



Slide 1: LIVING WITH CHRONIC MYELOID LEUKEMIA (CML)

Greetings and welcome to Living with Chronic Myeloid Leukemia (CML), telephone and web education program.

It is my pleasure to introduce your moderator Lizette Figueroa-Rivera.



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.

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Slide 2: WELCOMING REMARKS

Hello, everyone. On behalf of The Leukemia & Lymphoma Society, I'd like to welcome all of you.

For this program we would like to acknowledge and thank Abrale, Bristol Myers Squibb, and Novartis for support of this program.

Now, you'll hear a few words from Mel Mann, a CML survivor.



WELCOMING REMARKS
Living With Chronic Myeloid Leukemia (CML)



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

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Slide 3: WELCOMING REMARKS

Mel Mann:

Thank you, Lizette. And, I'd also like to add my welcome to the patients, caregivers, and healthcare professionals attending the program today.

My name is Mel Mann. I am a CML patient diagnosed since January 1995. At the time that I was diagnosed, I was given 3 years to live unless a bone marrow donor could be found. I was unable to find a donor, no one in my family matched, and no one else on the registry matched. And, despite me doing numerous bone marrow drives, I was unable to find a match.

I also started doing clinical trials and I was very fortunate to get on the Gleevec® clinical trial back in August of 1998. And, that is the drug that saved me, and I started the drug 3½ years after my diagnosis. And, a few months later I was able to start running and 10 months later I completed a 26.2 mile marathon for The Leukemia & Lymphoma Society, and also a 111 mile bike ride also for The Leukemia & Lymphoma Society's Team in Training, which raises money for future research. And, The Leukemia & Lymphoma Society played a significant role in funding Gleevec.

And, my leukemia was turned completely around and I'm here today, 26½ years later. The Leukemia & Lymphoma Society exists to find cures and ensures access to treatment to blood cancer patients. Our vision is a world without blood cancer. Until there's a cure, LLS will continue to fund promising research from bench to bedside. Today is World CML Day and we are one of many groups across the world that acknowledge the importance of CML awareness and continued research. LLS also acts as the voice for all blood cancer patients. Also, in honor of World CML Day, LLS is releasing its 100th podcast on The Bloodline, the LLS patient podcast, featuring Dr. Druker and myself, where I share my cancer journey. We speak of how Dr. Druker's work in CML has changed all of our lives. Please tune in at www.TheBloodline.org.

We are fortunate to have a presenter today, Dr. Charles Schiffer, who has dedicated so many years treating CML. We appreciate his dedication to supporting our mission. I'd like to thank him for providing us today with this important information on CML.

Thank you all. And for now, I'll turn the program back to Lizette.


Ms. Figueroa-Rivera:

Thanks, Mel. And, I hope you all get a chance to listen to our podcast with Mel.

If you're participating today by computer, Dr. Schiffer's slides will display as you see him via video and hear his audio through your computer. You can also view or print the slides from our website at www.LLS.org/Programs. Or, you can download and print the slides from the Materials tab on this program's web platform.

Following the presentation, we will take questions from the audience.


I am now pleased to introduce Dr. Charles Schiffer, Emeritus Professor of Oncology at Wayne State University School of Medicine at Karmanos Cancer Institute in Detroit, MI. Dr. Schiffer, I'm privileged to turn the program over to you.



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*).

BEATING CANCER IS IN OUR BLOOD.



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Slide 4: DISCLOSURES

Thank you very much.

This slide simply says that I've worked with many of the companies who have been important in the development of treatments for CML.

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

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Slide 5: AFTER 20+ YEARS OF IMATINIB, WHERE DO THINGS STAND IN CML?

So, it's a great privilege for me to be doing this, and in particular I think it's super cool that we're doing this on World CML Day, which is September 22 or 9/22 and I'll explain the 9/22 to you in a minute.

I've been involved in leukemia treatment for almost 50 years. And, we were one of the first, if not the only, center in the Midwest who had access to imatinib (Gleevec) and I think I treated my first patient in December of 1999, so that's a long time ago, a dramatic difference from the way things used to be and I'm going to be really pleased to describe this pathway of success to you and address a number of what I hope are clinically relevant issues for you, and leave time for lots of discussion.



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.

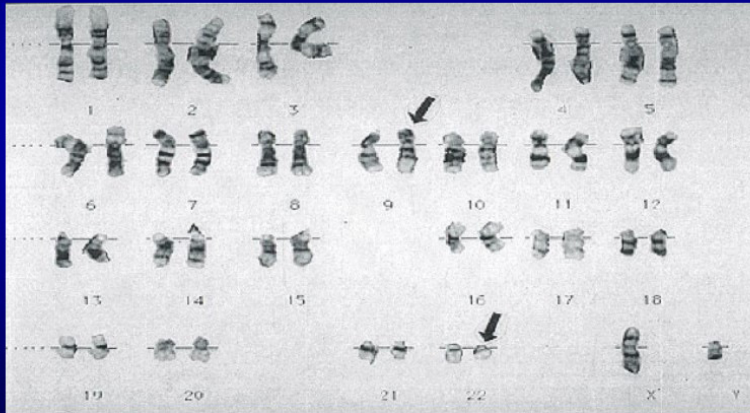
P.C. Nowell, D.A. Hungerford, University of Pennsylvania in Philadelphia

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

Slide 6: FIRST PAPER PUBLISHED IN 1960

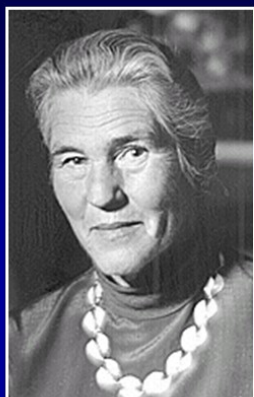
So, this is the first paper published in 1960 that described the Philadelphia chromosome. It came from investigators at the University of Pennsylvania, hence Philadelphia. And, this is the whole paper. Usually, scientific papers are dense and arcane and long and no fun to read, but I guess if you have something to say you can say it in just a few words

Cytogenetic Abnormality of CML: The Philadelphia Chromosome



Slide 7: Cytogenetic Abnormality of CML: The Philadelphia Chromosome

And, that is what they did cytogenetics, which was very new at the time, and their conclusion was that the findings suggest a causal relationship between the chromosome abnormality observed and chronic granulocytic leukemia, and what they observed was a very small chromosome where the arrow is.



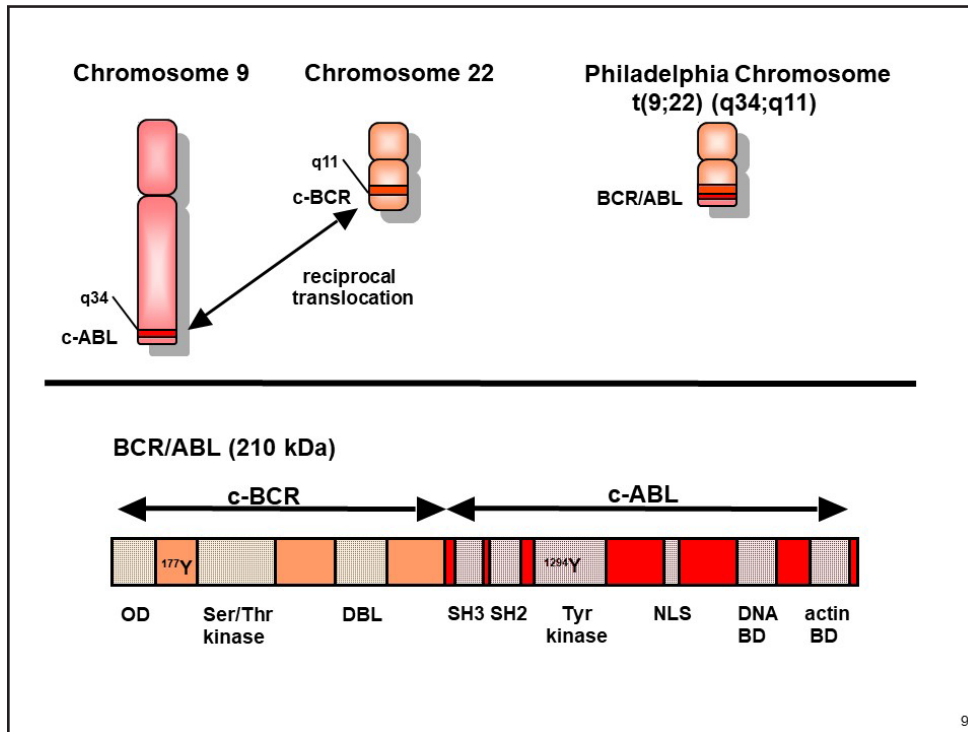
1973: translocation of chromosomal material

- 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...

