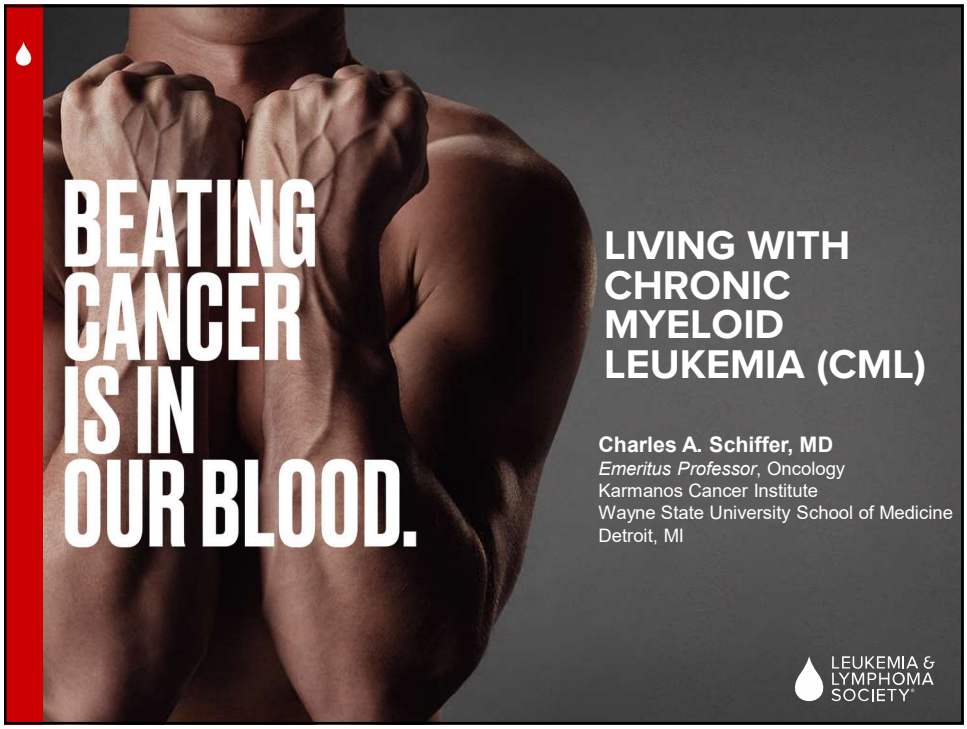

WELCOMING REMARKS

Living With Chronic Myeloid Leukemia (CML)

Lizette Figueroa-Rivera
Sr. Director, Education & Support
The Leukemia & Lymphoma Society

BEATING CANCER IS IN OUR BLOOD.

LEUKEMIA & LYMPHOMA SOCIETY

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WELCOMING REMARKS

Living With Chronic Myeloid Leukemia (CML)

Mel Mann, MBA, M.ED
CML Patient since 1995

DISCLOSURES

Living With Chronic Myeloid Leukemia (CML)

Charles A. Schiffer, MD, has affiliations with Agios, BMS, Merck, Novartis (*Consultant*); Takeda (*Grant Support*); Astellas, BMS/Celgene, Kartos, Syndax (*Data and Safety Monitoring Board*).

AFTER 20+ YEARS OF IMATINIB, WHERE DO THINGS STAND IN CML?

Charles A. Schiffer, MD
Professor Emeritus of Oncology
Karmanos Cancer Institute
Wayne State University School of Medicine

5

A Minute Chromosome in Human Chronic Granulocytic Leukemia

In seven cases thus far investigated (five males, two females), a minute chromosome has been observed replacing one of the four smallest autosomes in the chromosome complement of cells of chronic granulocytic leukemia cultured from peripheral blood. No abnormality was observed in the cells of four cases of *acute* granulocytic leukemia in adults or of six cases of acute leukemia in children. There have been several recent reports of chromosome abnormalities in a number of cases of human leukemia [including two of the seven cases reported here: Nowell and Hungerford, *J. Natl. Cancer Inst.* 25, 85 (1960)], but no series has appeared in which there was a consistent change typical of a particular type of leukemia.

Cells of the five new cases were obtained from peripheral blood (and bone marrow in one instance), grown in culture for 24–72 hours, and processed for cytological examination by a recently developed air-drying technique (Moorhead, *et al.*, *Exptl. Cell Research*, in press). The patients varied from asymptomatic untreated cases to extensively treated cases of several years duration in terminal myeloblastic crisis. All seven individuals showed a similar minute chromosome, and none showed any other frequent or regular chromosome change. In most of the cases, cells with normal chromosomes were also observed. Thus, the minute is not a part of the normal chromosome constitution of such individuals.

The findings suggest a causal relationship between the chromosome abnormality observed and chronic granulocytic leukemia.

PETER C. NOWELL
School of Medicine, University of Pennsylvania
DAVID A. HUNGERFORD
Institute for Cancer Research

1960

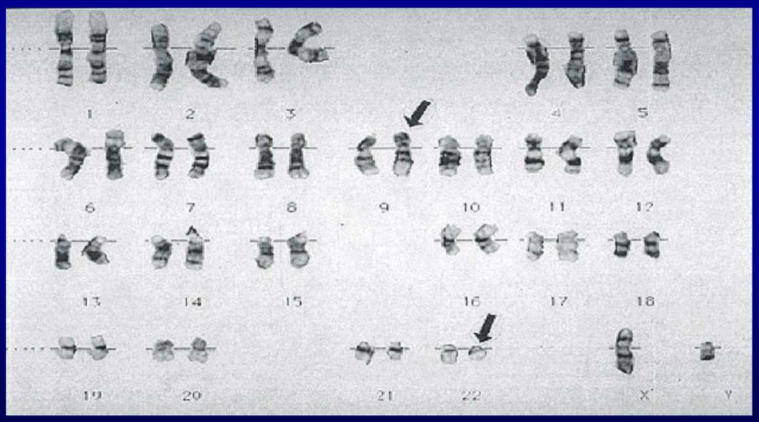
A minute chromosome in human granulocytic leukemia. Science 132, 1960, 1497.

