

CHRONIC MYELOID LEUKEMIA (CML): DIAGNOSIS, TREATMENT AND SIDE EFFECTS MANAGEMENT

BEATING CANCER IS IN OUR BLOOD.



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LEARNING OBJECTIVES

- Describe the symptoms and treatment 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 the various roles the pharmacist plays in contributing to the management of patients with CML
- Describe strategies to manage treatment side effects as well as potential long-term and late effects of treatments for CML
- Describe the ways that the social worker can contribute to the management of patients with CML

BEATING CANCER IS IN OUR BLOOD.



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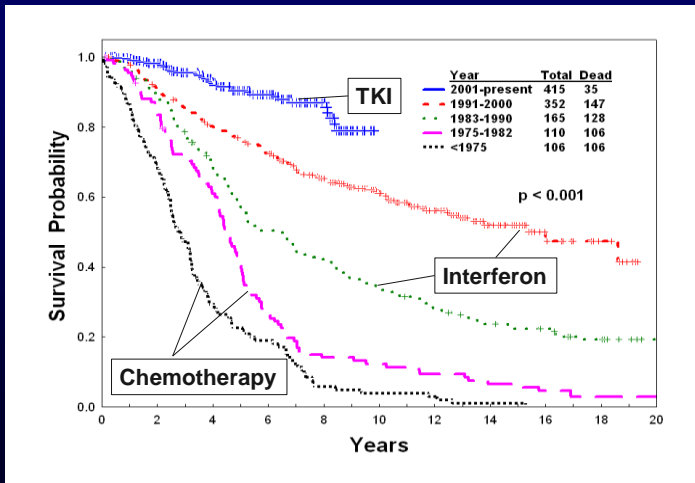
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CML: State of the Art

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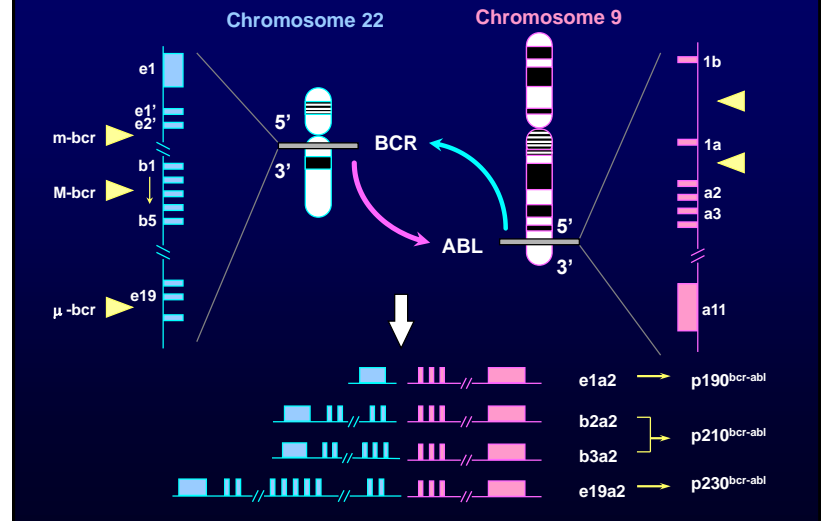
Survival in Early Chronic Phase CML



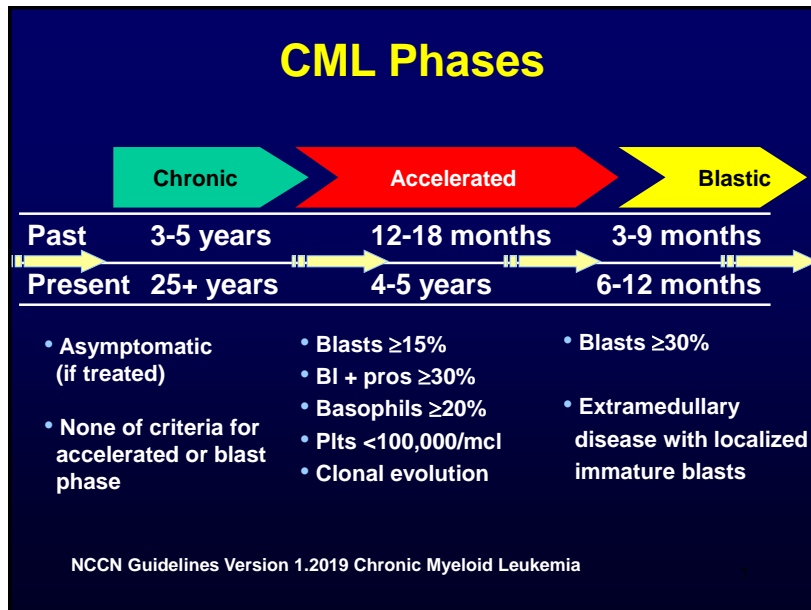
Kantarjian et al. Blood 2012; 119: 1981-7.

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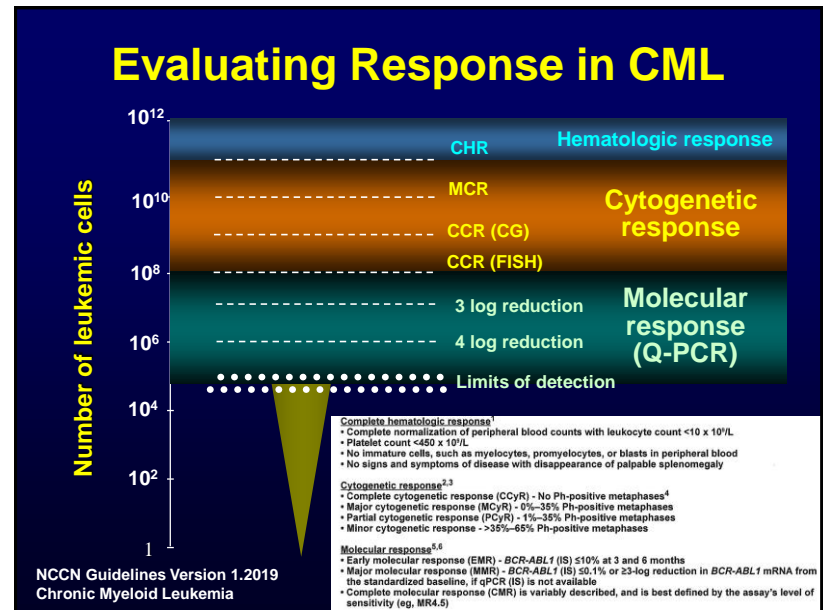
The Philadelphia Chromosome



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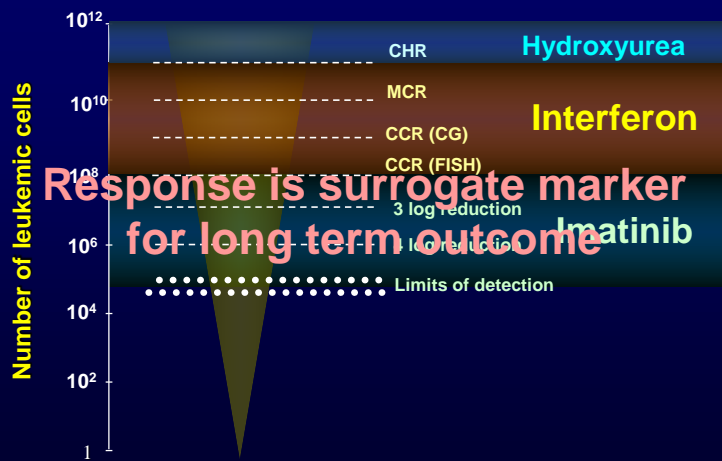


