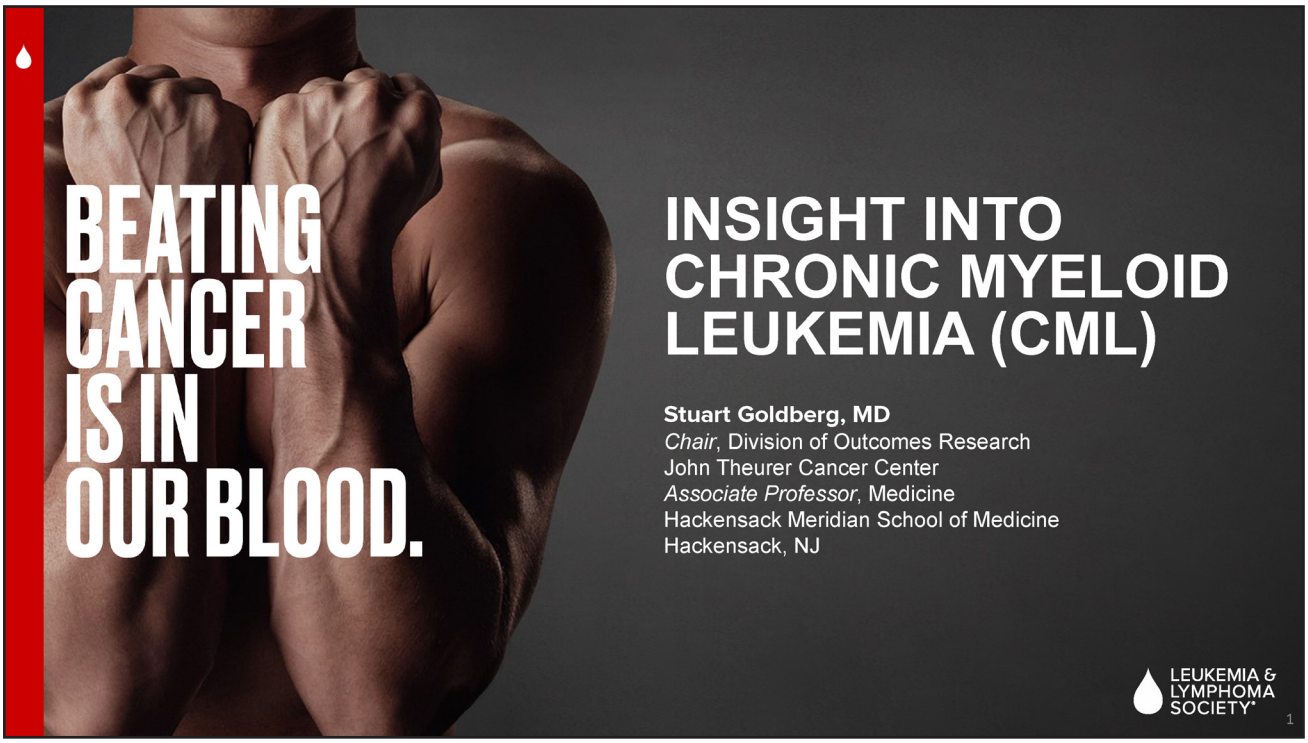


Slide 1: INSIGHT INTO CHRONIC MYELOID LEUKEMIA (CML)

Operator:

Hello everyone and welcome to today's ***Insight into Chronic Myeloid Leukemia*** free telephone and web education program. It is my pleasure to introduce your moderator, Ms. Figueroa-Rivera.

Lizette Figueroa-Rivera:

Hello everyone. On behalf of The Leukemia & Lymphoma Society, I'd like to welcome all of you. We have over 1,200 people participating from across the United States, as well as 18 other countries around the world. Welcome.

Special thanks to Dr. Stuart Goldberg for volunteering his time and expertise with us today, especially during these busy times.

Now, it is my pleasure to introduce WWE Superstar, actor and former professional football player, Joseph Anoai, who many may know as Roman Reigns. Roman will now provide a few welcoming remarks.