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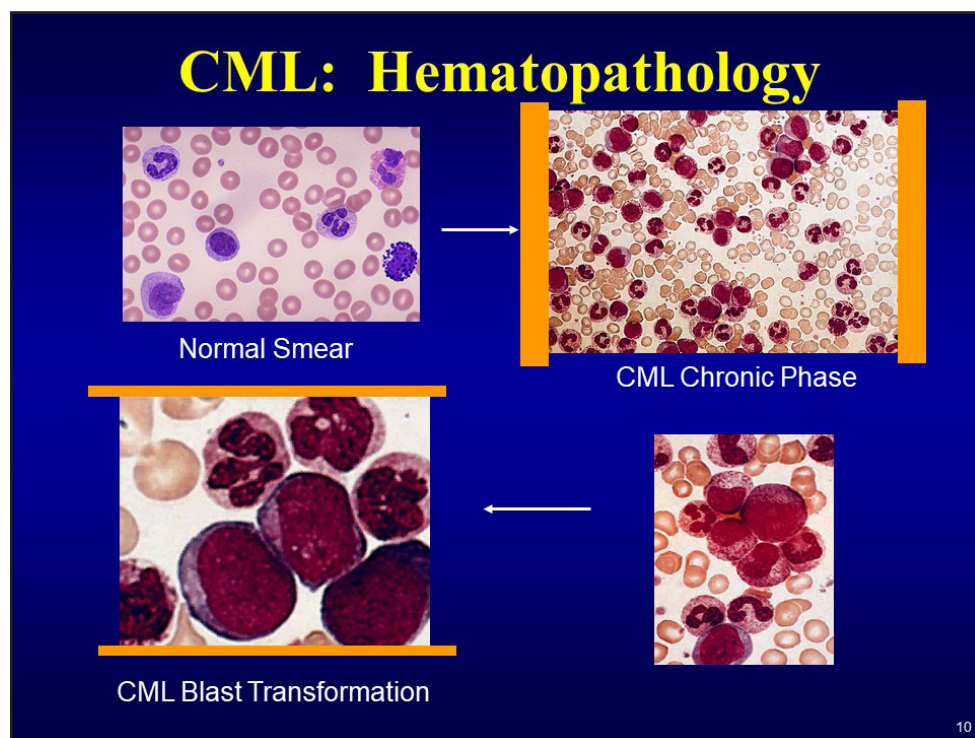
Slide 8: 1973: translocation of chromosomal material

The next major step was refining this. It wasn't just this small chromosome, but in fact a wonderful person and scientist named Janet Rowley in '73 using more sophisticated techniques noted that just an absence of material that created a small chromosome, but rather it was a transfer of material from chromosome 9 to chromosome 22 and back again. That's called a reciprocal translocation. And hence 9/22 and World CML Day today.



Slide 9: Really Understanding the Genetics and Chemistry

This prompted a huge amount of study to try to really understand the genetics and the chemistry as to what was going on, and this is a little complicated, but to simplify it, a piece of chromosome 9 containing the Abelson gene *ABL* was translocated to a piece of chromosome 22, the *BCR* region, hence the *BCR/ABL*. And, since it's putting 2 pieces of DNA together in places they do not belong and what they do is make an abnormal protein. What that abnormal protein did, and does, is it stimulates the growth and proliferation of white blood cells.



Slide 10: CML: Hematopathology

So, if this is an approximate normal number of white blood cells, what happens in CML chronic phase is that this expands dramatically, so if this normal white count is approximately 5000, this can be anywhere from 50,000 to 500,000, but in chronic phase it's an expansion of normal cells.

The analogy I sometimes make, it's like the thermostat on the furnace except because of this mutation, the furnace never takes off and keeps making abnormal cells.

Unfortunately, this is a genetically unstable state and on an average of 3 to 5 years, and we've heard from Mr. Mann why a transplant was recommended, this turns into an acute leukemia, which is very difficult to treat and was uniformly fatal, sometimes even with bone marrow transplant.

So before the availability of imatinib, this is essentially what happened to people. These were people who were treated with chemotherapy, drugs called hydroxyurea or busulfan. They very easily treated the elevated white count, but they never got rid of the Philadelphia chromosome, so it was like turning the thermostat down, but not turning it off.

This was what was a little bit better, therapy with a drug called interferon produced a lot of toxicity, but unfortunately it did not change the pattern of people dying of this disease and people were dying because of transformation to blast crisis. Notice this paper is in 1998, imatinib was 1999.

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.

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Slide 11: Italian Cooperative Study Group

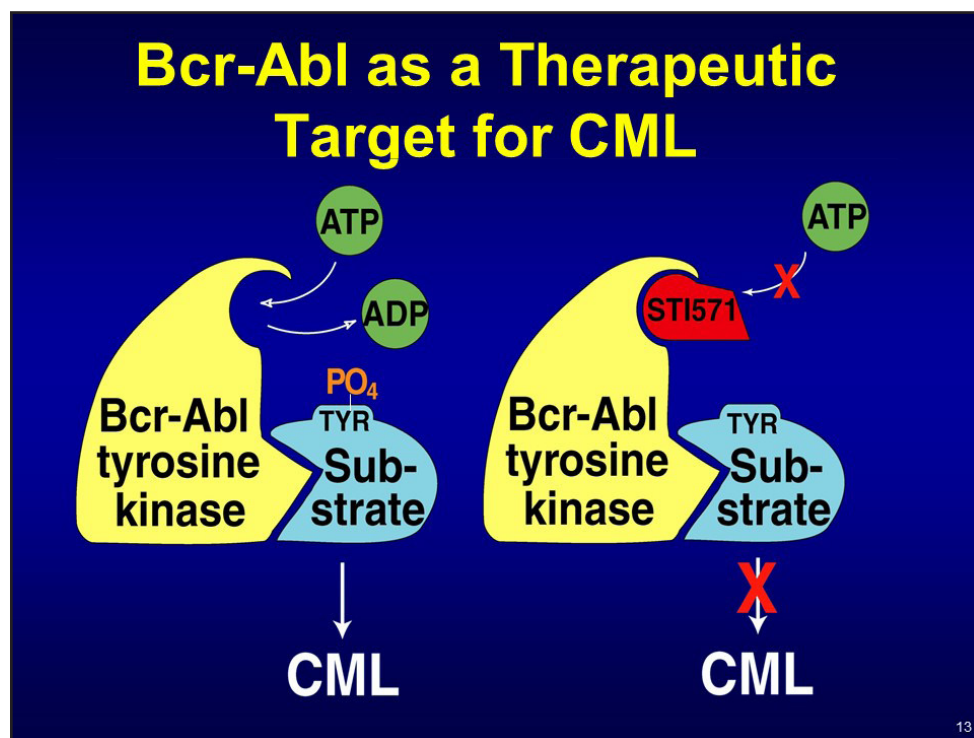
So, the status then was that transplantation from fully matched siblings was the only available curative therapy. Most people did not have HLA-matched siblings. We now have many different sources of donors for transplantation. But, at that time we did not and it was often limited.

We also had an age limit of 45 to 50. We were not nearly as good at it then and about a quarter of people actually died of the transplant within the first 2 to 3 months. And the results were, people would say, well this sounds terrible, I'd rather be transplanted the day before I turn into blast crisis. But unfortunately, the results were very poor if you did that. They were much better when you did it close to the time of diagnosis. So, it's possible actually that some people would have succumbed sooner had they undergone a non-successful transplant. Those were very difficult discussions to have with patients at that time because in general these patients did not have symptoms related to their CML.



Slide 12: Time Magazine

And then, along came imatinib, which was one of the most heralded findings in cancer medicine. At the time, this was Time magazine, this cover was replicated in dozens of magazines and this issue I think is in 2001. The early trials, as you heard from Mr. Mann, were done '98 to '99. Larger trials in 2000.

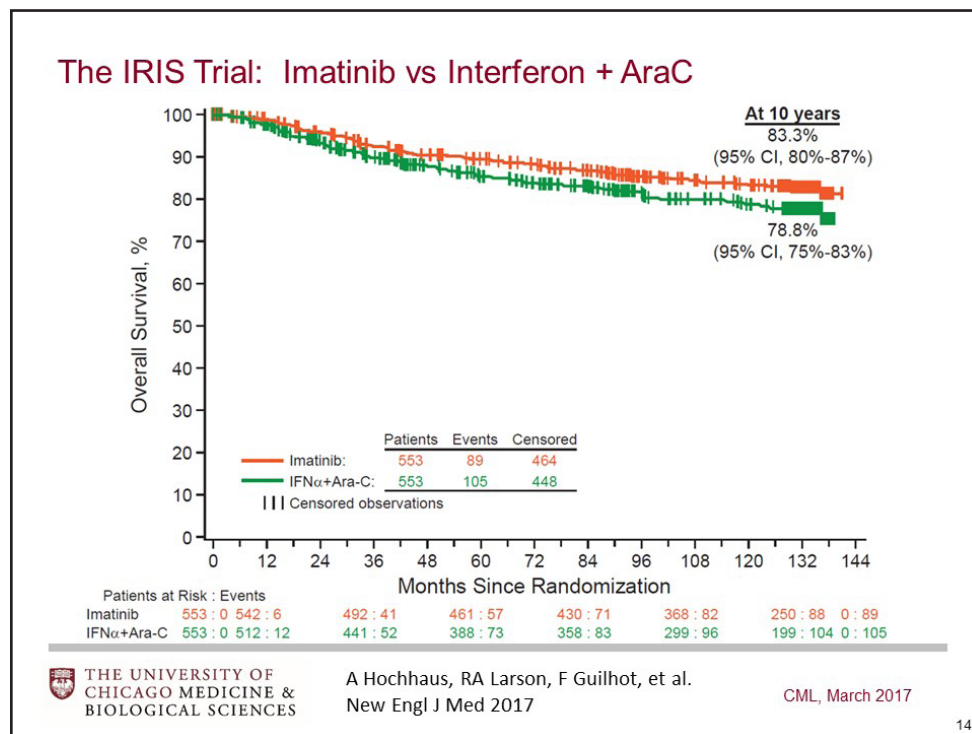


Slide 13: Bcr-Abl as a Therapeutic Target for CML

And what imatinib did, and imatinib was originally called STI571, it was a drug designed to stop signal transduction, but a good friend said what it really did was stop transplant immediately, because indeed that's what happened, because it was so successful.