P.C. Nowell, D.A. Hungerford, University of Pennsylvania in Philadelphia

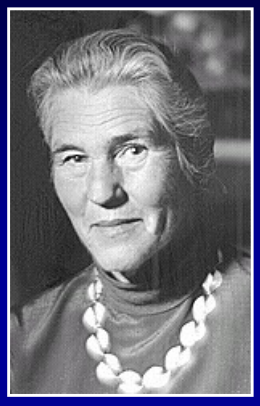
*…the findings **suggest a causal relationship** between the chromosome abnormality observed and chronic granulocytic leukemia…*

6

Cytogenetic Abnormality of CML: The Philadelphia Chromosome



7

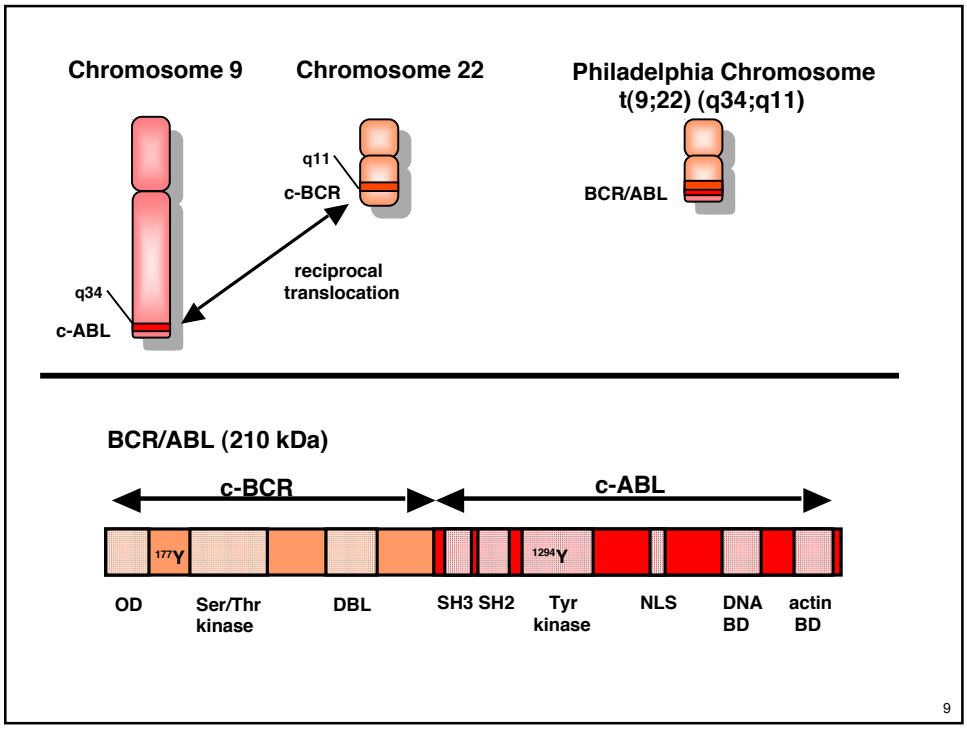


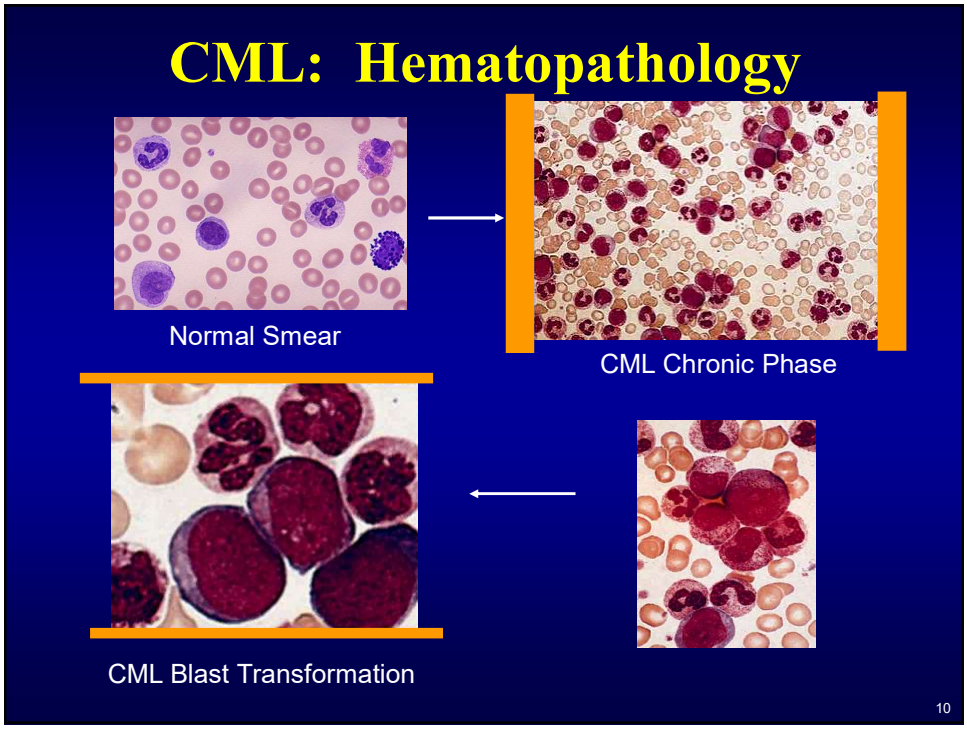
1973: translocation of chromosomal material

- Rowley JD: A new consistent chromosomal abnormality in chronic myelogenous leukemia identified by quinacrine fluorescence and Giemsa staining. Nature, 243, 290-293, 1973

- *…suggesting that there may be a hitherto undetected translocation between the long arm of 22 and the long arm of 9, producing the 9q+ chromosome…*

8


Chromosome 9
Chromosome 22
Philadelphia Chromosome
t(9;22) (q34;q11)
q11
c-BCR
BCR/ABL
reciprocal
translocation
q34
c-ABL
BCR/ABL (210 kDa)
c-BCR
c-ABL
177Y
1294Y
OD
Ser/Thr
kinase
DBL
SH3 SH2
Tyr
kinase
NLS
DNA
BD
actin
BD
9


