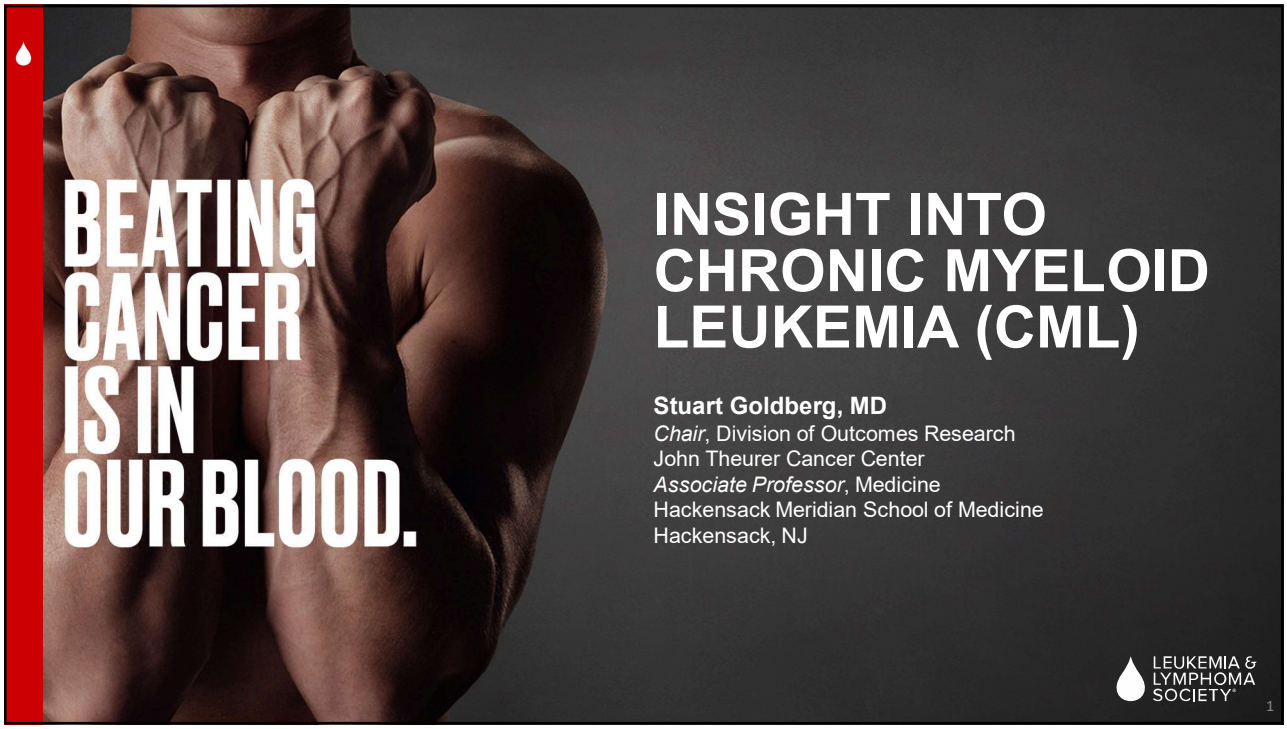

INSIGHT INTO CHRONIC MYELOID LEUKEMIA (CML)

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DISCLOSURES

Insight Into Chronic Myeloid Leukemia (CML)

Stuart Goldberg, MD, has affiliations with COTA, Inc., for Equity.

