What's on the Horizon for Chronic Myeloid Leukemia?

LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers
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Welcome & Introductions

Dr. Mauro's slides are available for download at www.LLS.org/programs

Wednesday, September 27, 2017 1

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1884

What's on the Horizon for Chronic Myeloid Leukemia?

Michael J. Mauro, MD
Clinical Director, Leukemia Service
Leader, Myeloproliferative Neoplasms Program
Memorial Sloan Kettering Cancer Center, New York, NY

CYCLE FOR SURVIVAL · THE NATIONAL CML SOCIETY · LEUKEMIA & LYMPHOMA SOCIETY® · TEAM IN TRAINING · TEAM922 · What Is My PCR? · ASK ME · MyPCR.org · MEMORIAL SLOAN KETTERING CANCER CENTER · FRED'S TEAM · IMAGINE A WORLD WITHOUT CANCER · iCMLf · H. JEAN KHOURY CURE CML CONSORTIUM · The Max Foundation

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SEPTEMBER is Blood Cancer Awareness Month.

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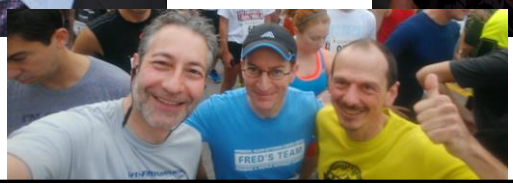
Disclosure

Michael J. Mauro, MD, has affiliations with Bristol Myers Squibb and Pfizer *(Consulting);* Novartis Oncology and Takeda *(Grant Support).*

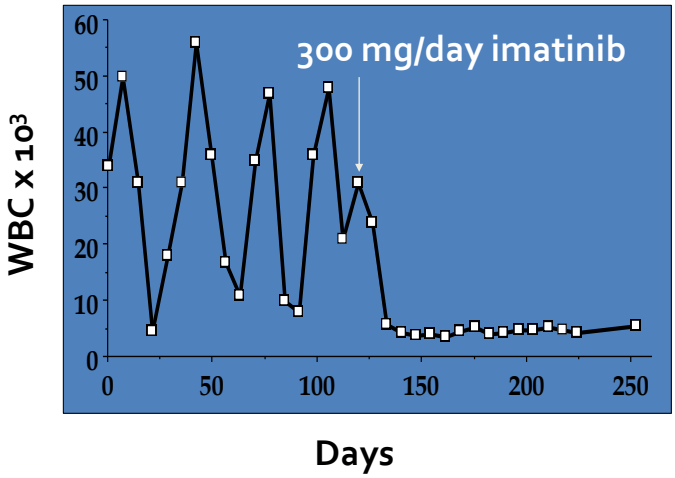
Prof. H. Jean Khoury, Atlanta

Dedicated to CML Leaders Lost in 2017

Prof. Tessa Holyoake, Glasgow



Almost 20 y have passed:
STI571 pt 0101 (first Portland patient, 1998)
from chaos to rapid hematologic response



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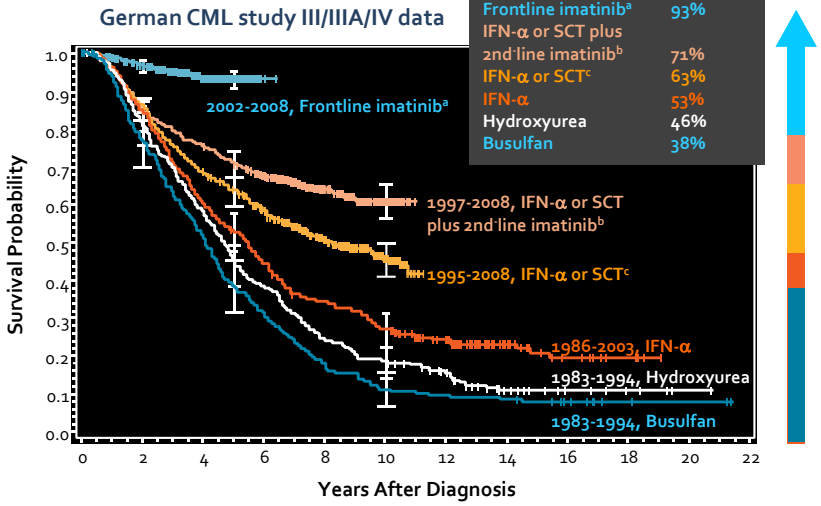
Imatinib changed the way we treated CML and was the beginning of a new era

German CML study III/IIIA/IV data

Best available therapy	*5-year OS*
Frontline imatinib[a]	93%
IFN-α or SCT plus 2nd line imatinib[b]	71%
IFN-α or SCT[c]	63%
IFN-α	53%
Hydroxyurea	46%
Busulfan	38%



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Adapted from Hehlmann R., German CML Study Group.

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

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

First description of CML

Fowlers's solution -1% arsenic trioxide

Staining methods for blood

Radiotherapy

Busulfan

Hydroxyurea

BMT

Interferon

Imatinib

Dasatinib

Nilotinib

Bosutinib

Ponatinib

Generic Imatinib

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

1960: Nowell & Hungerford describe the Philadelphia Chromosome

1973: Janet Rowley describes the 9:22 translocation

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

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

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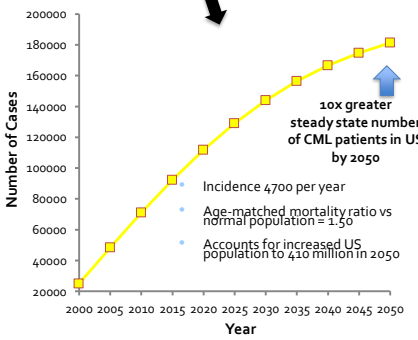
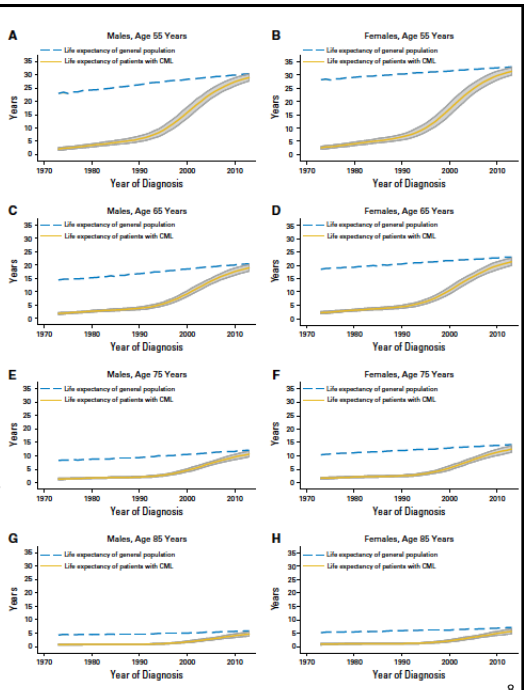
CML is an increasingly prevalent and survivable cancer

lifespan ➡

prevalence ⬇





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

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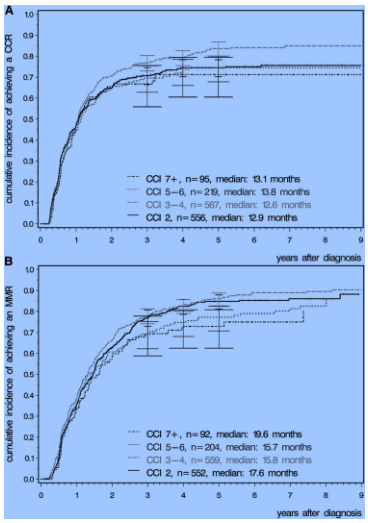
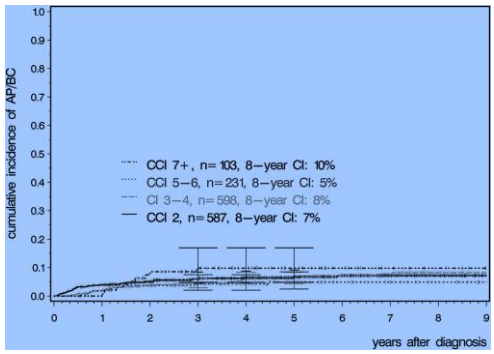
CML response not different in presence of other health problems: 'Comorbidity Index' Study



