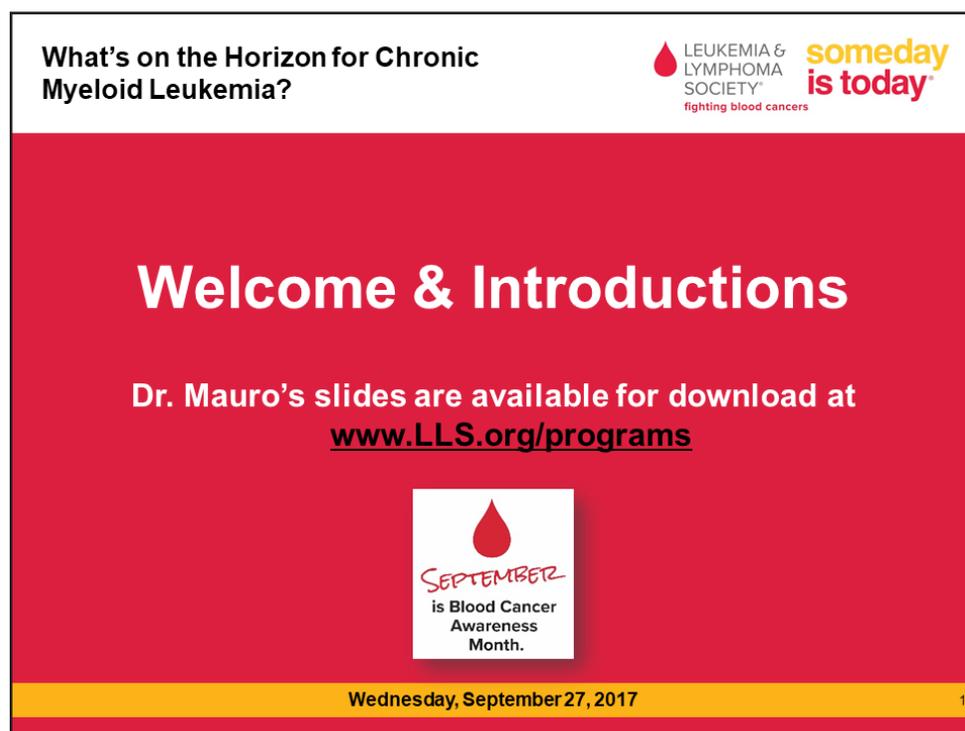


Transcript



What's on the Horizon for Chronic Myeloid Leukemia?

LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

someday is today™

Welcome & Introductions

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

SEPTEMBER
is Blood Cancer
Awareness
Month.

Wednesday, September 27, 2017

1

Slide 1. Welcome & Introductions

Lizette Figueroa-Rivera:

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

We have over 600 people participating from across the United States and several countries around the world, including Australia, Bangladesh, Canada, New Zealand, Peru, Trinidad and Tobago, and the United Kingdom.

And special thanks to Dr. Michael J. Mauro for volunteering his time and expertise with us today.

Before we begin, I'd like to introduce Nicole Bell, The Leukemia & Lymphoma Society's Executive Director of our Field Patient Access, who will share a few words. Nicole, please go ahead.

Nicole Bell:

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

The Leukemia & Lymphoma Society exists to find cures and ensure access to treatment for 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.

Last Friday on World CML Day, we were one of the many groups across the world that acknowledged the importance of CML awareness and continued research. LLS is proud to be one of the four CML advocate network member organizations representing the United States of America.

As this program demonstrates, we are a leading source of free blood cancer information, education, and support, and we touch patients in their communities throughout our 56 chapters in the United States.

LLS also acts as the voice for all blood cancer patients. We advocate for patients and survivors and their families, helping them navigate their cancer treatment and ensure that they have access to quality, affordable and coordinated care.

As I oversee our patient access efforts throughout the country, I also wanted to make sure that CML patients in affected areas by the recent hurricane know about our LLS Hurricane Relief Program. Please visit our website at www.LLS.org to find out if the area you live in qualifies.

We are fortunate to have a presenter today, Dr. Michael Mauro, one of the nation's leading experts in CML. We appreciate

What's on the Horizon for Chronic Myeloid Leukemia?

September 27, 2017

Speaker: Michael J. Mauro, MD

his dedication to supporting our mission and his commitment to caring for patients living with blood cancer. I'd like to thank him for providing us today with this wonderful and important information on CML.

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

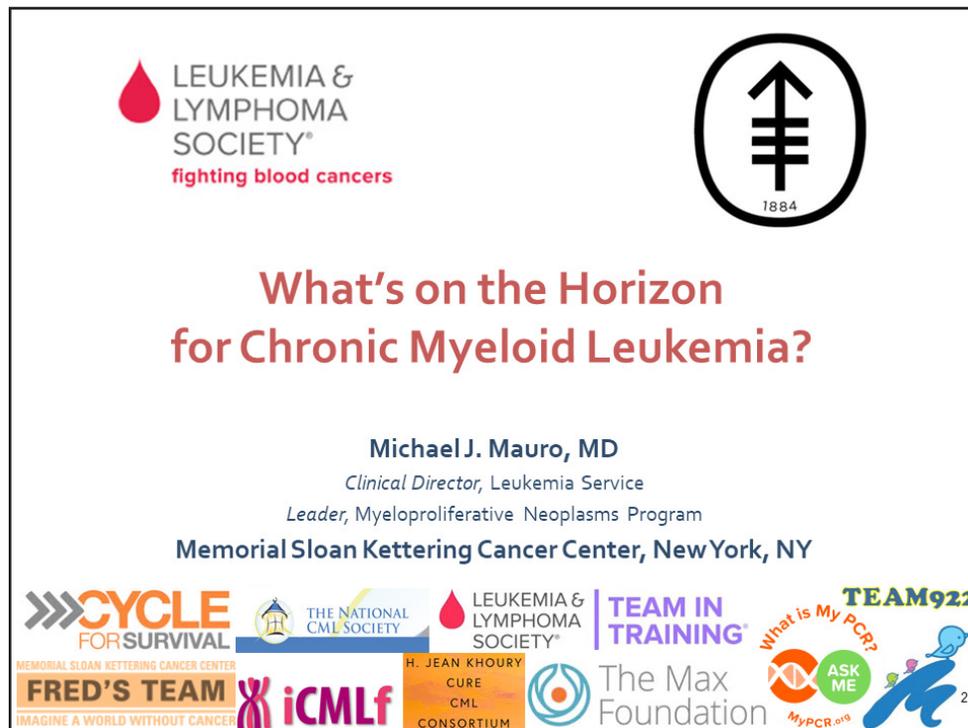
Lizette Figueroa-Rivera:

Thank you, Nicole.

And support for this program is provided by Bristol-Myers Squibb, Novartis, and Takeda Oncology.

I'm now pleased to introduce Dr. Michael Mauro from Memorial Sloan-Kettering Cancer Center in New York, New York.

Dr. Mauro, I'm privileged to turn this program over to you.



LEUKEMIA &
LYMPHOMA
SOCIETY®
fighting blood cancers



**What's on the Horizon
for Chronic Myeloid Leukemia?**

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

CYCLE FOR SURVIVAL | THE NATIONAL CML SOCIETY | LEUKEMIA & LYMPHOMA SOCIETY® | TEAM IN TRAINING® | TEAM922 | What is My PCR? | ASK ME | MyPCR.org

FRED'S TEAM | iCMLf | H. JEAN KHOURY CURE CML CONSORTIUM | The Max Foundation

Slide 2. What's on the Horizon for Chronic Myeloid Leukemia?

Dr. Michael Mauro:

Thank you, everyone.

Thank you to the LLS team for asking me to do this and for the kind introductions and thank you to the sponsors for supporting LLS.

Just a quick word, the LLS was a partner in my research, in my work, from the very beginning. The very first clinical trial efforts to prove that targeted treatment in CML with Gleevec® was possible and would be successful, was supported by The Leukemia & Lymphoma Society, and I've been privileged to worked with the organization since many years in Portland, Oregon and now in New York City and on the local boards and with the patient groups.

So, my task today is to tell you what's on the horizon for CML. I've been working in this field for almost 20 years now and we've seen such tremendous progress. We still have many questions to answer and I'll go through that with you in the next half hour or so.



The slide features a red background with white text. At the top left, it says 'SEPTEMBER is Blood Cancer Awareness Month.' with a red blood drop icon. At the top right, it says 'LEUKEMIA & LYMPHOMA SOCIETY fighting blood cancers' and 'someday is today' with a red blood drop icon. The main text in the center reads: 'Disclosure' followed by 'Michael J. Mauro, MD, has affiliations with Bristol Myers Squibb and Pfizer (Consulting); Novartis Oncology and Takeda (Grant Support)'. At the bottom, a yellow bar contains the date 'Wednesday, September 27, 2017' and the number '3'.

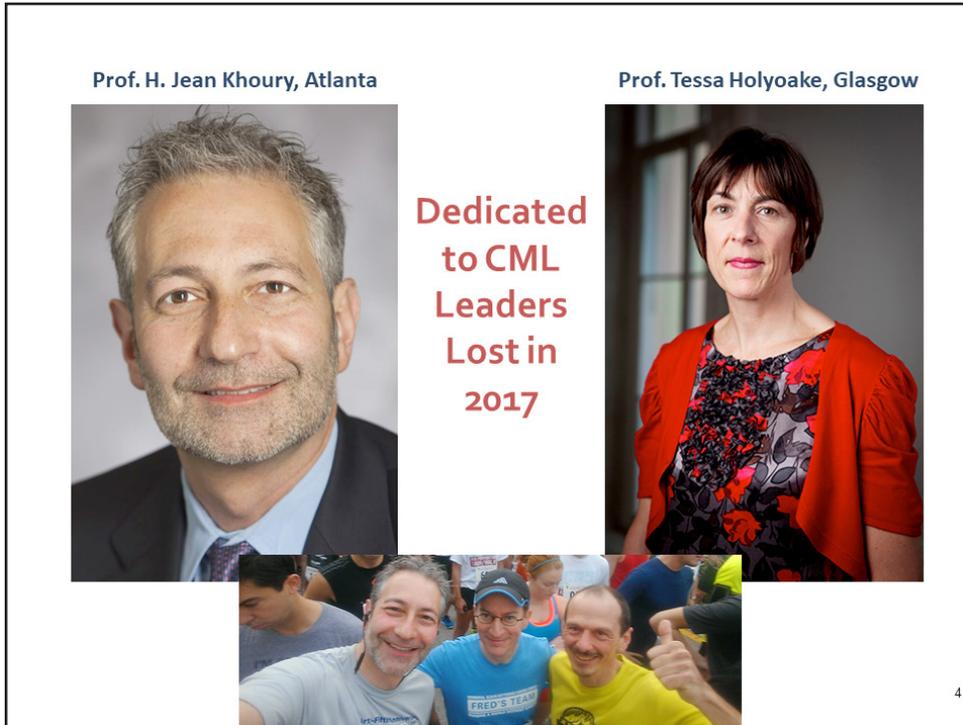
Slide 3. Disclosure

My disclosures are that I have consulted with the main companies that have developed the medications that many patients take and that you're aware of, including Bristol-Myers Squibb and Pfizer and research that's ongoing at my cancer center, Memorial Sloan-Kettering, is supported by Novartis Oncology and Takeda.