CML: Hematopathology
Normal Smear
CML Chronic Phase
CML Blast Transformation
10

Italian Cooperative Study Group

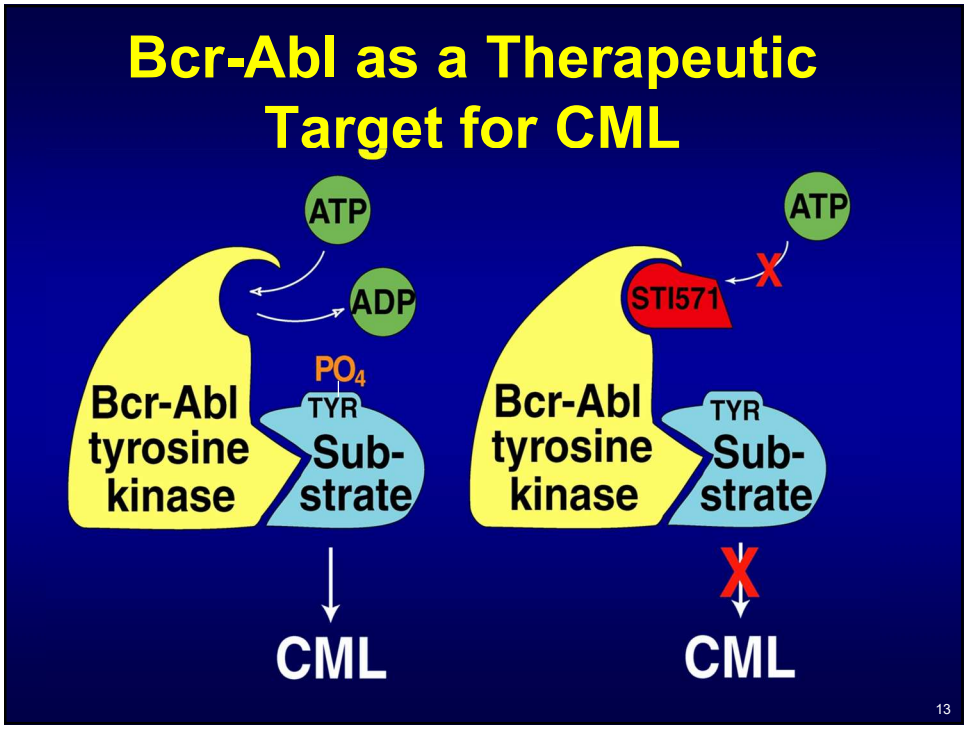
- Allogeneic transplantation from HLA fully matched siblings was the only available curative therapy
- But…
  - Age limit of 45-50 years
  - ~ 25% TRM
  - Results were better when done soon after diagnosis such that an unsuccessful transplant could actually shorten survival

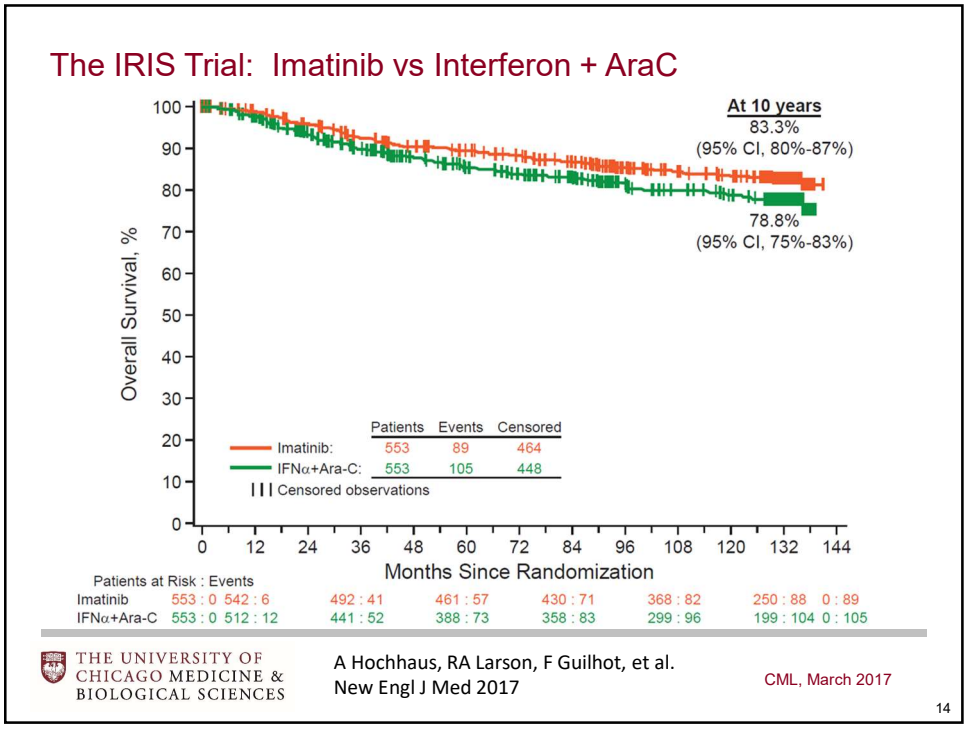
	Years										
IFN	218	203	188	162	137	117	101	83	68	49	17
CHT	104	99	88	74	56	45	31	26	22	17	5

Blood. 1998; 92:1541.

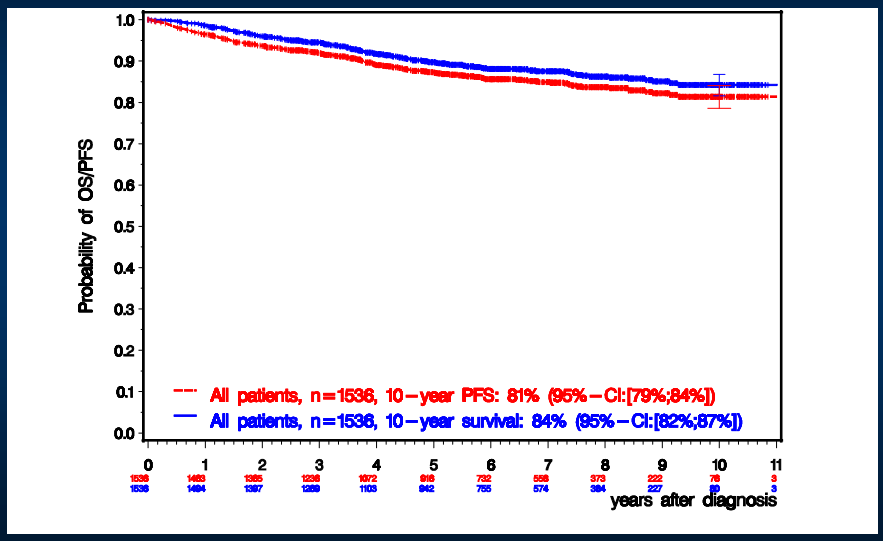
11

12


Bcr-Abl as a Therapeutic Target for CML
ATP
ADP
PO4
TYR
Bcr-Abl tyrosine kinase
Sub-strate
CML
ATP
STI571
X
Bcr-Abl tyrosine kinase
TYR
Sub-strate
X
CML
13