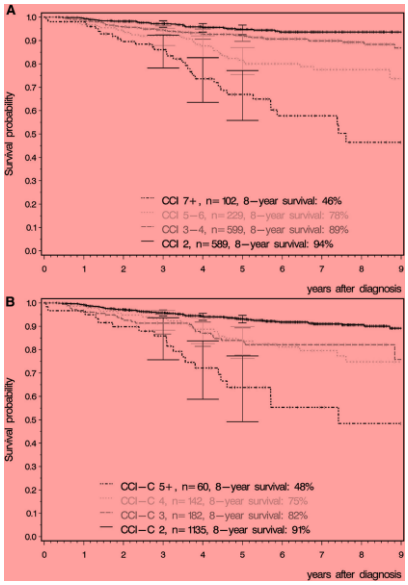


As measured by the Charleson Comorbidity Index (CCI)

blood 9

Saußele S et al. Blood 2015;126:42-49

Living with CML: Other health issues *more* important (impact longevity)



Charlson Comorbidity Index (CCI) calculated *age included*

Internist before Hematologist: Taking care of the *whole* patient

Charlson Comorbidity Index (CCI) calculated *age not included*

blood 10

Saußele S et al. Blood 2015;126:42-49

How common are other health problems in CML patients?

Table 3. All countries, chronic phase, baseline characteristics, recorded before any therapy ($n = 2388$)

Hematologic values		*Spleen*		*Comorbidities (n = 2360)*	
Hb (g/dl), males, median ($n = 1\,286$)	12.5	**Spleen, cm**[@], median ($n = 2331$)	0	Hypertension	25.7%
Hb, males, < 8.0	3.0%	Spleen, cm[@], 0 (non palpable)	53.5%	Cardiovascular disorders	17.2%
Hb, males, 8.0–12.0	39.7%	Spleen, cm[@], >0–4	19.6%	Diabetes mellitus, all types	9.5%
Hb, males, >12.0	57.3%	Spleen, cm[@], >4 ⩽ 10	11.8%	Neurologic disorders	6.9%
Hb (g/dl), females, median ($n = 1\,095$)	11.7	Spleen, cm[@], ⩾ 10	15.2%	Behavior disorders	2.3%
Hb, females, < 8.0	5.1%	**Cytogenetic data**		Chronic renal disease	2.6%
Hb, females, 8.0–11.0	32.9%	CCA/Ph+ ($n = 2018$)	9.4%	Chronic liver disease	2.2%
Hb, females, >11.0	62.0%	Variant translocations ($n = 2057$)	3.7%	Others, or unspecified	31.7%
Platelet count, $\times 10^9$**/l**, median ($n = 2\,381$)	395.0	**Molecular data—type of transcript ($n = 1533$)**			
Platelet count, $\times 10^9$/l, < 150	5.9%	b2a2	38.9%	Patients without comorbidities	44.5%
Platelet count, $\times 10^9$/l, 150 ⩽ 450	52.0%	b3a2+b2a2/b3a2	56.6%	Patients with one comorbidity	28.7%
Platelet count, $\times 10^9$/l, 450 ⩽ 1000	34.7%	Other	4.5%	Patients with two comorbidities	15.3%
Platelet count, $\times 10^9$/l, ⩾ 1000	7.4%			Patients with >2 comorbidities	11.5%
WBC count $\times 10^9$**/l**, median ($n = 2\,388$)	84.6				
WBC count $\times 10^9$/l, < 50	32.7%	***Sokal score (n = 2300)***		**ECOG/WHO score ($n = 2280$)**	
WBC count $\times 10^9$/l, 50 ⩽ 100	23.0%	Sokal low	34.5%	0–asymptomatic	57.1%
WBC count $\times 10^9$/l, 100 ⩽ 200	24.1%	Sokal intermediate	40.8%	1–symptomatic, compl. ambulatory	37.0%
WBC count $\times 10^9$/l, ⩾ 200	20.3%	Sokal high	24.7%	2–symptomatic, < 50% in bed/day	4.2%
Blast cells, %, median ($n = 2356$)	1.0	***EURO score (n = 2292)***		3–symptomatic, >50% in bed/day	1.2%
Basophils, %, median ($n = 2359$)	3.0	EURO low	37.4%	4–bedbound	0.5%
Eosinophils, %, median ($n = 2353$)	2.0	EURO intermediate	51.8%		
		EURO high	10.8%		
		EUTOS score (n = 2307)			
		EUTOS low	88.2%		
		EUTOS high	11.8%		

Abbreviations: CCA, clonal chromosome abnormalities; ECOG, Eastern Cooperative Oncology Group; EUTOS, European Treatment and Outcome Study for chronic myeloid leukemia; WBC, white blood cell; WHO, World Health Organization. @ cm below costal margin.

56% with comorbidities
42% Cardiovascular

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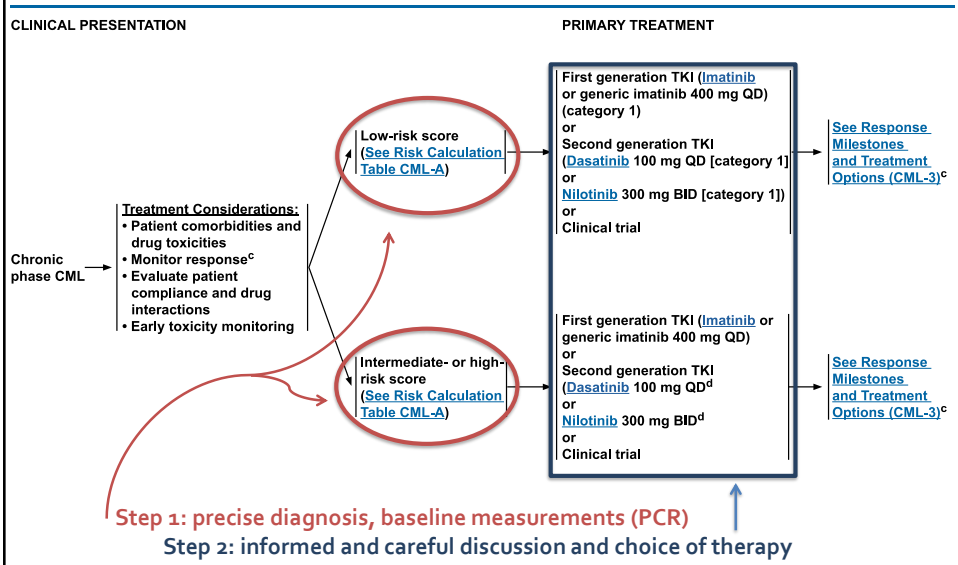
Hoffmann VS et al, Leukemia 29 1336-43, 2015

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018
Chronic Myeloid Leukemia

Initial Management



Step 1: precise diagnosis, baseline measurements (PCR)
Step 2: informed and careful discussion and choice of therapy

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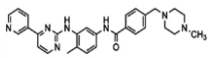
At present, *five* oral, small molecular kinase inhibitors approved in the US for Ph+ Leukemia: a 'spoil of riches'; more on the way?

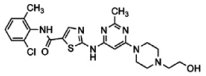
1st Gen. TKI



Imatinib (STI571)

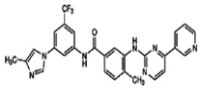
2001
Novartis
(1st line)

2nd Gen. TKIs



Dasatinib (BMS354825)

2007/2010
BMS
(1st, 2nd line)



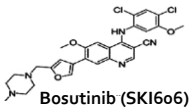
Nilotinib (AMN107)

2007/2010
Novartis
(1st, 2nd line)

South Korea only

Radotinib (IY5511)

2012/2015
IL-YANG:
(1st, 2nd line)

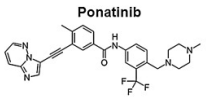


Bosutinib (SKI606)

2012
Pfizer
(2nd/3rd line)

2017:
1st/2nd/3rd line?