Prof. H. Jean Khoury, Atlanta

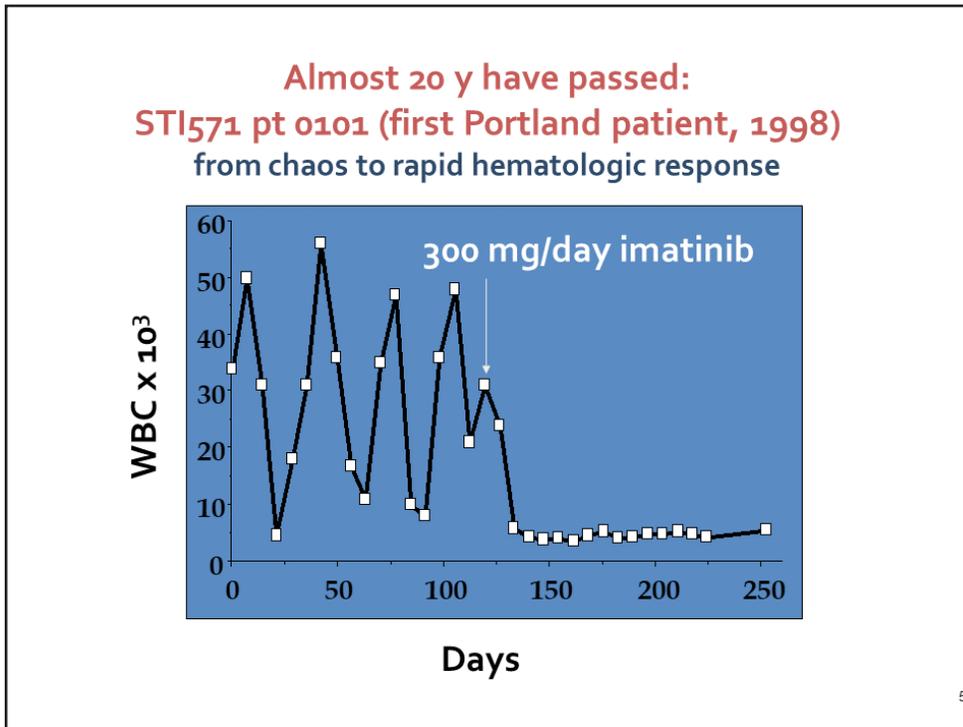
Prof. Tessa Holyoake, Glasgow

Dedicated
to CML
Leaders
Lost in
2017

The slide features two portraits at the top: Prof. H. Jean Khoury on the left and Prof. Tessa Holyoake on the right. In the center, the text 'Dedicated to CML Leaders Lost in 2017' is displayed in red. Below the portraits is a photograph of three men running a race, with one man in a blue shirt wearing a 'FRED'S TEAM' bib. A small number '4' is in the bottom right corner of the slide frame.

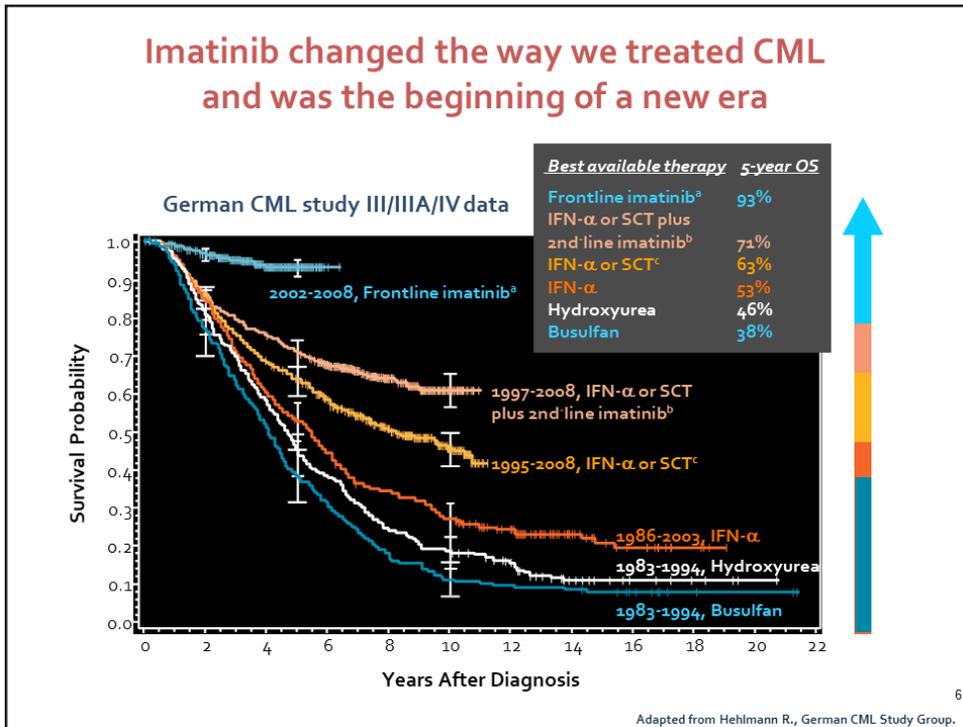
Slide 4. Dedicated to CML Leaders Lost in 2017

The other thing I'd like to say is as the field has progressed and time has passed, unfortunately we've lost a few of our leaders in the field and I just want to acknowledge the unfortunate loss of Professor Jean Khoury from Atlanta, who was a tremendous researcher and just the kindest of gentlemen, who lost his battle with cancer this year himself, as did Professor Tessa Holyoake from Scotland, who was one of the early researchers in this field, particularly stem cell biology. And these folks were both great athletes, I ran many races with them in my recreational time, and I just wanted to acknowledge their loss.



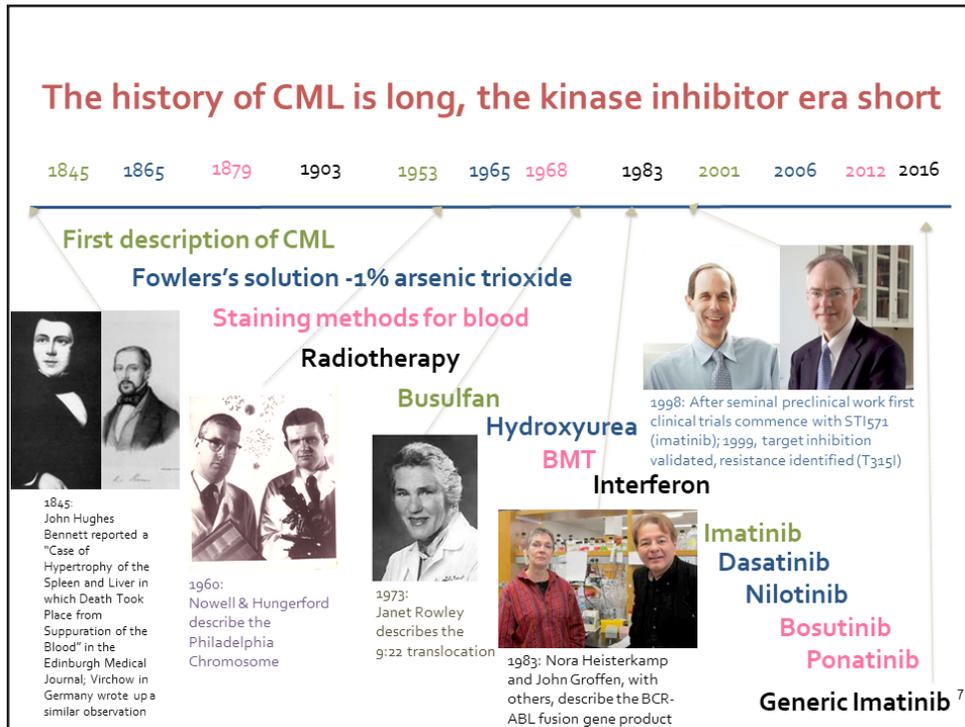
Slide 5. Almost 20 y have passed: STI571 pt 0101 (first Portland patient, 1998)

You know, it's been almost 20 years since the first patients began treatment with imatinib or STI571 as it was previously known. This is a graph which shows you how someone's blood counts might have looked as they entered the very first clinical trials for CML with Gleevec. And the modest dose of 300 milligrams a day was able to quickly, you know, change chaos into blood remission and deeper remissions thereafter. So the story began on a very high note and it's continued in that vein.



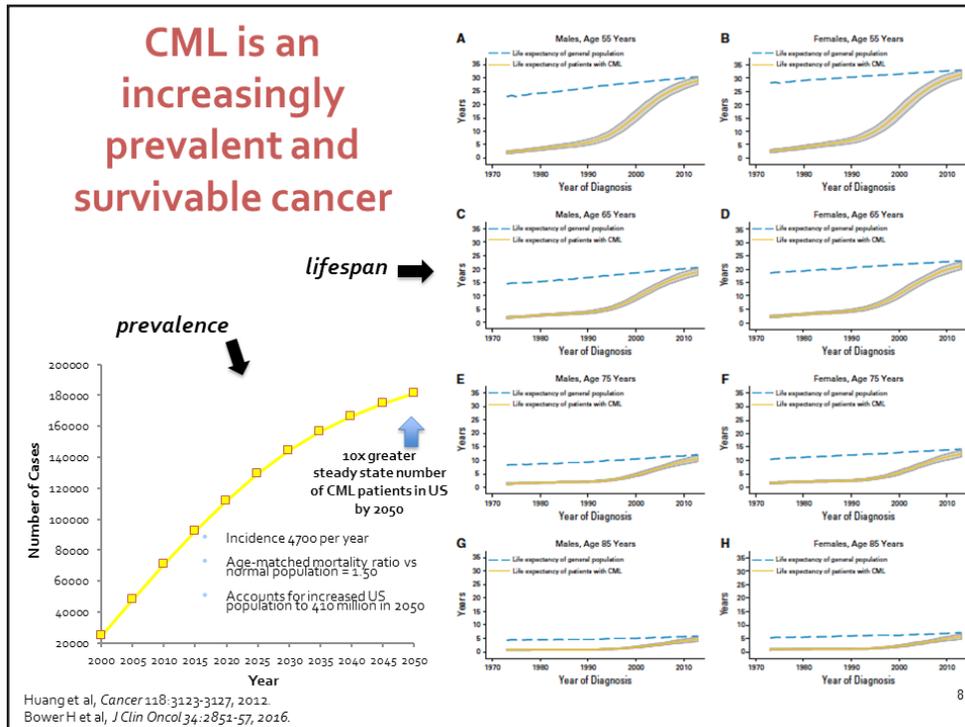
Slide 6. Imatinib changed the way we treated CML and was the beginning of a new era

The impact of targeted therapy, particularly imatinib and all of the drugs that have come after has had on the natural history of CML is illustrated by this graph. If you even just step back and don't look at the legend, you can tell that there's quite a difference between the shorter curve on top, which is the likelihood of surviving CML for patients in the era of kinase inhibitor therapy or imatinib, versus people who use other treatments, well back into the era when we didn't have very successful options such as simple alkylating drugs called busulfan and hydroxyurea. Interferon was an advance, but it was modest. Bone marrow transplant added a significant gain, but unfortunately the long term outcomes, there was still deterioration and only a fraction of patients were able to access them. So, the era of imatinib and targeted therapy has really changed the natural history of CML.



Slide 7. The history of CML is long, the kinase inhibitor era short

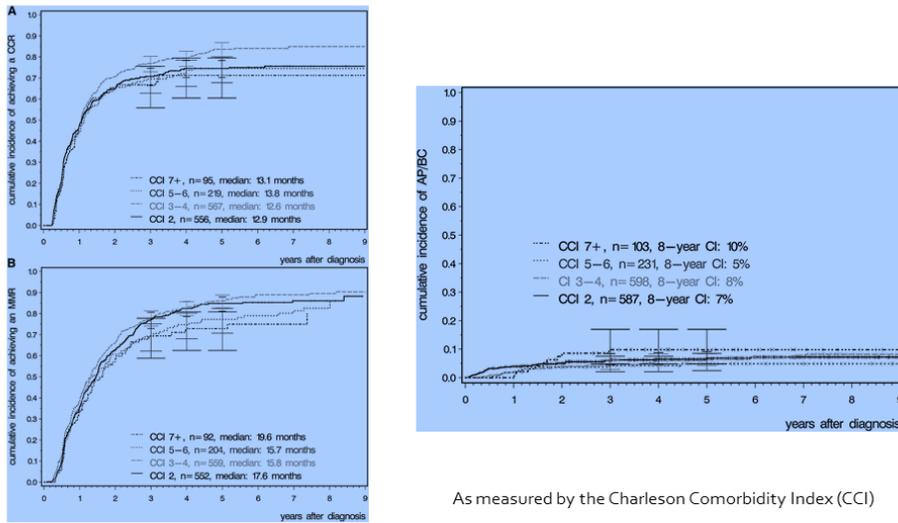
We're proud to say that we've been researching for a long time and the pace has picked up. This is a historical time line that just goes through how CML really has been unraveled and all of us stand on the shoulders of giants. In particular, in the early reports of CML, there was not much understanding, but in 1960 really a simple observation about the Philadelphia chromosome, the genetic marker for CML, was identified, and then scientists, simple cytogeneticist Janet Rowley, who also we lost in the last few years, described Philadelphia chromosome being a 9;22 translocation. Key scientists worked tirelessly in the lab to understand what made that genetic swap cause cancer, and it became one of the best understood cancers. And my mentor and colleague, Brian Druker in Oregon, Charles Sawyers here at Memorial Sloan-Kettering, some of the first partners to bring targeted drug, STI571, the first candidate drug to clinical trials, the first to identify how resistance could develop, and the story unfolds from there. We now have five FDA approved drugs, including a generic form of imatinib available, so the landscape is quite good.