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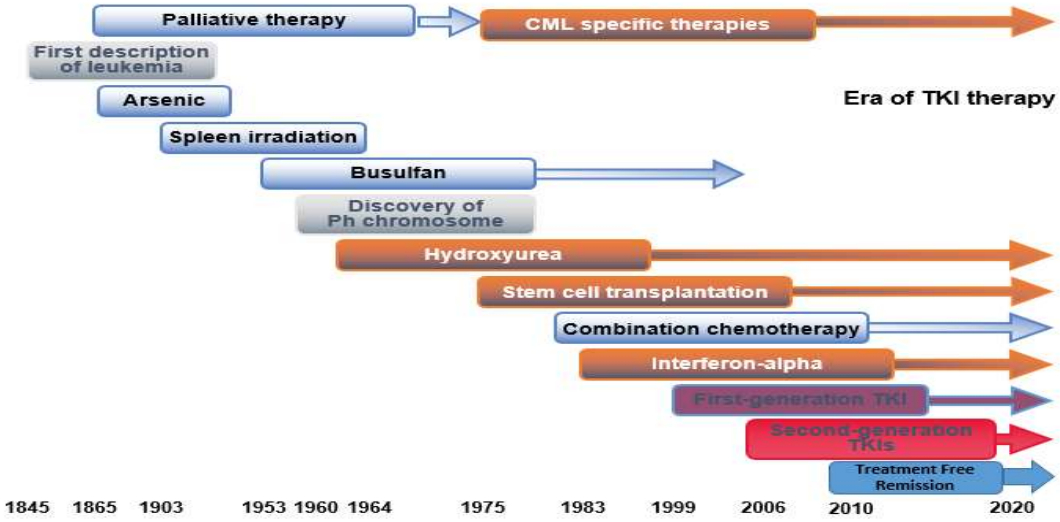
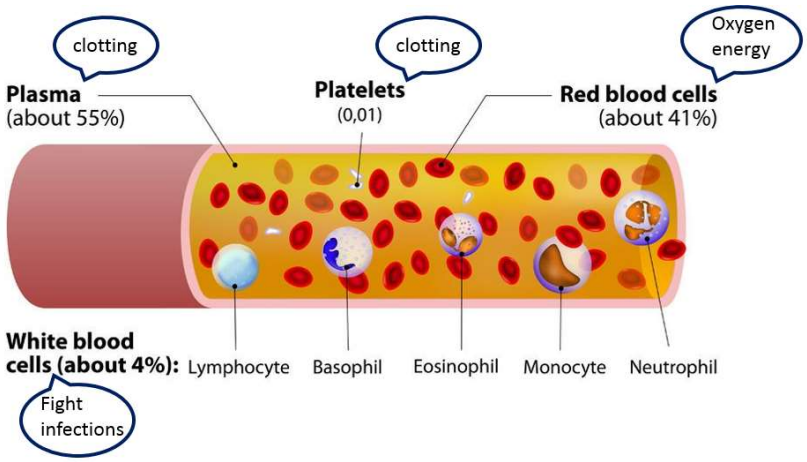
CML: A disease of "firsts"



Bumbea H et al. *J Med Life*. 2010;3(2):162-166 and Wapner J. The Philadelphia Chromosome

3

What is blood?



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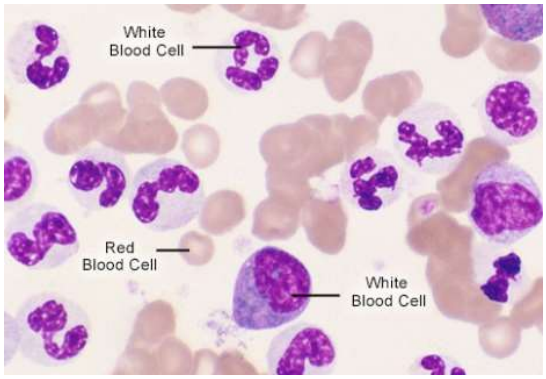
What is Chronic Myeloid Leukemia ?

- Leukemia: "white blood" cancer
- Myeloid (Myelogenous): type of white blood cell
- Chronic (vs Acute): aggressiveness of cancer: "numbers not function"



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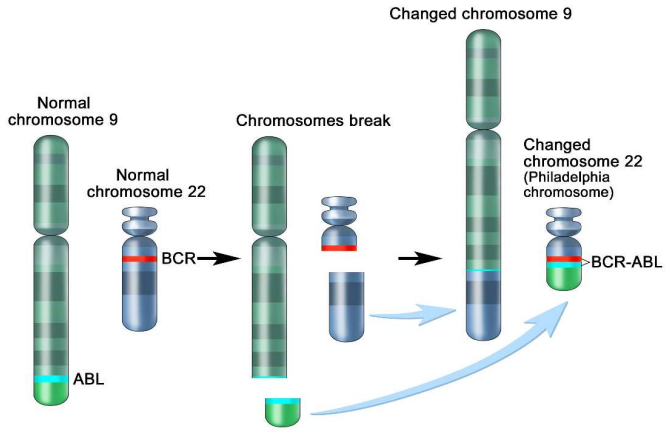
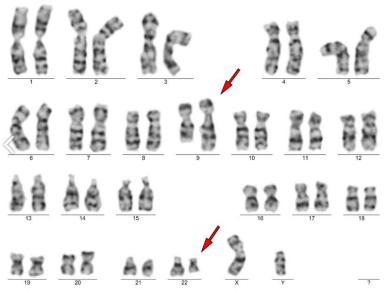
The Philadelphia Chromosome