The IRIS Trial: Imatinib vs Interferon + AraC
At 10 years
83.3%
(95% CI, 80%-87%)
78.8%
(95% CI, 75%-83%)
Overall Survival, %
Patients Events Censored
Imatinib: 553 89 464
IFNα+Ara-C: 553 105 448
Censored observations
Months Since Randomization
Patients at Risk : Events
Imatinib 553 : 0 542 : 6 492 : 41 461 : 57 430 : 71 368 : 82 250 : 88 0 : 89
IFNα+Ara-C 553 : 0 512 : 12 441 : 52 388 : 73 358 : 83 299 : 96 199 : 104 0 : 105
THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES
A Hochhaus, RA Larson, F Guilhot, et al.
New Engl J Med 2017
CML, March 2017
14

10-year OS and PFS
CML-Study IV, all patients



German CML Study Group, unpublished

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OUTCOMES IN LESS DEVELOPED COUNTRIES

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JCO® Global Oncology
An American Society of Clinical Oncology Journal

Novel Humanitarian Aid Program: The Glivec International Patient Assistance Program—Lessons Learned From Providing Access to Breakthrough Targeted Oncology Treatment in Low- and Middle-Income Countries – *P. Garcia-Hernandez et al 1:35, 2015*

Albania	Botswana	Ecuador	Honduras	Mali	Nigeria	Saint Lucia	Thailand
Argentina	Burkina Faso	El Salvador	India	Mauritius	Pakistan	Senegal	Togo
Armenia	Cambodia	Ethiopia	Indonesia	Mexico	Panama	Seychelles	Turkey
Azerbaijan	Cameroon	Fiji	Jamaica	Moldova	Papua New Guinea	Singapore	Uganda
Bahamas	Chile	Gabon	Kazakhstan	Mongolia	Paraguay	Solomon Islands	Uruguay
Bangladesh	China	Georgia	Kenya	Morocco	Peru	South Africa	Uzbekistan
Belarus	Colombia	Ghana	Kyrgyzstan	Namibia	Philippines	Sri Lanka	Venezuela
Benin	Cote d'Ivoire	Guatemala	Madagascar	Nepal	Republic of Congo	Sudan	Vietnam
Bhutan	Dominican Republic	Guinea	Malawi	Nicaragua	Russia	Surinam	Zambia
Bolivia	East Timor	Haiti	Malaysia	Niger	Rwanda	Tanzania	Zimbabwe

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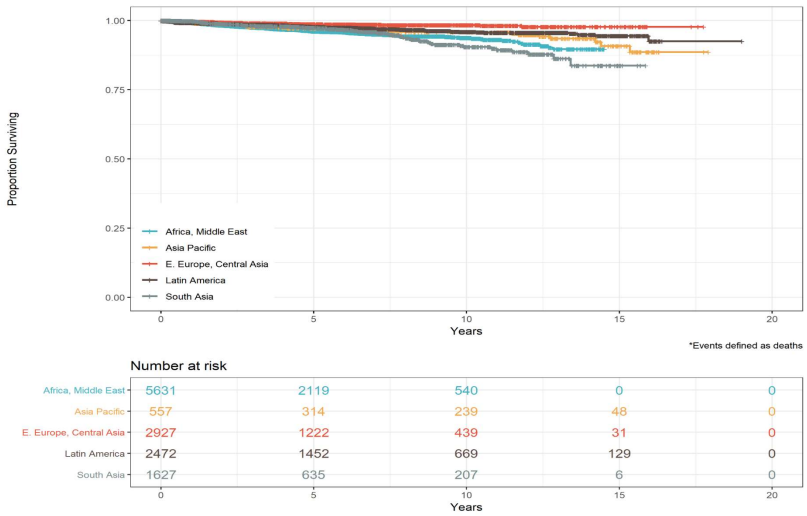
Overall survival (OS) CML patients receiving first line glivec



18

Imatinib (1999-2000):
and within a couple of years….

- Nilotinib
- Dasatinib

And a few years later…

- Bosutinib
- Ponatinib

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The Chemical Structure of TKIs

$$

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PERHAPS THE MOST CRITICAL COMPONENT OF CML CARE WITH TKIs

- COMPLIANCE
- COMPLIANCE
- COMPLIANCE

22


“ON TARGET”
23


“OFF TARGET”
MULTI-TARGETED?
24

Major Treatment Decisions

- Initial therapy
  - imatinib
- Dose adjustment of TKIs because of intolerance
- Stopping treatment

25

Poster 2924

Long-Term Outcomes in Patients with Chronic Myeloid Leukemia in Chronic Phase Receiving Frontline Nilotinib vs Imatinib: ENESTnd 10-Year Analysis

Timothy P. Hughes,[1] Giuseppe Saglio,[2] Richard A. Larson,[3] Hagop Kantarjian,[4] Dong-Wook Kim,[5] Surapol Issaragrisil,[6] Philipp le Coutre,[7] Gabriel Etienne,[8] Carla Boquimpani,[9] Richard E. Clark,[10] Viviane Dubruille,[11] Ian W. Flinn,[12] Slawomira Kyrcz-Krzemien,[13] Ewa Medras,[14] Maria Zanichelli,[15] Israel Bendit,[16] Manu Sondhi,[17] Ksenia Titorenko,[18] Claire Nourry-Boulot,[19] Paola Aimone,[19] and Andreas Hochhaus[20]

[1]South Australian Health and Medical Research Institute, Adelaide, SA, Australia; [2]Division of Internal Medicine & Hematology, University of Turin, Turin, Italy; [3]Department of Medicine, Section of Hematology/Oncology, University of Chicago, Chicago, IL; [4]The University of Texas MD Anderson Cancer Center, Houston, TX; [5]Seoul St. Mary's Hospital, College of Medicine, Catholic University of Korea, Seoul, South Korea; [6]Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, THA; [7]Charité - Universitätsmedizin Berlin, Berlin, Germany; [8]Hematology Department, Institut Bergonié, Bordeaux, France; [9]HEMORIO - Institute of Hematology in Rio de Janeiro and Oncoclínica Rio de Janeiro, Rio de Janeiro, Brazil; [10]Royal Liverpool University Hospital, Liverpool, United Kingdom; [11]Clinical Hematology, Nantes University Hospital, Nantes, France; [12]Sarah Cannon Research Institute, Nashville, TN; [13]Department of Hematology and Bone Marrow Transplantation, Medical University of Silesia, Katowice, Poland; [14]Department of Hematology, Blood Neoplasms and Bone Marrow Transplantation, Wroclaw Medical University, Wroclaw, Poland; [15]Instituto de Tratamento do Câncer Infantil, Instituto da Criança, Hospital das Clínicas, Universidade de São Paulo, São Paulo, Brazil; [16]Serviço de Hematologia do Hospital das Clínicas da FMUSP, São Paulo, Brazil; [17]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [18]Novartis Pharmaceuticals Corporation, Moscow, Russian Federation; [19]Novartis Pharma AG, Basel, Switzerland; [20]Univerisitätsklinikum Jena, Jena, Germany