3rd Gen. TKI



Ponatinib (AP24534)

2012
Ariad
(2nd?/3rd line)

4th Gen. TKI (allosteric): ABL001

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Choosing your tools: comparing TKI toxicity in CML

Issue	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib
Dosing	QD/BID, with food	BID, without food (2h)	QD, w/ or w/o food	QD, with food	QD, w/ or w/o food
Long term safety	Most extensive	Extensive; Emerging toxicity	Extensive; Emerging toxicity	Extensive, No emerging toxicity	More limited but increasing; Emerging toxicity
Heme toxicity	intermediate	least	Most severe; ASA-like effect; lymphocytosis	~dasatinb in 2nd, 3rd line; ~nilotinib in 1st line	↑thrombocytopenia ASA-like effect
Non-Heme toxicity	Edema, GI effects, ↓Phos	↑lipase, ↑bili, ↑chol, ↑glu Black box: QT prolongation; screening req'd	Pleural / pericardial effusions	Diarrhea; transaminitis	↑lipase, pancreatitis; rash; hypertension; Black box: vascular occlusion, heart failure, and hepatotoxicity
Emerging toxicities	early question re: CHF; ?late renal effects	Vascular events (ICVE, IHD, PAD)	PAH (pulmonary arterial hypertension)	? Mild renal effects	Vascular events (ICVE, IHD, PAD, VTE)

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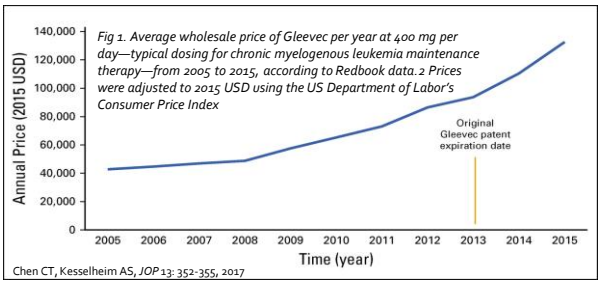


Fig 1. Average wholesale price of Gleevec per year at 400 mg per day—typical dosing for chronic myelogenous leukemia maintenance therapy—from 2005 to 2015, according to Redbook data. 2 Prices were adjusted to 2015 USD using the US Department of Labor's Consumer Price Index

Chen CT, Kesselheim AS, *JOP* 13: 352-355, 2017

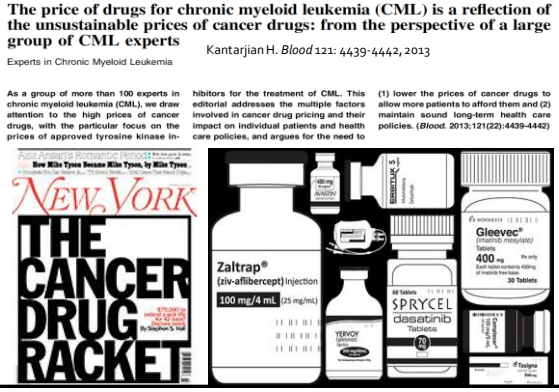
Reality check: Cost of Therapy


The New York Times

Business Day

Doctors Denounce Cancer Drug Prices of $100,000 a Year

Pollack A, *NY Times*, Published 4/25/13


The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts

Experts in Chronic Myeloid Leukemia

Kantarjian H. *Blood* 121: 4439-4442, 2013

As a group of more than 100 experts in chronic myeloid leukemia (CML), we draw attention to the high prices of cancer drugs, with the particular focus on the prices of approved tyrosine kinase inhibitors for the treatment of CML. This editorial addresses the multiple factors involved in cancer drug pricing and their impact on individual patients and health care policies, and argues for the need to (1) lower the prices of cancer drugs to allow more patients to afford them and (2) maintain sound long-term health care policies. (*Blood*. 2013;121(22):4439-4442)

NEW YORK

THE CANCER DRUG RACKET

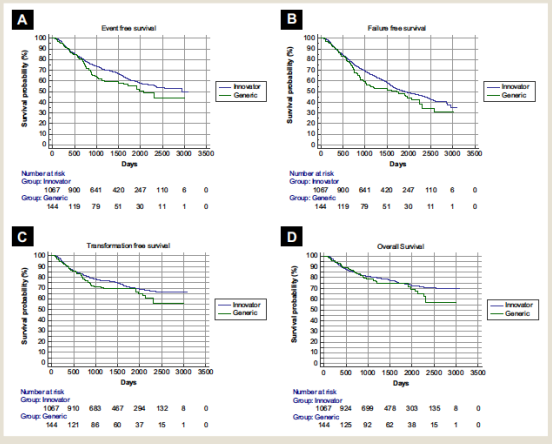
Hall S, *New York Magazine*, Published 10/20/13

What do we know about generic imatinib?

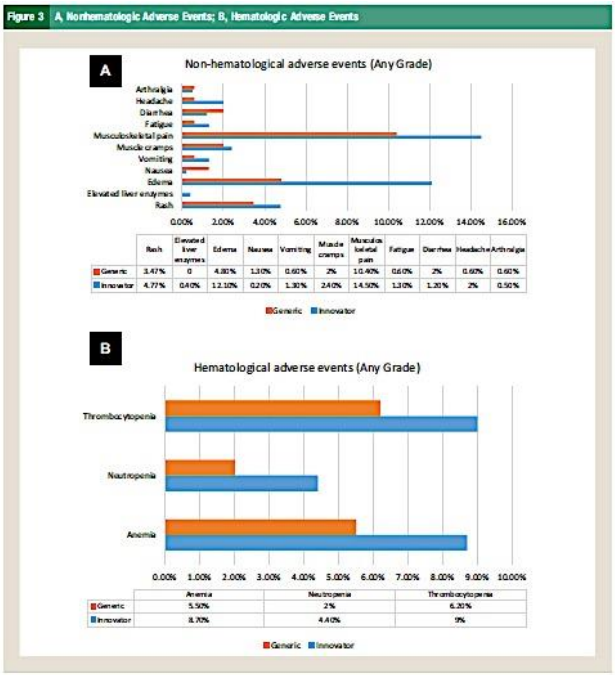
Table 1 Patient Demographics and Clinical Characteristics of Study Patients

Characteristic	Innovator Imatinib (n = 1067)	Generic Imatinib (n = 144)
Age, y		
Median	40	36
Range	10-68	2-75
Gender, n (%)		
Male	620 (58)	87 (60)
White cell count, /mm^3		
Median	169,600	142,670
Range	2800-828,000	4500-619,000
Platelet count, /mm^3		
Median	360,000	341,000
Range	20,000-2,130,000	70,000-1,370,000
Hemoglobin, g/dL		
Median	9.9	10.2
Range	3.1-18.6	5.2-18.3
Peripheral blood blasts, %		
Median	2	2
Range	0-31	0-12
Peripheral blood basophils, %		
Median	3	2
Range	0-41	0-15
Splenomegaly, n (%)	663 (62)	74 (51)

Figure 2 A, Kaplan-Meier Curves of Event-free Survival in Those Receiving Frontline Innovator/Generic Imatinib; B, Kaplan-Meier Curves of Failure-free Survival in Those Receiving Frontline Innovator/Generic Imatinib; C, Kaplan-Meier Curves of Transformation-free Survival in Those Receiving Frontline Innovator/Generic Imatinib; D, Kaplan-Meier Curves of Overall Survival in Those Receiving Frontline Innovator/Generic Imatinib



Danthala M et al. Clin Lymph, Myel, Leuk 17(7), 457-62, 2017



Danthala M et al. Clin Lymph, Myel, Leuk 17(7), 457-62, 2017

Branded *vs.* generic imatinib: toxicity

- Remember generic substitutions can rotate (different manufacturer with each Rx)
- Closer side effect monitoring prudent
- Shorter term PCR monitoring after switch may be advisable also