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Evaluating Response in CML



Response is surrogate marker for long term outcome

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Monitoring Procedures in CML

- **CG**: looks at all chromosomes; **but**: tedious; needs metaphases; only 20 cells counted (SD \pm 15%); painful BM biopsy
- **FISH**: faster; 200 cells; PB; **but**: false + up to 5%-10%; no information on other chromosomes
- **PCR**: most sensitive; PB; evaluable in CCyR; predicts for relapse; **but**: not standardized; no information on other chromosomes; variability up to 0.5 log; use 1 source (PB) and 1 reliable lab

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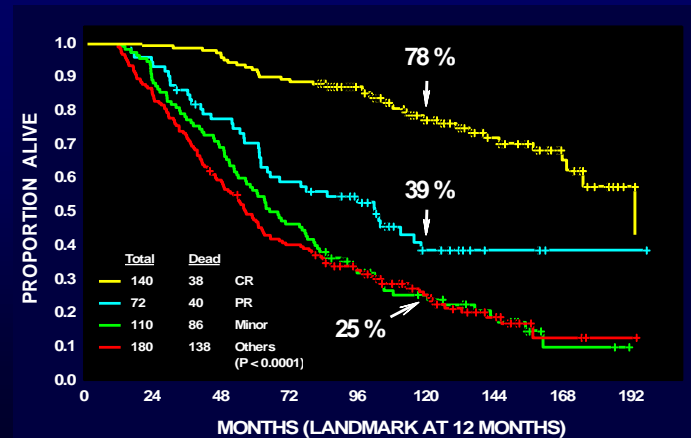
Definitions of Cytogenetic Response

Response	Criteria
Complete Hematologic Response	WBC $<10 \times 10^9/L$ Platelets $<450 \times 10^9/L$ PB myelo + metamyelo $<5\%$ No PB blasts + promyelo PB basophils $<20\%$ No extramedullary involvement
Cytogenetic*	% Ph+ Metaphases
Complete	0
Partial	1-35
Minor	36-95
	} Major

*Based on standard karyotype, 20 metaphases (not FISH)

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IFN α in CML Survival by CG Response



Kantarjian et al. Cancer 2003; 97: 1033.

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Molecular Response in CML*

- Real time PCR = BCR-ABL/control x 100
- Major molecular response (MMR)
 - BCR-ABL/control <0.1% (IS)
 - 3-log reduction (from standardized baseline)
 - Using reduction from individual baseline not validated
- Deeper responses:
 - MR4 ≤0.01%, MR4.5 ≤0.0032%
- Undetectable (“PCRu”) = PCR “negative”, sensitivity 4- to 5-log
 - CMR – controversial

* See Appendix 2 in transcript for further details on International Scale

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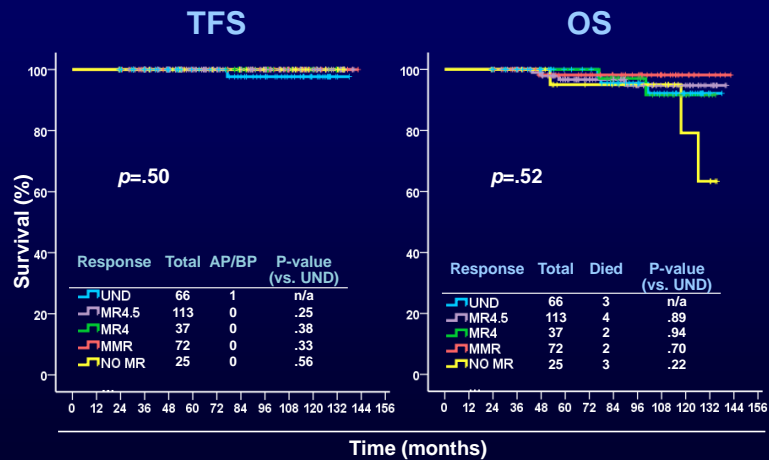
7-Year Outcome by Molecular Response – Only Patients With CCyR

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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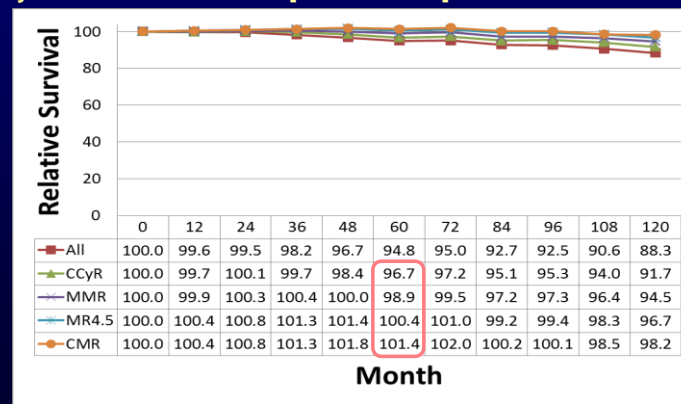
Molecular Response in CML TFS and OS by MR at 24 Months



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Relative Survival With TKI by Response to Therapy

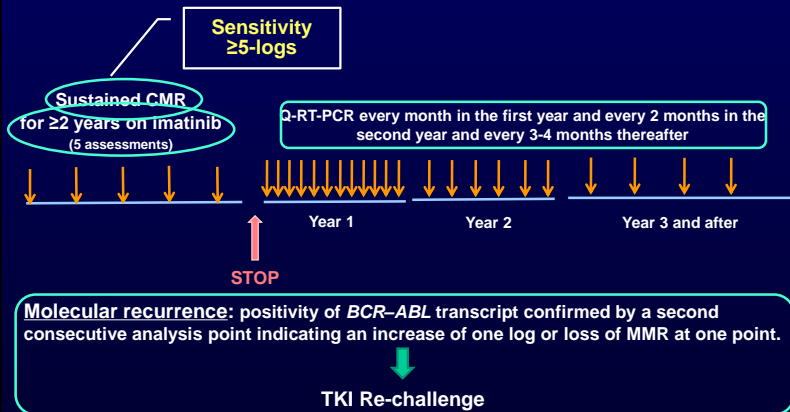
- 483 pts with CML treated with imatinib 400 mg (n=71), imatinib 800 mg (n=201), dasatinib (n=111), or nilotinib (n=101)
- 5-yr relative survival 94.8% [92.1% - 97.4%]



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Stop Imatinib (STIM) Study Design

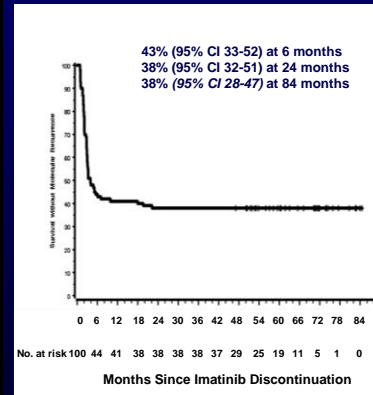
- 100 pts included
- Median follow-up 65 months



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

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STIM - Molecular Recurrence-Free Survival



- Median follow-up 65 mo
- No recurrence: 39 pts
 - 16 stable CMR
 - 23 intermittent positive
- Median time to recurrence: (n=61) 2.5 mo
- 17 lost MMR
- 57 restarted Rx:
 - 55 regained CMR
- Predictors of recurrence: sex, Sokal*

*See Transcript for definition of Sokal Scale

Etienne G, et al. *Blood.* 2015;126 [abstract 345].