It blocks an enzymatic pocket in which phosphate is transferred from ATP to ADP. This is called a tyrosine kinase enzyme. And by sticking this in there, it blocks the signal for white blood cells to grow. Here they grow uncontrolled, this stops it.

The initial results quite frankly were staggering. And, those of us were accustomed to seeing the previous problems we have in managing people with CML.

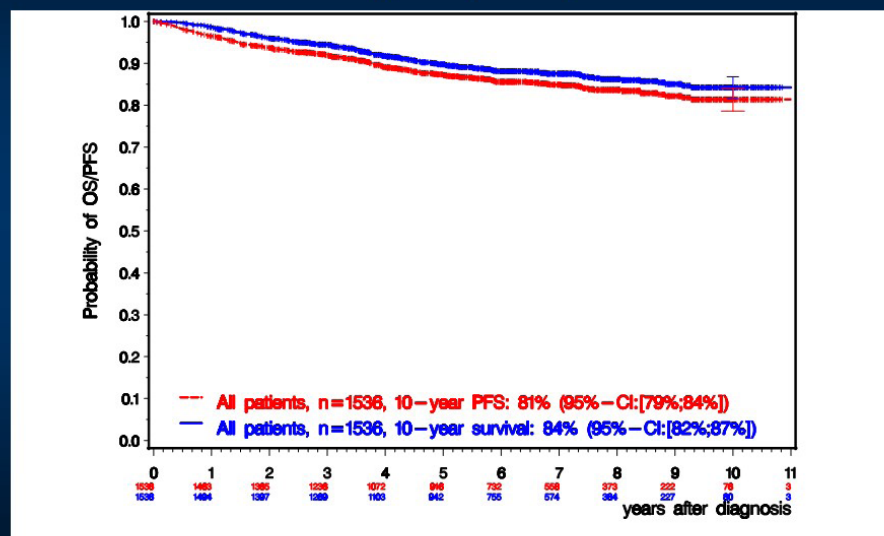


Slide 14: The IRIS Trial: Imatinib vs Interferon + AraC

After it was clear that it was an active drug, in order to get it approved for newly diagnosed patients, a number of randomized trials were done. This was the first randomized trial. It was called the IRIS Trial and people received either imatinib or what was considered to be the standard, but the standard was very poor therapy, and that was interferon and AraC. And, this is overall patient survival.

The study, the randomization to the interferon, was stopped after about a year and a half. I was actually on the data monitoring committee for this trial. And, it was stopped because the results were so inferior. And, the reason that these patients did so well, which is the green curve, is because they were allowed to be switched to the imatinib.

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



German CML Study Group, unpublished

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Slide 15: 10-year OS and PFS CML-Study IV, all patients

So at 10 years, this is about an 85% overall survival, a minority of these deaths were actually due to CML. The median age of patients in this study was about 55. And, some people died of other illnesses.

Look at this curve compared to the one I had showed you before.

This was replicated in a number of studies. This was about 1500 patients treated with imatinib in Germany. And importantly, when you compare this with the survival of age-matched control, it was approximately the same. So, this disease, which was uniformly fatal without a transplant, with an inexorable death rate, is now not curable, approximates normal survival in people who respond and almost everybody responds.

OUTCOMES IN LESS DEVELOPED COUNTRIES

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Slide 16: OUTCOMES IN LESS DEVELOPED COUNTRIES

These results were actually duplicated in less developed countries. All the original trials were in the US and the western world.

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

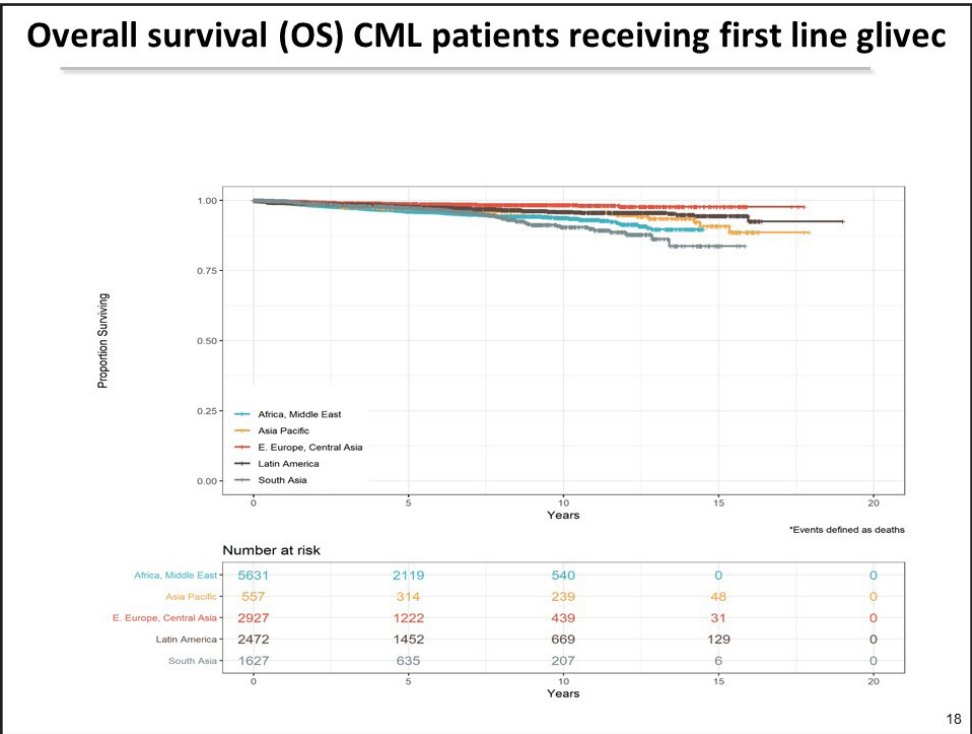


Albania	Botswana	Ecuador	Honduras	Mali	Nigeria	Saint Lucia	Thailand
Argentina	Burkina Faso	El Salvador	India	Mauritius	Pakistan	Senegal	Togo
Armenia	Cambodia	Ethiopia	Indonesia	Mexico	Panama	Seychelles	Turkey
Azerbaijan	Cameroon	Fiji	Jamaica	Moldova	Papua New Guinea	Singapore	Uganda
Bahamas	Chile	Gabon	Kazakhstan	Mongolia	Paraguay	Solomon Islands	Uruguay
Bangladesh	China	Georgia	Korea	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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Slide 17: JCO® Global Oncology

This was a study done, in the shaded areas, in countries with less developed health systems. This was an incredible accomplishment led by Pat Garcia-Hernandez. It was called the MAX program, (www.themaxfoundation.org) and with the help of Novartis, provided medications with CML in this part of the world.



Slide 18: Overall survival (OS) CML patients receiving first line glivec

These are the survival curves of this study. They look remarkably like what I just showed you, an extraordinary change in the course of the disease and all over the world.

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

- Nilotinib
- Dasatinib

And a few years later...

- Bosutinib
- Ponatinib

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Slide 19: Imatinib (1999-2000)

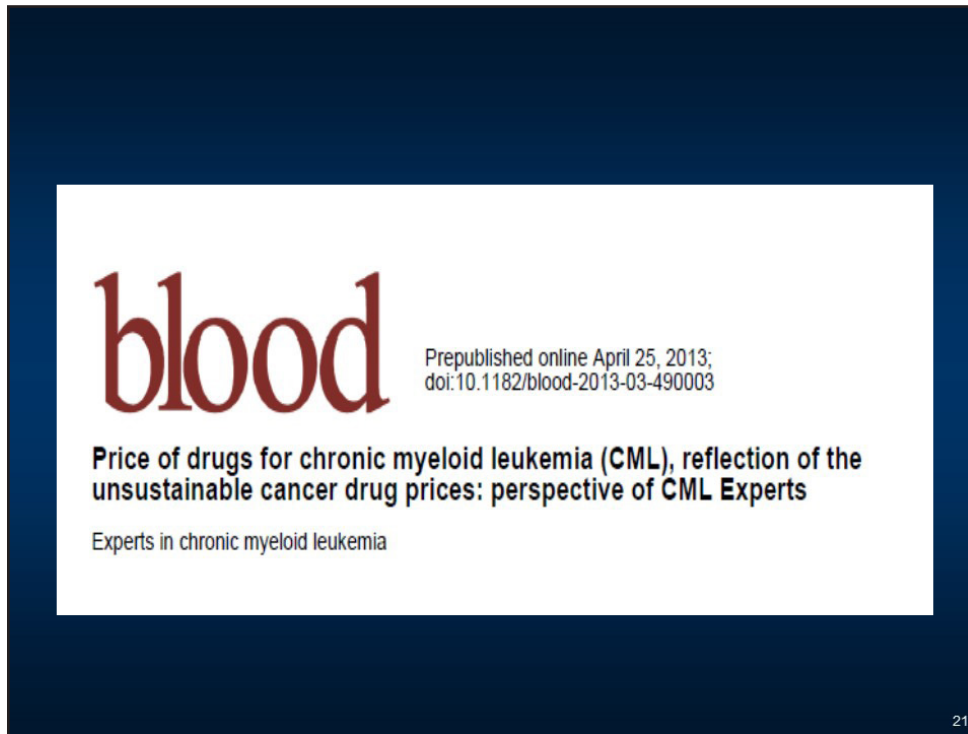
What happened next was, once the chemists got it partially right it was possible to tweak these molecules and within just a couple of years 2 other drugs, nilotinib and dasatinib were developed for people who either the Gleevec did not work sufficiently or who had side effects. And, a few years later bosutinib and ponatinib were developed and all are on the market in the US. There are other TKIs which have been approved in other parts of the world. This was the chemical structure of the TKIs.