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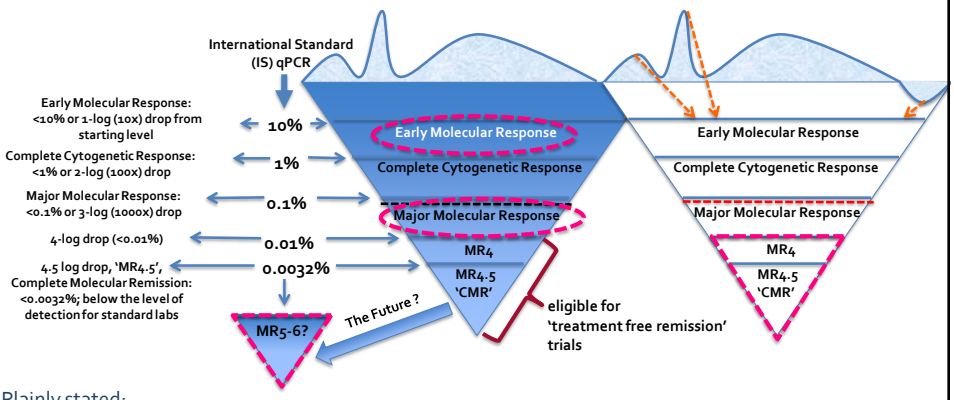
'Shrinking the iceberg': response expectations



Plainly stated:

1. PCR at diagnosis = very important, like a timing chip when you run a race (where did you start?)
2. Early response at 3mo should be 'on track', 10x lower than start, ~10% (if you start ~100%)
3. Complete cytogenetic response (~1% on the PCR scale; 100x lower) is very important and protective
4. Major molecular response (MMR, ~0.1% on the PCR scale; 1000x lower) adds further protection
5. Deep Molecular remission: aiming for 0.01% or lower (10,000x lower than start) and staying that way

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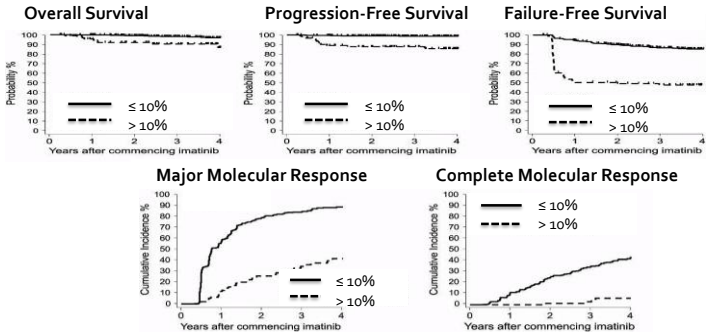
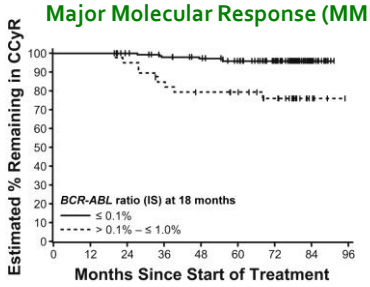
Early Molecular Response (EMR)

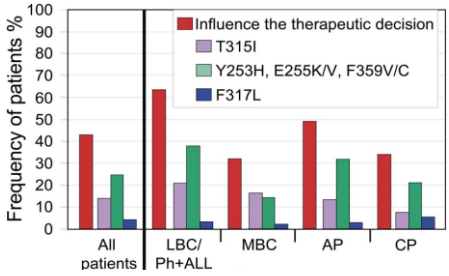
Predictive molecular tools in CML



Major Molecular Response (MMR)



Mutation Status



Branford S et al. Blood 2014;124:511-518; Hughes T, et al. *Blood* 2010; 116(19):3758-65; Branford S et al, *Blood* 2009

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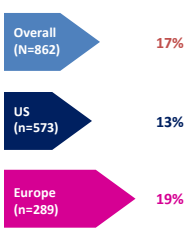
Monitoring for CML response needs improvement

About 1 in every 5 patients are not tested for MR at 12 months and almost half are not tested for CyR

Patients not tested for CyR at 12 months[1]

Patients not tested for MR by 12 months[1]



Age <65 years at initiation of first-line TKI, patients who had switched from first-line TKI and those seen in academic centres were more likely to be monitored by 12 months ($p<0.05$)[2]

1. Goldberg SL, Cortes J, Gambacorti-Passerini C, et al. Cytogenetic and molecular testing in patients with chronic myeloid leukemia (CML) in a prospective observational study (SIMPLICITY). J Clin Oncol. 2014;32:5s (suppl; abstr 7050).
2. Goldberg SL, Cortes J, Gambacorti-Passerini C, et al. Predictors of performing response monitoring in patients with chronic-phase chronic myeloid leukemia (CP-CML) in a prospective observational study (SIMPLICITY). J Clin Oncol. 2014;32:(suppl 30; abstr 116).

simplicity

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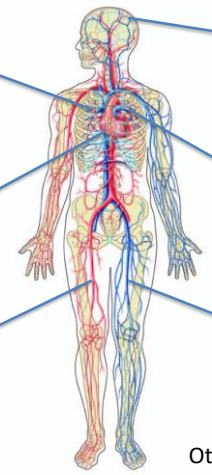
The most significant 'late effects': CML TKI Associated Cardiovascular Adverse Effects



- **Cardiomyopathy / Congestive Heart Failure**
  - Cardiomyocyte Injury?
- **Coronary Heart Disease / Myocardial Infarction**
  - Endothelial Dysfunction? Atherosclerosis?
- **Peripheral Arterial Disease**
  - Endothelial Dysfunction? Atherosclerosis?
- **Cerebrovascular Disease**
  - Endothelial Dysfunction? Atherosclerosis?
- **Pulmonary Arterial Hypertension**
  - Endothelial Dysfunction?
- **Venous Thrombosis**
  - Platelet dysfunction? Prothrombotic state?

Other:
- Fatigue
- Musculoskeletal Sx / Cramping
- Exercise-Induced Symptoms

➔ Morbidity and mortality; ? Effect on survival observations in front-line studies?

➔ ? Delay/deferral of advantageous therapy both in front-line and salvage

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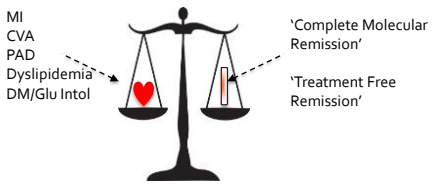
EUROPEAN SOCIETY OF CARDIOLOGY®

HEART FAILURE ASSOCIATION OF THE ESC

International CardiOncology Society

Guidelines in active development for CML patients and CV risk



'ABCDE' Step Approach to CV Intervention
A: Awareness of cardiovascular disease signs and symptoms
A: Aspirin (in select patients)
A: Ankle-brachial index measurement at baseline and follow-up to document peripheral arterial disease
B: Blood pressure control
C: Cigarette/tobacco cessation
C: Cholesterol (regular monitoring and treatment if indicated)
D: Diabetes mellitus (regular monitoring, dose of radiation/chemotherapy, and treatment if indicated)
D: Diet and weight management
E: Exercise (echocardiogram)

Barber M, Mauro M and Moslehi J, *in press*

✓ = Recommended + = As clinically indicated	Imatinib	Bosutinib	Dasatinib	Nilotinib	Ponatinib
Baseline Assessment					
Cardiovascular assessment	✓	✓	✓	✓	✓
Blood pressure check	✓	✓	✓	✓	✓
Fasting glucose	+	+	+	✓	✓
Fasting lipid panel	+	+	+	✓	✓
Echocardiogram	+	+	+*	+	+
Electrocardiogram	✓	✓	✓	✓	✓
Ankle-brachial index	+	+	+	✓	✓
1-month follow up					
Cardiovascular assessment	+	+	✓	✓	✓
Blood pressure check	+	+	+	+	✓
3- to 6-month follow-up					
Cardiovascular assessment	✓	✓	✓	✓	✓
Blood pressure check	+	+	+	✓	✓
Fasting glucose	+	+	+	✓	+
Fasting lipid panel	+	+	+	✓	✓
Echocardiogram	+	+	+*	+	+
Electrocardiogram	+	+	+	✓	✓
Ankle-brachial index	+	+	+	✓	✓

*Patients treated with dasatinib should be considered for echocardiogram if cardiopulmonary symptoms are present.