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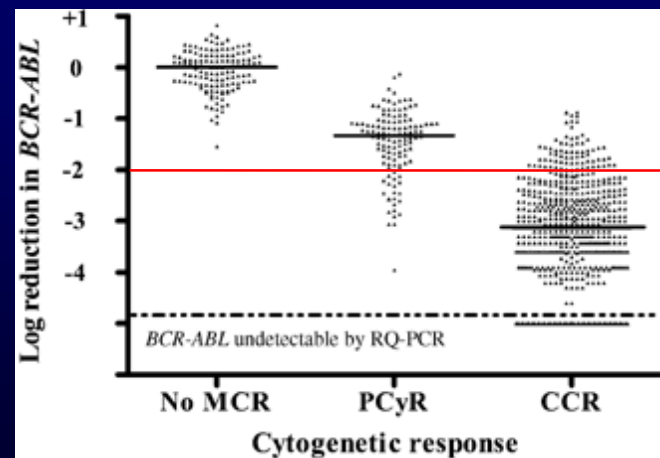
Monitoring Recommendations for CML According to the ELN 2013

When	What
At diagnosis	<ul style="list-style-type: none"> •CG (BM aspiration) •FISH (in case of Ph-) •Qualitative PCR
During treatment	<ul style="list-style-type: none"> •PCR (IS) every 3 mo until MMR, then every 3-6 mo •CG at 3, 6, and 12 mo (until CCyR) – Not needed if adequate PCR •FISH once CCyR achieved
Failure, progression	<ul style="list-style-type: none"> •PCR (IS), mutational analysis, cytogenetics •Immunophenotype for BP
Warning	<ul style="list-style-type: none"> •PCR and CG more frequently

Baccarani et al. Blood 2013; 122: 872-84.

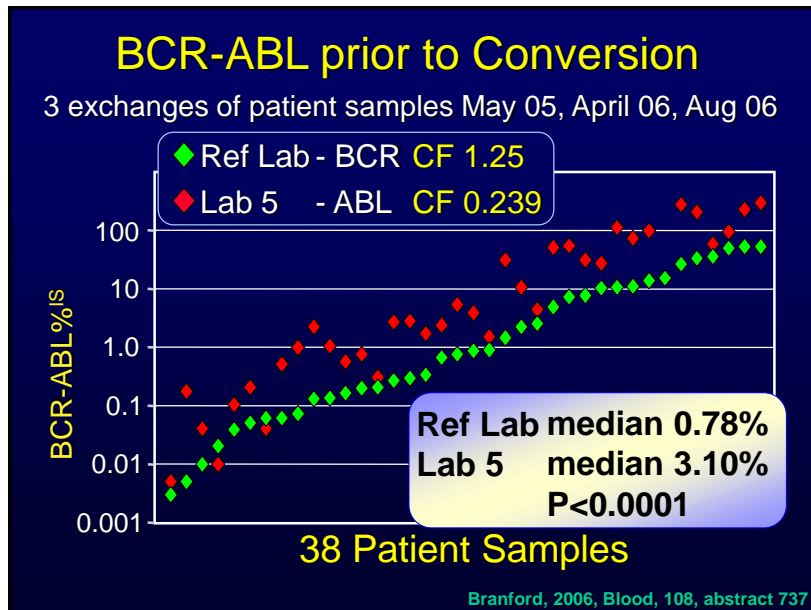
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Can PCR Replace Cytogenetic Analysis?

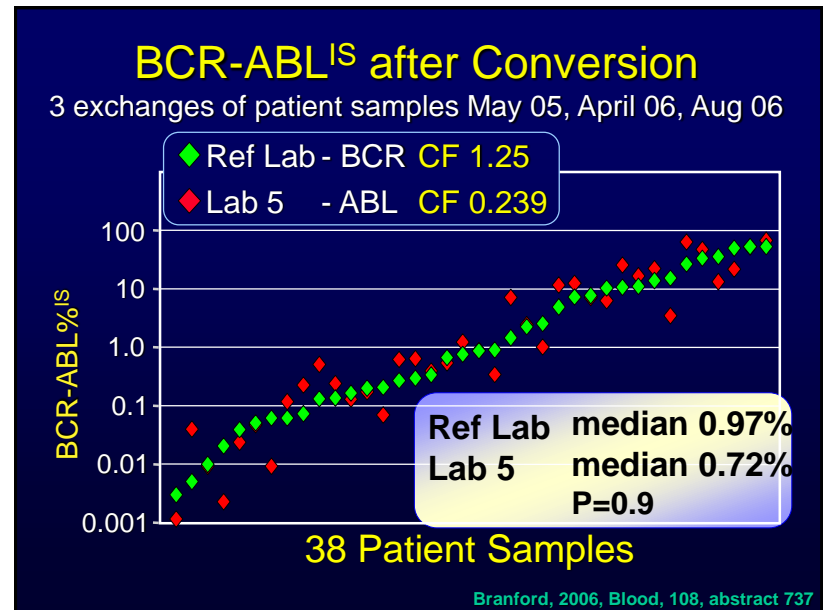


Ross DM et al. Leukemia 2006; 20: 664-70.

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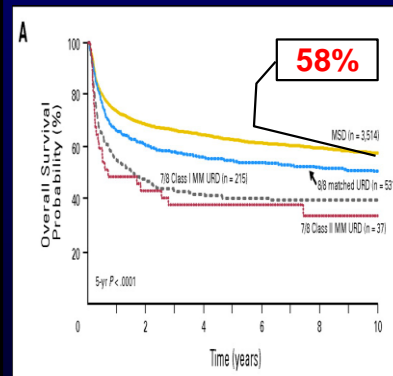
Frontline Therapy in CML

- Standard-dose imatinib
- High-dose imatinib
- Imatinib-based combinations
- Second-generation TKI
 - Dasatinib
 - Nilotinib
 - Bosutinib
- Stem cell transplant

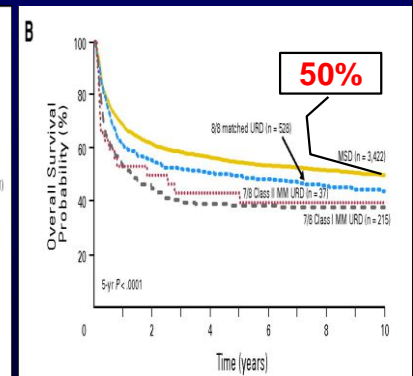
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SCT is Curative (for Some)