The Philadelphia Chromosome (and the protein bcr-abl) is the cause of CML. It is acquired (not hereditary) and largely unknown why it develops

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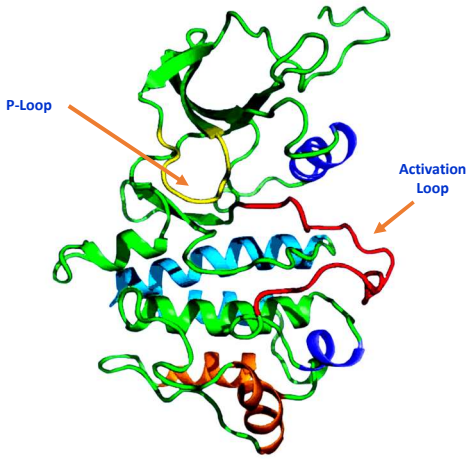
The bcr-abl fusion protein



- The Philadelphia Chromosome codes for the bcr-abl fusion protein
- This abnormal protein turns on the cell and causes cancer cells to grow rapidly.
- Blocking the function of the bcr-abl protein slows the disease
- Measuring bcr-abl transcripts in the blood or bone marrow allows monitoring of disease status

1. Sawyers CL. *N Engl J Med.* 1999;340:1330-1340.
2. Melo JV, Deininger MWN. *Hematol Oncol Clin North Am.* 2004;18:545-568.

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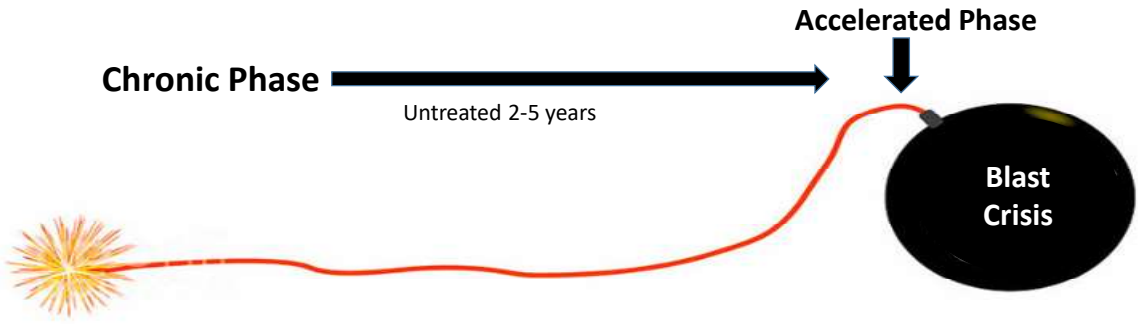
The Phases of CML

(Or why to treat since I felt well before the diagnosis)



Goal is to prevent Blast Crisis by slowing or stopping the fuse (lengthen chronic phase)

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How do we know treatment is working?

Has the fuse really been lengthened?

- **Good blood counts DO NOT indicate that treatment is working!!!**
- **Suppression of the Philadelphia chromosome correlates with improved survival ----**
- **Reduction of the bcr-abl transcripts is a good indicator of success!!!**

- **PCR tests from the blood can measure the bcr-abl transcripts**
  - **100% IS is the average amount of "cancer" bcr-abl transcripts in a new patient**
  - **1-2% IS is where the Philadelphia chromosome disappears = survival (CR)**
  - **0.1% IS is a nice cushion (MMR)**
  - **0.01 IS (MMR4) or 0.003 (MMR4.5) is where so little cancer treatment might stop**

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Treatment milestones	at 3 months	at 6 months	at 12 months	at 15 months or more
PCR bcr-abl >10% IS	Possible TKI resistance	TKI resistance	TKI resistance	TKI resistance
PCR bcr-abl 1-10% IS	Milestone met	Milestone met	Possible TKI resistance	TKI resistance
PCR bcr-abl <1% IS	Milestone met	Milestone met	Milestone met	Milestone met

PCR monitoring is performed every 3 months
GREEN = continue current therapy
YELLOW = time for concern
RED = time to switch