Slide 8. CML is an increasingly prevalent and survivable cancer

The best news I can say for patients and for those that take care of it, that while the number of people around in the United States and in Europe and in everywhere, living with CML, continues to increase. So, the prevalence, meaning not how many people get CML, but how many people are living with CML, has increased quite steadily. The life span expectations for those with CML, irrespective of your age, whether you are in your 50s, 60s, 70s, 80s, and indeed there are patients of course younger and even older than this, the expectation is of a normal life span. And this is published data, using our best available information from our experience of now almost 20 years with targeted therapy.

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



As measured by the Charleson Comorbidity Index (CCI)

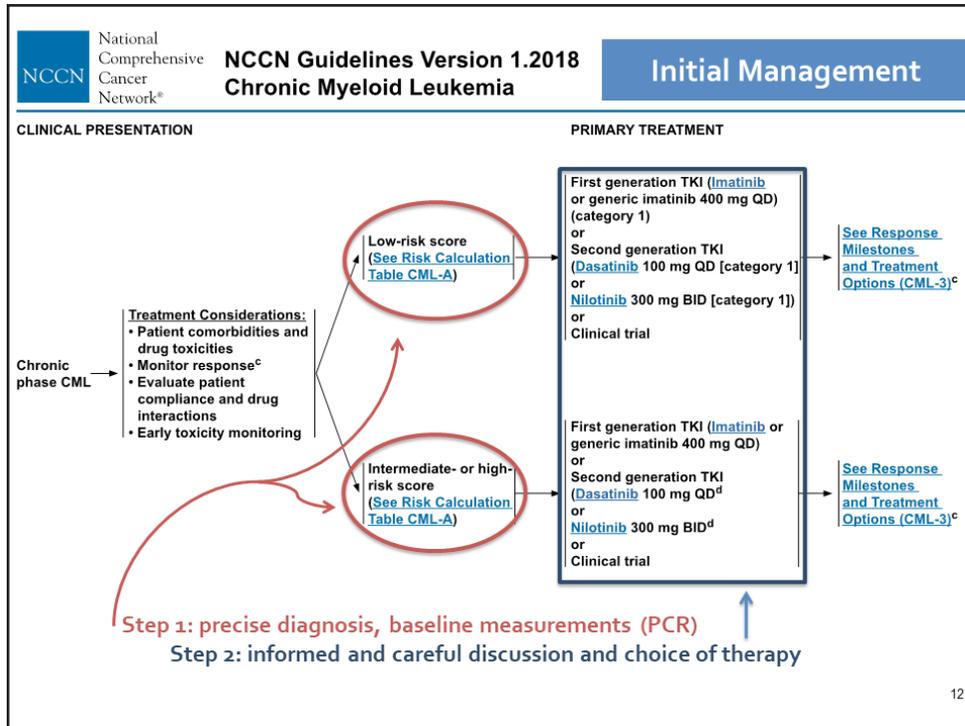


Saußele S et al. Blood 2015;126:42-49

Slide 9. CML response not different in presence of other health problems: 'Comorbidity Index' Study

The other research that's been done lately shows us the important notion that taking care of the whole patient really matters, and that the CML response doesn't differ if you have different health problems, so we shouldn't treat people who were of older age or have different health problems necessarily differently. We may choose different medications, we may need to manage side effects differently, but patients of different comorbid scores or having different medical problems do equally well, there's no difference between their likelihood of getting a cytogenetic or a molecular remission, which is on the left, or the low risk they have of, heaven forbid, having their leukemia transform.

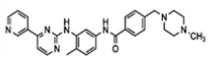
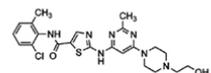
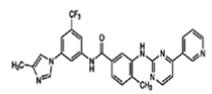
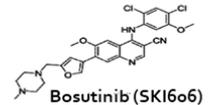
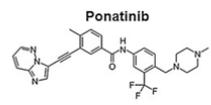
2,000 plus patients and about half the patients had other medical problems and a little under half had a cardiovascular-related problem, and that's become a particular area of focus as we look at the side effects of certain medications and how to manage that risk. So you have to pay attention to everything.



Slide 12. NCCN Guidelines Version 1.2018 Chronic Myeloid Leukemia

The guidelines on how we treat CML in the United States are by an organization called the NCCN (National Comprehensive Cancer Network). Memorial Sloan-Kettering is one of the centers that contributes to this effort to look at our best data and come up with rational evidence-based guidelines to say how do we treat CML. And this is the latest iteration of how to approach a new diagnosis of CML, showing that of course we have to – before this slide there's instructions on how to evaluate a patient via blood, bone marrow testing, to properly make the diagnosis – but once we have all the information we can actually strategize or assign a bit of a risk score to say whether the CML may have smaller or potentially greater chance of developing resistance or having treatment not be initially successful. And then we see the next step is fairly broad and open-ended, the Step 2, which is an informed and careful discussion and choice of therapy. And there are not one, not two, but three different options, and you can see there isn't a choice 1, choice 2, choice 3. It's one or the other or the other. So there needs to be a very open and honest discussion between patients and healthcare providers and family members about where is my CML, what's best for me, if not this option, what are the other options? And I encourage people to ask questions and to have those dialogues with their healthcare team, not just in the beginning, but as a constant thread because CML is a long journey, it's a marathon as I like to refer to it, and frequently reassessing response and options is important to discuss amongst the healthcare team.

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

1st Gen. TKI		2001 Novartis (1 st line)	
	Imatinib (STI571)		
2nd Gen. TKIs		2007/2010 BMS (1 st , 2 nd line)	
	Dasatinib (BMS354825)		2007/2010 Novartis (1 st , 2 nd line)
South Korea only		2012/2015 IL-YANG: (1 st , 2 nd line)	
	Radotinib (LY5511)		2012 Pfizer (2 nd /3 rd line)
			2017: 1 st /2 nd /3 rd line?
3rd Gen. TKI		2012 Ariad (2 nd ?/3 rd line)	4th Gen. TKI (allosteric): ABL001
	Ponatinib (AP24534)		








Slide 13. At present, five oral, small molecular kinase inhibitors approved in the US for Ph+ Leukemia: a 'spoil of riches'; more on the way

The palette of drugs we have is quite broad. Now this is a bit of a busy slide, but it shows you that we have five small molecule kinase inhibitors approved. It's often called the spoil of riches, that's a great problem to have. And to let you know there's even some that aren't available in the United States, that aren't necessarily – we're not missing out, they're drugs that are similar in capacity and in ways – some are similar in side effects, but there's five in the U.S. and even more in other places in the world. And in the lower right you see the mention of the drug ABL001, which is probably one of the most promising drugs in development, another oral medication, much like some of its predecessors, but different enough and I'll tell you a little bit more about that as we get into the talk a little bit further.

The last thing I didn't mention on the previous slide is that we may see broader options in the front-line setting with recent data with bosutinib, as a drug we now use in the second and third choice category, potentially being offered as a first choice, based on some good research showing that it may offer advantages over Gleevec for certain patients or as an alternative choice. So, it may get to be even a more complicated, but yet good problem, that we may have four options to think of at diagnosis.

Choosing your tools: comparing TKI toxicity in CML

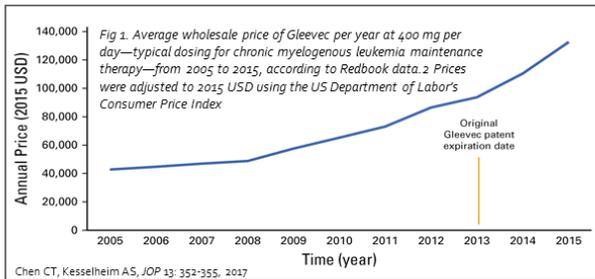
Issue	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib
Dosing	QD/BID, with food	BID, without food (zh)	QD, w/ or w/o food	QD, with food	QD, w/ or w/o food
Long term safety	Most extensive	Extensive; Emerging toxicity	Extensive; Emerging toxicity	Extensive, No emerging toxicity	More limited but increasing;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

14

Slide 14. Choosing your tools: comparing TKI toxicity in CML

I've left this slide up to give you a chance to ponder it, which is that there are different side effects with different medications. As you look across this image you see that the way the medications are taken or dosed is different. We know that we have different time lines with regards to how much safety or knowledge about side effects we have. We know there are blood count side effects, that's called heme toxicity. We know there are non-blood side effects such as changes in some things we see in the blood such as fats in the blood sugar in the blood, salts in the blood. There are side effects such as fluid retention called pleural and pericardial effusions that are internal fluid accumulations. GI side effects such as diarrhea. Liver side effects. All of these need to be vetted and managed because some of them are not infrequent and some of them are obviously important and can cause problems.

On the bottom we have some particular questions about things we've seen as we study medications over longer periods of time, what we might call emerging or later toxicities. Or specifically cardiovascular side effects. It's true that the patients with – the typical person with CML may have some cardiovascular risk, we all do as we grow older, and it's important to just simply know how that risk is and how it may play into treatment choice and how risks can be managed if certain medications are indicated or really the right choice for a patient or necessary. Even despite having some of these side effects. And they included blocked arteries or worsening of cardiovascular side effects or conditions. A condition where high blood pressure develops blood flow between the heart and the lungs, called pulmonary hypertension. So many things to look for. These are the kind of questions you need to ask in the clinic and that your physician should be aware of and should be reviewing with you, just to make sure your health is obviously fully known. These questions are addressed and side effects reviewed in the context of some of these side effects that could be medicine-related.



Reality check: Cost of Therapy

The New York Times

Business Day

WORLD | U.S. | NY REGION | BUSINESS | TECHNOLOGY | SCIENCE | HEALTH | SPORTS | OPINION

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



Pollack A, NY Times, Published 4/25/13
Hall S, New York Magazine, Published 10/20/13

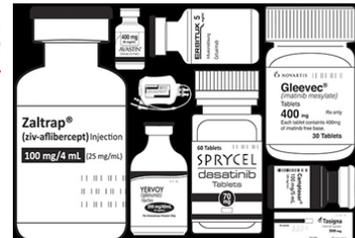
The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts

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

Experts in Chronic Myeloid Leukemia

As a group of more than 100 experts in chronic myeloid leukemia (CML), we draw attention to the high prices of cancer drugs, with the particular focus on the prices of approved tyrosine kinase inhibitors for the treatment of CML. This editorial addresses the multiple factors involved in cancer drug pricing and their impact on individual patients and health care policies, and argues for the need to

(1) lower the prices of cancer drugs to allow more patients to afford them and (2) maintain sound long-term health care policies. (*Blood* 2013;121(22):4439-4442)



Slide 15. Reality check: Cost of Therapy

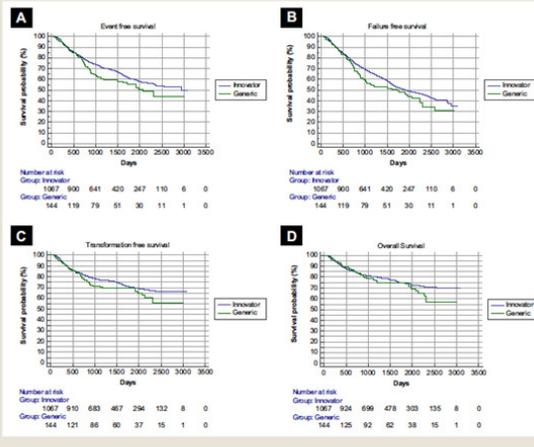
Now turning to a little bit more of a reality check, I think those on the patient side and advocacy side and caregiver side, I think we probably worry almost equally about the cost and managing access to treatment. And clearly, we know that forces that play with pharmaceutical partners and sponsors as businesses, there are price changes and analysis that's done on how these medications are priced. And we see, for example, that the cost of Gleevec, the original drug, has risen steadily and actually the pace of rising cost picked up as we got closer to a generic drug and this is not uncommon. We know that certain drugs were priced at north of \$100,000 per year, if it was purchased out-of-pocket, which seems quite high. Of course, the way these prices are set isn't something we look at in academia or something we are involved in, this is a business decision and it's a part of our healthcare system and the way it works. And some may say our U.S. healthcare system needs a lot of help and I agree, but as experts in the field, you'll see in the middle, led by one of our colleagues, Hagop Kantarjian, we've tried to open up a dialogue in the literature to say that we need to look at these prices. We have such a good paradigm with ability to treat leukemia so well, currently with a need to treat it over several years, in theory indefinitely, but maybe with hope it'll become more limited and be several years of treatment, but that's still a great expense, and for some patients access becomes a real challenge and that's a grave injustice if patients have difficulty with access or are unable to access a curative, potentially curative therapy, or a highly active therapy like the medications I've just mentioned. And other drugs have fallen under the same type of criticism, so we're not blind to this issue, even in academia.