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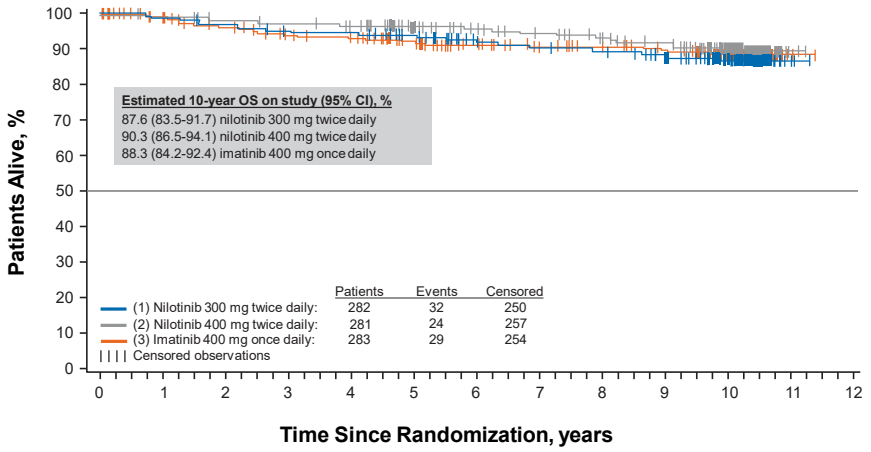
Figure 6. KM-Estimated Overall Survival[a]



No. at risk:events

(1)	282:0	271:2	263:7	254:13	249:16	232:17	214:21	207:25	204:27	194:31	152:31	2:32	0:32
(2)	281:0	270:2	264:6	261:8	256:9	235:10	221:11	211:14	200:17	192:21	148:23	2:24	0:24
(3)	283:0	274:2	262:10	250:16	245:18	225:22	208:23	199:24	192:24	184:26	141:29	2:29	0:29

[a] OS was defined as death due to any cause during the core or extension phase (including follow-up after discontinuation of treatment).

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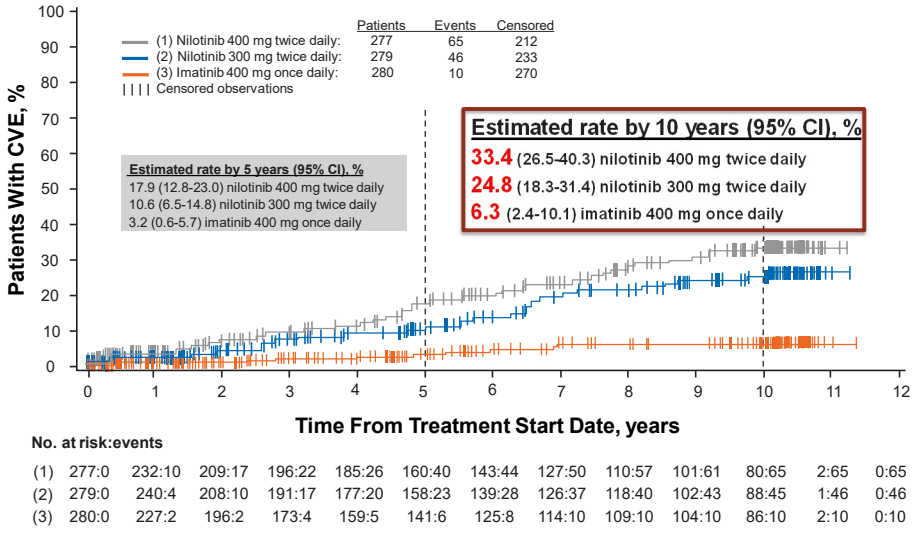
INITIAL THERAPY -- IMATINIB

- All randomized trials comparing imatinib with second generation TKIs (nilotinib, dasatinib, bosutinib) have shown results similar to this with faster responses but no survival advantage
- ~ 30-40% of patients are switched from their original TKI to alternatives because of real or perceived inadequate response or toxicity
- Many patients are maintained long term using doses lower than the original “standard” dose
- Treatment free remission (TFR) was not assessed in any of the large trials

28

KM-Estimated Time to First Cardiovascular Event

- Cardiovascular event (CVE) rates in the first 5 years in each arm were similar to the rates beyond 5 years (**Figure 8**)



No. at risk:events

(1)	277:0	232:10	209:17	196:22	185:26	160:40	143:44	127:50	110:57	101:61	80:65	2:65	0:65
(2)	279:0	240:4	208:10	191:17	177:20	158:23	139:28	126:37	118:40	102:43	88:45	1:46	0:46
(3)	280:0	227:2	196:2	173:4	159:5	141:6	125:8	114:10	109:10	104:10	86:10	2:10	0:10

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LONGER TERM FOLLOW-UP OF SECOND GENERATION TKIs

Dasatinib - late pleural effusions, pulmonary hypertension; T/NK cells

Nilotinib – hyperglycemia, peripheral arterial occlusive disease, other arterial thromboses

Bosutinib – less information

Ponatinib - MAJOR arterial thrombotic issues

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MONITORING RESPONSE WITH PCR

- Test blood rather than repeated bone marrows
- Can detect a single abnormal transcript among ~ 100,000 normal cells
- Initially every 3 months stretching to every 6 months in long term responders