Increase in pcr by 1 log also equals resistance

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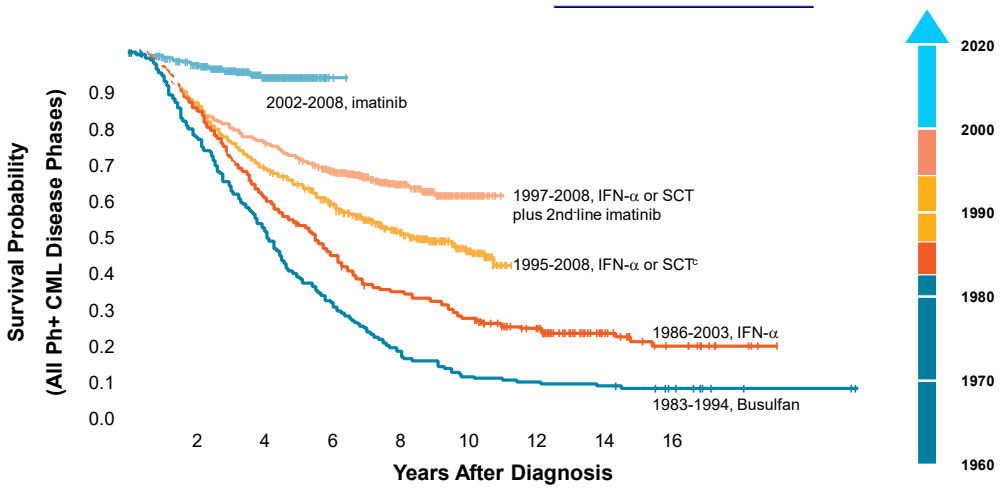
Treatment Has Improved Survival. Most new patients can expect a NORMAL lifespan with current TKI therapy



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Current Treatments for CML

- Tyrosine kinase inhibitors
  - Imatinib (Gleevec) } 1st generation
  - Dasatinib (Sprycel)
  - Nilotinib (Tasigna)
  - Bosutinib (Bosulif) } 2nd generation
  - Ponatinib (Iclusig) } 3rd generation

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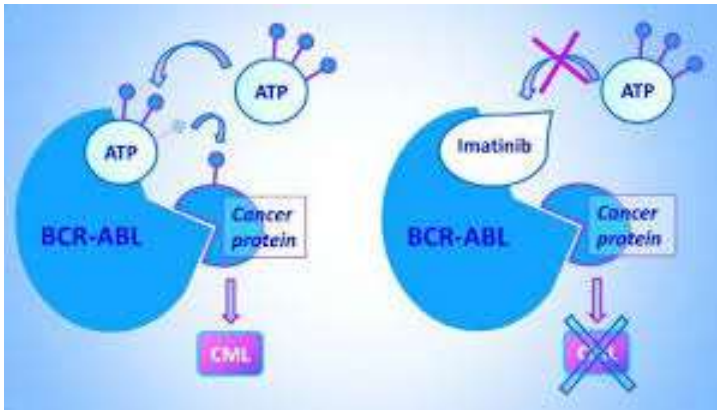
How TKI's work



The bcr-abl protein causes abnormal phosphorylation (energy transfer) of proteins turning on cell growth
The TKI's physically block entry of ATP (energy) into the bcr-abl protein, halting growth

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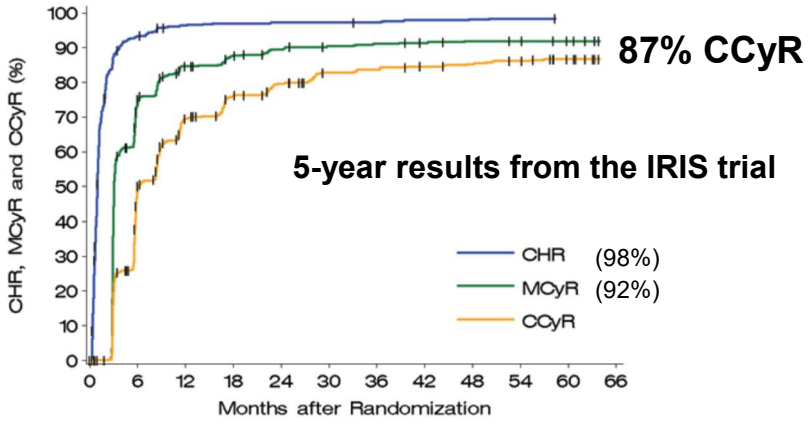
Imatinib (Gleevec) and the IRIS study. Most are still in remission more approaching 20 years



CCyR=complete cytogenetic response.
Druker BJ, et al. *N Engl J Med*. 2006;355:2408.