What do we know about generic imatinib?

Table 1 Patient Demographics and Clinical Characteristics of Study Patients

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

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

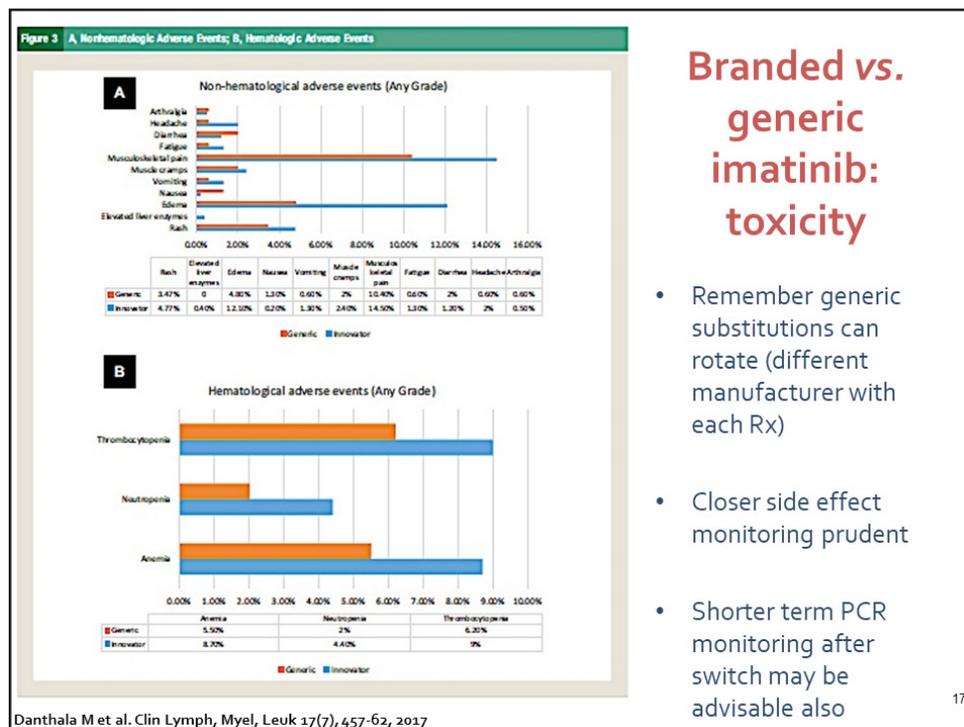


Danthalha M et al. Clin Lymph, Myel, Leuk 17(7), 457-62, 2017

16

Slide 16. What do we know about generic imatinib?

Many people fret about the advent and the integration of generic Gleevec. That's a natural occurrence, it happens after a drug passes its expiry date with regards to patents, and in this case, there was a little bit of a longer time frame before the patents were up, and there are other forces at play, which are surprising to people, such as the fact that a single manufacturer has an exclusive right for several months and the initial cost of generic was not much different than branded drug, and copay issues still abound.



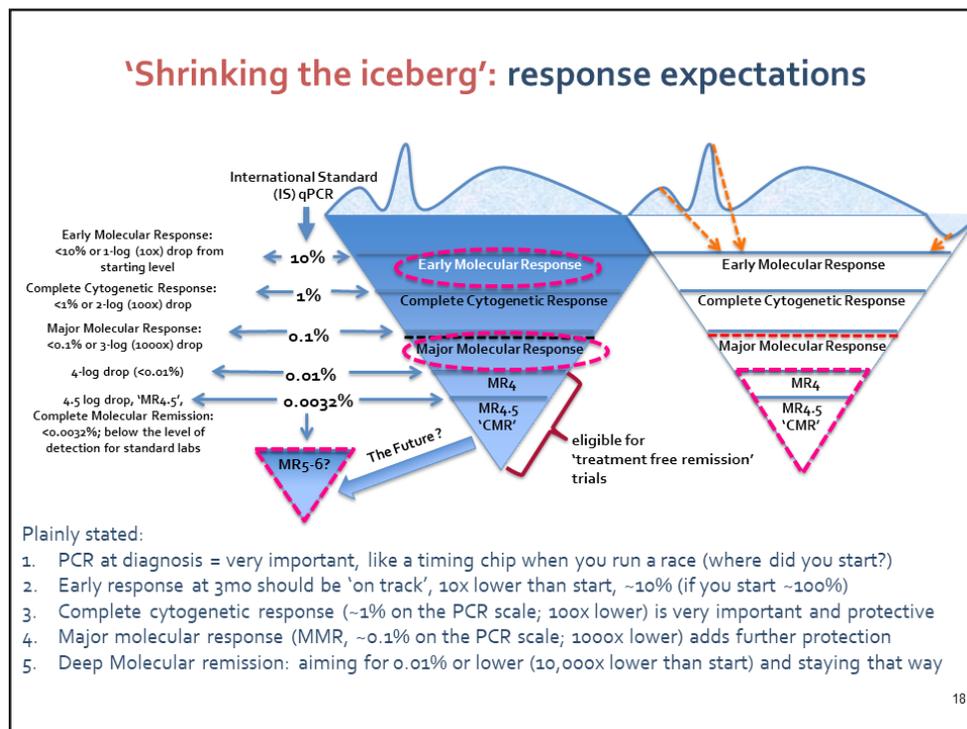
Branded vs. generic imatinib: toxicity

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

Slide 17. branded vs. generic imatinib: toxicity

What I'm showing you here are things that I think are important to know, that when response rates are looked at and patients treated with generic imatinib or the imatinib mesylate, the Gleevec branded drug, in this case these are patients from India where they were given the drug at low or no cost through a program sponsored by Novartis called GIPAP™ (Glivec International Patient Assistance Program), which is a very kind and its persistent effort now championed by the Max Foundation. Bottom line is that response rates and survival is really no different between the brand and the generic drug, which is very important information to know.

That being said, there can be subtle differences in side effects with the generic versus the branded drug. In this case, interestingly, the generic compound sometimes had some lower rates of blood-related side effects and other side effects on the top which are not blood-related. I encourage anyone who's moved to a generic or has questions about it, to recognize that they can rotate, they can come from different manufacturers. You need to pay close attention to side effects and we also need to remember that if there's any question about response, it's always – not unreasonable to think about an interval test, a PCR test, which is our workhorse, our blood-based test to show degree of response, which is most informative across the board, whether you're early or late in disease, and that can be advisable in the case of a switch when we want to have reassurance that response is not any different on a different drug, meaning a brand versus generic.



Slide 18. 'Shrinking the iceberg': response expectations

You know, the way we approach CML, this is a figure I often bring to the clinic to share with my patients, I always describe treating CML like shrinking an upside-down iceberg, where we have a lot of CML at the beginning, and we knock it down logarithmically. And this is a marathon again that runs over several years, but we need to start and run at a certain pace. PCR gives us these numbers, these percent numbers, which are in the near left of the figure. And arbitrarily – and most patients fall close to a level of 100% when they begin treatment – and we first look for what's called an early molecular response, reduction in the PCR to roughly 10%, and that's an estimate or a guide. There is very good data, which I'll show you, that tell us how important it is to have a reduction like that, but where you start is important, it's like running a race, as I make in point one. It's like a timing chip. You know, if you're in the back of the pack you may not cross the starting line right away and you need to be timed where you started and to see how your pace is individually.

We next look for – to see if that early response is on track, should be ten times lower, down to 10% roughly, if you started at 100% in theory. The next step is a complete cytogenetic response, where if we did bone marrow testing we would no longer see evidence of leukemia by a test called cytogenetics or FISH. This is where the PCR comes down 1%. It's 100 times lower than the starting level. And this is one of the most important and protective response milestones. And it should come in the first year or 18 months, really in the first year.

We then look for molecular responses. And many people are familiar with this from either themselves or as providers or involved in healthcare or having loved ones with CML, where we're looking for deep molecular remissions, .1% on the PCR scale, which is 1,000 times lower than the start, and is a very – considered at another important milestone, offers additional advantages beyond cytogenetic remission, further protection against complications developing. And then, of course, deeper molecular remission, where the PCR numbers are very low, 10,000 or more times lower than start, where the PCR number is below .01% on a standard scale, can even become undetectable. And there's a term called complete molecular remission which is not used as often because it's really just a line in the sand where the tests often can't detect anything any longer and that's a bit arbitrary. I think we focus more on deeper molecular remissions and how long they've been ongoing and that they've stayed below certain key thresholds in order for us to think about options for patients, which I'll share with you in a bit.

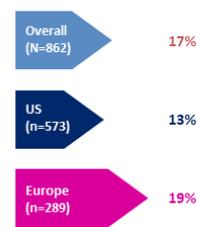
Monitoring for CML response needs improvement

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

Patients not tested for CyR at 12 months¹



Patients not tested for MR by 12 months¹



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

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



Slide 20. Monitoring for CML response needs improvement

We've learned an important lesson from a trial I've been proud to be part of, called the SIMPLICITY study and that's unfortunately, the truth is, is that patients are not monitored as much as they should be. In a large study of thousands of patients in the U.S. and Europe there is unfortunately about half the patients were not tested for cytogenetic response within the first year of treatment about 1 in 8 patients not tested for molecular response, and that's not right. That means we're not following guidelines or recommendations for monitoring. So, I encourage all people at this button on the right, which was a campaign championed by the Max Foundation, where overseas many patients don't actually hear about their results from their doctor and they were encouraged to be quite blunt about it and say what is my PCR. You need to be asked and to be monitored appropriately for us to be successful with CML. And I think data like this coming from this important study, called the SIMPLICITY study, really has shed light on the fact that we can do better with monitoring and this is a group effort. It can come from the patient and the family and the healthcare team, working together to get these tests done on time and interpreted and everybody on the same page.

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

**Cardiomyopathy
Congestive Heart Failure**
Cardiomyocyte Injury?

**Coronary Heart Disease
Myocardial Infarction**
*Endothelial Dysfunction?
Atherosclerosis?*

Peripheral Arterial Disease
*Endothelial Dysfunction?
Atherosclerosis?*

Cerebrovascular Disease
*Endothelial Dysfunction?
Atherosclerosis?*

Pulmonary Arterial Hypertension
Endothelial Dysfunction?

Venous Thrombosis
*Platelet dysfunction?
Prothrombotic state?*

Other:

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

→ Morbidity and mortality; ? Effect on survival observations in front-line studies?
→ ? Delay/deferral of advantageous therapy both in front-line and salvage

21

Slide 21. The most significant 'late effects': CML TKI Associated Cardiovascular Adverse Effects

A little bit more about something that I'm particularly interested in as many others in my field are, and that's that some of these side effects that are related to the cardiovascular system can hit really any part of the cardiovascular system. We don't understand exactly what changes are happening in the blood vessels or the platelets, if it's hardening of the arteries or atherosclerosis, is it the blood vessels themselves. This also travel through the blood and platelets and other changes. We know that of interest many patients have fatigue or other symptoms that might be linked to these things and we're concerned that this may be affecting the burden of patients with CML, morbidity and heaven forbid even mortality. Some of the vascular events have been dangerous, have been fatal, maybe these are having an impact on how successful our first line treatment options are when we use more potent treatments, and is it causing a delay or a deferral of people taking advantage of more potent drugs like ponatinib, for example, which is Iclusig® – which is a very potent and very active drug for patients with resistant leukemia, but it has some of the highest rates of side effects in this arena, so a lot of attention needs to be paid to this.