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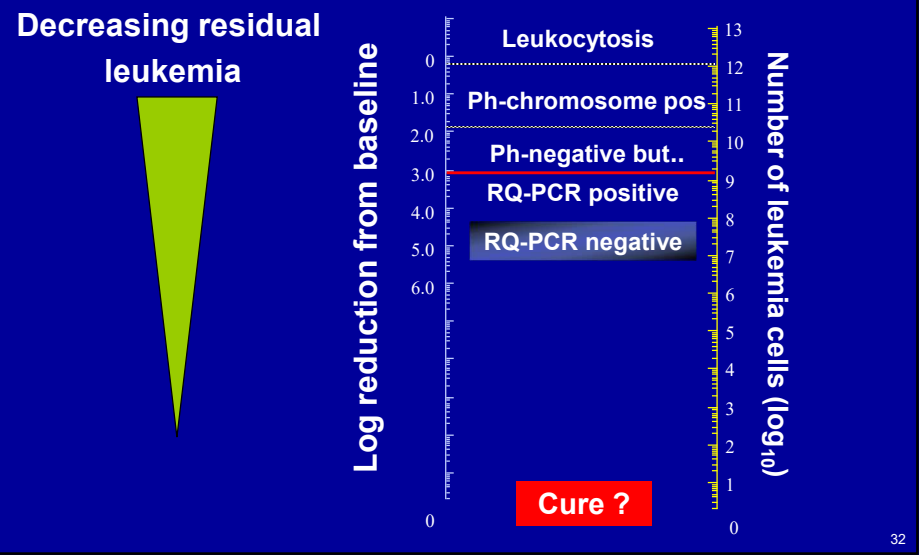
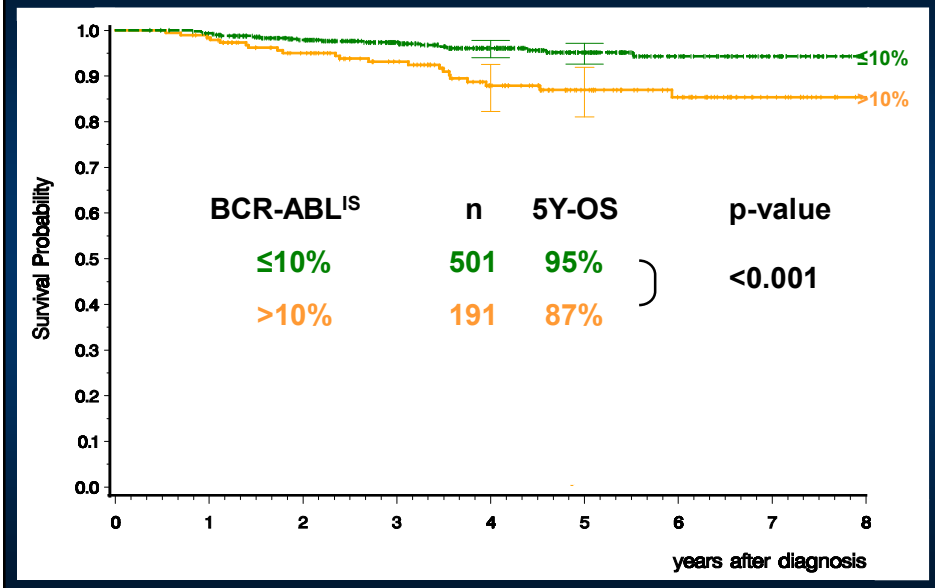
BCR-ABL transcript numbers expressed as log reduction in responding CML patients



32

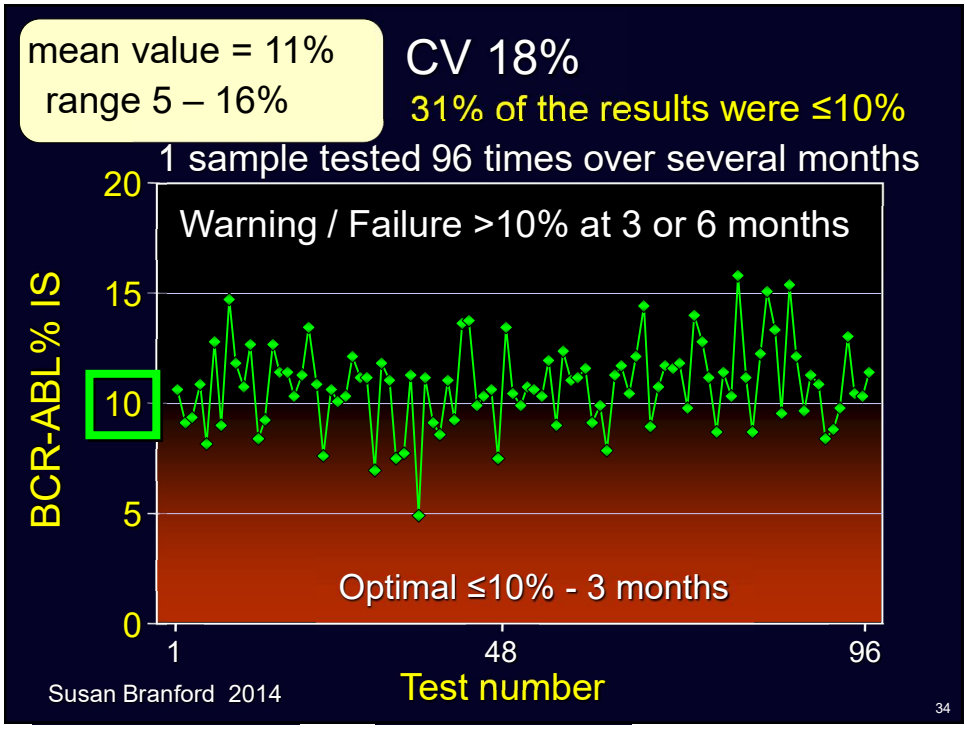
Overall Survival (OS) by BCR-ABL^{IS} at 3 months ≤10% vs. >10%



BCR-ABL^{IS}	n	5Y-OS	p-value
≤10%	501	95%	<0.001
>10%	191	87%	

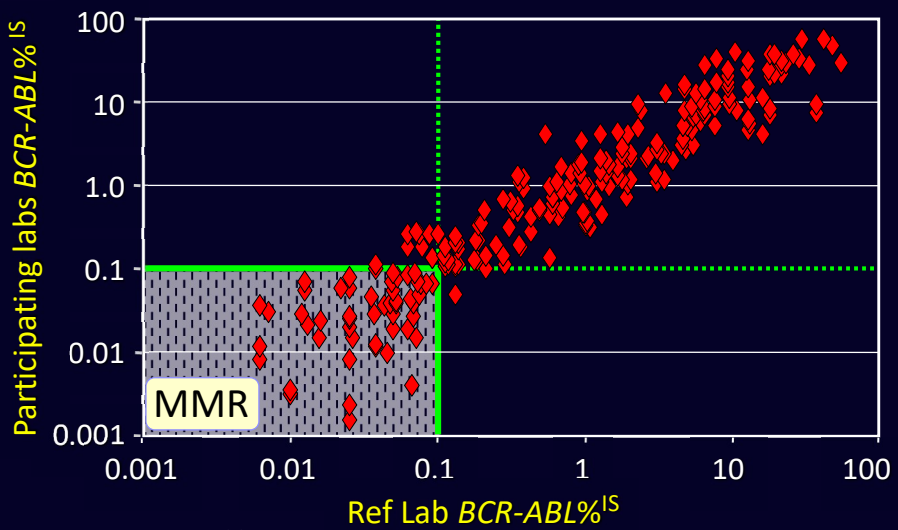
Hanfstein B, et al. Leukemia. 2012 Sep;26(9):2096-102.