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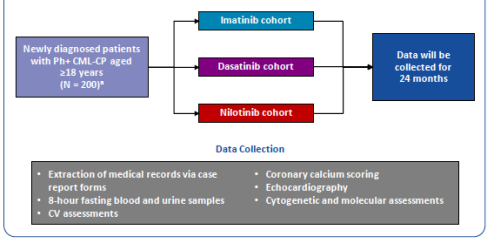
Figure 1. CA180-653 Study Design



Prospective study of cardiovascular and metabolic risk in newly diagnosed CML (CA180-653, sponsored by BMS)

Table 2. Clinical Assessments at Routine Office Visits

Procedure	Baseline	Every 3 months	Month 6 only	Month 24 only
Physical exam[a]	X			
Targeted physical exam[a]		X		
Electrocardiogram	X	X		
Medical history[b]	X	X		
Vital signs[c]	X	X		
Ankle-brachial index	X	X		
AE assessments	Continuous			
Clinical assessments[d]	X	X		
Echocardiogram	X		X	X
Coronary calcium scoring	X		X	X
Hematology and chemistry panels[e]	X	X		
Investigational blood biomarker collection[f]	X	X		
Urine collection[g]	X	X		

[a]Includes height, weight, and BMI. [b]Includes Sokal score, Framingham Coronary Heart Disease Score, smoking status, history of hypertension, hyperlipidemia, and hyperglycemia. [c]Includes blood pressure and heart rate. [d]Includes disease status and mutational analysis. [e]Includes fasting blood glucose, HbA_{1c}, fasting lipid panels, and all SOC laboratory assessments (8 hours of fasting required). [f]Includes different metabolites, cytokines, chemokines, and other biomarkers (8 hours of fasting required). [g]Includes increased albuminuria test (8 hours of fasting required).
BMI = body mass index; HbA_{1c} = glycated haemoglobin; SOC = standard of care.

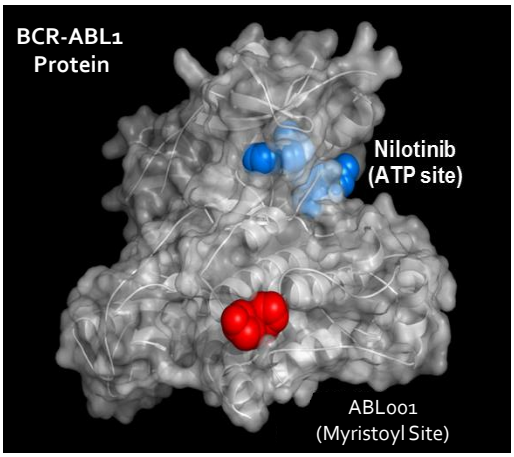
Table 3. Summary of Collected CV and Metabolic Risk Variables

Variables	Data Collected
Targeted CV events	• Development of arrhythmia, cardiac dysfunction, cerebrovascular ischemic disease, coronary death, coronary insufficiency, heart failure, left ventricular systolic function, myocardial infarction, peripheral artery occlusive disease, pulmonary arterial hypertension, QT prolongation, ischemic or hemorrhagic stroke, transient ischemic attack, venous thromboembolism, other vascular occlusive events, and Framingham Coronary Heart Disease Score • Subclinical changes that lead to development of new risk factors or exacerbation of known risk factors (newly diagnosed diabetes, newly diagnosed hypertension, progressive symptoms of disease)
Targeted metabolic events	• Diagnosis of diabetes mellitus, impaired fasting glucose, elevated HbA_{1c}, metabolic syndrome, abnormal laboratory values for events of special interest
Hematologic	• Collection of fasting blood glucose, HbA_{1c}, fasting lipid panel • Changes from baseline will be calculated
Metabolic	• Collection of BMI, metabolites, cytokines, and chemokines from biomarker panels, and moderately increased albuminuria levels • Changes from baseline will be calculated
Diagnostic	• Collection of echocardiogram, ankle-brachial index, and coronary calcium scoring assessments • Changes from baseline will be calculated

23

ABL001: Novel 3rd generation ABL kinase inhibitor

- ABL001 is a new potent, specific inhibitor for CML with a distinct 'allosteric' mechanism of action
- Binds a *different and separate* region of the kinase domain: the myristate-binding pocket, holding Bcr-Abl in the inactive conformation
- Has potential to be combined with the currently available TKIs – the first instance where there is rationale for combinations…



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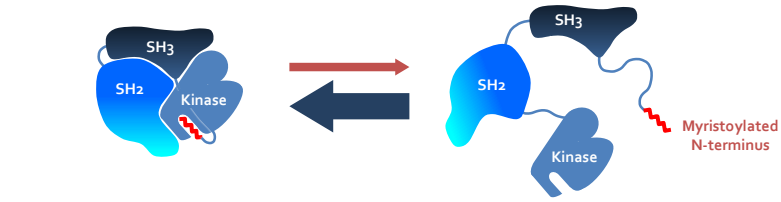
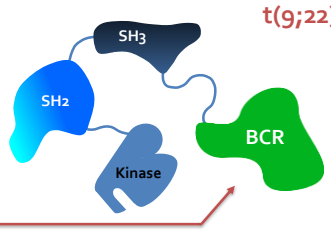


INACTIVE

ACTIVE

In the case of CML / t(9:22) and Bcr-Abl fusion the inactivation of the kinase is blocked

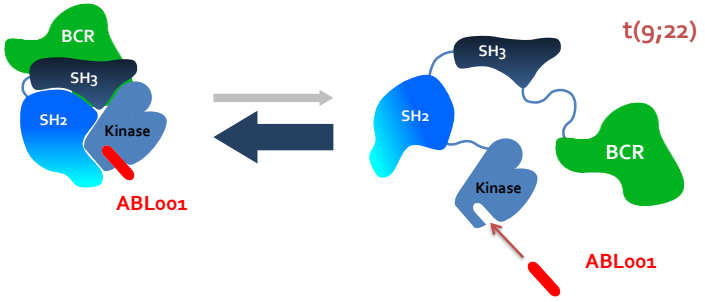


ACTIVE

How ABL001 works

25

ABL001 allosterically blocks BCR-ABL1 kinase activity



- **ABL001 in cells in the lab selectively inhibits (blocks) Bcr-Abl**
- **In animal studies it was able to prevent resistance development**
- **In human cells when very small amounts of ABL001 were added, smaller amounts standard TKIs were needed to block Bcr-Abl**

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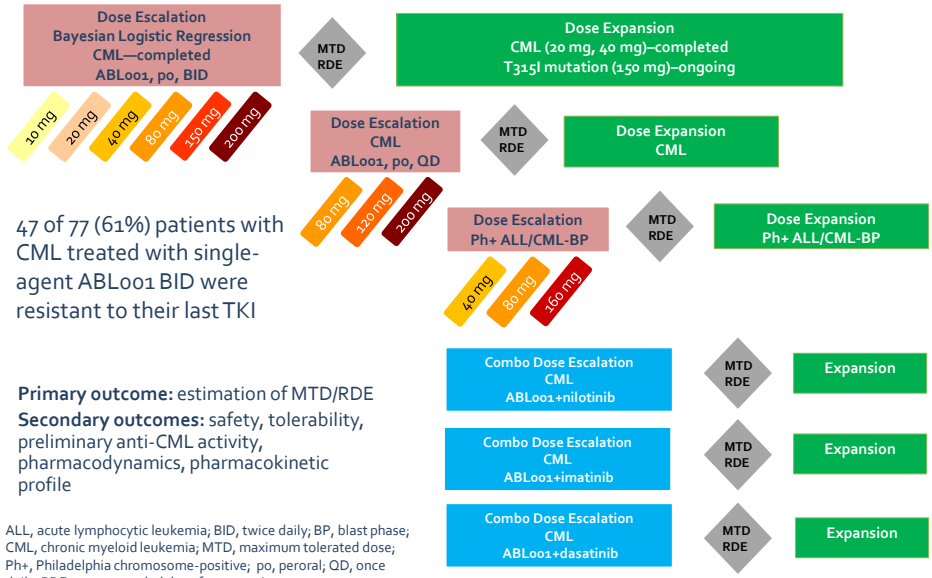
ABL001X2101: Study Design