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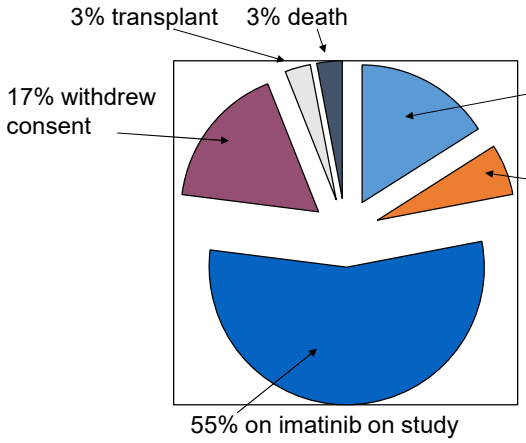
However up to 20%-35% of Patients With CML on Imatinib (Gleevec) IRIS Study Required Changes in Treatment



8 year follow up of the IRIS Trial

A second study from the UK estimated that only 63% of patients would be still be on imatinib and in cytogenetic remission at 5 years

AE=adverse event.

Deininger M. *Blood*. 2009:114 (abstr 1126); de Lavallade et al. *J Clin Oncol*. 2008;26:3358.

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Sometimes the bcr-abl protein changes its shape and the TKI cannot fit into the groove (mutation)

If the protein mutates, we need a new TKI

The second and third generation TKIs

2nd: Dasatinib, Nilotinib, Bosutinib
- **more potent in the test tube**
- **fit into mutated bcr-abl**

3rd : Ponatinib
- **most potent**
- **fits into difficult mutations**
- **most side-effects**

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Can Mutational Studies Aid in Selection?

In vitro sensitivity patterns of ABL-kinase domain mutations to TKIs

Although patients harboring a high IC50 mutation tend to respond poorly, the IC50 values alone might not be predictive of drug selection

		IC50-fold increase (WT=1)			
		Bosutinib	Imatinib	Dasatinib	Nilotinib
	Parental	38.31	10.78	>50	38.43
	WT	1	1	1	1
P-LOOP	L248V	2.97	3.54	5.11	2.80
	G250E	4.31	6.86	4.45	4.56
	Q252H	0.81	1.39	3.05	2.64
	Y253F	0.96	3.58	1.58	3.23
	E255K	9.47	6.02	5.81	6.69
	E255V	5.53	16.99	3.44	13.31
C-Helix	D276G	0.60	2.18	1.44	2.00
	E279K	0.95	3.55	1.64	2.05
ATP binding region (drug contact sites)	V299L	26.10	1.54	8.65	1.34
	T315I	45.42	17.50	75.03	39.41
	F317L	2.42	2.60	4.46	2.22
SH2-contact	M351T	0.70	1.76	0.88	0.44
Substrate binding region (drug contact site)	F359V	0.93	2.86	1.49	5.16
A-LOOP	L384M	0.47	1.28	2.21	2.33
	H396P	0.43	2.43	1.07	2.41
	H396R	0.81	3.91	1.63	3.10
	G398R	1.16	0.35	0.69	0.49
C terminal lobe	F486S	2.31	8.10	3.04	1.85

Sensitive	<2
Moderately resistant	2.01-4
Resistant	4.01 - 10
Highly resistant	>10

Redaelli S, et al. *J Clin Oncol*. 2009;27:479.

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Why doesn't everyone get a 2nd gen TKI first?

- Yes they are more potent and get CML patients into remission faster
- Yes they are good at mutated bcr-abl

- However, imatinib works --- similar long term survival
- And possibly more side-effects?

- Current guidelines: consider if higher risk CML (Sokal score)
- Certainly use if prior therapies aren't working or if side-effects

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Representative Results of 1st line TKIs

	Imatinib	Nilotinib	Dasatinib	Bosutinib
CCyR 2 years	77-82%	85%	86%	77% @ 1 year
MMR 5years	69-64%	77%	76%	39% @ 1 year
PFS 5 years	86- 94.7%	95.8%	85%	-
OS	90-91.7%	96.2%	91%	-
Progression AP/BP	12 (2 between 3-5 years)	3	0 (between 3-5 years)	4 (1 year)

Cortes JE, et al. *J Clin Oncol.* 2016;34(20):2333-2340. Hochhaus A, et al. *Leukemia.* 2016;30(5):1044-1054. Cortes JE, *J Clin Oncol.* 2018;36(3):231-237.

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CML patients get a Second Chance at Success

	First Line PFS	Second Line PFS
Dasatinib	90% at 5 years	40-50% at 6 years
Nilotinib	90-95% at 5 years	55% at 4 years
Bosutinib	88% EFS at 2 years	80% at 2 years (only 40% remain on at 5 years)
Ponatinib	100% at 2 years	55% at 5 years

hah NP, et al. *Blood.* 2014;123(15):2317-2324. Kim DD, et al. *Br J Haematol.* 2013;160(5):630-639. Cortes JE, et al. *Blood.* 018;132(4):393-404. Gambacorti-Passerini C, et al. *Haematologica.* 2018;103(8):1298-1307. Jain P, et al. *Lancet Haematol.* 015;2(9):e376-383.