33



34

RT-qPCR results at low levels are inevitably more variable than those at high levels



Branford S, et al. Blood 2008;112(8):3330–3338

35

Can you rely on a single assessment?

Technical issue:

- Duplicate values are .98% and 1.2%, which gets reported as 1%

For the > 1- 10% group:

- Does 1.01 = 9.99?
- Is .99 different than 1.01?

36

PCRITIS

Side effects

- Confused physicians
- Inappropriate dose increase
- Inappropriate referral for transplantation
- Inappropriate switch to new TKI
- Patient anxiety

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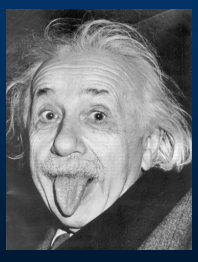
"Not everything that counts can be counted, and not everything that can be counted, counts."

Albert Einstein



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Treatment Free Remission (TFR)

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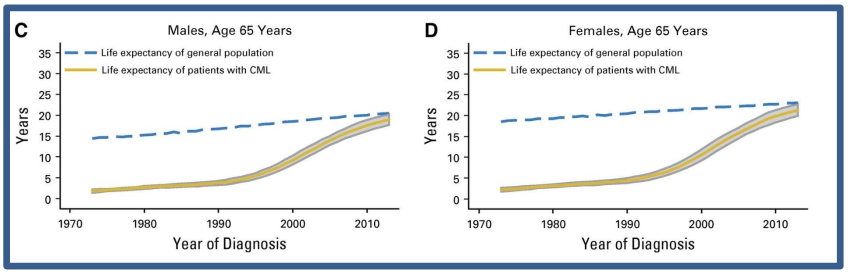
POTENTIAL BENEFITS OF STOPPING TKIs

- It's better not to take medications you don't need
- Pregnancy
- Reduction or elimination of TKI toxicities
  - Low grade, chronic
  - More severe side effects which haven't happened yet (particularly cardiovascular)
- The allure of the concept of "cure"
- **COST**

40

Life Expectancy of Patients with CML



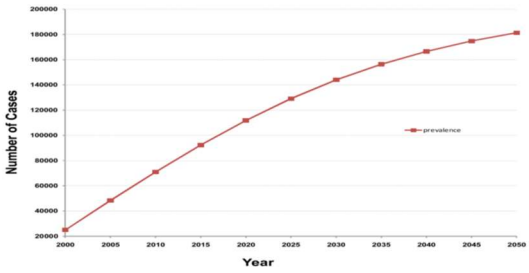
Patients of all ages diagnosed with CML will lose < 3 life-years as a result of CML

Bower et al. J Clin Oncol.2016 Aug 20;34(24):2851-7

MEDICAL COLLEGE OF WISCONSIN

41

CML Prevalence in the US



- By 2050 the prevalence of CML will plateau at 180,000
- Current prevalence ≅ 30,000 patients
- Current annual cost of TKI's is ≅ $100,000
- Annual cost of drugs alone in the US: 30,000 x $100,000 ≅ $3,000,000,000

Huang X et al. Cancer. 2012 June 15; 118(12): 3123–3127.

MEDICAL COLLEGE OF WISCONSIN

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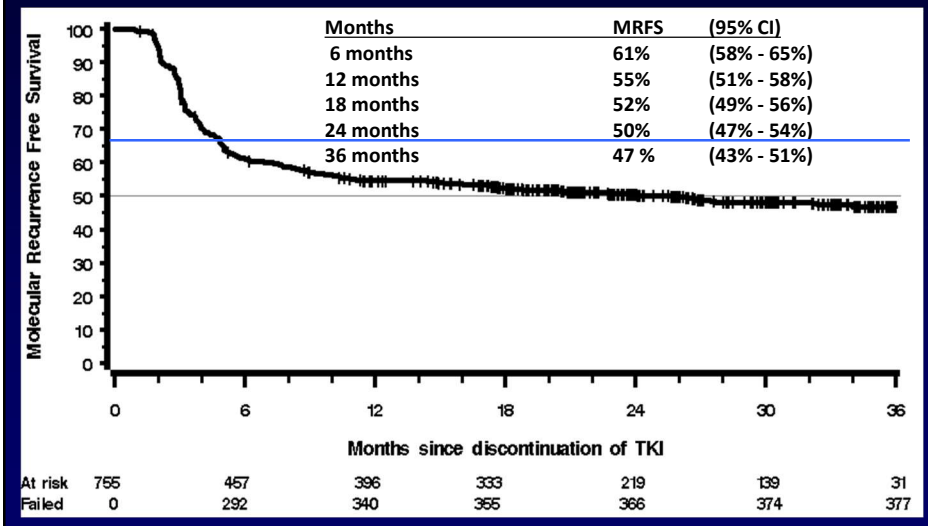
EURO-SKI Study

Molecular recurrence-free survival (n=755)



Months	MRFS	(95% CI)
6 months	61%	(58% - 65%)
12 months	55%	(51% - 58%)
18 months	52%	(49% - 56%)
24 months	50%	(47% - 54%)
36 months	47 %	(43% - 51%)

EURO-SKI presented by FX Mahon at ASH 2016

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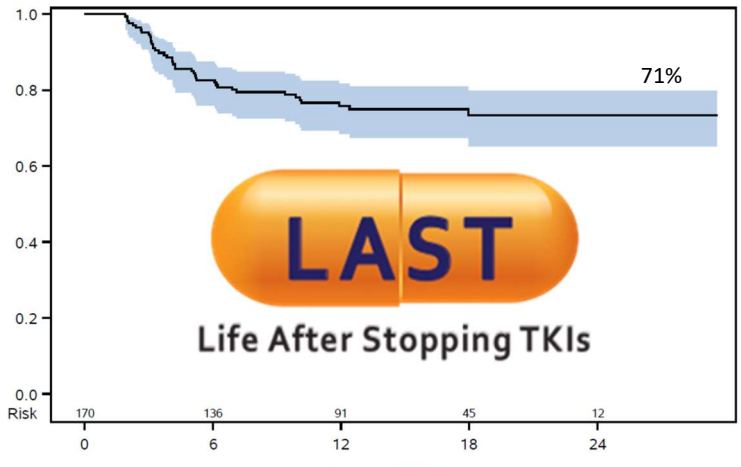
Molecular Recurrence Free Survival