Overall Survival



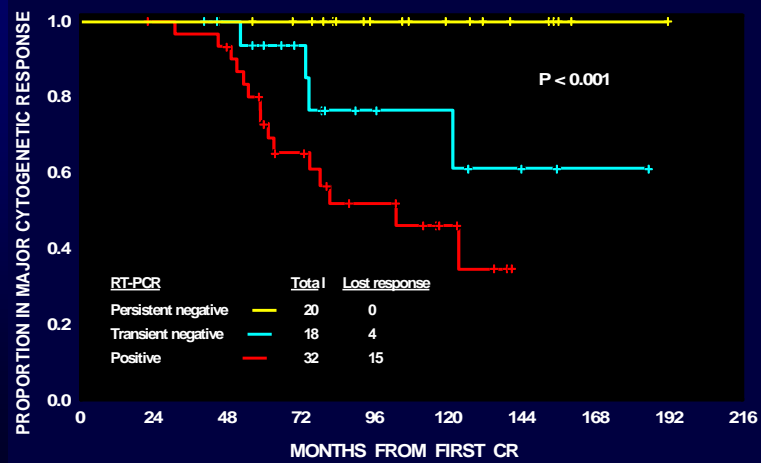
Leukemia-Free Survival



Arora et al. JCO 2009; 27: 1644-52.

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SCT is NOT the Only Curative Treatment for CML

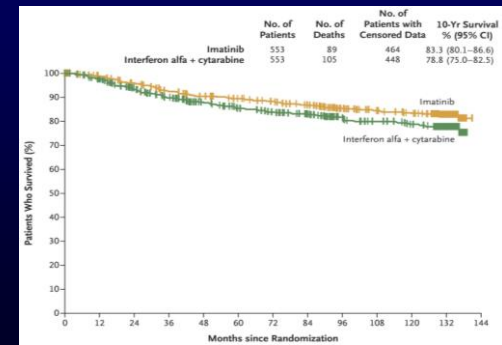


Kantarjian et al. Cancer 2003; 97: 1033.

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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%



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

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DASISION – The Final Report

- 519 pts randomized to dasatinib (n=259) or imatinib (n=260)
- Minimum follow-up 5 yrs

Outcome (%)	Dasatinib	Imatinib	P value or HR
Discontinued	39	37	
12m cCCyR	77	66	P=0.007
5y MMR	76	64	P=0.0022
5y MR4.5	42	33	P=0.025
3m <10%	84	64	
5y AP/BP	4.6	7.3	
5y OS	91	90	HR 1.01
5y PFS	85	86	HR 1.06

Cortes et al. ASH 2014; Abstract #154.

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ENESTnd – The 6-Year Report

- 846 pts: nilotinib 600 (n=282), nilotinib 800 (n=281), or imatinib (n=283)
- Minimum follow-up 6 yrs

Outcome (%)	Nil 600	Nil 800	Imatinib	P value or HR
Discontinued*	40	38	50	
5y MMR*	77	77	60	P<0.0001
6y MR4.5	56	55	33	P<0.0001
3m <10%	91	89	67	
6y AP/BP	3.9	2.1	7.4	P=0.06/0.003
5y OS*	94	96	92	HR 0.8/0.44
5y EFS*	95	97	93	HR 0.61/0.37

* 5-yr data from Larson et al ASCO 2014; Abstract #7073

Larson RA, et al. Blood. 2014; Abstract #4541.

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BFORE – The Initial Report

	% (95% CI)		OR (95% CI)	P Value
	BOS	IM		
MMR at 12 mo	47.2 (40.9–53.4)	36.9 (30.8–43.0)	1.55 (1.07–2.23)	0.02
BCR-ABL1 ≤10% at 3 mo	75.2 (69.8–80.6)	57.3 (51.0–63.5)	NA	<0.0001
BCR-ABL1 ≤1% at 6 mo	65.9 (59.9–71.8)	50.2 (43.9–56.5)	NA	<0.0001
CCyR by 12 mo	77.2 (72.0–82.5)	66.4 (60.4–72.4)	1.74 (1.16–2.61)	<0.01

- MMR rate at 12 mo higher with BOS vs IM in all Sokal risk groups: high (34% vs 17%), intermediate (45% vs 39%), and low (58% vs 46%)
- MMR rate at 12 mo similar in ITT population: BOS 47% vs IM 36%; $P=0.01$

NA=not available. High Sokal risk group: n=53 BOS, n=54 IM; intermediate: n=107 BOS, n=92 IM; low: n=86 BOS, n=95 IM.

Cortes et al. JCO 2017 [Epub ahead of print].

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TKI Frontline Therapy in CML Treatment Discontinuation

	Percentage			
	F/U (mo)	IM400	Nilotinib	Dasatinib Bosutinib
ENESTnd**‡	>50	49	38	
DASISION	>48	35		33
BELA	>24	29		37

* Nilotinib 300 mg BID shown.

‡ Includes patients who discontinued into extension study; rates are 34% imatinib and 29% nilotinib if all excluded

Saglio G, et al. ASH 2013; 92; Cortes et al. ASH 2013; 653; Cortes et al. ASH 2011; Abstract #455.

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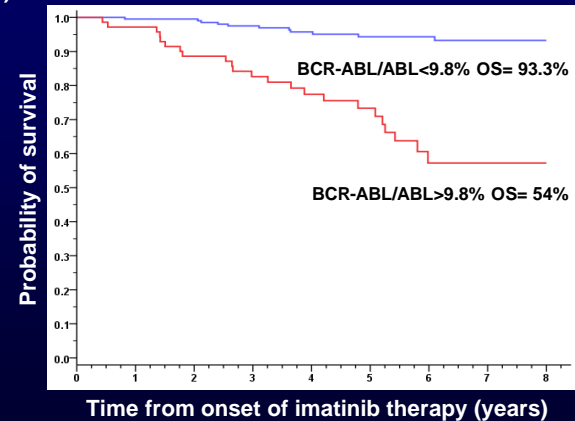
Factors Influencing Early Discontinuation of 2nd Generation TKI

- Adverse events
- Lack of efficacy
- Availability of alternative options
- Decrease tolerance to adverse events (AE)
- Unreasonable expectations regarding toxicity
- Suboptimal management of AEs
- Lack of familiarity

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Survival After Imatinib Therapy by Molecular Response Achieved at 3 Months

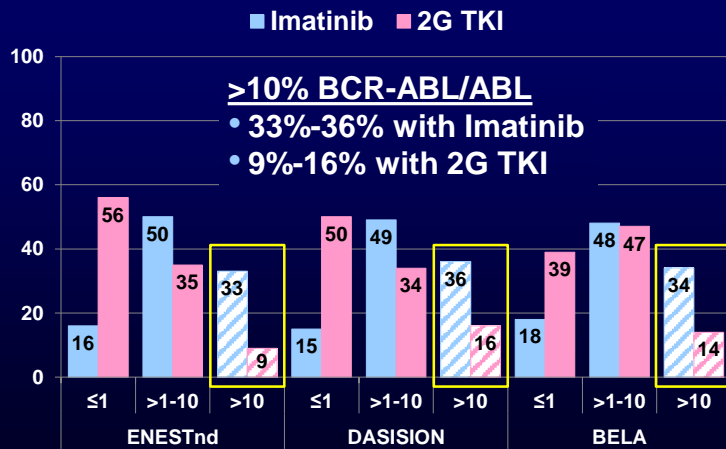
- Optimal PCR value determined by receiver Operating Characteristic (ROC) curve



Marin D, et al, *J Clin Oncol*. 2012; 30(3):232-238.