International **CardiOncology** Society

Guidelines in active development for CML patients and CV risk

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

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

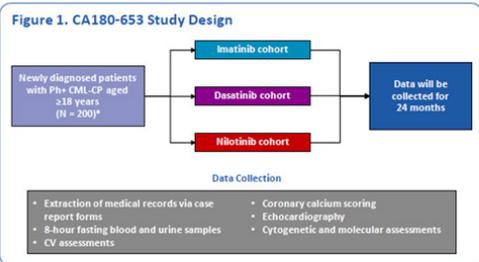
22

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

Slide 22. Guidelines in active development for CML patients and CV risk

Now this next slide gives some guidance to doctors and this is on the right a table which isn't published yet, but will be in the next few months for hematologists at the American Society of Hematology (ASH) meeting and gives some not exactly what they are required to do, but what we might suggest people have done before they start a certain medication for CML and they're all listed there, what they might do at a one month checkup or a 3 to 6 month checkup, and these are the kind of things that a cardiologist or internal medicine physician, and often the hematologist as well, things like simple blood pressure checks can be done. And this would probably, if this alone were done it would make a difference in that we would recognize cardiovascular changes or perhaps undiagnosed cardiovascular conditions and be able to intervene. Much like the ABCDE approach – one of my colleagues, Javid Moslehi, a cardio-oncologist, had written in one of his papers, it's quite a simple equation. We know what causes cardiovascular disease and we know at a minimum we can start with having a hard look at how that interacts with patients who have CML or are on treatment, and right away get hopefully some traction and some improvement on some of the side effects we have seen and the complications we've seen. And this is all a collaborative effort between a field called cardio-oncology and hematology-oncology. If you didn't know it, there's actually a specialist within cardiology called a cardio-oncologist. Maybe it should have been called an onco-cardiologist because it's actually a heart specialist who treats cancer patients and is familiar with cancer-related treatment complications to the heart and the vascular system. So, if you're having complications and you need help, there are specialists that your hematologist can help find for you that is an emerging field.

Figure 1. CA180-653 Study Design



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

Table 2. Clinical Assessments at Routine Office Visits

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

^aIncludes height, weight, and BMI. ^bIncludes Sokal score, Framingham Coronary Heart Disease Score, smoking status, history of hypertension, hyperlipidemia, and hyperglycemia. ^cIncludes blood pressure and heart rate. ^dIncludes disease status and mutational analysis. ^eIncludes fasting blood glucose, HbA_{1c}, fasting lipid panels, and all SOC laboratory assessments (8 hours of fasting required). ^fIncludes different metabolites, cytokines, chemokines, and other biomarkers (8 hours of fasting required). ^gIncludes increased albuminuria test (8 hours of fasting required). ^hBMI = body mass index; HbA_{1c} = glycated hemoglobin; SOC = standard of care.

Table 3. Summary of Collected CV and Metabolic Risk Variables

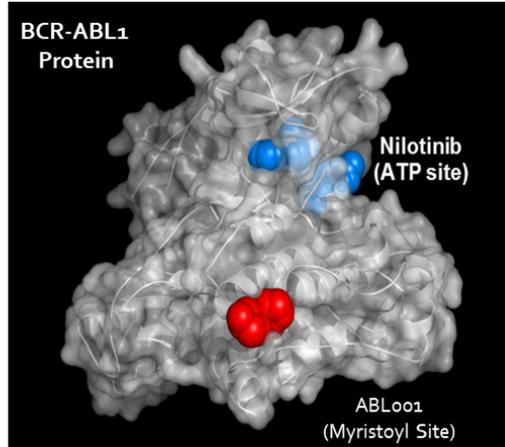
Variables	Data Collected
Targeted CV events	<ul style="list-style-type: none"> Development of arrhythmia, cardiac dysfunction, cerebrovascular ischemic disease, coronary death, coronary insufficiency, heart failure, left ventricular systolic function, myocardial infarction, peripheral artery occlusive disease, pulmonary arterial hypertension, QT prolongation, ischemic or hemorrhagic stroke, transient ischemic attack, venous thromboembolism, other vascular occlusive events, and Framingham Coronary Heart Disease Score Subclinical changes that lead to development of new risk factors or exacerbation of known risk factors (newly diagnosed diabetes, newly diagnosed hypertension, progressive symptoms of disease)
Targeted metabolic events	<ul style="list-style-type: none"> Diagnosis of diabetes mellitus, impaired fasting glucose, elevated HbA_{1c}, metabolic syndrome, abnormal laboratory values for events of special interest
Hematologic	<ul style="list-style-type: none"> Collection of fasting blood glucose, HbA_{1c}, fasting lipid panel Changes from baseline will be calculated
Metabolic	<ul style="list-style-type: none"> Collection of BMI, metabolites, cytokines, and chemokines from biomarker panels, and moderately increased albuminuria levels Changes from baseline will be calculated
Diagnostic	<ul style="list-style-type: none"> Collection of echocardiogram, ankle-brachial index, and coronary calcium scoring assessments Changes from baseline will be calculated

Slide 23. Prospective study of cardiovascular and metabolic risk in newly diagnosed CML (CA180-653, sponsored by BMS)

To that end, if it's possible and you're at a center where such a study exists, there is a study which we're just opening, I've been glad to be part of the development and the launching of this study, where Bristol-Myers Squibb has sponsored for newly diagnosed CML patients, a study where people starting any of the TKIs, Gleevec, Sprycel®, Tasigna®, are put into a program where they have non-invasive, but important cardiovascular testing regularly during their treatment, and I think this wouldn't be a hard sell for people to potentially be part of this study, because it tells you a lot about your cardiovascular health and it may help us learn what markers and what things we might be able to see before problems happen, how they relate to different medications and different patient populations and how we can move on. So, this is an important study which has just begun and the first patients have been enrolled and I encourage you to look for such research to help move the field forward.

ABL001: Novel 3rd generation ABL kinase inhibitor

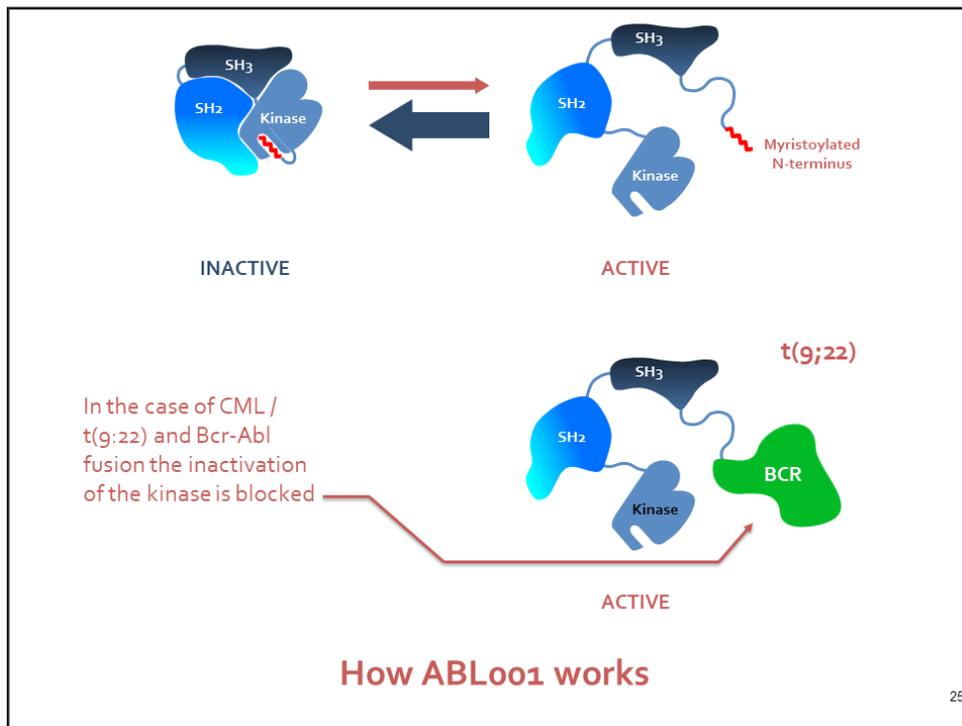
- ABL001 is a new potent, specific inhibitor for CML with a distinct 'allosteric' mechanism of action
- Binds a *different and separate* region of the kinase domain: the myristate-binding pocket, holding Bcr-Abl in the inactive conformation
- Has potential to be combined with the currently available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



24

Slide 24. ABL001: Novel 3rd generation ABL kinase inhibitor

I'm going to spend a little bit of the end of the talk here talking about some advances and some future perspectives and I want to highlight what I think is one of the most promising new drugs on the horizon, which is ABL001, perhaps a novel third generation drug or maybe even what we might call a fourth-generation drug.



25

Slide 25. How ABL001 works

It works in a slightly different way than the medications we currently use. If you look at this cartoon of the BCR-ABL protein, which is a structure, you see that where Tasigna or nilotinib blocks the protein, is different than the place where ABL001 blocks or changes something, which tells you right off the bat that these drugs wouldn't compete with each other, it binds a

separate and different region, something called the myristate binding pocket, so it has the potential to be combined. It's the first new medication that is the same type of drug, BCR-ABL inhibitor, that potentially could be used with the drugs we have available.

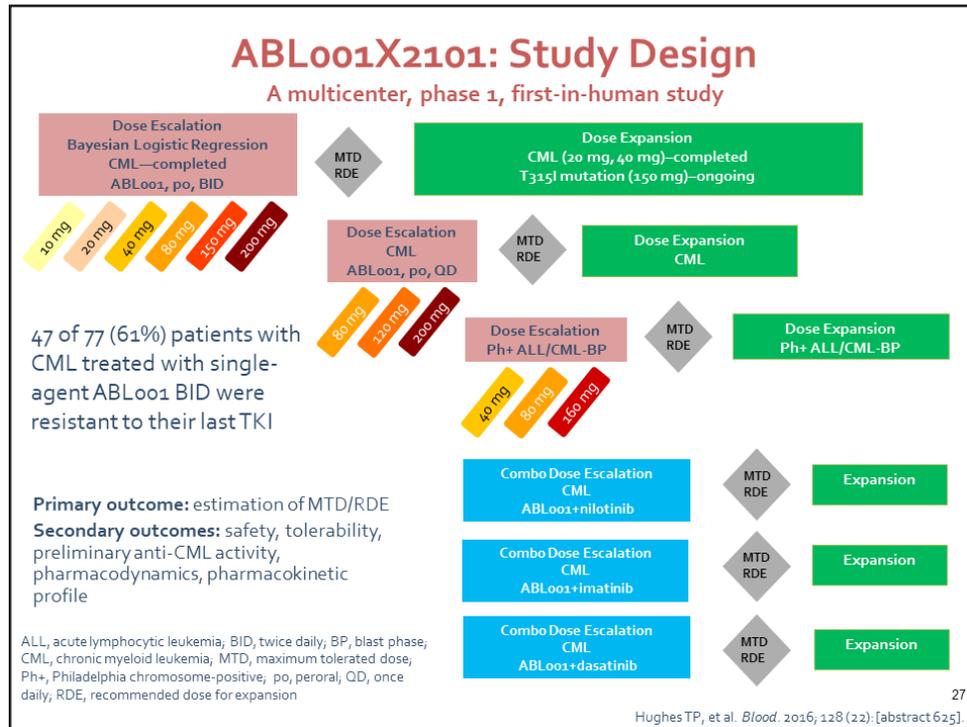
ABL001 allosterically blocks BCR-ABL₁ kinase activity

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

26

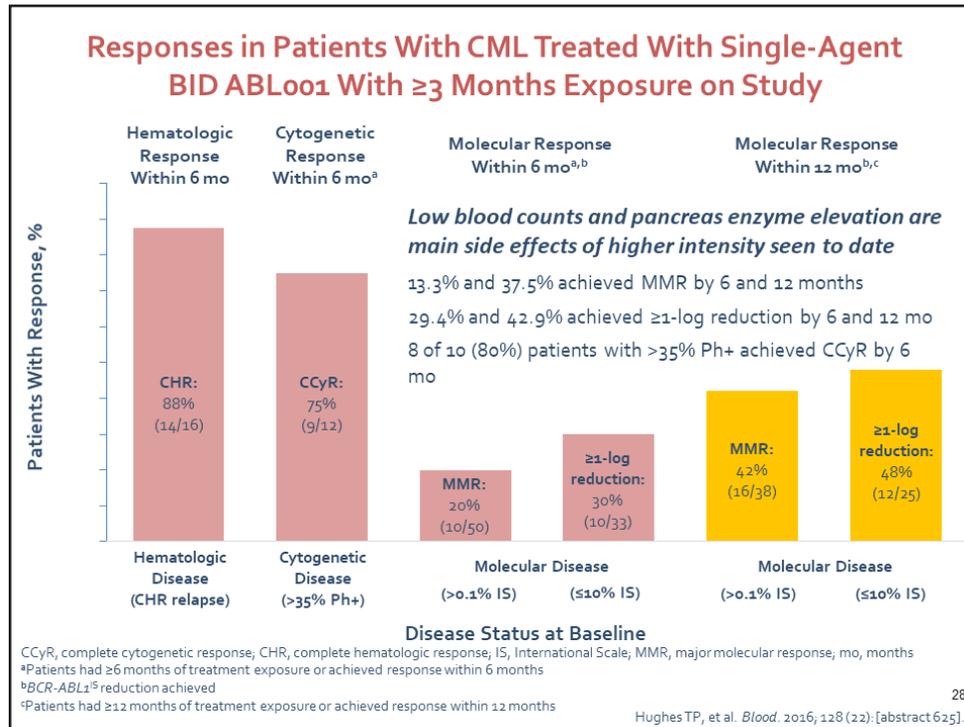
Slide 26. ABL001 allosterically blocks BCR-ABL₁ kinase activity