Roman Reigns:

My name is Joe. Many of you might know me as WWE Superstar Roman Reigns. In October 2018, I stepped into the ring and announced to a packed arena and millions of viewers that I had to relinquish my WWE Universal Championship Title that I worked so hard for, so I could take time to deal with my leukemia, which had returned after 11 years in remission.

I was first diagnosed with chronic myeloid leukemia (CML) in 2007 at age 22. Like you, I know all too well the effects of having a blood cancer and how important it is to have a good support system and access to trusted information.

Last year, WWE and I teamed up with The Leukemia & Lymphoma Society in the fight against cancer. We're proud to partner to support the work they are doing to support blood cancer patients, families, and caregivers, and to drive forward groundbreaking research in the search for cancer cures. I'm especially proud of the LLS's Children's Initiative, which is addressing the important need for better and more effective treatment options for pediatric blood cancer patients around the world.

My own journey with leukemia has inspired me to do whatever I can to help other cancer patients. I know firsthand how tough it is to deal with cancer and I want to show people that even someone like me can be knocked down. But, with the right treatment and support, we can get back up and keep moving forward. My partnership with LLS is part of my commitment to keep fighting for cancer patients and families.

Today, you'll have the opportunity to learn from Dr. Stuart Goldberg, who has volunteered his time to speak with you and we appreciate his dedication to supporting LLS's mission and commitment to caring for patients living with blood cancers.

Thank you for joining us.

Lizette Figueroa-Rivera:

Thanks again to Roman for his support and partnership. You may find out more about his journey with CML on our recent podcast that was released on World CML Day 2 days ago. You may listen to this episode at **TheBloodline.org**.

For this program, we would like to acknowledge and thank Bristol-Myers Squibb, Pfizer, Novartis, and Takeda Oncology for support of this program.

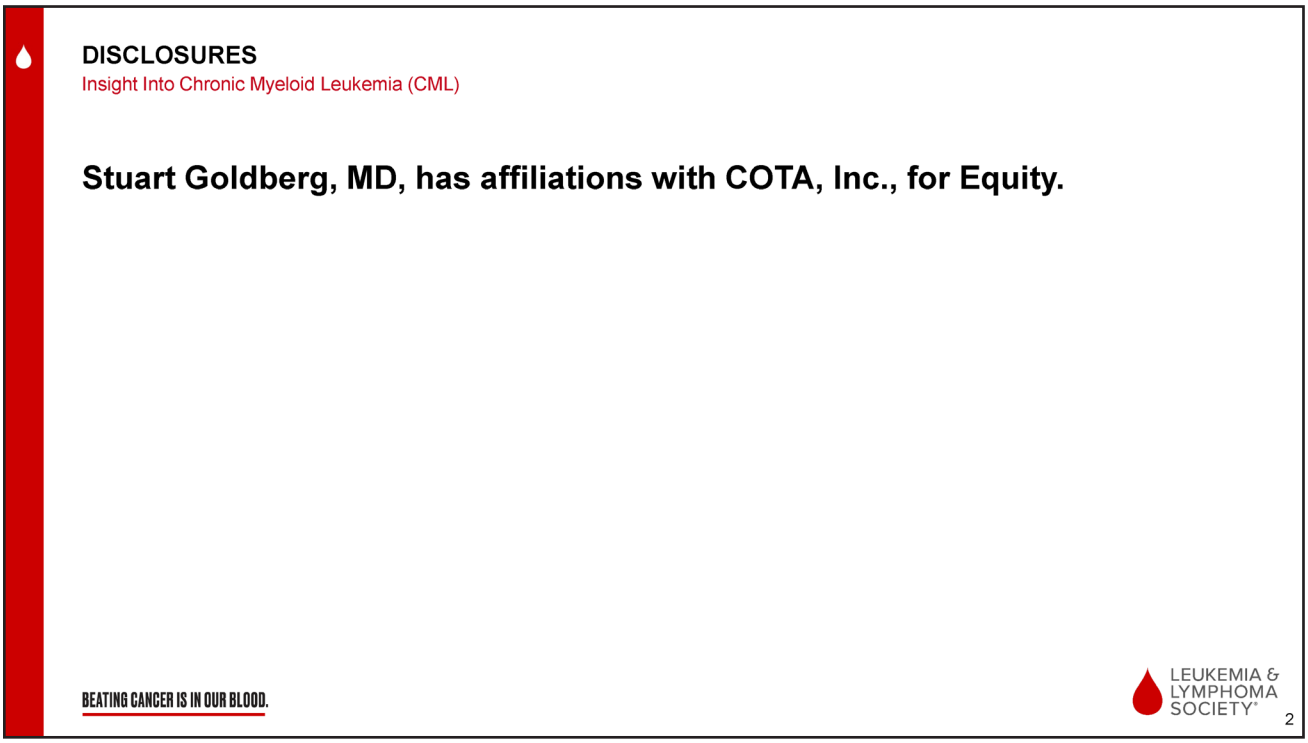
If you are participating today by computer, Dr. Goldberg's slides will display as you listen to the program. You can also view or print the slides from our website at **LLS.org/Programs**. Or, you can download and print the slides from the Materials tab on this program's web platform.