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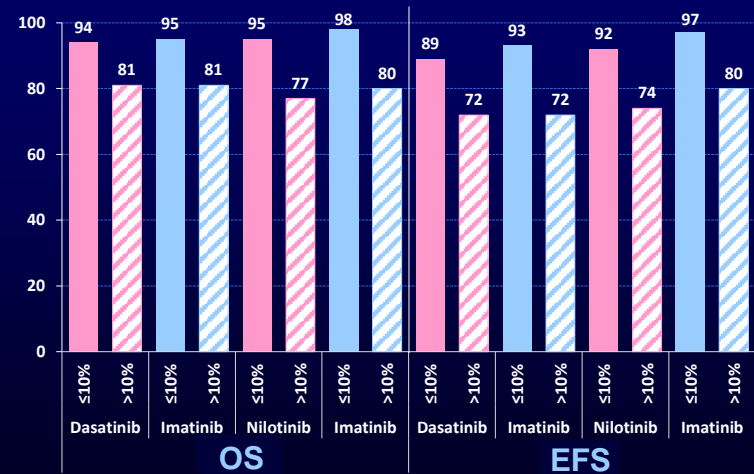
Molecular Response at 3 Months by Therapy



Hochhaus A, et al. *Blood*. 2012; 120:Abstract 167. Saglio G, et al. *Blood*. 2012; 120:Abstract 1675. Brummendorf TH, et al. *Blood*. 2012;120: Abstract 69.

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OS and EFS by 3-Month Response in DASISION and ENESTnd



Larson et al. *Blood*. 2014; Abstract #4541; Cortes et al. *JCO* 2016; 34: 2333-40.

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Early Response to TKI: 3 Months or 6 Months?

- 58/489 (12%) pts on frontline TKI had no MCyR at 3 months
- 5-y EFS 77%, OS 88%, TFS 94%
- By 6 months, 52 (90%) still on TKI (4 intolerance, 1 loss CHR, 1 BP)

5-yr Outcome	% by Response at 6 months	
	MCyR	No MCyR
OS	100	79
EFS	85	66
TFS	95	94

- **Conclusion: Waiting for 6 month response better discriminates for poor outcome.**

Nazha et al. Haematologica 2013; 98: 1686-8.

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Effect of Reduced Dosing on 3 Month PCR by Total Dose and Number of Missed Days

Percent prescribed dose	Imatinib		Dasatinib	
	No. (%) (N=327)	3 mo PCR <10%	No. (%) (N=315)	3 mo PCR <10%
100%	272 (83)	78%	222 (71)	96%
80%-99%	42 (13)	62%	48 (13)	85%
<80%	13 (4)	46%	45 (4)	80%
Total missed days	13.5 (1-48)		14 (1-58)	
median (range)				
0	272 (83)	78%	222 (71)	96%
0-14	41 (13)	59%	48 (15)	85%
>14	14 (4)	57%	45 (14)	80%

- Probability of achievement of RQ-PCR <10% decreases with increased numbers of missed doses and decreased total dosing

Apperley JF, et al. Blood. 2013;122: Abstract 93.

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Dasatinib in CML Chronic Phase After Imatinib Failure

- 670 pts randomized to 4 dasatinib schedules
- 6-year follow-up

Outcome (100 mg/d)	Percent
MCyR / CCyR (within 2 yr)	63 / 50
IM Resistant	59 / 44
IM Intolerant	77 / 67
MMR	37
6-yr OS	71
6-yr PFS	49
6-YR TFS	76
Discontinued treatment	69

Shah et al. Blood 2014 [Epub ahead of print].

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Nilotinib in CML Chronic Phase Post Imatinib Failure

- 321 pts with imatinib resistance (71%) or intolerance (29%)
- Minimum 48 mo follow-up
- Nilotinib 400 mg PO BID

Outcome	Percent
- CHR	85
- MCyR / CCyR	59 / 45
Resistant*	56 / 41
Intolerant*	66 / 51
- 48-month OS	78
- 48-month PFS	57
Discontinued treatment	70

- Median dose intensity 789 mg/d

* 24 mo data; no additional MCyR after 24 mo; 5 pts improved from MCyR to CCyR after 24 mo.

Kantarjian et al. Blood 2011; 117: 1141-5.
Giles et al. Leukemia 2013; 27: 107-12.

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2nd-line Bosutinib in CP- CML: 8-Year Update Efficacy Summary

- Phase 1/2 bosutinib 500 mg/d
- 284 pts: imatinib resistant 195, intolerant 89
- Median age 53 y (18-91 y), prior IFN 35%, SCT 3%

n (%)	Imatinib-resistant	Imatinib-intolerant	Total
Cytogenetic responses			
Evaluable patients [†]	182	80	262
MCyR	110 (60)	48 (60)	158 (60)
CCyR	89 (49)	41 (51)	130 (50)
Survival outcomes			
Cumulative incidence of progression [‡] or death	57 (29)	10 (11)	67 (24)
Deaths	40 (21)	11 (12)	51 (18)

- New toxicities year 5-8: renal (14%), diarrhea 1 (0.8%), liver 7 (6%)
- Vascular events (per 100 pt/year): cardiovascular 0.008, cerebrovascular 0.005, peripheral vascular 0.001

Brummendorf et al. ASH 2017; abstract #900.

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2nd-Generation TKI in CP CML Post Imatinib Failure

Toxicity	Dasatinib	Nilotinib	Bosutinib
Pleural effusion	++	-	-
Liver	+	+	+
Transaminases	+	+	++
Bilirubin	-	++	-
Rash	+	+	++
Diarrhea	-	-	++
Lipase	- (+)	++	-
Glucose	-	++	-
Hypophosphatemia	++	++	+
Bleeding	+	-	-
QTc	++	++	-

Shah et al. Haematologica 2010; 95: 232-40; Kantarjian et al. Blood 2011; 117: 1141-45.
Cortes et al. Blood 2011; 118: 4567-76.

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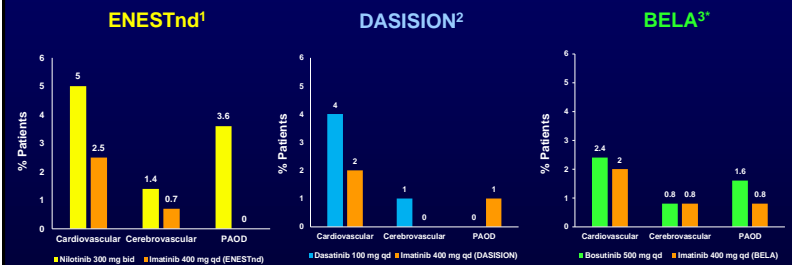
2nd-Generation TKI in CP-CML Post Imatinib Failure

Toxicity	Dasatinib	Nilotinib	Bosutinib
Anemia	13	11	13
Neutropenia	35	31	18
Thrombocytopenia	23	30	24

Shah et al. Haematologica 2010; 95: 232-40.
Kantarjian et al. Blood 2011; 117: 1141-45.
Cortes et al. Blood 2011; 118: 4567-76.