The Chemical Structure of TKIs



Slide 20: The Chemical Structure of TKIs

Imatinib originally started at approximately \$30,000 to \$35,000 a year, but within a few years went up to \$120,000 to \$130,000 per year. And, this in fact sort of set the baseline for all oral cancer drugs, any of which are approved now start at \$120,000, \$130,000, \$140,000 a year.



Slide 21: 2013 Editorial

This is something that obviously affects availability. It affects patients to an amazing extent. It affects patients on Medicare to a huge extent. And, many of us found this intolerable. About 125 of us wrote this editorial in the biggest hematology journal in the world. This was 2013. And it was a little bit of a diatribe or a complaint about the price of drugs for CML, the perspective of CML experts. Despite this paper and God knows how many lectures many of us gave on this subject, this is still an enormous problem. It's currently being debated in Congress, and I would suggest that patients participate as actively as possible in the lobbying to get drug prices down. I think the word obscenity is a modest epithet for what is going on in drug pricing at the moment.

PERHAPS THE MOST CRITICAL COMPONENT OF CML CARE WITH TKIs

- **COMPLIANCE**
- **COMPLIANCE**
- **COMPLIANCE**

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Slide 22: PERHAPS THE MOST CRITICAL COMPONENT OF CML CARE WITH TKIs

So, how about some clinical stuff for patients? There are many aspects of management of patients with CML that you have to be aware of. But perhaps the most critical component, and the one we address every time we see patients on a 3-month visit, is compliance, compliance, compliance. Imatinib was heralded as the first targeted drug and I had a very dear, smart friend who was a cancer pharmacologist, who reminded us that the first target of targeted therapy is the mouth. If it doesn't hit the mouth and it doesn't hit the mouth consistently, it doesn't work.



Slide 23: ON TARGET

This young man, my grandson, is now 17 years old. He probably wouldn't think it cute that I'm showing this slide.



Slide 24: OFF TARGET

And neither would his brother. Often because of price and side effects, patients reduce their intake of the drug. They skip doses and this is sort of an off-target effect if you will.

Now let's talk a little science, is off-target. This TKI drug and the whole family don't just affect what we want it to affect. They don't just affect the BCR-ABL, but they affect a whole host of other tyrosine kinases. And, some of the side effects that people experience are a consequence of these off-target effects. You want to hit BCR-ABL and you do, but unfortunately you hit some other things as well.

Major Treatment Decisions

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

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Slide 25: Major Treatment Decisions

So, there're major treatment decisions you have to make when you see people with CML. The first decision is obviously what drug do you use because 3 drugs were approved in the United States at the moment. I'll talk a little about dose adjustment and reduction of dose when it's necessary. And I'll talk a lot about the possibility of stopping treatment, which I know many of you are interested in.

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 Kyrz-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 Hochhaus²⁰

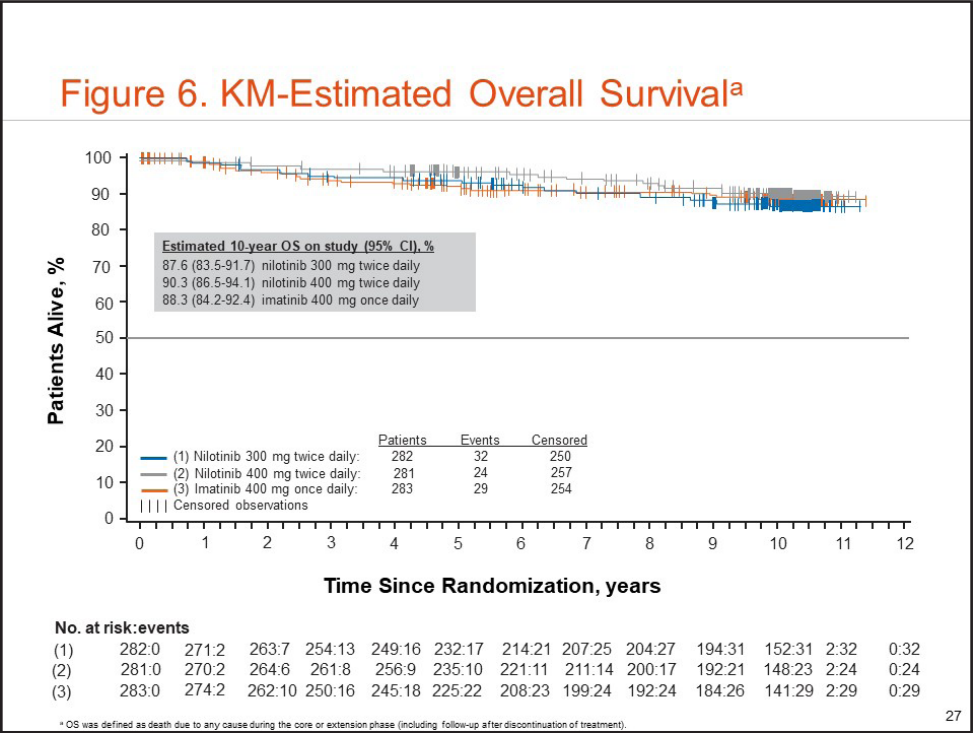
¹South Australian Health and Medical Research Institute, Adelaide, SA, Australia; ²Division of Internal Medicine & Hematology, University of Turin, Turin, Italy; ³Department of Medicine, Section of Hematology/Oncology, University of Chicago, Chicago, IL; ⁴The University of Texas MD Anderson Cancer Center,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

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Slide 26: Long-Term Outcomes in Patients with Chronic Myeloid Leukemia in Chronic Phase Receiving Frontline Nilotinib vs Imatinib: ENESTnd 10-Year Analysis

I'm going to show you the results of just one study, which is representative of essentially all randomized trials. Randomized trials, half the people get one thing, half the people get the other.

And, this was a trial that compared treatment of newly diagnosed patients with either imatinib or nilotinib. It was called, the ENESTnd trial.



Slide 27: Figure 6. KM-Estimated Overall Survival^a

And, this is the 10-year results. This is the 10-year survival. And, you can see that it is absolutely identical to all the curves shown to you previously, there were 2 doses of nilotinib studied, standard dose of imatinib.

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

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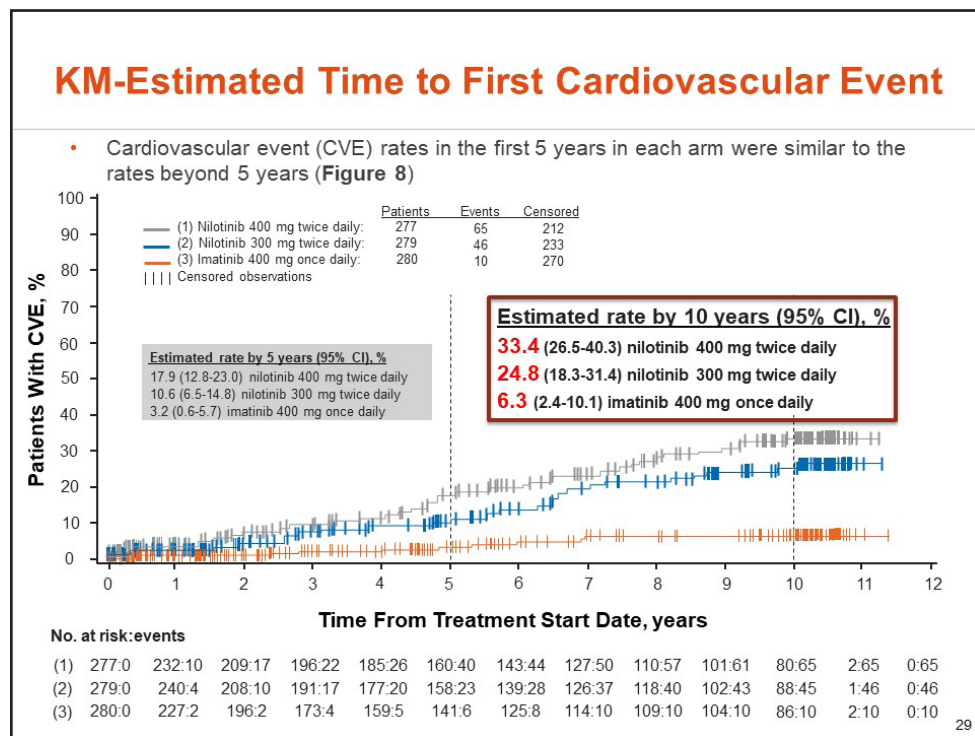
Slide 28: INITIAL THERAPY -- IMATINIB

If you summarize all the randomized trials comparing imatinib with other TKIs, nilotinib, dasatinib, and bosutinib, the results are essentially identical to this. The second generation or newer TKIs produce reductions in the BCR-ABL faster and a little bit deeper, but as I just showed you, there's no survival advantage and survival is excellent.

You have to remember that about a third of people are switched from their original drug to one of the alternatives because of real, and I say sometimes perceived inadequate response, because doctors don't always know when to switch therapy or because of legitimate side effects.

It's also important to remember, that while people start on a certain dose, because of side effects, it's often necessary to decrease the dose and when you do decrease the dose, it's important to monitor very carefully to make sure that the responses are sustained at the lower dose.

None of these trials studied treatment-free remission, that is whether you can take people off the drug and indeed until recently, the standard approach was to keep people on the drug forever.