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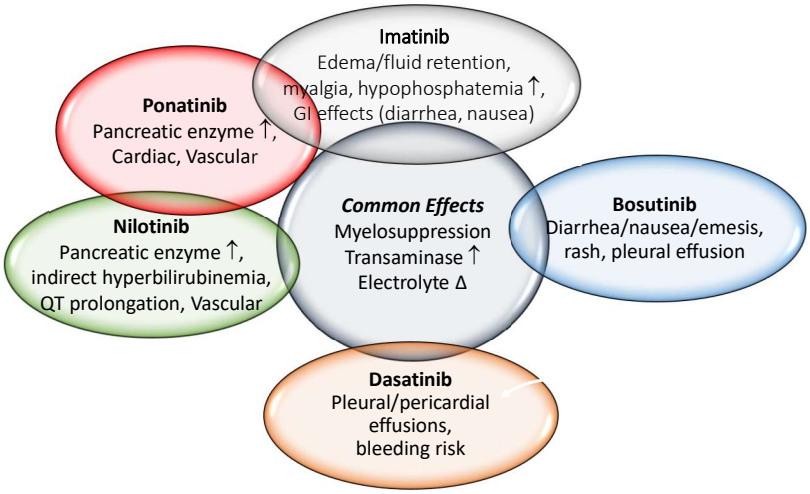
Although TKIs are generally well tolerated they can have side effects



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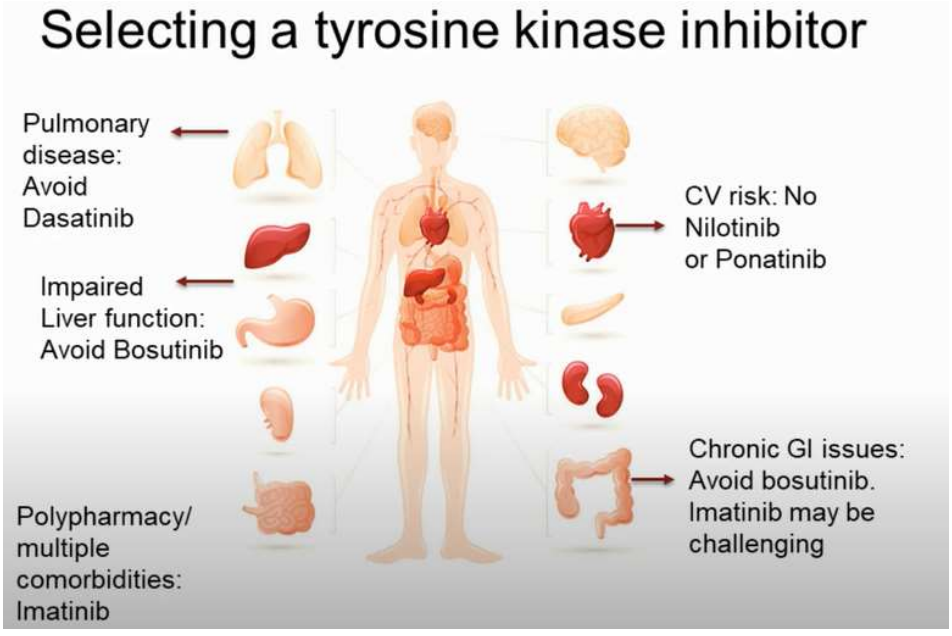
Selecting a tyrosine kinase inhibitor



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What about Generic Imatinib?

- Generic imatinib has the same medication so ----
- IT WORKS

- However, it has different coatings and fillers so ---
- Absorption may be slightly different
- Side-effects may be slightly different

- Costs are different
  - (but unfortunately in the US, not a dramatic reduction)