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Ischemic Events by TKI From Randomized Trials



* Median exposure 55 months (0.03-69.4)

¹Hochhaus et al. Leukemia 2016; 30: 1044-54; ²Cortes et al. JCO 2016; 34: 2333-40;
³ Cortes JE, et al. Am J Hematol. 2016;91(6):606-616.

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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.

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Sensitivity of Mutations to TKI

	IC ₅₀ -fold increase (WT=1)			
	Imatinib	Bosutinib	Dasatinib	Nilotinib
WT	1	1	1	1
L248V	3.54	2.97	5.11	2.80
G250E	6.86	4.31	4.45	4.56
Q252H	1.39	0.31	3.05	2.64
Y253F	3.58	0.96	1.58	3.23
E255K	6.02	9.47	5.61	6.69
E255V	16.99	5.53	3.44	10.31
D276G	2.18	0.60	1.44	2.00
E279K	3.55	0.95	1.64	2.05
V299L	1.54	26.10	8.65	1.34
T315I	17.50	45.42	75.03	39.41
F317L	2.60	2.42	4.46	2.22
M351T	1.76	0.70	0.88	0.44
F359V	2.86	0.93	1.49	5.16
L384M	1.28	0.47	2.21	2.33
H396P	2.43	0.43	1.07	2.41
H396R	3.91	0.81	1.63	3.10
G398R	0.35	1.16	0.69	0.49
F486S	8.10	2.31	3.04	1.85

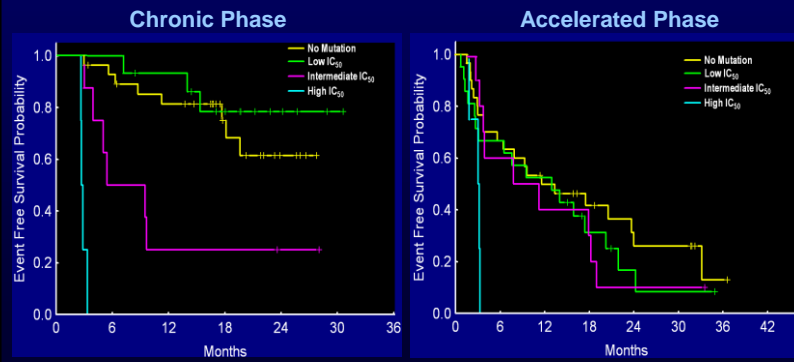
Highly Resistant / Resistant / Sensitive

Redaelli et al. JCO 2009; 27: 469-71.

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CCyR by Mutations in CML Treated with 2nd Generation TKI after IM Failure

- 86/169 (51%) pts treated had mutation
 - CP 30/59 (51%), AP 41/71 (58%), BP 15/39 (38%)
- IC₅₀ for dasatinib, nilotinib predictive for response in CP and AP



Jabbour et al, Blood 2009; 114: 2037-43.

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Response to Bosutinib 3rd – Line Therapy

- Dual Src & Abl inhibitor, no effect over c-kit or PDGFR
- 114 pts who failed imatinib (600 mg) & dasatinib or nilotinib

Response, %	IM + D resistant (n=37)	IM + D intolerant (n=50)	IM + NI resistant (n=27)
CHR	68	76	76
MCyR	39	42	38
CCyR	22	40	31
PCyR	17	2	7
MMR	3	25	11
2-yr PFS	65	81	77

IM, imatinib; D, dasatinib; NI, nilotinib.

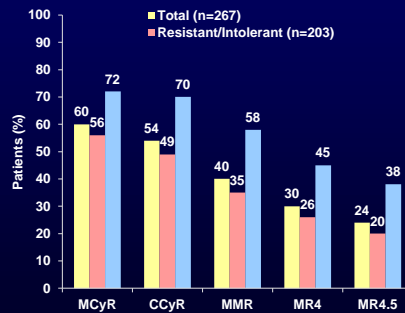
Gambacorti-Passerini et al. ASH 2014; abstract 4559.

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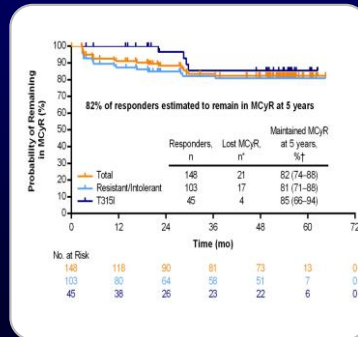
Efficacy of Ponatinib in CP-CML

- 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 018.2.

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Omacetaxine for CP-CML After Failure to ≥ 2 TKI

- 122 pts with CP-CML (n=81) or AP-CML (n=41) with ≥ 2 prior TKI
- Omacetaxine 1.25 mg/m² BID x 14d, then x 7d

Response, %

	CP N=81	AP N=41
--	------------	------------

Primary endpoint	MCyR 20%	MaHR 27%
	CCyR 10%	CHR 24%
Median duration, mo	17.7	9
Median PFS, mo	9.6	4.7
Median OS, mo	33.9	16

- 11 pts (9 CP, 2 AP) ongoing response
- Median 35 cycles over median 39 months
- Median response duration: 14 mo CP, 24 mo AP

Kantarjian et al. Blood 2012; Abstract #2787.

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Optimizing Frontline CML Therapy in 2018

- Excellent therapy for CML available
- Optimizing therapy is much more than comparing drugs
- Progress in management lagging progress in treatment
- Clinical trials still needed
- CML not a disease of the past

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Questions?

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Pharmacist's Role in Managing Patients with Chronic Myeloid Leukemia

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THE UNIVERSITY OF TEXAS
MDAnderson
Cancer Center
Making Cancer History®

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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
 - Medication access
 - Patient and caregiver education
 - Patient and provider information resource

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Patient Case

- MM is an 71-year-old female with a diagnosis of CML since 2002. 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.

CML, chronic myeloid leukemia; CMR, complete molecular response; PCR, polymerase chain reaction

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Screening for Drug-Drug Interactions

- All TKIs are metabolized via cytochrome P450 enzymes, especially CYP3A4
 - All are major CYP3A4 substrates except ponatinib
 - Metabolism affected by concomitant moderate or strong CYP3A4 inducers or inhibitors
- Avoid concomitant QT interval prolonging agents with nilotinib
- Concomitant acid-reducing medications can affect nilotinib, dasatinib, and ponatinib absorption
- Drug-Food Interactions
 - Nilotinib must be taken on an empty stomach
 - Avoid foods that inhibit CYP3A4 (grapefruit, star fruit, Seville oranges)

CYP, cytochrome P450; TKI, tyrosine kinase inhibitor

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Screening for Drug-Disease Interactions

- QT prolongation (nilotinib, dasatinib, bosutinib)
 - EKG monitoring recommended for nilotinib
- Cardiac and vascular toxicities
 - All TKIs may lead to an increased risk of one or more CV toxicities such as CHF, thrombosis, hypertension
 - POAD most reported with nilotinib and ponatinib
 - Manage CV risk factors, monitor closely
- Pancreatitis (nilotinib, ponatinib)
 - 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)

CHF, congestive heart failure; POAD, Peripheral occlusive arterial disease; CV, cardiovascular; EKG, electrocardiogram;
TKI, tyrosine kinase inhibitor
Saglio G, et al. *Blood* 2010; 116: 3430 (abstract).