Slide 29: KM-Estimated Time to First Cardiovascular Event

However, there were difficulties and differences in other aspects of the drug in this trial. The bottom line is imatinib, the other lines are 2 doses of nilotinib. And what this shows is over time there is an increased incidence of cardiovascular events, such as cardiovascular, heart attacks, strokes, or difficulty with circulation to peripheral extremities. These are big deal events, occasionally fatal, fortunately usually not.

This with imatinib approximates what you might expect with an age-matched population, although we're not certain of that because there's never been a randomized trial of imatinib compared to nothing.

So, obviously the decision about what TKI to use initially has to be predicated on both responses, and I showed you that the survivals are similar with all of these drugs, as well as side effects.

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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Slide 30: LONGER TERM FOLLOW-UP OF SECOND GENERATION TKIs

And, each of the available drugs have characteristic side effects. They all have overlapping side effects, sometimes with nausea, diarrhea, which fortunately usually goes away, and fatigue. But, dasatinib is uniquely characterized by pleural effusions, both early and occasionally late pleural effusions, fluid around the lung presenting with shortness of breath and unusually with something called pulmonary hypertension, which is a very serious lung and heart problem.

Nilotinib can produce hyperglycemia, indeed it can induce diabetes in pre-diabetics. I told you and showed you the data about the very appreciable incidence of vascular events.

Bosutinib is the newest, there's less information about this, but it's likely that there's a mild increase in cardiovascular events with this drug as well. And, remember these are off-target effects of the treatment. Remember grandson number 2.

And ponatinib, which is by far the most potent of all of these drugs, has a very large, huge incidence actually, up to about 35% to 40% of major arterial thrombotic events, and is now only used in circumstances where none of the other drugs are effective.

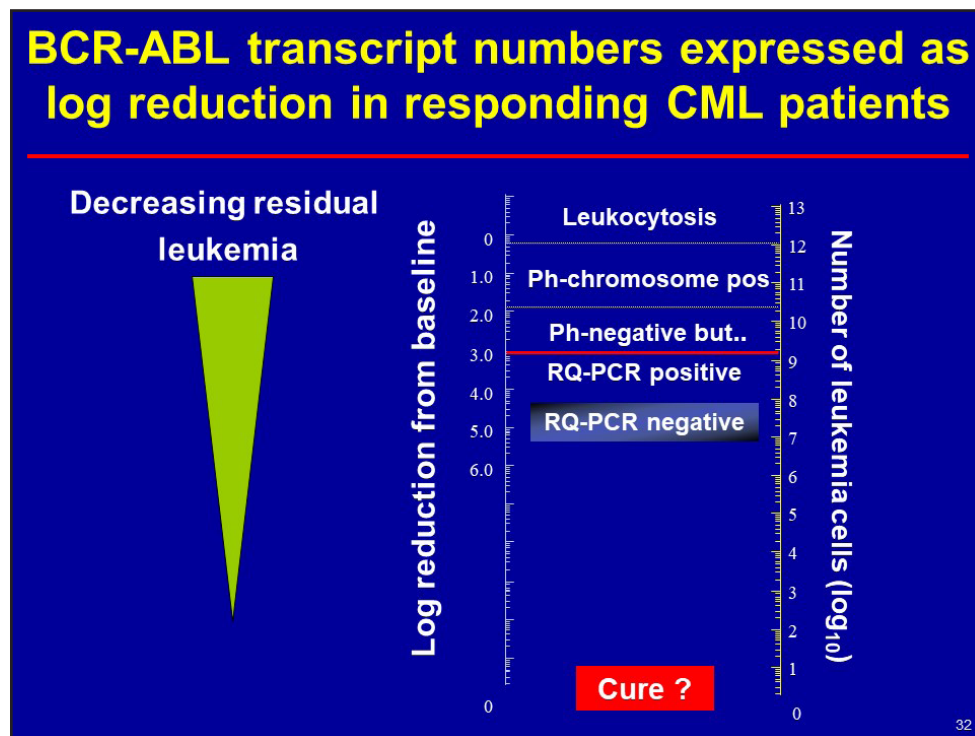
MONITORING RESPONSE WITH PCR

- **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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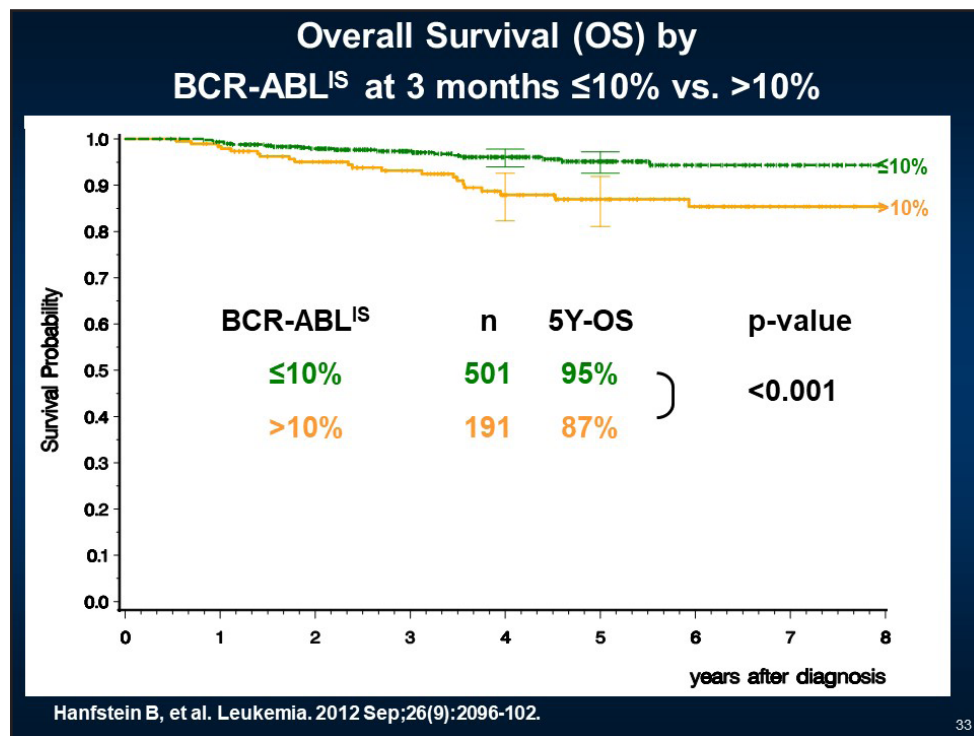
Slide 31: MONITORING RESPONSE WITH PCR

Now, as you all know, appropriate care requires serial monitoring: Is the drug working? Monitoring in the beginning is easy. You just measure blood counts and the disappearance of the spleen. And, the blood counts normalize in about 98% of patients within a month. But, what you're really trying to do is get rid of the Philadelphia chromosome and by that, in the past you had to do repeat bone marrows in order to do cytogenetics because that needed dividing cells. But fortunately, for at least the past decade, there's been a test called PCR or polymerase chain reaction which can be done in the blood so that patients do not need bone marrows. It's very, very specific, can detect a single abnormal cell amongst 100,000, and we recommend it initially every 3 months, stretching to every 6 in long-term responders, but that varies from patient to patient.



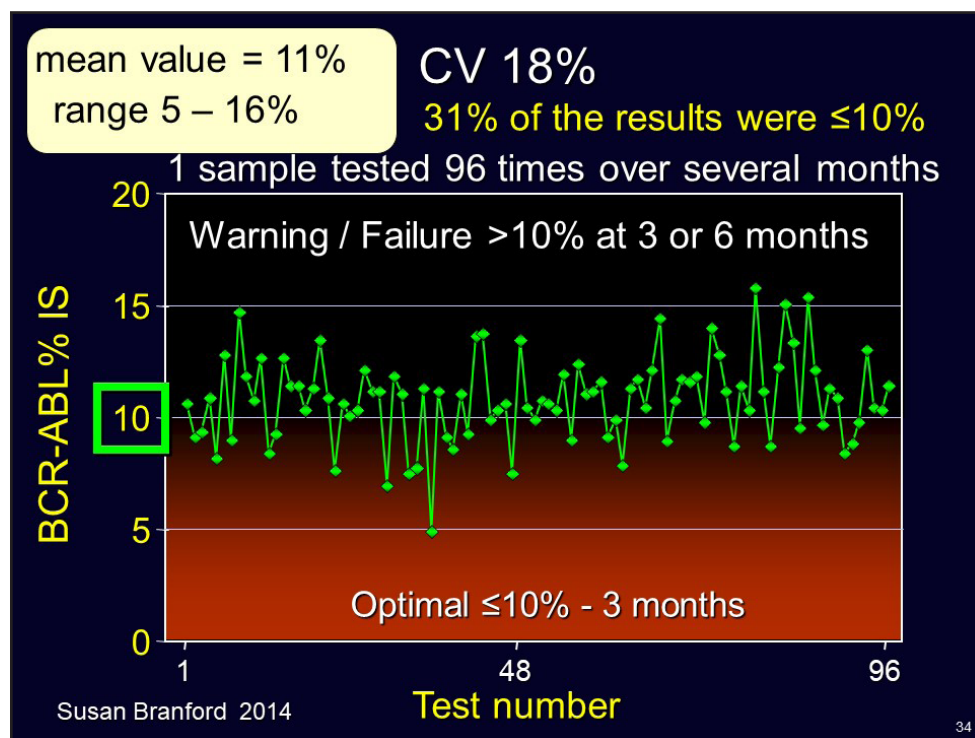
Slide 32: BCR-ABL transcript numbers expressed as log reduction in responding CML patients

I think I'm going to skip this slide, but what it essentially reminds us of is that there are trillions of cells at the time of diagnosis. If you get rid of 2 logs or 100-fold of those cells, you cannot detect the Philadelphia chromosome any longer. But, you need 4 to 5 log reduction, that is 10,000 to 100,000 log reductions to become PCR-negative. But PCR-negative does not mean that there are no CML cells. It means we can't detect them with our current technology.