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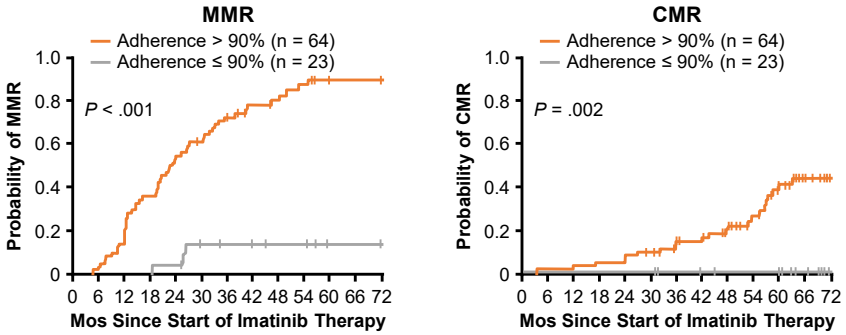
Can I miss doses?
Adherence to Imatinib Is Critical for Achieving Molecular Response

Missing just 3 DAYS per MONTH (10%) lowered the chance of newly diagnosed patients obtaining deep remissions. PLEASE take your medications;

If you are having side-effects tell your team, maybe something can be done.



Marin D, et al. J Clin Oncol. 2010;28:2381-2388.

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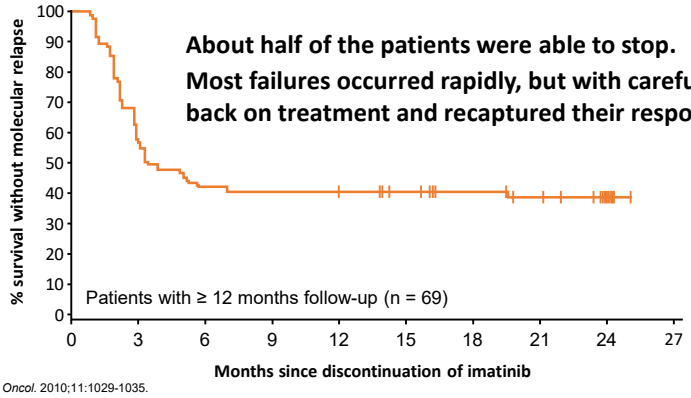
I am in remission: Can I stop my TKI?

TKI discontinuation is now a real goal and no longer research

Stop Imatinib Trial (STIM) is now more than 10 years old



About half of the patients were able to stop.

Most failures occurred rapidly, but with careful monitoring, went back on treatment and recaptured their response

Mahon F-X, et al. *Lancet Oncol.* 2010;11:1029-1035.

25

Criteria to Consider TKI discontinuation

- **In a deep remission for a minimum of 2 years**
  (MMR4 or MMR 4.5 : pcr bcr-abl <0.01% IS or <0.003% IS)
- **No history of resistance or advanced phase**
- **Willing to be closely monitored**
  (pcr tests every 1-2 months for the first year)

- **Additional features that lead to success**
  - **Long prior treatment >8 years**
  - **Rapid initial response**
  - **Certain bcr-abl transcript types**
  - **Lower initial Sokal score**

- **Second attempts have succeeded at approximately 25% rate**

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I am in remission, and don't want to stop What else?

- You are not alone
- If you are doing fine, great --- but take your medication and get monitored
- If you are having side-effects, don't accept it –
  - Consider decreasing dose with approval of your doctor, followed by monitoring
  - Don't just skip doses
  - If that fails, consider changing TKIs – they all have different side-effects
- If you are having cost issues, talk to your medical team

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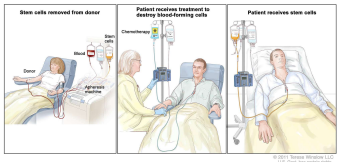
Other Treatments for CML

- Allogeneic (donor) hematopoietic stem cell transplants
  - Today used mostly is advanced phases of disease or very resistant disease



- Interferon
  - Used mostly during pregnancy

- Omacetaxine (Synribo)
  - Used in resistant disease

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Newer Medications on the Horizon???

TKI	Features	Current status
ABL-001	Allosteric inhibitor	• Completed phase 1, single agent and combination • Pivotal phase 3 3rd line v bosutinib started
Radotinib	2nd generation	• Approved in South Korea 1st and 2nd line • Pending studies elsewhere
PF-114	Ponatinib analog, not binding VEGFR	• Nearing MTD Starting phase 2
K0706	3rd generation	• Phase 1 started

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Remaining Challenges?