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

I am now pleased to introduce Dr. Stuart Goldberg from John Theurer Cancer Center in Hackensack Meridian School of Medicine in Hackensack, NJ. Dr. Goldberg, I'm privileged to turn the program over to you.

Dr. Stuart Goldberg:

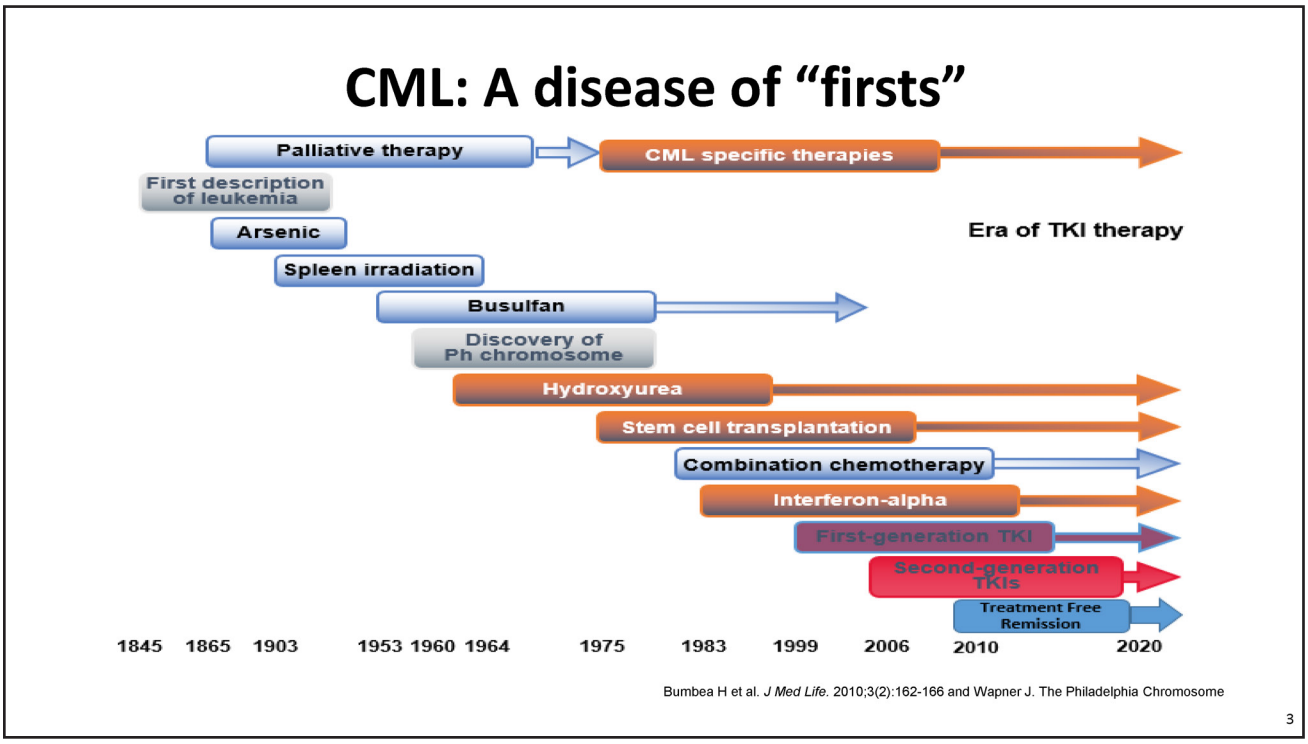
Well, thank you everyone, and it's a pleasure for me to be able to speak on behalf of The Leukemia & Lymphoma Society on chronic myeloid leukemia. I wanted to also start by thanking The Leukemia & Lymphoma Society, not just for this honor, but for all of the great work they do in supporting patients with CML and other blood cancers. I hope that many of you realize that all of those little quarters that have been donated, actually benefitted you directly because of The Leukemia & Lymphoma Society, their grants to the researchers helped to develop the drug imatinib or Gleevec® that many of you may be on. So, this is one of those times when we have a direct link between the patient donations and giving us a therapy that now works. And, so let's talk a little bit about CML and how we got through this great journey and how we're doing well for many of our patients.