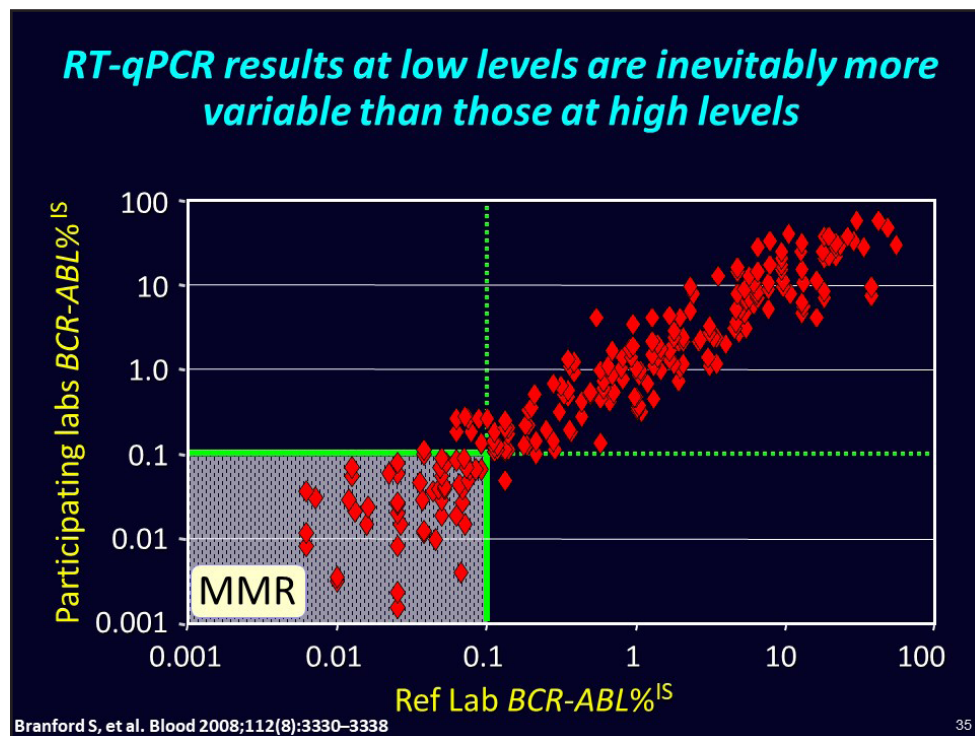
Slide 33: Overall Survival (OS) by BCR-ABL^{IS} at 3 months $\leq 10\%$ vs. $>10\%$

This is a slide that shows that early response probably matters. If you get your PCR to less than 10%, you do a lot better than greater than 10%, and some guidelines recommend that you might want to consider changing therapy. You have to understand however, what the variability of the PCR is.



Slide 34: 1 sample tested 96 times over several months

This is a bunch of samples from the same patient in which the thing was repeated over several months, same lab, the best lab in the world. Actually, same lab, same sample, look at the variability in results. If you're less than 10% you're supposed to do great. If you're higher you're supposed to do more poorly.



Slide 35: RT-qPCR results at low levels are inevitably more variable than those at high levels

The same thing happens at the lower end of the spectrum, which is what we're going to be talking about when we're talking about treatment-free remission. Duplicate samples are not necessarily exactly the same. Simply an issue of the variability in the test.

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?

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Slide 36: Can you rely on a single assessment?

So, you can have something that's greater than 10%, which could be 10.01 or it could be 20. And, those are very, very different numbers. But the point being that you cannot rely on a single test.

PCRITIS

Side effects

Confused physicians

Inappropriate dose increase

Inappropriate referral for transplantation

Inappropriate switch to new TKI

Patient anxiety

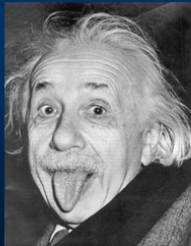
37

Slide 37: PCRITIS

I call this disease PCR-itis. It confuses physicians and I've seen physicians inappropriately increase doses based on a single test, even inappropriately refer for transplant on a single test, or inappropriately switch to a different drug. It makes patients appropriately incredibly anxious. And, the important point is that you cannot rely on a single test. If you have a worrisome result or even an excellent result, it has to be repeated. CML is a marathon, it's not a sprint, and you rarely react to a single PCR value.

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

Albert Einstein



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Slide 38: Albert Einstein

Albert Einstein said, "Not everything that counts can be counted, and not everything can be counted, counts". You have to know what you're doing

Treatment Free Remission (TFR)

Perspectives



Moving treatment-free remission into mainstream clinical practice in CML

Timothy P. Hughes and David M. Ross

128:17, 2016

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Slide 39: Treatment Free Remission (TFR)

So, how about treatment-free remission? The standard had been to continue treatment forever. There were some initially very bold clinical trials, now about 5 or 6 years old, which people had therapy stopped.

POTENTIAL BENEFITS OF STOPPING TKIs

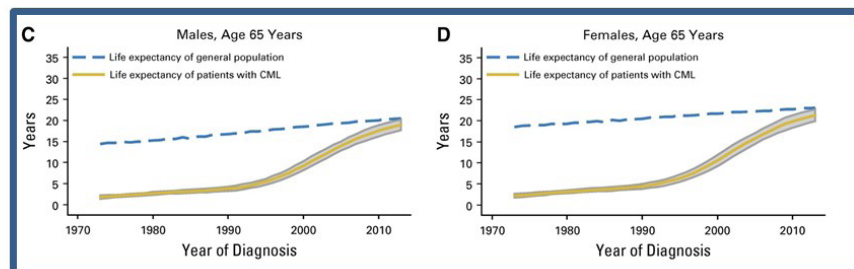
- It's better not to take medications you don't need
- Pregnancy
- Reduction or elimination of TKI toxicities
 - Low grade, chronic
 - More severe side effects which haven't happened yet (particularly cardiovascular)
- The allure of the concept of "cure"
- **COST**

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Slide 40: POTENTIAL BENEFITS OF STOPPING TKIs

Why do you want to stop? It's better not to take medications you don't need. Younger people think about pregnancy, the drugs are teratogenic and pregnancy is a no-no while you're taking the drug. Many patients have low-grade, chronic toxicities. Prominent perhaps with imatinib is fatigue and muscle cramps. It's likely that continuation will result in an increase in the incidence of more severe side effects, which I've already talked about. And of course, the issue of cost.

Life Expectancy of Patients with CML



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

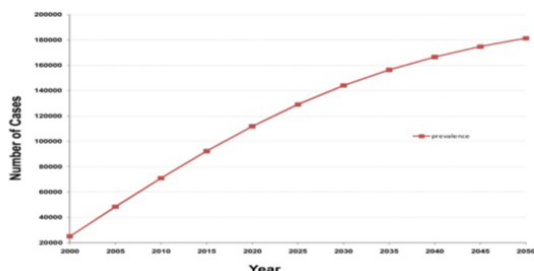
Bower et al. J Clin Oncol. 2016 Aug 20;34(24):2851-7



Slide 41: Life Expectancy of Patients with CML

The life expectancy of patients with CML has increased, as I showed you, to the point where it's almost normal in responders.

CML Prevalence in the US



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

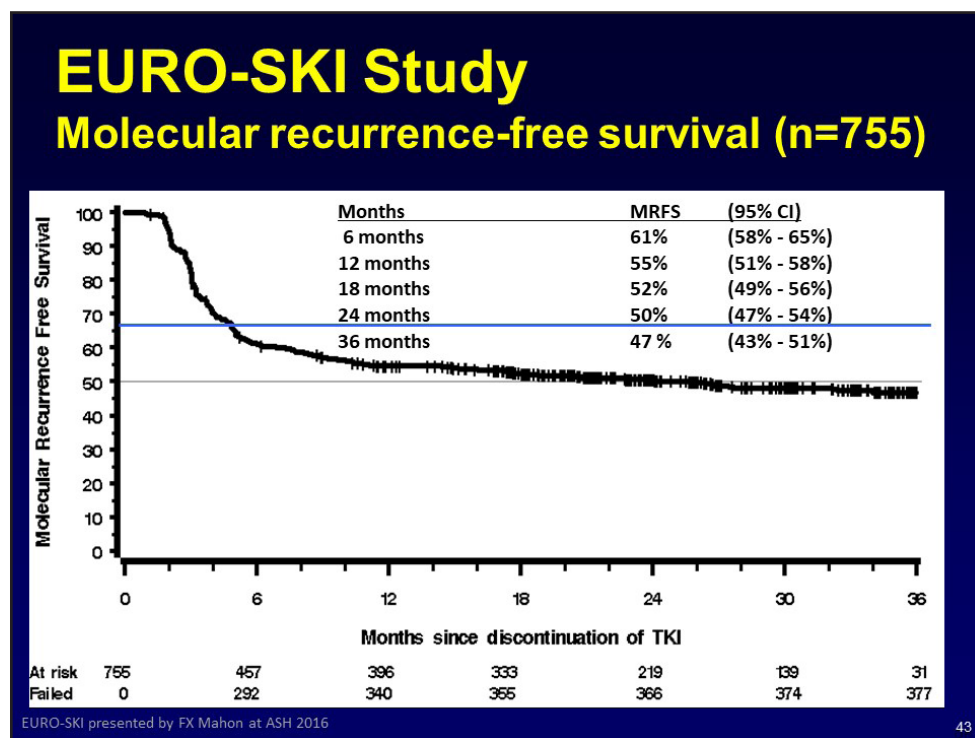
Huang X et al. Cancer. 2012 June 15; 118(12): 3123–3127.