This drug has been in development for several years now and this cartoon kind of describes how it works. On the top you see what normally happens, where there's a structure as part of the BCR-ABL protein that changes, fits into a space and keeps a balance between an active and inactive form. Hopefully more of an inactive form because overactive proteins are generally not good. When BCR-ABL fusion happens, a certain region is lost, so the ability to inactivate BCR-ABL is now changed. So now we're keeping the protein more active and constitutive activation or automatic activation of BCR-ABL is what causes CML. So, the way this drug was developed is it's able to kind of restore that ability to turn off BCR-ABL by putting it back in an active formation, even with BCR-ABL there, even in the leukemia cell where the normal element that would do that is gone. So, this medicine in the laboratory is shown to really selectively block cells with BCR-ABL. In animals it was able to treat leukemia and actually stop resistance. And that's in mice or rats and I think we have to always take that in stride, but it was a very powerful study. But in humans it seemed that very small amounts were able to be added to standard medications and really boost the ability of blocking BCR-ABL, so there's synergy, as we say, or at least additive effects of the 2 drugs.



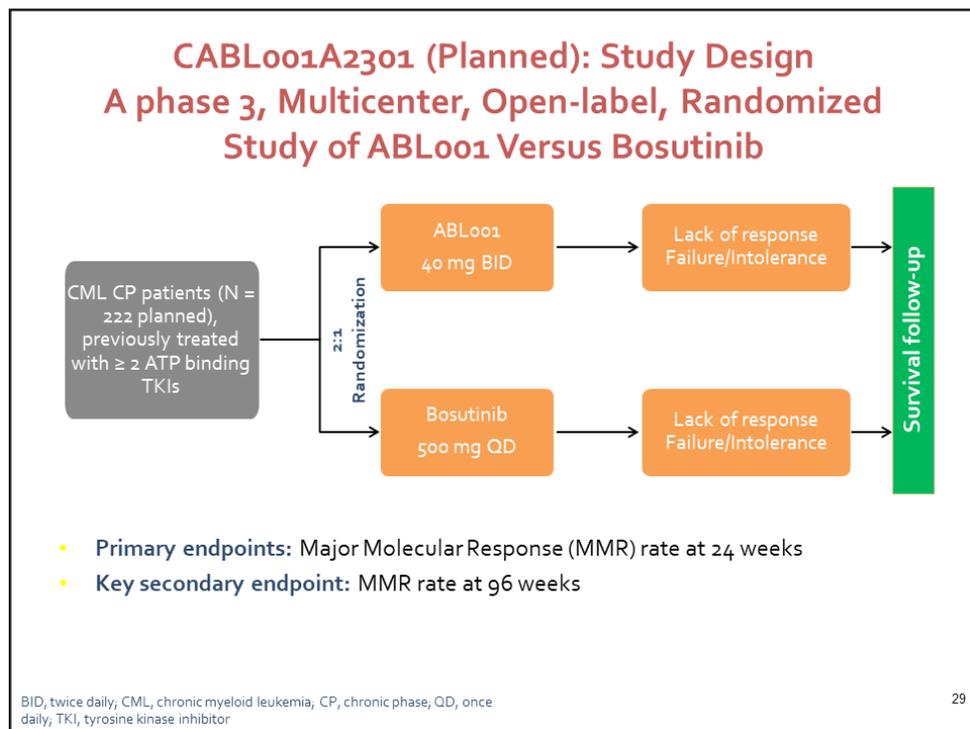
Slide 27. ABL001X2101: Study Design A multicenter, phase 1, first-in-human study

There's a large study that continues, over 200 patients as part of this Phase I study of ABL001. And this is a complicated slide, but it shows you the schema where patients have gotten different doses of the medicine, either once or twice a day, different types of CML patients, either chronic or even patients with advanced forms like PH-positive ALL, which is really a disease in and of itself, or blast phase CML. And then combinations on the lower right as I mentioned. This is probably one of the most interesting parts, in that this medication probably can be combined with available medications, and we're still early and we're understanding how those drugs combine, the safety and the interactions, which is important to know, and of course how they might boost response or bring people back into remission if they've haven't gotten success with available medications.



Slide 28. Responses in Patients With CML Treated With Single-Agent BID ABL001 With ≥3 Months Exposure on Study

These are some of the initial results which have been presented and in public domain at the American Society of Hematology meeting. And again, this is a Phase I trial so it wasn't designed to look at response, but we can see that it's very active, that blood remissions called CHR or complete hematologic responses are very common, as is cytogenetic and molecular response, and deeper molecular responses are clearly possible.



Slide 29. CABL001A2301 (Planned): Study Design A phase 3, Multicenter, Open-label, Randomized Study of ABL001 Versus Bosutinib

Some of the main side effects are low blood counts and pancreas enzyme elevation, which we see with other TKIs. But you can see that the number of patients achieving cytogenetic and molecular responses is quite good. The safety seems very good and this trial will continue in development and a new trial is opening, so if you haven't had access to that trial and it's a good fit, there's a trial where patients who have had a few medications already and are looking or need an alternative option, there's a trial where they can get either bosutinib or this ABL001 in what's called a randomized trial. And of course, that means no placebo of course, but different arms, so it's important to talk to your healthcare team and of course if this is a good choice for you, these are both active medications after other medicines have failed, and I think it'll show us how active ABL001 might be in this type of patient. And so look for this study as well. I'm a big advocate for research as you are probably getting a sense for.

Cumulative incidence of MR

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

EURO-SKI: Survival without loss of MMR
 n=200; MR4 or greater, >2y (inclusion)
 Relapses, n=86
 Relapses within 6 months, n=77

Relapse-free survival at 6 months: 61% (54-68)

A Cancer Drug Gave Me This Life. Can I Survive Without It?

Since she was 23, Erin Zennett Ruddy has swallowed a daily pill to keep her leukemia at bay. Now she has a choice: stay the course or ditch the drug. Find out what she'll do next.

fantastic therapy + careful selection + good monitoring = fantastic outcomes... 'treatment free remission'

Slide 30. Fantastic therapy + careful selection + good monitoring = fantastic outcomes... 'Treatment free remission'

The next slide gives a bit of another chapter in the story, which is the question of treatment-free remission. And I use the title fantastic therapy and careful selection plus good monitoring equals fantastic outcomes and treatment-free remission.

This is an article written by one of my patients about how she was brave enough to enter one of the clinical trials, where she stopped her medication to see if it would be successful. And on the right – upper right, upper left – are some of the outcomes for people who have entered studies and under the right circumstances, when a patient has had treatment long enough, has had a deep enough response, has been monitored very carefully, hasn't had resistance or other complications, there may be an opportunity to stop treatment. And it seems that once there's an initial 6 period where about half of the patients see their CML return and need to be retreated, but thereafter there seems to be a clearing or patients being in the clear and being very unlikely to have their CML return and be in what's called a treatment-free remission. On the left, upper left, is the very long follow-up from one of the first studies of a small number of patients and on the right, the curve flips, but the numbers mean the same, that it's about a 50-50 success rate, in this upper right it's 61%, it's a bit closer to 50 with a bit more time, but that's a very large study coming out of Europe called the EURO-SKI trial.

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

Age ≥ 18 years.

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

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

Prior evidence of quantifiable BCR-ABL₁ transcript.

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

No history of resistance to any TKI.

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

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

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

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

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

- Any significant adverse event believed to be related to treatment discontinuation.
- Progression to accelerated or blast phase CML at any time.

31

Slide 31. Criteria for consideration of treatment free remission (TKI cessation): *the rules as noted by the National Comprehensive Cancer Network (NCCN)*

So, we're really cracking into this nut, as we say, to understand how successful this experiment can be, is it possible that we can offer treatment cessation to a good number of patients, if not everyone. And this is sort of just out for prime time. It's actually been incorporated into what's called the National Comprehensive Cancer Network Guidelines, the body that helps give doctors in the U.S. guidance, based on evidence, as to what – how to handle CML, how to treat – and this is a busy slide, but it goes through the rules and many patients of course have questions, but I see many patients to talk about this option.

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

Age ≥ 18 years.

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

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

Prior evidence of quantifiable BCR-ABL₁ transcript.

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

No history of resistance to any TKI.

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

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

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

- Any significant adverse event believed to be related to treatment discontinuation.
- Progression to accelerated or blast phase CML at any time.

32

Slide 32. Criteria for consideration of treatment free remission (TKI cessation): *patient specifics*

So, to break it down, for the patients who are potentially this is something to consider, would be these criteria. Adults, chronic phase CML, never had advanced CML, are on 1 of the approved medications for at least 3 years, they have obviously a BCR-ABL transcript that can be measured, and they have no history of resistance.

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

Age ≥ 18 years.

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

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

Prior evidence of quantifiable BCR-ABL₁ transcript.

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

No history of resistance to any TKI.

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

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

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

- Any significant adverse event believed to be related to treatment discontinuation.
- Progression to accelerated or blast phase CML at any time.

33

Slide 33. Criteria for consideration of treatment free remission (TKI cessation): *PCR criteria and assay*

For the kind of monitoring we need to do, we need to show – and this is important – a stable deep molecular response for more than two years on several tests, performed at the right, you know, spaced out properly, and of course access to being able to repeat that test over time, frequently.

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

Age ≥ 18 years.

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

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

Prior evidence of quantifiable BCR-ABL₁ transcript.

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

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

- Any significant adverse event believed to be related to treatment discontinuation.
- Progression to accelerated or blast phase CML at any time.

34

Slide 34. Criteria for consideration of treatment free remission (TKI cessation): *monitoring rules*

The kind of monitoring that's required for such an endeavor is busy. Patients need to have monthly testing for the first six months, followed by every two months for the next 18 months. And then continue at the same pace they had previously, which is quarterly, at least for the time being. And of course, they need to be for certain strict rules about restarting treatment for what we call loss of deep molecular remission, where people cross back over major molecular remission. And they need to be followed carefully thereafter.

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

Age ≥ 18 years.

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

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

Prior evidence of quantifiable BCR-ABL₁ transcript.

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

No history of resistance to any TKI.

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

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

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

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

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

- Any significant adverse event believed to be related to treatment discontinuation.
- Progression to accelerated or blast phase CML at any time.

35

Slide 35. Criteria for consideration of treatment free remission (TKI cessation): *CML specialty center / NCCN feedback*

And lastly, we need to still learn from this endeavor and we need to have reporting by doctors and patients through healthcare teams, whoever is available, about any adverse events and of course, heaven forbid, any patients who lose control of their CML. I want to answer that question which may come up. That has been exceeding rare and in published clinical trials there are probably only two out of thousands of patients who due to probably certain circumstances did have their CML move forward into a more advanced stage as a result of taking part of this type of endeavor. But it's still viewed as safe, given the very, very low likelihood of that happening and with careful monitoring hoping we can eliminate or avoid that entirely.

Do Adverse Events Occur With TKI Withdrawal?

N=200; 222 AEs in 98 patients were reported

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

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

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

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

Mahon FX et al, Blood 2014 124:151

36

Slide 36. Do Adverse Events Occur With TKI Withdrawal?

Interestingly, stopping treatment doesn't always mean things always get better. There is what's been described as a withdrawal syndrome, where people have some side effects from stopping their TKIs, and again it's mostly Gleevec patients that have stopped. There are a few reports in the literature where people have had arthritic type symptoms, a few other symptoms, which generally are short-lived, but can be noticeable and part of this endeavor to consider treatment-free remission, so it's not always perfect, just to give full disclosure.