Slide 2: DISCLOSURES

Dr. Stuart Goldberg:

Let's start by talking a little bit about my disclosures. I actually work with a company that does medical data research called COTA, but that will not affect today's program.



Slide 3: CML: A disease of "firsts"

So, where to begin? Well, it's always good to look at the history to understand where you're going, and best to look at where you've been. And, CML is actually one of those diseases with a very, very colorful history. It's often been called a disease of firsts. You can see from this slide, we first discovered or first described CML back in the 1840s and you can see very early on one of the first effective uses of the chemotherapy drug arsenic, an old poison, that we still use today for some patients with CML, but more commonly in the acute leukemias. But, a drug that actually did work, helped a little bit. Then we see an early use of splenic irradiation at the turn of the century in the 1900s.

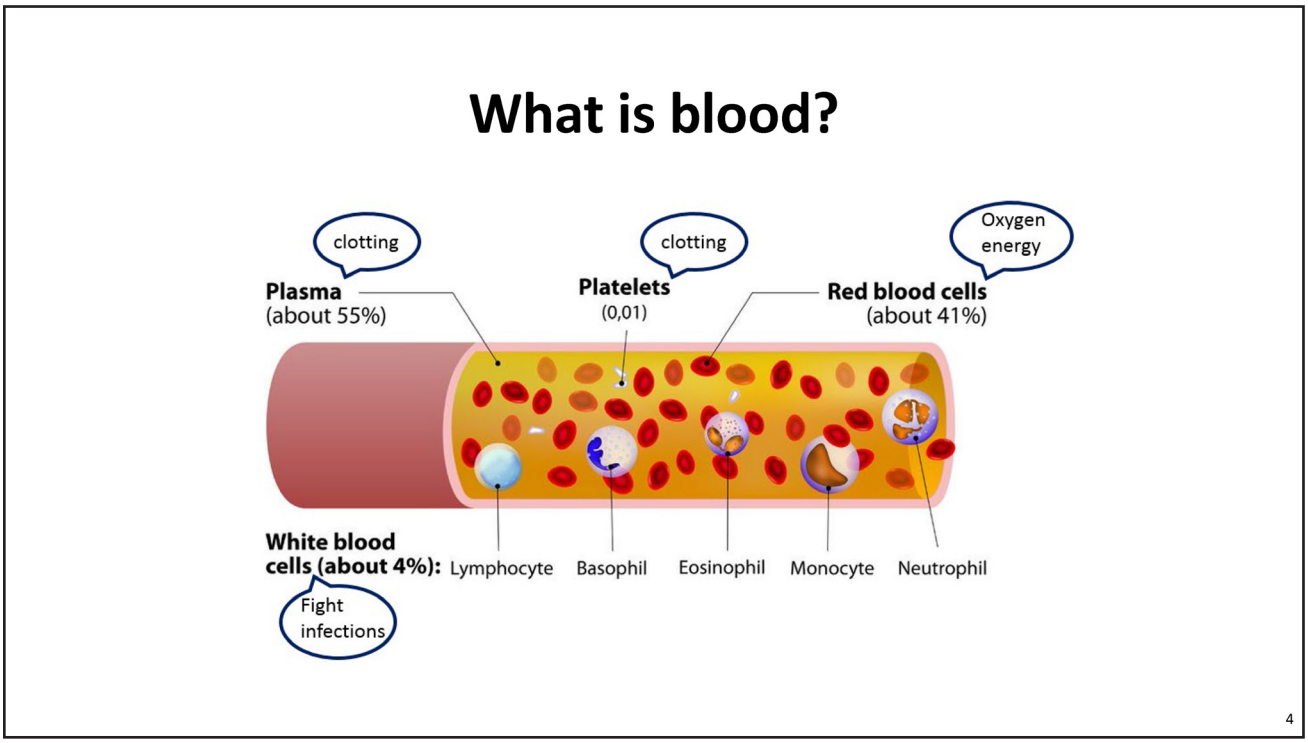
But, the real break and the real change in the management of CML came in the early '60s with the discovery of the Philadelphia chromosome, which we'll talk about in quite detail.