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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 to:
 - discontinue medications (aRR = 1.7; 95% CI 1.3-2.22)
 - be nonadherent (aRR = 1.42; 95% CI 1.19-1.69).

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.

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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

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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 adverse effects (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 with 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 – affects 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 ($\leq 90\%$ vs $>90\%$) was the only independent predictor of CMR on multivariate analysis (RR = 19.35; $p = 0.004$).
- Pharmacist-managed oral anticancer therapy program in CML patients (N = 56)
 - Higher adherence rate (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.

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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.

INR, international normalized ratio; CML, chronic myeloid leukemia; GI, gastrointestinal

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

AE, adverse event

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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
 - 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)
 - UpToDate (www.uptodate.com)
- 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 (www.mascc.org/maatt)
 - ONS (<https://www.ons.org/practice-resources/toolkits/oral-adherence>)

ASCO, American Society of Clinical Oncology; NCCN, National Comprehensive Cancer Network; MASCC, Multinational Association of Supportive Care in Cancer; ONS, Oncology Nursing Society; PCR, polymerase chain reaction.

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
 - medication access
 - patient and caregiver education, or
 - guiding patients and providers to appropriate resources.

CML, chronic myeloid leukemia.

CML: TKI SIDE EFFECTS and MANAGEMENT

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Adverse Effect Profiles

Class Effects

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

Agent Specific Effects

- **Imatinib**: *hepatotoxicity, pancreatitis, 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*

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

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Imatinib (Gleevec®) 1

- **Fatigue:**
 - Can occur with all TKIs
 - Hydration and exercise can decrease intensity
 - Try adjusting time of administration
- **Nausea:**
 - Improves over time
 - Give antiemetics prior to medication
 - Take medication with a cracker or ginger candy
- **Fluid retention:**
 - Periocular, worse in AM
 - Cold compresses and application of hydrocortisone cream
 - Extremity or abdominal fluid
 - Low-sodium diet and diuretics can help
- **Muscle cramping:**
 - Most common long-term side effect
 - Adequate hydration; tonic water, tomato juice
 - Potassium supplements, magnesium supplements



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Imatinib (Gleevec®) 2

- **Weight gain:**
 - Low carbohydrate diet to decrease weight/prevent gain
- **Diarrhea:**
 - OTC antidiarrheals, probiotics
- **Increase in serum creatinine**



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Imatinib (Gleevec®) 3

• Generic vs. branded form of imatinib:

- Studies show very little difference in efficacy¹
- Little difference in cost
- Financial assistance may be available for copay from Novartis Pharmaceuticals Corporation (Novartis), maker of Gleevec (imatinib)
- After insurance company denial for branded drug, other support may be available from Novartis
- The Leukemia & Lymphoma Society offers financial guidance. Visit lls.org/support/financial-support



¹ Kozaric, Amina Kurtovic et al "The Comparison of Efficacy Between Generic and Branded Imatinib in Achievement of Overall Survival and Cytogenetic Responses in CML Patients in Bosnia and Herzegovina." *Blood* 128.22 (2016): 5451. Web. 28 Nov. 2018.

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Nilotinib (Tasigna®) 1

- Elevated blood sugar:
 - Avoid administering to known diabetic patients
- Abnormal liver enzymes, specifically indirect bilirubin:
 - May require dose adjustment
 - Direct bilirubin is normally not affected
- Increased cholesterol:
 - Monitor every 6 months
 - Monitor EKGs
 - Potentially avoid use in patients with history of cardiac events
- Skin rash:
 - Occurs with most TKIs to varying degrees
 - Moisturizing skin creams with mild exfoliant, hyaluronic acid, or salicylic acid
 - Avoid prolonged sun exposure



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Nilotinib (Tasigna®) 2

- Avoid drug-food interactions (applies to all TKIs):
 - No grapefruit, star fruit, and Valencia oranges
 - These foods can increase the amount of TKI in the bloodstream
- Avoid drug-drug interactions:
 - Most common are fluconazole, ciprofloxacin, diltiazem, verapamil -> increased TKI
 - Many HIV medications will *increase* the amount of the TKI in the blood stream
 - Rifampin, nafcillin, St. John's wort all *decrease* the amount of the TKI in the bloodstream

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Dasatinib (Sprycel®)-1

- Headache:
 - Acetaminophen or NSAIDs in moderation
- Diarrhea:
 - OTC antidiarrheal, probiotic
 - Adequate hydration, mild foods
 - Avoid spicy foods, fatty foods, and decrease caffeine
- Nausea and vomiting:
 - Frequent, small amounts of fluid
 - Mild foods (BRAT diet)
 - Antiemetics



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Dasatinib (Sprycel®)- 2

- Low blood counts:

- Do not panic with high white blood cell counts, dasatinib will bring that down quickly
- With too much hydroxyurea while waiting to start the dasatinib, there will be a start and stop syndrome, when the counts are too low, which may lead to drug resistance and delay of the MMR. So keep the WBC in the 35k-40k range

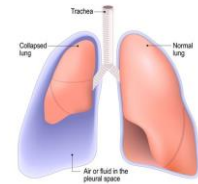


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Dasatinib (Sprycel®)- 3

- Pleural effusions:

- Specific to this TKI; may occur at any time
- Possible slight increase in the incidence after a respiratory viral infection
- Early identification is important
- Watch for decreased breath sounds at the bases and a persistent dry cough on deep inspiration



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Dasatinib (Sprycel®)- 4



• Pleural effusion:

- Chest X-ray for confirmation
- If positive, medication must be stopped
- Possible interventions: diuretics, steroids, antibiotics
- Based on PCR level, resume dasatinib at the same or lower dose after effusion clears

• Possible prevention:

- Saline nasal wash BID to each nostril – to wash off the virus from the nasal passages

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Bosutinib (Bosulif®) - 1



• Diarrhea:

- Decreases over time
- On medication start day, caution to stay at home; diarrhea onset is very rapid
- Keep hydrated, OTC antidiarrheals – may take 6 to 8 pills/day
- Eat mild foods
- Use with caution with renally impaired patients

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Bosutinib (Bosulif®) - 2

- **Stomach pain:**
 - All TKIs are best absorbed in the presence of stomach acid, so to prevent delayed and malabsorption, avoid pantoprazole, esomeprazole, omeprazole, or rabeprazole
 - 2 hours pre or post the medication you can give Maalox® (aluminum hydroxide, magnesium hydroxide, and simethicone), cimetidine, famotidine, ranitidine, or Tums® (calcium carbonate)
- **Rash:**
 - May be severe during the first month of therapy, requiring discontinuation of the medication
 - Skin assessment with lab assessments

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Concomitant Acid Suppressive Therapies

- **Imatinib***: no recommendations to avoid any acid suppressing therapies
- **Dasatinib**: avoid concomitant use of H2As and PPIs; avoid use of antacids 2 hours before or after any dasatinib dose
- **Nilotinib***: avoid concomitant use of PPIs; avoid use of H2As 10 hours before or 2 hours after any nilotinib dose; avoid use of antacids 2 hours before or after any nilotinib dose
- **Bosutinib***: consider alternatives to concomitant PPIs; avoid use H2As or antacids 2 hours before or after any bosutinib dose
- **Ponatinib**: concomitant acid suppressive therapy should be avoided if possible
- It may not be possible to avoid concomitant acid suppressive therapy. In that case, monitor patients closely for signs of reduced efficacy of the TKI.