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




INFECTIOUS DISEASE

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

Mayra Garcia,¹ Arik Cooper,¹ Wei Shi,¹ William Bornmann,² Ricardo Carrion,³ Daniel Kalman,¹ Gary J. Nabel^{1*}

Ebola virus causes a fulminant infection in humans resulting in diffuse bleeding, vascular instability, hypotensive shock, and often death. Because of its high mortality and ease of transmission from human to human, Ebola virus remains a biological threat for which effective preventive and therapeutic interventions are needed. An understanding of the mechanisms of Ebola virus pathogenesis is critical for developing antiviral therapeutics. Here, we report that productive replication of Ebola virus is modulated by the c-Abl1 tyrosine kinase. Release of Ebola virus-like particles (VLPs) in a cell culture cotransfection system was inhibited by c-Abl1-specific small interfering RNA (siRNA) or by Abl-specific kinase inhibitors and required tyrosine phosphorylation of the Ebola matrix protein VP40. Expression of c-Abl1 stimulated an increase in phosphorylation of tyrosine 13 (Y13) of VP40, and mutation of Y13 to alanine decreased the release of Ebola VLPs. Productive replication of the highly pathogenic Ebola virus Zaire strain was inhibited by c-Abl1-specific siRNAs or by the Abl-family inhibitor nilotinib by up to four orders of magnitude. These data indicate that c-Abl1 regulates budding and release of filoviruses through a mechanism involving phosphorylation of VP40. This step of the virus life cycle therefore may represent a target for antiviral therapy.

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

Christopher M. Coleman,¹ Jeanne M. Sisk,¹ Rebecca M. Mingo,¹ Elizabeth A. Nelson,¹ Justin M. White,¹ Matthew S. Frenkel,¹ Department of Microbiology and Immunology, University of Maryland, Baltimore, Maryland, USA; ²Department of Cell Biology, University of Virginia, Charlottesville, Virginia, USA*

ABSTRACT
The highly pathogenic severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) cause significant morbidity and mortality. There is currently no approved therapeutic for highly pathogenic coronaviruses, even as MERS-CoV is spreading throughout the Middle East. We previously screened a library of FDA-approved drugs for inhibitors of coronavirus replication in which we identified Abelson (Abl) kinase inhibitors, including the anticancer drug imatinib, as inhibitors of both SARS-CoV and MERS-CoV *in vitro*. Here we show that the anti-CoV activity of imatinib occurs at the early stages of infection, after internalization and endosomal trafficking, by inhibiting fusion of the virions at the endosomal membrane. We specifically identified the imatinib target, Abelson tyrosine-protein kinase 2 (ABL2), as required for efficient SARS-CoV and MERS-CoV replication *in vitro*. These data demonstrate that specific approved drugs can be characterized *in vitro* for their anticoronavirus activity and used to identify host proteins required for coronavirus replication. This type of study is an important step in the repositioning of approved drugs for treatment of emerging coronaviruses.

Repurposing imatinib: other Abl targets

IMATINIB AMELIORATES NEUROINFLAMMATION IN A RAT MODEL OF MULTIPLE SCLEROSIS BY ENHANCING BLOOD-BRAIN BARRIER INTEGRITY AND BY MODULATING THE PERIPHERAL IMMUNE RESPONSE

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Abstract
Central nervous system (CNS) disorders such as ischemic stroke, multiple sclerosis (MS) or Alzheimer's disease are characterized by the loss of blood-brain barrier (BBB) integrity. Here we demonstrate that the small tyrosine kinase inhibitor imatinib enhances BBB integrity in experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis (MS). Treatment was accompanied by decreased CNS inflammation and demyelination and especially reduced T-cell recruitment. This was supported by downregulation of the chemokine receptor CXCR2 in CNS and lymph nodes, and by modulation of the peripheral immune response towards an anti-inflammatory phenotype. Interestingly, imatinib ameliorated neuroinflammation, even when the treatment was initiated after the clinical manifestation of the disease. We have previously shown that imatinib reduces BBB disruption and stroke volume after experimentally induced ischemic stroke by targeting platelet-derived growth factor receptor- α (PDGFR- α) signaling. Here we demonstrate that PDGFR- α signaling is a central regulator of BBB integrity during neuroinflammation and therefore imatinib should be considered as a potentially effective treatment for MS.

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

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

Slide 37. Repurposing imatinib: other Abl targets

You know, in the last slide here, I want to say that this field and the development of targeted therapy, Gleevec was really one of the first targeted therapies. When it was being studied the only other medicine that was targeted in cancer was hormonal therapy for breast cancer, which would be tamoxifen, you know, anti-estrogen therapy, or a drug called Herceptin®, which is an antibody for patients with breast cancer. If you read the newspaper or the science journals you know, looking at targeted therapy for cancer – it's a literal explosion, and there are hundreds, if not thousands of drugs available or in development for different targets in different cancers. So, we really set an example about what we could do if we understand a cancer best, unravel it, come up with a smart therapy that is specific and narrow enough, and this slide shows you the beauty of when you have a very well developed, rationally designed what we call a targeted drug, you may uncover other purposes for it.

Imatinib or Gleevec, if you didn't know it, probably may have a role in blocking viral transmission of serious infections including Ebola and MERS and SARS. It can have effects in the central nervous system in patients with multiple sclerosis and Parkinson's. There's at least preclinical and animal data that support this. There have been some clinical studies. We haven't the answer as to exactly if these medications can be used or if other versions of them can be used, but we're thankful goodness able to sometimes even borrow targeted therapies from one disease into another. And this has happened in other cancers as well, so it's been a tremendous advance, not only in knowledge, but in therapy, if you follow the CML story.

H. JEAN KHOURY
CURE
CML
CONSORTIUM

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



www.curecml.org

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

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- Duke Cancer Institute
- Weill Medical College of Cornell University
- Barbara Ann Karmanos Cancer Institute
- UCSF Helen Diller Family Comprehensive Cancer Center
- Roswell Park Cancer Institute
- Dana-Farber Cancer Institute

38

Slide 38. H. Jean Khoury Cure CML Consortium

So, a bit of a shameless plug is that I'm part of a consortium called the H. Jean Khoury Cure CML Consortium, and this is named in honor of Jean Khoury, who unfortunately passed this year. Given his really fire-starting us to get this consortium going. And this is – many of the large cancer centers in the U.S. have gotten together and actually executed one of the first treatment-free remission or treatment discontinuation trials in the U.S. and we're working hard to try to really amplify and light a fire under CML research in the United States, as we can work together better than as we can alone.



We need your help to better our research

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

HAS YOUR LIFE BEEN AFFECTED BY CML?

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

The 5-10 minute survey is voluntary and anonymous.

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39

Slide 39. We need your help to better our research: Go to www.curecml.org and click on 'survey'

And if you have the time I'd encourage everyone to maybe jot this down or take note of probably not a hard website to

remember, www.curecml.org. There's a survey available and it will help us guide what patients, caregivers, physicians, anyone interested, feels like the research priority should be in CML. It's a quick survey and if you can I'd encourage you to try to look for this and take care of this for us as we want to move the field forward.

CML in 2017 and beyond...

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



40

Slide 40. CML in 2017 and beyond...

So, the story, what's on the horizon and what's in the future, is that CML is a highly treatable and a functionally curable disease. Each time I see a new patient I try to encourage them to use that as their mantra – it's my mantra, and is hopefully theirs, too. We know that generic imatinib is here, we have to let science overcome fears, it's a powerful drug whether it's in a generic or branded form. TKIs should be chosen carefully between patients and physicians. Side effects are important, other health problems are important, response is obviously very important. Monitoring needs to happen, it can't be underdone. Mutations testing can be an important part of that. And resistance is treatable. It doesn't mean that all is lost. There are new agents on the horizon, including ABL001, which may fit nicely into our armamentarium.

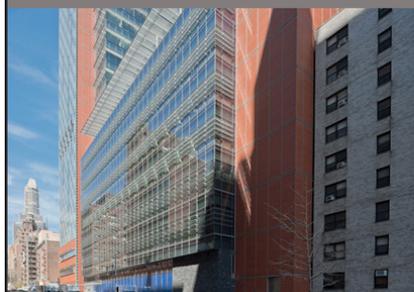
We don't talk much about bone marrow transplant, but it's still a curative option, and for certain patients it's really something to talk about early and to understand and to sort out options. So, it's not thought of too late and it's not a too little-too late type of scenario.



Thank you for your attention!

Questions?

212-639-3107

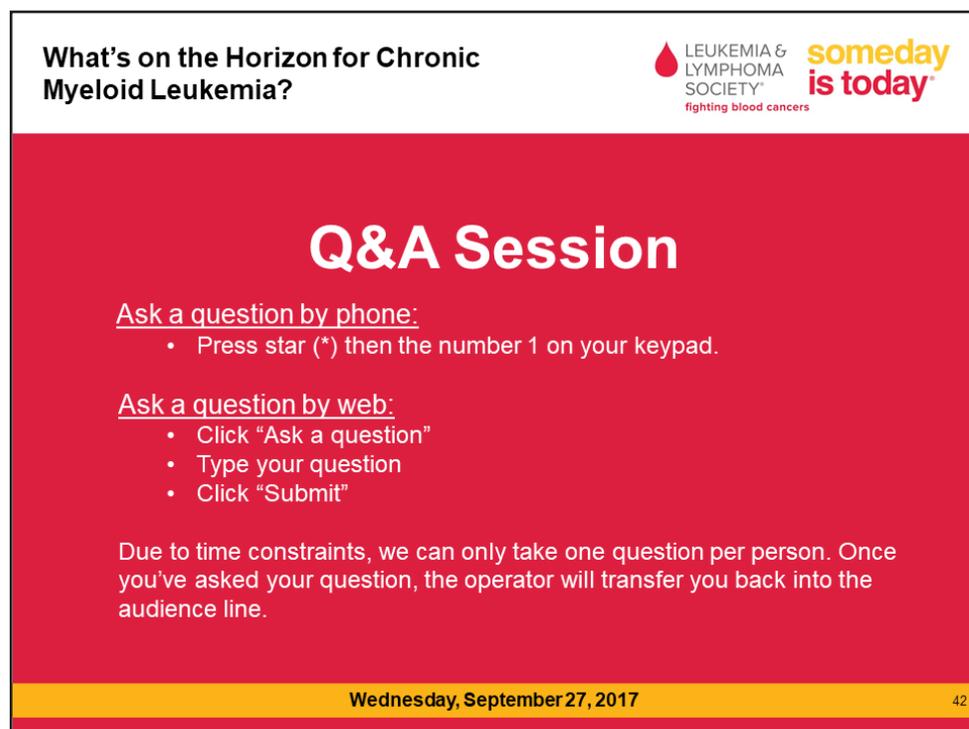


Slide 41. Thank you for your attention! Questions?

But the past and the future have been very bright. It's many years since Gleevec was on the cover of the Time Magazine, but I think we have a great story. And I just want to thank you for your participation and your attention and I wanted to leave enough time for questions, so I'll end my presentation there.

Lizette Figueroa-Rivera:

Thank you so much, Dr. Mauro, for providing us with so much information today.



The slide features a red background with white text. At the top left, it repeats the title 'What's on the Horizon for Chronic Myeloid Leukemia?'. To the right are the Leukemia & Lymphoma Society logo and the slogan 'someday is today' with 'fighting blood cancers' underneath. The main heading 'Q&A Session' is centered in large white font. Below it, instructions for asking questions by phone and web are listed. A note states that only one question per person can be asked. At the bottom, a yellow bar contains the date 'Wednesday, September 27, 2017' and the slide number '42'.

Slide 42. Q&A Session

Operator:

It's now time for our question and answer portion of our program.

Lizette Figueroa-Rivera:

We'll take the first question from our web audience. Doctor, Susan and T.J. are asking about fluctuating BCR-ABL numbers. They're asking, when do you have to start worrying?