Then you see in the 1970s and the 1980s, the birth of biological therapies, such as interferon, one of the first uses of a biological natural chemical to basically stimulate the immune system to fight the leukemia, and then bone marrow transplant, the rise of a new therapy at the time in the 1980s and 1990s, that really was the first major cure type therapy for CML. In fact, up until 2000, the most common reason to have a bone marrow transplant in the United States was CML.

And, CML changed the way we even think about transplant as we learned that it wasn't the chemotherapy, the high doses of chemotherapy in the transplant, but rather the new donor cells, the immune system that was fighting the cancer, and that led us to new ways of thinking about whole transplant, donor lymphocytes, and so-called mini-transplants. CML really is responsible for revolutionizing the way we think about transplantation.

And then, the biggest break at the turn of the century, as we enter the 2000s, was the discovery and treatment of a targeted therapy that goes directly after the CML fusion protein, called imatinib or TKIs (tyrosine kinase inhibitors).

So, let's go into detail.



Slide 4: What is blood?

So, before we can talk about really what is CML, we have to understand what is blood. Now for many of you, you think of blood as that red stuff that runs through our arteries and veins, but blood is much more complex, it has 4 major elements. Certainly, there are the red cells. The red cells, their job is to be the trucks that carry the oxygen and energy. They're what give us our strength, they carry oxygen from the lungs, feed our muscles and feed our tissues and allow us to have energy and to walk around and do all the things we want to do.

In men, we measure the amount of blood in what is called hemoglobin, and in men about one gram of hemoglobin equals one pint and men will have about 14 grams or basically 14 pints of blood. Women will have about 12 grams or 12 pints of blood to give that energy.

The next major cells are the clotting cells and they come in 2 pieces. The bricks are the platelets, they seal in the hole, and the serum or the plasma is the glue that holds those platelets in place. A normal platelet count is usually between 150 and 400,000 and in a patient with newly diagnosed CML, we pay a lot of attention to the platelet count because if the platelet count is very, very high that indicates to the doctors that this may be a more aggressive disease, so it actually is part of the scoring system when we first see a patient to look at the platelet count as opposed to looking at the white count.