A multicenter, phase 1, first-in-human study



47 of 77 (61%) patients with CML treated with single-agent ABL001 BID were resistant to their last TKI

Primary outcome: estimation of MTD/RDE
Secondary outcomes: safety, tolerability, preliminary anti-CML activity, pharmacodynamics, pharmacokinetic profile

ALL, acute lymphocytic leukemia; BID, twice daily; BP, blast phase; CML, chronic myeloid leukemia; MTD, maximum tolerated dose; Ph+, Philadelphia chromosome-positive; po, peroral; QD, once daily; RDE, recommended dose for expansion

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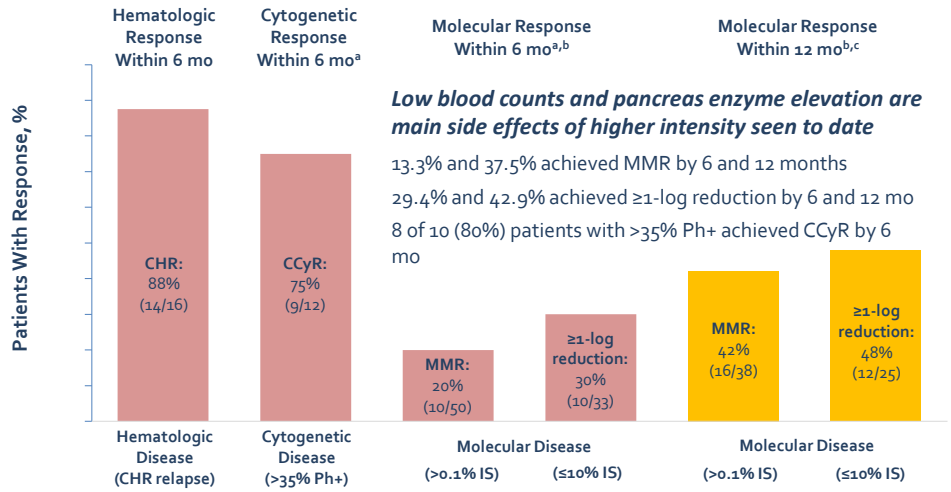
Hughes TP, et al. *Blood*. 2016; 128 (22): [abstract 625].

Responses in Patients With CML Treated With Single-Agent BID ABL001 With ≥3 Months Exposure on Study



Low blood counts and pancreas enzyme elevation are main side effects of higher intensity seen to date

13.3% and 37.5% achieved MMR by 6 and 12 months

29.4% and 42.9% achieved ≥1-log reduction by 6 and 12 mo

8 of 10 (80%) patients with >35% Ph+ achieved CCyR by 6 mo

CCyR, complete cytogenetic response; CHR, complete hematologic response; IS, International Scale; MMR, major molecular response; mo, months

[a]Patients had ≥6 months of treatment exposure or achieved response within 6 months

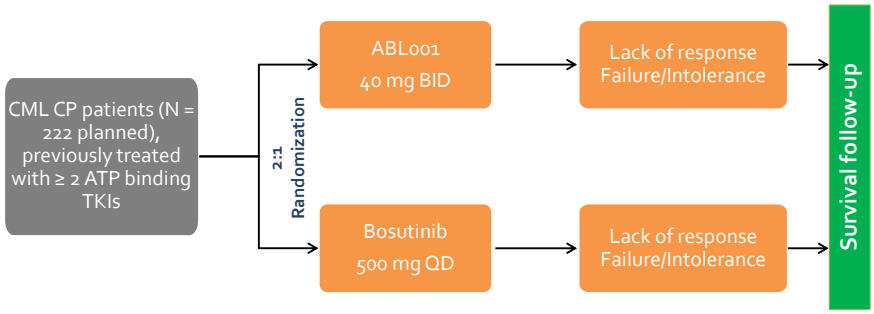
[b]*BCR-ABL1*^{IS} reduction achieved

[c]Patients had ≥12 months of treatment exposure or achieved response within 12 months

28

Hughes TP, et al. *Blood*. 2016; 128 (22): [abstract 625].

CABL001A2301 (Planned): Study Design
A phase 3, Multicenter, Open-label, Randomized Study of ABL001 Versus Bosutinib



- **Primary endpoints:** Major Molecular Response (MMR) rate at 24 weeks
- **Key secondary endpoint:** MMR rate at 96 weeks

BID, twice daily; CML, chronic myeloid leukemia; CP, chronic phase; QD, once daily; TKI, tyrosine kinase inhibitor

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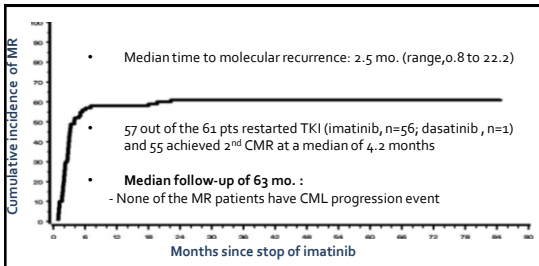
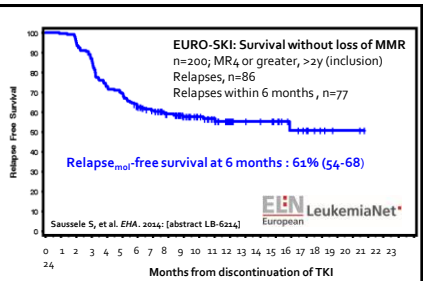


- Median time to molecular recurrence: 2.5 mo. (range,0.8 to 22.2)
- 57 out of the 61 pts restarted TKI (imatinib, n=56; dasatinib , n=1) and 55 achieved 2nd CMR at a median of 4.2 months
- **Median follow-up of 63 mo. :**
  - None of the MR patients have CML progression event



fantastic therapy + careful selection + good monitoring = fantastic outcomes…

'treatment free remission'

30

Criteria for consideration of treatment free remission (TKI cessation) : *the rules as noted by the National Comprehensive Cancer Network (NCCN)*

Age ≥18 years.

Chronic phase CML. No prior history of accelerated or blast phase CML.

On approved TKI therapy (imatinib, dasatinib, nilotinib, bosutinib, or ponatinib) for at least three years.

Prior evidence of quantifiable BCR-ABL1 transcript.

Stable molecular response (MR4; ≤0.01% IS) for ≥2 years, as documented on at least four tests, performed at least three months apart.

No history of resistance to any TKI.

Access to a reliable QPCR test with a sensitivity of detection of ≥4.5 logs that reports results on the IS and provides results within 2 weeks.

Monthly molecular monitoring for the first six months following discontinuation, bimonthly during months 7–24, and quarterly thereafter (indefinitely) for patients who remain in MMR (MR3; ≤0.1% IS).

Consultation with a CML Specialty Center to review the appropriateness for TKI discontinuation and potential risks and benefits of treatment discontinuation, including TKI withdrawal syndrome.

Prompt resumption of TKI, with a monthly molecular monitoring for the first six months following resumption of TKI and every 3 months thereafter is recommended indefinitely for patients with a loss of MMR. For those who fail to achieve MMR after six months of TKI resumption, BCR-ABL1 kinase domain mutation testing should be performed, and monthly molecular monitoring should be continued for another six months.

Reporting of the following to a member of the NCCN CML panel is strongly encouraged:

-Any significant adverse event believed to be related to treatment discontinuation.

-Progression to accelerated or blast phase CML at any time.

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Criteria for consideration of treatment free remission (TKI cessation): *patient specifics*

Age ≥18 years.