Dr. Michael Mauro:

That's a great question. Clearly, it's a very sensitive test and as you get down to hopefully some of the lower levels, we can see fluctuations. I think we have to focus on some of the thresholds that we don't want to cross over. I'd say to focus on, when it comes to PCR what's called major molecular response, if the number's fluctuating and moves north of .1% on the International Scale, that's a bit of a concern and probably should trigger evaluation. Fluctuations lower than that are probably not uncommon and may not be a manifestation of anything to worry about. We do focus on deep molecular remission and, for example, I talk to patients in the clinic about whether their numbers are consistently in what's a 4-log reduction or MR4. There's probably much more noise down in that end of the spectrum. I think – my best advice is to take a step back and to look at the overall trend. If the slope is negative, as they say, meaning that the numbers are generally falling, it can sometimes be a sawtooth. It's important to make sure people don't rise and cross over key thresholds like major molecular response. And then of course, be dialed in with your healthcare team to understand what the full interpretation of the results are, what their view is, and to know your PCR and know exactly how it's being measured and then scale it's on.

Lizette Figueroa-Rivera:

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

Operator:

Our next question comes from Jaclyn from Maryland. Please state your question.

Jaclyn:

Yes, I'm on a medication called Sprycel. And I want to know is constantly bleaching my skin, is there unnecessary ingredients in this? I've been on it for 7 years.

Dr. Michael Mauro:

Well, that's a very interesting question. I think there definitely have been reports of changes in skin pigmentation, hair pigmentation, in both directions, lightening of the skin, darkening of the hair. More with Gleevec than with Sprycel. But I think it's possible with any of the medications. And there are expert dermatologists out there that can sort that out, to maybe make sure it's not more than 1 thing happening at once, but there clearly can be that side effect. And I know it's disconcerting, but don't believe we have any concern of it causing any serious conditions, but it certainly can be cosmetically not favorable or surprising. So, I might again open up the discussion with your hematologist and maybe a dermatologist who can make sure there's nothing else going on, and see if we can manage this situation. But hopefully it's in the setting of a good response to treatment.

Lizette Figueroa-Rivera:

Thank you, Doctor. And our next question comes from our web audience. Zel asks, can you comment on dose reduction versus cessation, the risks and successes?

Dr. Michael Mauro:

Another great question. So, it's surprising to many people to hear that why would you just quit cold turkey, maybe you should slow down or cut the dose down. There have been some studies that have deliberately lowered the doses. There's probably one important study from England called the DESTINY trial, where people who were in a good remission, a major molecular response, and on the three commonly initiated first drugs, had their dose of drug cut in half, and the results were very encouraging, that it was very unusual, almost absent, for people to lose response when they had doses of Tasigna and Sprycel cut down, and very rare on Gleevec. And that's not surprising because cutting the Gleevec dose in half is probably much more of a true dose reduction than cutting the dose of one of the more potent drugs in half.

So, it's possible that that may evolve as our strategy rather than quitting cold turkey, as you might say. But on the other hand, we have a lot of experience with patients who have been treated long enough, and the thinking there is hold enough pressure or treat long enough to render the CML unable to proliferate or grow again, and then you may not need any treatment. There's a little bit of science that in the laboratory sometimes you don't like to lower the dose of medications down because you may actually foster resistance, you may allow for escape or emergence of something that can grow, that can essentially squeeze through the pressure of having some medication, but not the full dose.

So, at the moment we still think about treatment cessation as our strategy for this treatment-free remission, but there's data from a number of different studies, including that important trial, showing that dose reductions may be also feasible and may be a compromise for many patients for reducing side effects, or the prelude to potentially treatment-free remission.

Lizette Figueroa-Rivera:

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

Operator:

Our next question comes from Richard from Tennessee. Please state your question.

Richard:

Yes. I started with Tasigna and went to Sprycel and they both seemed to work well and I'm in molecular recession. But I'm having a tinny taste in my mouth and slight stomach – like I'm almost hungry all the time. Is that normal?

Dr. Michael Mauro:

I'm glad to hear that those medications are effective and those are both good drugs. So, some of the more subtle side effects are sometimes hard to pin down. I do hear a lot about GI effects and Sprycel can have some GI effects, although it is a bit more mild. Gleevec may be a little bit heavier in that regard. That's probably one that's got to get back to the healthcare team because you always have to think broadly. I always encourage tackling each problem by stepping back to say – first I never assume anything's normal. If it was not there, now it's there, and it's affecting your quality of life. And then second, I think we always want to consider could it be the leukemia, could it be the treatment, could it be some other issue in the setting of treatment for the leukemia that is now unmasked. And it may be quite a simple solution. So, I'd probably encourage kind of a multi-faceted approach with even maybe a gastroenterologist and certainly internal medicine and hematology tackle that. Fortunately, it doesn't sound risky, but I'd tackle it from a multidisciplinary approach, much like any of the sort of hard to difficult side effect questions we often get.

Lizette Figueroa-Rivera:

Thank you, Doctor. And our next question is from our web audience. Acreddie and Shawna are both asking about pregnancy and fertility during CML treatment for women as well as men.

Dr. Michael Mauro:

Well, that's a definite area of interest for me. I am a strong advocate for women who have been treated for CML, under the appropriate circumstances – if you've just heard me talk about a scenario where I think patients are potentially able to stop their treatment, that's going to open the door for them to potentially be able to consider pregnancy. The fast facts are that we generally don't consider it safe to take these medications at all during pregnancy. There may be some patients who've been treated late in pregnancy when the child is quite far along in development, when there may not be as much risk, but overall, it's not recommended at all. So, it means stopping treatment. So, my general recommendations are for a woman to – if they can, to achieve that deep remission and that time in deep remission, where they're potentially at that point where they might consider stopping the treatment, not just for pregnancy. That gives us the confidence to potentially move forward.

I've managed many women in whom that experiment wasn't successful and there were some limited relapse during pregnancy, but this is a very careful and deliberate discussion that needs to take place. I encourage women to talk to their specialist or find a specialist – I'm one of them – who is interested in this and who's supportive of this. Many unfortunately aren't. Because achieving pregnancy while you're still being treated for your leukemia is a very tricky discussion and there may be some ways to do that. We're hopefully going to put some more firm guidelines in the literature for doctors to have. But essentially, it's possible to potentially achieve pregnancy and minimize or eliminate altogether the taking of medications when you're pregnant, even if it's just for a few days, based on careful plan with your doctor. But the principles are that treatment shouldn't – can't take place during pregnancy. Monitoring should take place as if people have stopped treatment, like these treatment-free remission trials that I've explained. The status of someone who can get maybe the green light to think about pregnancy should be similar to the status of people who were given the green light to think about stopping the treatment.

And then lastly in a word for men, initially we had concerns about effects on males, you know, the male element, if you will, during conception, about spermatogenesis infertility. There probably is a bit of effect on male fertility from some of the medications, perhaps Sprycel more than others, but overall I tell men that they can father children, but any pregnancy, obviously if it's with a woman who's pregnant with CML and probably if it's the male partner, should be considered higher risk and getting high risk obstetrics and very meticulous prenatal and early pregnancy-related testing done to make sure the baby's healthy and well to help the couple decide, is very important.

Lizette Figueroa-Rivera:

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

Operator:

Our next question comes from George from Texas. Please state your question.

George:

I'm on Sprycel 50. Started on Gleevec 400, went to Sprycel 50, and for the last ten months I've been with a rash, really not too bad a rash, but it's always there and itches all the time. Have any suggestions as to what would stop it? I've tried a little bit of everything.

Dr. Michael Mauro:

Another one of those very specific side effect questions that probably needs the multi-faceted approach. There are skin side effects with all the medications. I probably would say for Sprycel we generally see more of like an acne type reaction in the face and hairline and upper body and it may be itchy, it may be inflamed. And there may be things where you treat something like that like you'd treat an eruption in the skin, if it wasn't from Sprycel, where it might be quite effective, but you probably need a dermatologist that's knowledgeable about these drugs or at least cancer-related therapy and side effects to tackle it.

I failed to mention with the other question regarding GI side effects that the other gentleman had, you know, everything's important, everything can be a quality of life-impairing side effect. People shouldn't have to live with adverse events, even if they're lower intensity. So, this definitely has to be an open discussion with the healthcare team to say is this something we can fix, is this something that isn't going to go away and it's not bearable. Because if it deteriorates your ability to take the

medication, it's serious. So the best advice, though, is to probably have a multi-faceted approach with a dermatologist, and if you've tried a little bit of everything I think you probably need a higher level of expert opinion.

Lizette Figueroa-Rivera:

Thank you. And our next question comes from our web audience. Liz and David both ask, how do you treat the anemia associated with Gleevec?

Dr. Michael Mauro:

So, the anemia related to Gleevec may be part and parcel to the drug itself. There may be – there's anemia with all of the medications to some degree and I would explain it in that once you've had CML, when your marrow is now no longer burdened by CML, it may never recover completely too normal. Many people have slightly low white blood cell counts, platelet counts, anemia with Gleevec is probably the most – is more common than with some of the other drugs. It may be because of a subtle effect on a normal pathway called KIT, because the red blood cell size, the MCV number on the CBC reports also increases.

This is another one of those situations where you want to make sure nothing is being missed. Is there any reason why the marrow in the body can't recover fully? Is there an issue with the kidneys, with the level of hormone in the blood called erythropoietin, that makes blood? Is there anything related to nutritional deficiencies, iron, folic acid, B12? All those things need to be checked.

In many cases we can't reverse it. I can give you a glimmer of hope that we do when we've had patients enter treatment-free remission, I've seen the anemia go away. So, if it's temporary and treatment is for a finite period of time, there's hope on the horizon that you may not have to live with anemia forever, if potentially you're able to have a defined duration of treatment.

Lizette Figueroa-Rivera:

Thank you, Doctor. And our next question comes from our web audience. Ramona is asking what test results determine whether a patient is in accelerated phase of CML? And what are the names of the tests that numbers classify CML as accelerated?

Dr. Michael Mauro:

Very good question. So accelerated phase can be something that can be the situation when the CML is first recognized or it can be something that evolves. Probably the strongest indicators of accelerated phase would be excess numbers of cells in the blood called blasts or basophils. Very significant growth in the spleen. There are some more – so those are things in the CBC and on examination really or even an ultrasound.

Genetically if there's something called clonal evolution or more complicated chromosome changes, not just the Philadelphia chromosome, but something else, that's an element of accelerated phase.

And then just a specific – you know, if the platelet count is low, not because of treatment, that's often a sign of accelerated phase CML as well. So, it's really a constellation of findings.

The biggest predictor, which is part of some of the more current risk models, would be the basophil count, the size of the spleen and the blast cells in the blood. So those are the key things to look for, to know whether the CML is behaving in an accelerated fashion or is an accelerated phase.

Lizette Figueroa-Rivera:

Thank you, Doctor. And our last question today comes from Heather and she's asking if a transplant, a bone marrow transplant, is a curative option for CML.

Dr. Michael Mauro:

That's probably a good place to end, to remind everyone that prior to the availability of the medications and the story I've just painted, CML was one of the most treatable diseases with bone marrow transplant. It had some of the highest success rates, it was really what many called the poster child condition for bone marrow transplant. It still is a very serious undertaking with risks both in the short and the long term that can change someone's life, but it is a curative procedure. When it works it works beautifully. And it's why we shouldn't for certain push it too far back. We need to think about it early when we have signs of poor response to treatment. Clearly if we have CML is starting to advance or behave like in an accelerated or blast phase, those are real almost certainties where that's probably one of the best long-term options.

My partner and director here, Sergio Giral, at MSK, always reminds patients that he sees in consultation that bone marrow transplants an option. It may not be a must. And particularly in CML I think it's an option. So, it's a discussion that has to take place early. And in the right circumstances it definitely is a cure.



What's on the Horizon for Chronic Myeloid Leukemia?

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someday is today

SUPPORT RESOURCES

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

Wednesday, September 27, 2017 43

Slide 43. Support Resources

Lizette Figueroa-Rivera:

Well, thank you, Heather, for that question, which was our final question today.

And thank you also, Dr. Mauro, for your continued dedication to patients. For those of you who participated in today's program, we hope the information presented today will assist you and your family in your next steps.

If you were not able to get your question answered today, please speak to an LLS Information Specialist at 1-800-955-4572 from 9 AM to 9 PM Eastern Time, or reach us by email at infocenter@LLS.org. Information Specialists are available to answer your questions about treatment including clinical trials, or answer other questions you may have about support, including financial assistance for treatment.

Again, thanks to our supporters, Bristol-Myers Squibb, Novartis, and Takeda Oncology.

Dr. Mauro, thank you again for volunteering your time with us today. And on behalf of The Leukemia & Lymphoma Society, thank you all for joining us. Goodbye and we wish you well.