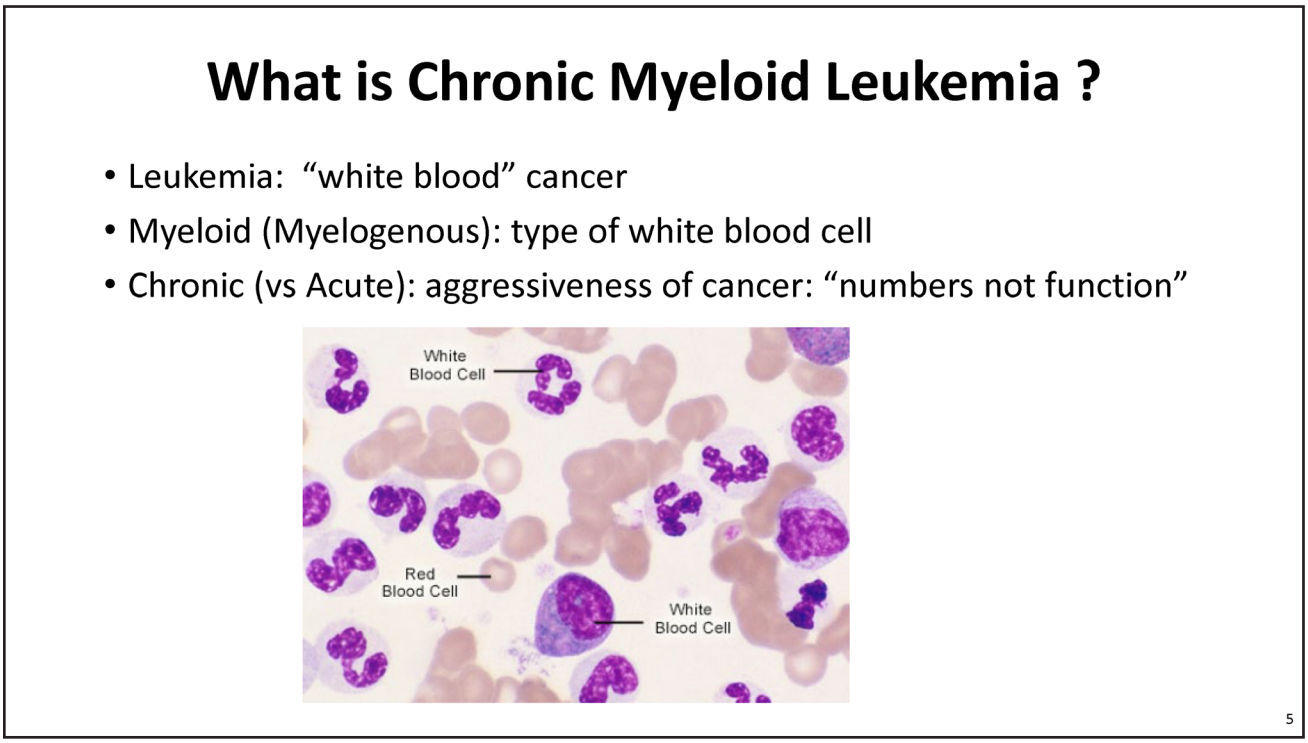
And then, the third major element, the third major piece of blood, is the white cells. And the white cells, they're the immune system, they're the part that fights infections and keeps you from getting infections and fighting those infections that you do get.

And, as you can see on the bottom, white cells come in different flavors. Because if you were building an army to fight something you wouldn't just throw out soldiers, you'd have all different pieces. And so, all the way on the right-hand side you see something called a neutrophil, that white cell with a little red squiggly thing in the middle, that's called a neutrophil or a polyneutrophil or granulocyte, has a whole bunch of different names, but that is the key myeloid cell that fights bacteria. That's the white cell that does the day-to-day fighting against bacteria and that actually is the cell that gets affected in CML.

And, there're other white cells that actually do other things, for example, all the way on the left-hand side you see the lymphocyte. Lymphocytes, they come in 2 big flavors, the Bs and the Ts. The B cells are like the generals that memorize an old infection and then put out antibodies so you don't get the same infection twice, so they like memorize an old battle, and so make antibodies. You're hearing a lot about antibodies because of COVID. It's the B cells that are going to be the ones that we educate with a vaccine.

And, another type of lymphocyte is the T cell. They're like the spies, they go out looking for infections. You don't hear as much about T cells when we talk about CML. There is something called a CAR-T cell, CART, C-A-R-T transplant. These are sort of taking the rage in some of the other kinds of leukemia, where we're educating those T cells to fight the other types of cancers. But for CML, not really something we've really been able to explore because of some medical technical issues.

Okay, so that's what blood is. What is CML? Well, let's break down chronic myeloid leukemia.



Slide 5: What is Chronic Myeloid Leukemia?

So, the word leukemia in Greek means white blood. And so, leukemia are cancers of the white blood cells. So, if you have white cells in your immune system, those white cells are now abnormal, either made too many or not made properly, but it's cancers of those white cells, the immune system cells.