Chronic phase CML. No prior history of accelerated or blast phase CML.

On approved TKI therapy (imatinib, dasatinib, nilotinib, bosutinib, or ponatinib) for at least three years.

Prior evidence of quantifiable BCR-ABL1 transcript.

Stable molecular response (MR4; ≤0.01% IS) for ≥2 years, as documented on at least four tests, performed at least three months apart.

No history of resistance to any TKI.

Access to a reliable QPCR test with a sensitivity of detection of ≥4.5 logs that reports results on the IS and provides results within 2 weeks.

Monthly molecular monitoring for the first six months following discontinuation, bimonthly during months 7–24, and quarterly thereafter (indefinitely) for patients who remain in MMR (MR3; ≤0.1% IS).

Consultation with a CML Specialty Center to review the appropriateness for TKI discontinuation and potential risks and benefits of treatment discontinuation, including TKI withdrawal syndrome.

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Reporting of the following to a member of the NCCN CML panel is strongly encouraged:

-Any significant adverse event believed to be related to treatment discontinuation.

-Progression to accelerated or blast phase CML at any time.

32

Criteria for consideration of treatment free remission (TKI cessation): *PCR criteria and assay*

Age ≥18 years.

Chronic phase CML. No prior history of accelerated or blast phase CML.

On approved TKI therapy (imatinib, dasatinib, nilotinib, bosutinib, or ponatinib) for at least three years.

Prior evidence of quantifiable BCR-ABL1 transcript.

Stable molecular response (MR4; ≤0.01% IS) for ≥2 years, as documented on at least four tests, performed at least three months apart.

No history of resistance to any TKI.

Access to a reliable QPCR test with a sensitivity of detection of ≥4.5 logs that reports results on the IS and provides results within 2 weeks.

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Reporting of the following to a member of the NCCN CML panel is strongly encouraged:

-Any significant adverse event believed to be related to treatment discontinuation.

-Progression to accelerated or blast phase CML at any time.

33

Criteria for consideration of treatment free remission (TKI cessation): *monitoring rules*

Age ≥18 years.

Chronic phase CML. No prior history of accelerated or blast phase CML.

On approved TKI therapy (imatinib, dasatinib, nilotinib, bosutinib, or ponatinib) for at least three years.

Prior evidence of quantifiable BCR-ABL1 transcript.

Stable molecular response (MR4; ≤0.01% IS) for ≥2 years, as documented on at least four tests, performed at least three months apart.

No history of resistance to any TKI.

Access to a reliable QPCR test with a sensitivity of detection of ≥4.5 logs that reports results on the IS and provides results within 2 weeks.

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Reporting of the following to a member of the NCCN CML panel is strongly encouraged:

-Any significant adverse event believed to be related to treatment discontinuation.

-Progression to accelerated or blast phase CML at any time.

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Criteria for consideration of treatment free remission (TKI cessation): *CML specialty center / NCCN feedback*

Age ≥18 years.

Chronic phase CML. No prior history of accelerated or blast phase CML.

On approved TKI therapy (imatinib, dasatinib, nilotinib, bosutinib, or ponatinib) for at least three years.

Prior evidence of quantifiable BCR-ABL1 transcript.

Stable molecular response (MR4; ≤0.01% IS) for ≥2 years, as documented on at least four tests, performed at least three months apart.

No history of resistance to any TKI.

Access to a reliable QPCR test with a sensitivity of detection of ≥4.5 logs that reports results on the IS and provides results within 2 weeks.

Monthly molecular monitoring for the first six months following discontinuation, bimonthly during months 7–24, and quarterly thereafter (indefinitely) for patients who remain in MMR (MR3; ≤0.1% IS).

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-Any significant adverse event believed to be related to treatment discontinuation.

-Progression to accelerated or blast phase CML at any time.

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Do Adverse Events Occur With TKI *Withdrawal?*

N=200; 222 AEs in 98 patients were reported

57 AEs in 31 patients were related to treatment stop, no grade 4

	Patients All Grade (n)	Patients Grade 3 (n)	AEs All Grade (n)	AEs Grade 3 (n)
Musculoskeletal pain, joint pain, arthralgia	23	3	39	6
Other (sweating, skin disorders, folliculitis, depressive episodes, fatigue, urticaria, weight loss)	8	0	18	3

Musculoskeletal pain in CML patients after discontinuation of imatinib: a tyrosine kinase inhibitor withdrawal syndrome?
J. Richter et al. J Clin Oncol. 2014 Sep 1;32(25):2821-3.

Tyrosine kinase inhibitor withdrawal syndrome: a matter of c-kit ?
Response to Richter et al.
Ph. Rousselot et al.

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Mahon FX et al, Blood 2014 124:151

www.ScienceTranslationalMedicine.org 29 February 2012 Vol 4 Issue 123

INFECTIOUS DISEASE

Productive Replication of Ebola Virus Is Regulated by the c-Abl1 Tyrosine Kinase

Mayra García,[1] Arik Cooper,[1] Wei Shi,[1] William Bornmann,[2] Ricardo Carrion,[3] Daniel Kalman,[4] Gary J. Nabel[1]*

Ebola virus causes a fulminant infection in humans resulting in diffuse bleeding, vascular instability, hypotensive shock, and often death. Because of its high mortality and ease of transmission from human to human, Ebola virus remains a biological threat for which effective preventive and therapeutic interventions are needed. An understanding of the mechanisms of Ebola virus pathogenesis is critical for developing antiviral therapeutics. Here, we report that productive replication of Ebola virus is modulated by the c-Abl1 tyrosine kinase. Release of Ebola virus–like particles (VLPs) in a cell culture cotransfection system was inhibited by c-Abl1–specific small interfering RNA (siRNA) or by Abl-specific kinase inhibitors and required tyrosine phosphorylation of the Ebola matrix protein VP40. Expression of c-Abl1 stimulated an increase in phosphorylation of tyrosine 13 (Y^{13}) of VP40, and mutation of Y^{13} to alanine decreased the release of Ebola VLPs. Productive replication of the highly pathogenic Ebola virus Zaire strain was inhibited by c-Abl1–specific siRNAs or by the Abl-family inhibitor nilotinib by up to four orders of magnitude. These data indicate that c-Abl1 regulates budding or release of filoviruses through a mechanism involving phosphorylation of VP40. This step of the virus life cycle therefore may represent a target for antiviral therapy.

Journal of Virology

Abelson Kinase Inhibitors Are Potent Inhibitors of Severe Acute Respiratory Syndrome Coronavirus and Middle East Respiratory Syndrome Coronavirus Fusion

Christopher M. Coleman,[a] Jeanne M. Sisk,[a] Rebecca M. Mingo,[b] Elizabeth A. Nelson,[b] Judith M. White,[b] Matthew B. Frieman[a]

Department of Microbiology and Immunology, University of Maryland, Baltimore, Maryland, USA[a]; Department of Cell Biology, University of Virginia, Charlottesville, Virginia, USA[b]

ABSTRACT

The highly pathogenic severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) cause significant morbidity and morality. There is currently no approved therapeutic for highly pathogenic coronaviruses, even as MERS-CoV is spreading throughout the Middle East. We previously screened a library of FDA-approved drugs for inhibitors of coronavirus replication in which we identified Abelson (Abl) kinase inhibitors, including the anticancer drug imatinib, as inhibitors of both SARS-CoV and MERS-CoV *in vitro*. Here we show that the anti-CoV activity of imatinib occurs at the early stages of infection, after internalization and endosomal trafficking, by inhibiting fusion of the virions at the endosomal membrane. We specifically identified the imatinib target, Abelson tyrosine-protein kinase 2 (Abl2), as required for efficient SARS-CoV and MERS-CoV replication *in vitro*. These data demonstrate that specific approved drugs can be characterized *in vitro* for their anticoronavirus activity and used to identify host proteins required for coronavirus replication. This type of study is an important step in the repurposing of approved drugs for treatment of emerging coronaviruses.