- **Most CML patients do well and can expect a normal lifespan**

- **Understand and reduce long term side effects**
- **Increase the pool of patients who obtain deep response to allow more TKI discontinuations**
- **Improve second attempts at TKI discontinuation**
- **Help those with resistant disease**
- **Improve treatment and monitoring in third world countries**
- **Grapple with escalating costs**

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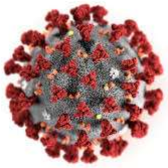

CML and Coronovirus

- At the present time there is no evidence to suggest that CML patients are at higher risk of contracting COVID-19 or having a more severe form of viral infection (American Society of Hematology)
- Some TKI medications prolong QTc (heart rhythm). Hydroxychloroquine and Azithromycin (medications being studied in coronavirus) also prolong QTc --- Use with caution.
- The iCMLf is collecting data on CML-COVID-19, check the website for updated details. The LLS is also providing updates as available.

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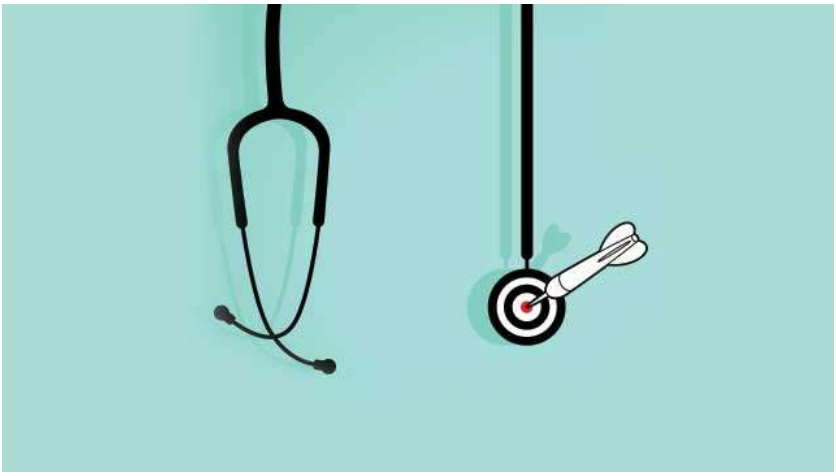
Thank you.
Questions?



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Q&A SESSION

Insight Into Chronic Myeloid Leukemia (CML)

- **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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To contact an **Information Specialist** about disease, treatment and support information, resources and clinical trials:

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Monday to Friday, 9 a.m. to 9 p.m. ET

Chat live online: www.LLS.org/InformationSpecialists
Monday to Friday, 10 a.m. to 7 p.m. ET

Email: infocenter@LLS.org
All email messages are answered within one business day.

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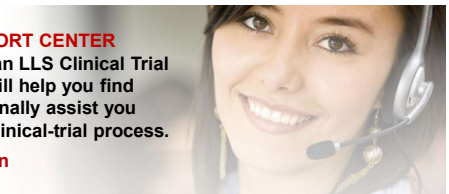
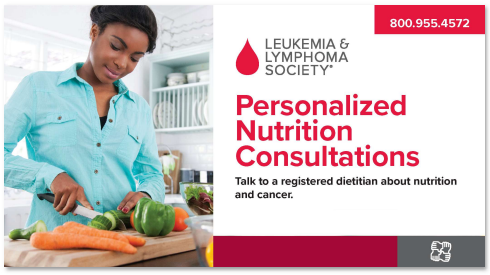
Work one-on-one with an LLS Clinical Trial Nurse Navigator who will help you find clinical trials and personally assist you throughout the entire clinical-trial process.

www.LLS.org/Navigation





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View our free education videos on disease, treatment, and survivorship. To view all patient videos, please visit **www.LLS.org/EducationVideos**.

Patient Podcast

The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit **www.thebloodline.org**.

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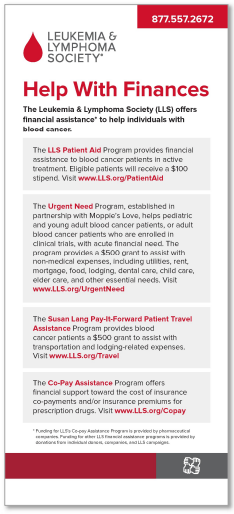
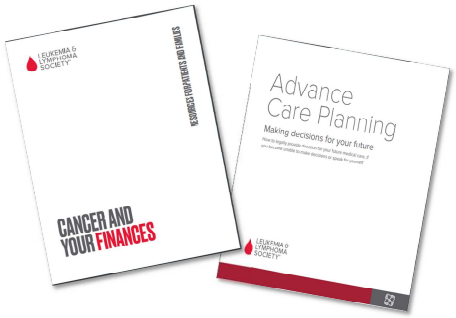


The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancer:
www.LLS.org/Finances



To order free materials: **www.LLS.org/booklets**

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THANK YOU
We have one goal: A world without blood cancers
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