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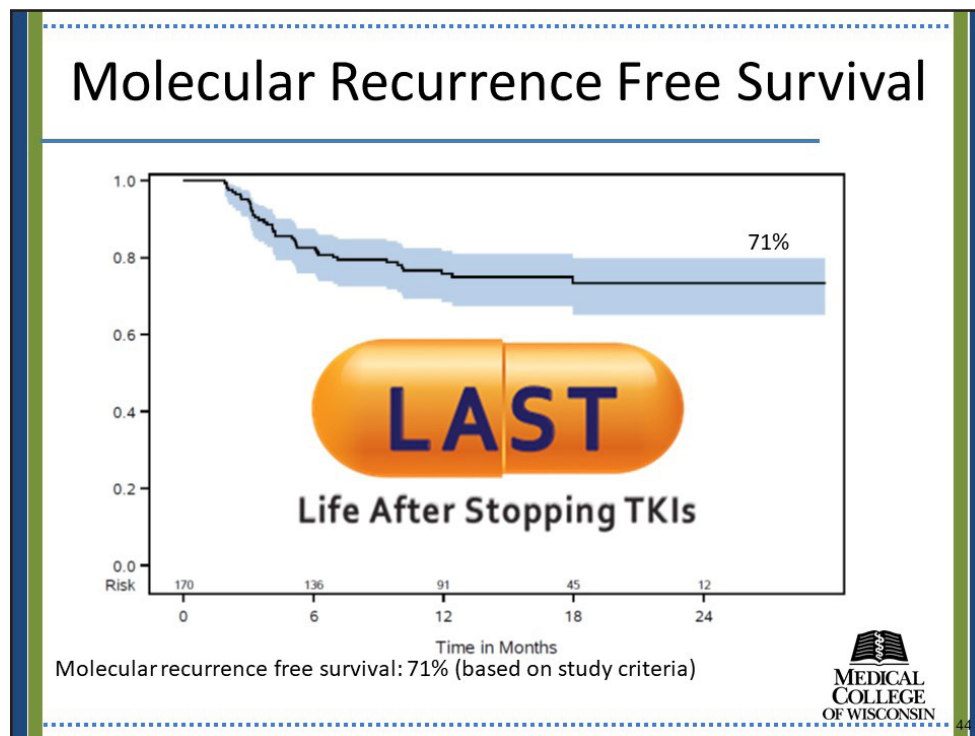
Slide 42: CML Prevalence in the US

So, the number of people alive with CML has dramatically increased, whereas unfortunately before, people died an average of 3 years after diagnosis. People do not succumb any longer. And so, the complication to the healthcare system of all these people being treated is obvious.



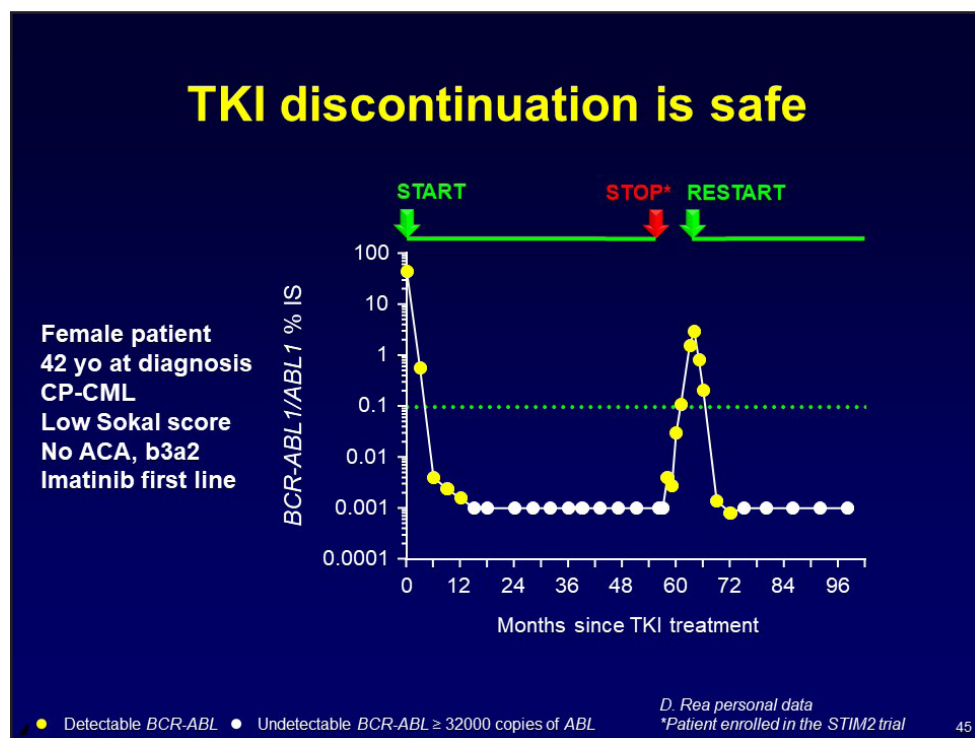
Slide 43: EURO-SKI Study: Molecular recurrence-free survival (n=755)

There've been a large number of so-called stopping studies. This is not the first, but it is the largest. It was done in Europe, 755 patients, and biologically it's absolutely fascinating. The happy part is here, that is about 50% of people have not had their disease come back with 3 years of follow-up. Now, through up to 5 years of follow-up. But unfortunately, about half of the people, and almost all of those relapses recur within the first 6 to 8 months and these are people who have had multiple negative tests with PCR and yet it's still there, you stop the drug and it comes back immediately.



Slide 44: Molecular Recurrence Free Survival

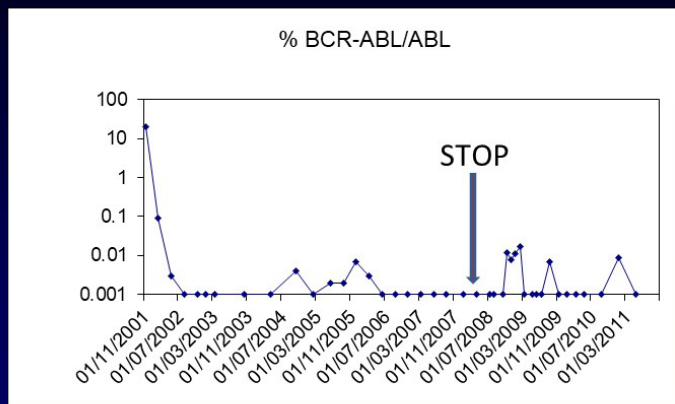
We don't understand the biology of why it doesn't come back and what this rapid relapse tells us is that the cells are still there but effectively put to sleep by the imatinib, so you don't know it clinically.



Slide 45: TKI discontinuation is safe

Same results in the study we did in the United States. We have to emphasize that this is very safe, this is a person who was started very low transcripts, stopped, transcripts recurred, drug restarted, control of the disease very, very quickly. And virtually everybody who restarts regains their previous level of response. It requires increased monitoring, but it is very, very safe.

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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Slide 46: Fluctuation of BCR-ABL detection after discontinuation

It's important for doctors and patients to know, this is someone who stopped, that you can have little blips in the PCR that come and go and don't necessarily require restarting unless they get to a certain level, which is up here, which is 100-fold higher than down here. So, you must be aware that this fluctuation can occur.

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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Slide 47: SUMMARY OF RESULTS OF “STOPPING” TRIALS

And, if I want to summarize all of these trials for you, the success rate is approximately 50%. There’s a very low but real rate of late relapse. Essentially all relapses can be successfully treated. There’s something called the withdrawal syndrome, which occurs in about 20% to 25% of patients. And this is sort of like a musculoskeletal ache sort of syndrome. Usually, mild. You can treat it with ibuprofen. Usually, self-limited. But, sometimes a bit more severe. We don’t know the mechanism. It’s probably related to you’re no longer inhibiting all of those other kinases. It’s possible that if you have a trial of discontinuation and it doesn’t work, you can try it again, but that’s usually not successful.

There are some factors which predict whether it’s going to be successful, but these are not absolute. People who’ve had deeper responses and people who’ve had longer durations of treatment have lower relapse rates, but this is like 60/40, 70/30, rather than 90/10.

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 dasatinib or nilotinib treatment

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

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Slide 48: HOW MANY PATIENTS WOULD BENEFIT FROM STOPPING?

I'm going to just summarize the bottom line of this slide to allow time for questioning.

If you take 100 people who walk in the door, the question is how many would successfully stop? You have to get a very deep response, it has to be maintained, and we've just seen that approximately 50% of patients relapse after they stop. If you just do this math, approximately 20 of those 100 patients who walk in the door will be able to stop successfully. It might be a little bit higher, although this has never been proven in a clinical trial, if you start with second generation, the more potent TKIs, but remember the survival is the same with these drugs and they have more profound long-term side effects, so almost all of us recommend imatinib as the initial therapy.

Necessary Ingredients to Safely Allow TKI Discontinuation

- Attempt to discontinue only in patients with **deep (at least MR4)** and **long-lasting (\geq 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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Slide 49: Necessary Ingredients to Safely Allow TKI Discontinuation

Who can you consider stopping? People with deep responses that have been long-lasting, at least 2 years. You have to have a good laboratory. You have to have a doctor who understands the results of the PCR test. And it means, of course, that you have to have been on the drug for quite some time before considering stopping, and as a consequence, you need a physician who's well-versed in how to deal with the side effects of these drugs.