Repurposing imatinib: other Abl targets

OPEN ACCESS Freely available online PLOS ONE

Imatinib Ameliorates Neuroinflammation in a Rat Model of Multiple Sclerosis by Enhancing Blood-Brain Barrier Integrity and by Modulating the Peripheral Immune Response

Milena Z. Adzemovic[1¶], Manuel Zeitelhofer[1¶*], Ulf Eriksson[2], Tomas Olsson[1,4], Ingrid Nilsson[2,4]

1 Neuroimmunology Unit, Department of Clinical Neuroscience, Center for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden, 2 Division of Vascular Biology, Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden

Abstract

Central nervous system (CNS) disorders such as ischemic stroke, multiple sclerosis (MS) or Alzheimers disease are characterized by the loss of blood-brain barrier (BBB) integrity. Here we demonstrate that the small tyrosine kinase inhibitor imatinib enhances BBB integrity in experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis (MS). Treatment was accompanied by decreased CNS inflammation and demyelination and especially reduced T-cell recruitment. This was supported by downregulation of the chemokine receptor (CCR) 2 in CNS and lymph nodes, and by modulation of the peripheral immune response towards an anti-inflammatory phenotype. Interestingly, imatinib ameliorated neuroinflammation, even when the treatment was initiated after the clinical manifestation of the disease. We have previously shown that imatinib reduces BBB disruption and stroke volume after experimentally induced ischemic stroke by targeting platelet-derived growth factor receptor -α (PDGFR-α) signaling. Here we demonstrate that PDGFR-α signaling is a central regulator of BBB integrity during neuroinflammation and therefore imatinib should be considered as a potentially effective treatment for MS.

SCIENTIFIC REPORTS

The c-Abl inhibitor, Nilotinib, protects dopaminergic neurons in a preclinical animal model of Parkinson's disease

Senthilkumar S. Karuppagounder[1,2,6], Saurav Brahmachari[1,2,6], Yunjong Lee[1,2,3,6], Valina L. Dawson[1,2,3,5,6], Ted M. Dawson[1,2,4,5,6]* & Han Seok Ko[1,2,7]*

[1]Neuroregeneration and Stem Cell Programs, Institute for Cell Engineering, The Johns Hopkins University School of Medicine, Baltimore, MD 21205. USA, [2]Department of Neurology, The Johns Hopkins University School of Medicine, Baltimore, MD 21205. USA, [3]Department of Physiology, The Johns Hopkins University School of Medicine, Baltimore, MD 21205. USA, [4]Department of Pharmacology and Molecular Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD 21205. USA, [5]Solomon H. Snyder Department of Neuroscience, The Johns Hopkins University School of Medicine, Baltimore, MD 21205. USA, [6]Adrienne Helis Malvin Medical Research Foundation, New Orleans, LA 70130-2685, USA, [7]Diana Helis Henry Medical Research Foundation, New Orleans, LA 70130-2685, USA.

c-Abl is activated in the brain of Parkinson's disease (PD) patients and in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-intoxicated mice where it inhibits parkin through tyrosine phosphorylation leading to the accumulation of parkin substrates, and neuronal cell death. In the present study, we evaluated the in vivo efficacy of nilotinib, a brain penetrant c-Abl inhibitor, in the acute MPTP- induced model of PD. Our results show that administration of nilotinib reduces c-Abl activation and the levels of the parkin substrate, PARIS, resulting in prevention of dopamine (DA) neuron loss and behavioral deficits following MPTP intoxication. On the other hand, we observe no reduction in the tyrosine phosphorylation of parkin and the parkin substrate, AIMP2 suggesting that the protective effect of nilotinib may, in part, be parkin-independent or to the pharmacodynamics properties of nilotinib. This study provides a strong rationale for testing other brain permeable c-Abl inhibitors as potential therapeutic agents for the treatment of PD.

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H. JEAN KHOURY CURE CML CONSORTIUM

We are a group of researchers from 17 world-class academic medical centers throughout North America committed to curing CML through innovative research. With feedback from advocates and patients, we strive to meet the needs of the CML community.

Fred Hutchinson Cancer Research Center

Huntsman Cancer Institute

H. Lee Moffitt Cancer Center & Research Institute

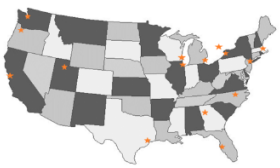
Medical College of Wisconsin

MD Anderson Cancer Center

Oregon Health & Science University

John Theurer Cancer Center at Hackensack University

Winship Cancer Institute of Emory University



www.curecml.org

'Galvanized by the spectacular collaboration created by the LAST study, the creation of a CML consortium was simply the next logical thing to do' -H. Jean Khoury

University of Chicago Comprehensive Cancer Center

Princess Margaret Cancer Centre

Memorial Sloan Kettering Cancer Center

Duke Cancer Institute

Weill Medical College of Cornell University

Barbara Ann Karmanos Cancer Institute

UCSF Helen Diller Family Comprehensive Cancer Center

Roswell Park Cancer Institute

Dana-Farber Cancer Institute

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We need your help to better our research

Go to www.curecml.org and click on 'survey'

HAS YOUR LIFE BEEN AFFECTED BY CML?

We want to know what you think the research priorities should be.

The 5-10 minute survey is voluntary and anonymous.

SURVEY LINK

mcw.edu/CMLsurvey

Scan QR code

MEDICAL COLLEGE OF WISCONSIN

QUESTIONS?
cureCML@mcw.edu
414.805.8745

H. JEAN KHOURY
CURE CML
CONSORTIUM

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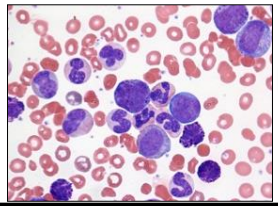
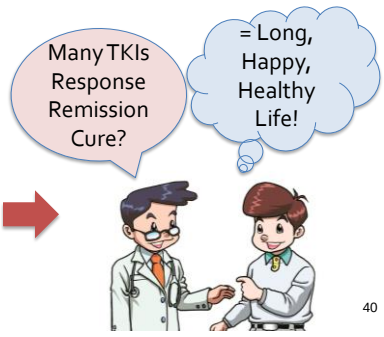
CML in 2017 and beyond…

- CML is highly treatable; 'functional cure' appears feasible
- Generic imatinib is here; let science overcome fears
- TKIs should be carefully chosen (risk/benefit)
- Monitoring needs to happen, mutations *can* drive treatment choice and resistance is treatable
- Even more new agents on the horizon (ABL001)
- SCT still needed as an option; don't under-utilize
- The past and the future have been VERY bright……





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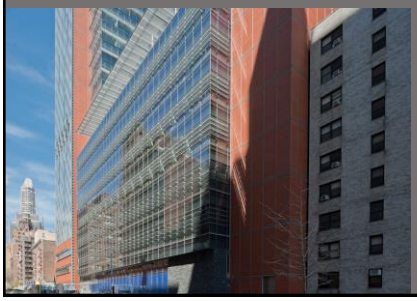
Thank you for your attention!
Questions?
212-639-3107



What's on the Horizon for Chronic Myeloid Leukemia?

LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers
someday is today®

Q&A Session

Ask a question by phone:

- Press star (*) then the number 1 on your keypad.

Ask a question by web:

- Click "Ask a question"
- Type your question
- Click "Submit"

Due to time constraints, we can only take one question per person. Once you've asked your question, the operator will transfer you back into the audience line.

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SUPPORT RESOURCES

- **LLS Community:** Online community of people living with or supporting someone with blood cancer: **www.LLS.org/community**
- **What to ask:** Questions to ask your treatment team: **www.LLS.org/whattoask**
- **Free education materials: www.LLS.org/booklets**
- **Past CML education programs: www.LLS.org/programs**
- **Online CML Chat: www.LLS.org/chat**
- **Information Resource Center:** Speak one-on-one with an Information Specialist who can assist you through cancer treatment, financial, and social challenges.
  - **EMAIL: infocenter@LLS.org**
  - **TOLL-FREE PHONE: (800) 955- 4572**