H2A – H2 antagonist, PPI – proton pump inhibitor

*Nilotinib must be taken on an empty stomach (no food 2 hours before or 1 hour after each dose). Imatinib and bosutinib are recommended to be taken with food. Dasatinib and ponatinib may be taken with or without food.

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Bosutinib (Bosulif®) -3

- Low blood counts:
 - With initial treatment, weekly counts to monitor trends
 - When counts stabilize, change to twice monthly, then progress to every 3-6 months
 - Initial PCR testing every 3 months, then every 6 months when stable
- Fluid retention:
 - May manifest as pericardial effusion, pleural effusion, pulmonary edema and/or peripheral edema. This is rare, but possible.



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Ponatinib (Iclusig®)-1

- Similar side effects with other TKIs:
 - Skin rash, fatigue, headache, stomach pain, and arthralgias
- It is the only TKI used in the resistance mutation T315I; also used in Ph+ ALL
 - The initial dose was 45 mg daily
 - Blood clots, arterial spasms, thromboembolic events, and hepatotoxicity were seen with this initial dosing

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Ponatinib (Iclusig®)-2

- Medication is used with caution.
 - Current dose is 30 mg daily which can be decreased to 15 mg daily
 - Evaluate signs and symptoms (S/S) such as pain (anywhere), shortness of breath, cramping
 - All these S/S need investigation and necessitate holding the medication



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New on the Block: TKI Discontinuation Syndrome-1

- Since the initial use of imatinib and the newer TKIs, people are living longer
 - Patients who have been PCR negative (totally negative) after 5 consecutive years may discontinue their medication
 - Should be monitored on a clinical trial
 - Monitor the PCR every 2 months for the first 2 years, then every 3 months
- If there is any detection of disease with the PCR test, a TKI is resumed
 - Can be resumed at a low dose and monitored for response



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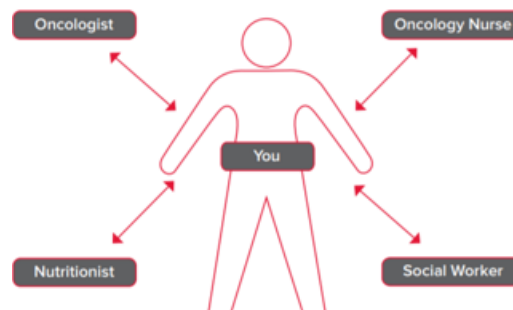
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PSYCHOSOCIAL IMPACT OF CML DIAGNOSIS AND TREATMENT



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PSYCHOSOCIAL IMPACT OF CML DIAGNOSIS/TREATMENT

□ Impact of *any* Cancer Diagnosis

- “You don’t look sick”!
- “You have the *good* (blood) cancer”
- All the “what ifs”

□ Treatment Choice/Side Effects/Adherence

- TKI choice/adherence
- Drug-food interactions – imatinib/sprycel vs nilotinib
- Adverse/side effects – communicate to healthcare team
- Monitoring guidelines – achieving “milestones” and “log reduction”
- Potential for lifelong TKI therapy

□ Resistant or Intolerant CML

- “Why me?”
- Considering clinical trials as treatment option
- Allo transplant for CURE??

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PSYCHOSOCIAL IMPACT OF CML DIAGNOSIS/TREATMENT CONT'D

□ Access and Financial Concerns

- Availability, but access challenges – currently no Co-Pay programs
- Financial toxicity...high out-of-pocket costs more likely to:
 - Discontinue medications
 - Be non-adherent
- Insurance plans when moving from Employer-based to Medicare

□ Treatment Free Remission/Discontinuation

- Is there a “right” time to discuss TFR?
- “If it ain’t broke”
- Relapse following TFR – frustration/fear/anger
- 2nd trial of TFR - anxiety
- TKI Withdrawal syndrome

□ Family Planning

- Currently issue for potential mother – need to PLAN
- Fertility preservation costs

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TEAM APPROACH TO PSYCHOSOCIAL ISSUES

When counseling and support from the team may be needed:

□ For the patient

- Concern about being unable to care for self, or others to extent prior to diagnosis.
- Concerns about physical side effects of treatment – fatigue, muscle cramps, nausea, rash, cytopenias
- Anxiety and/or depression
- Worry about lack or loss of income and cost of TKI
- Wonder when, if and how to reveal diagnosis to family members, friends, co-workers
- Family planning

□ For the family/loved ones:

- Concerns about balancing family responsibilities and caring for patient's initial needs
- Potentially caring for other family as well- children, elderly parents or relatives
- Frequent medical visits in early months
- Self-care for the caregiver
- Access/cost of TKIs

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WHAT PATIENTS/FAMILIES NEED TO KNOW

Frequently the following are the responsibility of the social worker:

- Providing clear directions for the patient and caregiver about what to expect, and what is expected of them, throughout cancer journey.
- Discussing family planning issues and identifying resources.
- Helping patient communicate with HCPs, family, friends, employers
- Working with patient to encourage staying physically active
- Recognizing and discussing (potential) financial impact on the patient and caregiver. Currently TKIs are lifelong treatment.
- Assessing for emotional impact of treatment on patients and caregivers - anxiety, depression, anger-and be prepared to provide support and resources.
- Discussing programs/services currently available and connecting families with full array of services offered at the institution (social work, nutrition, integrative medicine, support groups, financial assistance, etc.) and in the community.

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CURRENT AND RELEVANT INFORMATION

Supporting Patients and Loved Ones



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RESOURCES AND INFORMATION

□ National Organizations

- Leukemia & Lymphoma Society – www.LLS.org
- American Cancer Society – www.cancer.org
- Cancer Support Community – www.cancersupportcommunity.org
- National Cancer Institute – www.cancer.gov
- National Comprehensive Cancer Network - www.nccn.org

□ Help and Information - LLS

- Free Information Booklets
- Telephone/Web Education Programs
- Financial Assistance
 - Co-Pay
 - Travel Assistance
 - Referral to Medication Access programs
- Finding Support
 - Information Resource Specialists:
 - Phone: (800) 955-4572, M-F, 9 a.m. to 9 p.m. ET
 - Email: infocenter@LLS.org
 - Online Chat
 - LLS Chapters
 - LLS Community (social media platform)
 - Patti Robinson Kaufman First Connection Program (peer-to-peer)
 - One-On-One Nutrition Consultations (PearlPoint)

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IN SUMMARY

*With communication comes understanding and clarity;
With understanding, fear diminishes;
In the absence of fear, hope emerges;
And in the presence of hope, anything is possible.*

**Ellen Stovall
Past President & CEO,
National Coalition for Cancer Survivorship**



BEATING CANCER IS IN OUR BLOOD.



THANK YOU

BEATING CANCER IS IN OUR BLOOD.