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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Slide 50: WILL THERE BE LATE RELAPSES?

Will there be late relapses? You don't know why people haven't relapsed actually. Some of us think this might be related to immune suppression, that cancer is a failure of the immune system. If you get a cancer it's because your immune system has not recognized that it's foreign and controlled it. And, some of us wonder whether the fact that we're having long remissions is related to the fact that the immune system's taking control again. A hypothesis, no data.


There are occasionally relapses. It could be that we've pushed people to very low levels and that if you follow them for a long period of time, late relapses will happen. The only data that addresses this is that there was an increased incidence of CML after the atomic bombs in Hiroshima and Nagasaki. And, there was the development of CML, about 10 years after the bombings in survivors which continued to rise slowly. So, it's possible that in people in whom we've stopped the drug, the disease is still there hibernating and will recur late with long-term follow-up of a decade or 2, but we don't know. And as a consequence, almost everyone recommends continuing to do PCR monitoring long term every 6 to 8 months.



Slide 51: Last Slide

This is my last slide. My colleagues in solid tumors who treat solid tumors, which are much more aggressive, much more difficult to treat, tell me that this is what treating CML is like. It's easy, it's a pill, it's very well tolerated, and it's like sinking a putt in a hole this big. And, I used to try to argue this point, but instead what I said to myself is it's pretty darn cool, particularly on World CML Day, that this is the situation and we should be very pleased and proud about what's been accomplished and what's going to continue in the future.

So, I think I will stop here and take questions. Thanks for your attention.




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.

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Slide 52: Q&A SESSION

Ms. Figueroa-Rivera:

Thank you so much, Dr. Schiffer. It is now time for the question-and-answer portion of our program.

And, we'll take the first question from our web audience. Doctor, Mary asks, what effects do TKIs have on the GI system and are there non-medication ways to relieve the GI discomfort?

Dr. Schiffer:

Unfortunately, the biggest GI problem that people encounter is nausea first, and it's very important with imatinib that you take the drug with food. When the drug was originally prescribed in the early 2000s, in fact, it was recommended you take it on an empty stomach and there was a lot of nausea and vomiting. If you take it with food that generally goes away and is eliminated as a problem and very few people have to take antiemetics.

The other problem is diarrhea. With all of them actually. How do you address that? Many patients will discover that it's exacerbated by combinations with certain foods. And, a really important one is that a lot of us who are older are lactase deficient. We may not know it but when you combine 2 things, imatinib and milk, that gives you diarrhea, 2 plus 2 can equal 4. So, it's very important to review whether this is a problem because lactase deficiency is very common.

There are people in whom the diarrhea persists, and anti-diarrheal agents are almost always helpful.

Very occasionally you consider dose reduction in this circumstance.

Ms. Figueroa-Rivera:

Thank you. And, we'll take the next question from our telephone audience, please.

Operator:

Certainly. Suzanne from New York, go ahead.

Suzanne:

Yes Doctor, I was just wondering, with stopping the med that you happen to be on, what are the people that are 70s, 80s, how would you recommend that and how many have been taken off, if you know of any?

Dr. Schiffer:

Stopping is not an age thing. Simply having very, very low transcript levels for a certain period of time, the results are not better in younger people compared to older people. And, I think it's important to talk about stopping in all patients who seem to qualify. We're all following people who have extremely low and undetectable levels of transcripts. And, it's a safe maneuver. Requires a bit more monitoring the first year, but that's just blood draws. And, it's something that's almost mandatory that we should talk to all of the patients who seem to qualify.

Ms. Figueroa-Rivera:

Thank you. And, our next question Doctor comes from Jean Marie who is asking if the term remission is used in CML since it's a chronic disease and her doctor usually utilizes the term undetected?

Dr. Schiffer:

Well, I showed you in the slide, undetected there are still CML cells there and we know that from the stopping trials, right? Because these people have been undetected for years, you stop it and within the first few months it comes back. I don't know if the word remission means remission, we use it in cancer to describe people who are really doing well and the most important thing about doing well is feeling well and not dying prematurely. And, if you achieve a certain depth of response, that's why we monitor with the PCR, you have the opportunity for a near normal life span, and that's true if you have some small number of transcripts detectable, or if they're not detectable, so the word remission doesn't mean much. What you want, or at least to me, what you want to do is have low levels that are sustained. And, you're going to do very, very well.

Ms. Figueroa-Rivera:

Yes, thank you Doctor. And, we'll take the next question from the telephone audience, please.

Operator:

Thank you. The next question comes from Chethan from Texas, go ahead.

Cheaton:

Doctor, I am sorry if this was already covered, but I was detected with CML back home in India, like 8 years or so, I would like to see what the advancements that has come in the past. Currently, I'm taking the generic form of Gleevec. But, I'm just trying to see when, in a futuristic thing, what are the things that I need to be prepared for. I know there are cases where patients reappear with CML. Could you please comment anything, like are there any good hygiene or anything that have to keep in mind?

Dr. Schiffer:

That's a pretty open-ended question, a little difficult to answer. One important thing about continuing to do well is to continue the medication as prescribed, unless, you're a candidate for a trial of discontinuation. It's a little difficult to be more specific than that.

You did mention the word generic however and I forgot to include that in my lecture. As far as we know, there have been large numbers of studies done all over the world and I know sometimes patients get anxious because their

insurers switch from one generic to another because it's a couple of cents cheaper. All of the studies to-date have shown that the generics work and that they seem to work in the same fashion as the originator, Gleevec compound. And, that's very important for you all to know because almost everybody is taking generic imatinib now. And, there're going to be generics for the others coming in the next couple of years.

Ms. Figueroa-Rivera:

That's good to know, that was one of our next questions Doctor. And, there are also younger folks like the caller on that were diagnosed rather early, is there a consideration for younger folks that are diagnosed with CML? I know that we do have a couple of folks on the line that are asking about fertility.

Dr. Schiffer:

As I said, unfortunately all of these drugs are teratogenic for women. So, it's an absolute no-no to be pregnant while taking these drugs and should someone get pregnant, they have to tell their doctor immediately and that's another hour's lecture about what to do then.

There does not appear to be an issue with males taking the drug, so there's no prescription with respect to pregnancy of the wives of male patients.

But, there are a lot of younger women who are diagnosed with CML for whom future pregnancy is desirable, it's a big deal. These are certainly people who should be monitored carefully with respect to whether they're suitable for a trial of discontinuation.

The major subtlety which should be discussed with young women at the time of diagnosis, is which TKI? The survival is exactly the same. I showed you that half a dozen times. The issue though is that the responses are faster and a bit deeper, that is about 10% of more people will have a deeper response with the second generation TKIs. So without data, that is, no prospective trials, it certainly is a reasonable discussion with a young woman to say we could use second generation TKI, there's no effect on survival, it is possible that you will have perhaps a 10% increase in your ability to get to the point where a trial of discontinuation can be done. You have to balance that though by a different pattern of toxicity with those drugs.

So that's an important, sometimes difficult, conversation but that's the one circumstance in which even those of us who are major fans of imatinib have discussions about using the other drugs up front. It's not a sure thing, the relapse rate is still 50%, no matter what TKI you started with, but it's possible that a slightly higher percentage of people will get to the point where a trial of discontinuation would be appropriate.

There're a lot of other subtleties around this question, but that's sort of the overall thought.

Ms. Figueroa-Rivera:

Thank you, Doctor. And, the last question today, Lauri's asking, Does having CML make a patient have any unique factors or outcomes with COVID and are CML patients in chronic phase considered immunocompromised?

Dr. Schiffer:

Important question. No, fortunately. People with CML who are on TKIs do not appear to be immunocompromised in that they essentially never is, nothing's never, but not more than the normal population get unusual infections that you would associate with immunocompromised people. So, we do not consider such people immunocompromised. They would respond well to the vaccine and like every other person in the country and world, we recommend that they do be vaccinated.

There has been an international registry of what has happened to people with CML with respect to COVID, that is, is the incidence different and is the clinical course different. There are many problems with surveys of this type, but the general conclusion is that COVID is the same in terms of susceptibility and severity in CML patients compared to everybody else. Older is not as good as with everything. But, there are no differences. The COVID rules that are being provided for the general population should be the same for CML patients.

Ms. Figueroa-Rivera:

Thank you Doctor for addressing this.

And, I wanted to thank you, but Patricia, one of our participants today, I wanted to read her last comment, which says it better than I would. Patricia says thank you Dr. Schiffer and your colleagues for your caring and persistence. I cry from gratitude each time I hear how the drugs were developed. I'm so grateful.

Thank you, Patricia for your comment and I'm sure that we are all grateful, especially on World CML Day to see all of the advances that we have had for CML. And, we thank Dr. Schiffer for his involvement in those advances.

Dr. Schiffer:

Well, thank you. It's been a privilege for me to do this for you.



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Slide 53: LLS EDUCATION & SUPPORT RESOURCES


Thank you. And, if we weren't able to get to your question today or you want more information, you may speak to an LLS Information Specialist at 1-800-955-4572 from 9 AM to 9 PM Eastern Time or e-mail us at LLS.org/ContactUs.




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Slide 54: LLS EDUCATION & SUPPORT RESOURCES

And, as a reminder you can download and print the slides, as well as listen to today's program from our website at LLS.org/Programs.



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Slide 55: LLS EDUCATION & SUPPORT RESOURCES

Again, we acknowledge and thank Abrale, Bristol-Myers Squibb, and Novartis for support of this program.



Slide 56: THANK YOU

Again, thank you all for joining us on this World CML Day. Goodbye and we wish you well.