Molecular recurrence free survival: 71% (based on study criteria)

MEDICAL COLLEGE OF WISCONSIN

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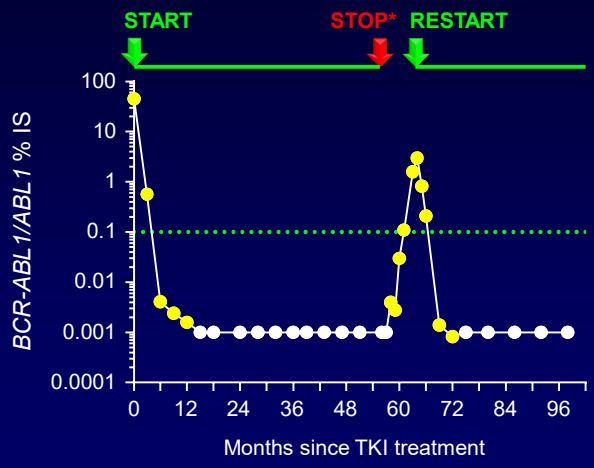
TKI discontinuation is safe

Female patient
42 yo at diagnosis
CP-CML
Low Sokal score
No ACA, b3a2
Imatinib first line



● Detectable *BCR-ABL* ● Undetectable *BCR-ABL* ≥ 32000 copies of *ABL*

D. Rea personal data
**Patient enrolled in the STIM2 trial*

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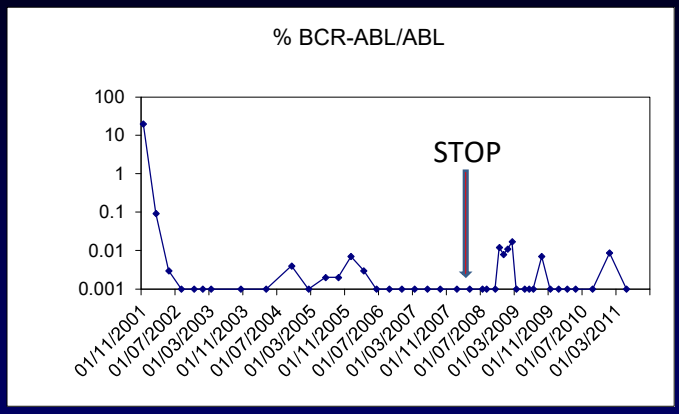
Fluctuation of BCR-ABL detection after discontinuation



Among the 39 pts without confirmed molecular relapse, 5 exhibited a fluctuation in BCR-ABL transcript detection

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SUMMARY OF RESULTS OF "STOPPING" TRIALS

- ~ 50% success rate independent of TKI
- Low, but real, rate of late relapse
- Virtually all relapses can be treated to level of original response
- "Withdrawal syndrome" in > 20% of patients
- If at first you don't succeed, you usually don't succeed later
- Prognostic factors
  - Depth of response
  - Duration of treatment

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HOW MANY PATIENTS WOULD BENEFIT FROM STOPPING?

If MMR is sufficient

CI of MMR at 5 years with imatinib is ~ 66%

If MR4.5 is necessary

CI of MR4.5 is ~ 30-40%

Assume ~ 60% of patients relapse….

Therefore a maximum of ~ 15% of imatinib patients will discontinue successfully, perhaps 5-10% more with dasatinb or nilotinib treatment

And, they will have to have received TKIs for a number of years before stopping

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Necessary Ingredients to Safely Allow TKI Discontinuation

- Attempt to discontinue only in patients with deep (at least MR4) and long-lasting (≥ 2 years) molecular responses
- Strictly monitor and rapidly resume treatment if MMR is lost
- PCR performed in a laboratory able to score deep molecular responses
- Proper interpretation of results by treating physicians

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WILL THERE BE LATE RELAPSES?

- The mechanism of sustained response is not known – immune mediated??
- Occasional late relapses have been seen and are likely under-reported
- Hiroshima/Nagasaki – CML incidence peaked ~ 10 years after the bombings in survivors and continued to rise slowly
- My approach is to continue to monitor long term, ~ every 6 months

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Q&A SESSION
Living With 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 have asked your question, the operator will transfer you back into the audience line.

BEATING CANCER IS IN OUR BLOOD.

LEUKEMIA & LYMPHOMA SOCIETY®

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LLS EDUCATION & SUPPORT RESOURCES

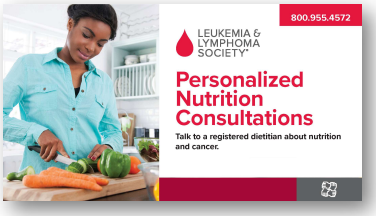
HOW TO CONTACT US:

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

Call: (800) 955-4572
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.



NUTRITION CONSULTATIONS
Our registered dietitian has expertise in oncology nutrition and provides free one-on-one consultations by phone or email.

www.LLS.org/Consult

CLINICAL TRIAL SUPPORT CENTER
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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LLS EDUCATION & SUPPORT RESOURCES

Online Chats

Online Chats are free, live sessions, **moderated by oncology social workers**. To register for one of the chats below, or for more information, please visit www.LLS.org/Chat

Education Videos

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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LLS EDUCATION & SUPPORT RESOURCES


877.557.2672

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Help With Finances

The Leukemia & Lymphoma Society (LLS) offers financial assistance* to help individuals with blood cancer.

The **LLS Patient Aid** Program provides financial assistance to blood cancer patients in active treatment. Eligible patients will receive a $100 stipend. Visit **www.LLS.org/PatientAid**

The **Urgent Need** Program, established in partnership with Moppie's Love, helps pediatric and young adult blood cancer patients, or adult blood cancer patients who are enrolled in clinical trials, with acute financial need. The program provides a $500 grant to assist with non-medical expenses, including utilities, rent, mortgage, food, lodging, dental care, child care, elder care, and other essential needs. Visit **www.LLS.org/UrgentNeed**

The **Susan Lang Pay-It-Forward Patient Travel Assistance** Program provides blood cancer patients a $500 grant to assist with transportation and lodging-related expenses. Visit **www.LLS.org/Travel**

The **Co-Pay Assistance** Program offers financial support toward the cost of insurance co-payments and/or insurance premiums for prescription drugs. Visit **www.LLS.org/Copay**

* Funding for LLS's Co-pay Assistance Program is provided by pharmaceutical companies. Funding for other LLS financial assistance programs is provided by donations from individual donors, companies, and LLS campaigns.

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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