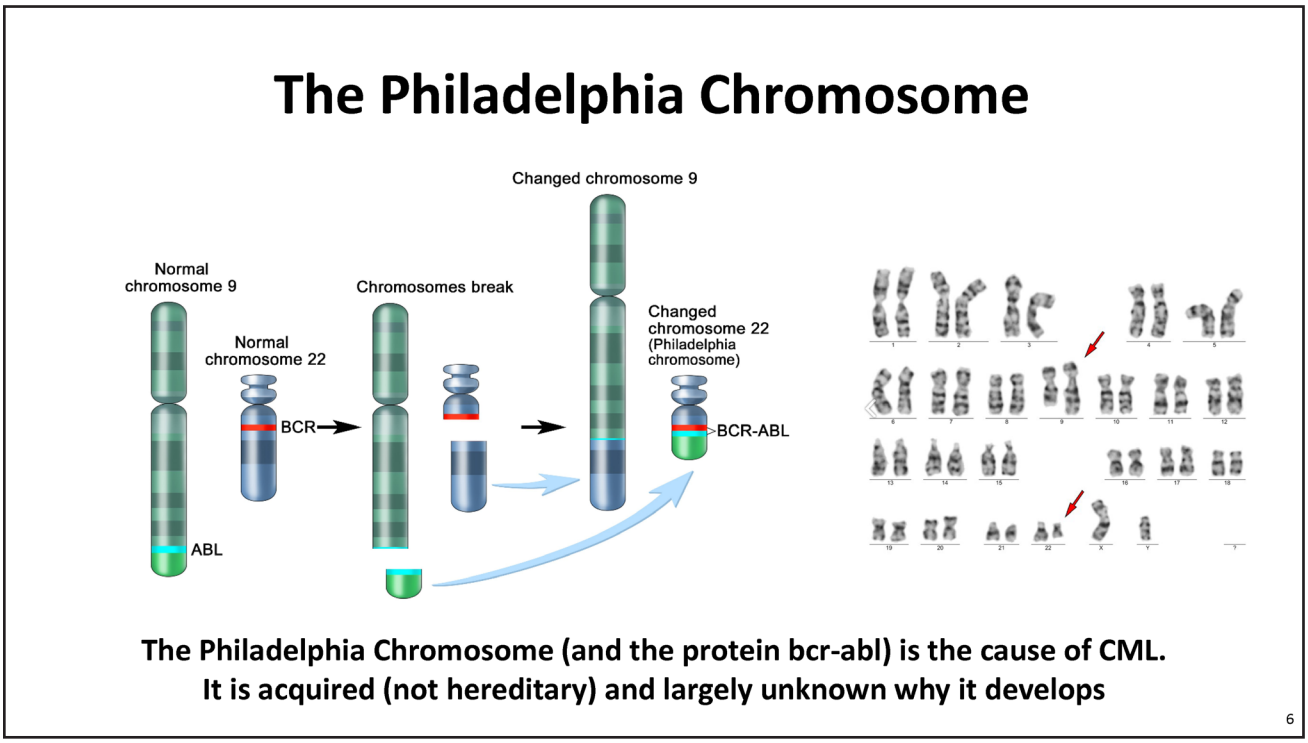
The word myeloid, I told you that there're different kinds of white cells, so the myeloid cells are the bacteria-fighting cells of the immune system. So, a myeloid leukemia would be a cancer of the myeloid or those bacteria-fighting white cells.

And then finally, the most important word is chronic. And, I don't mean chronic as in like lasts for a long time, but chronic in a medical sense is to be distinguished from the acute leukemias. We're looking more at the aggressiveness.

In the chronic leukemias, what you see is elevations of normal-looking white cells that actually work. In the acute leukemias, we're seeing more function problems, we're seeing elevations of white cells that look ugly under the microscopes that don't work. A cell called a blast. You never want to be hearing your doctors talking about blasts because blasts are non-functioning white cells and if you have a non-functioning white cell, patients with lots of blasts don't fight infections as well and they get into trouble.

So, chronic myeloid leukemia, in summary, would be a disease, a cancer of the white cell, where you have lots and lots and lots of healthy-looking functional bacteria-fighting myeloid cells. So, that's what CML would be if you just went from a big standpoint.

But, how do we know it's really CML and not some other disease where the white cell is being made over? We can go inside the cell.



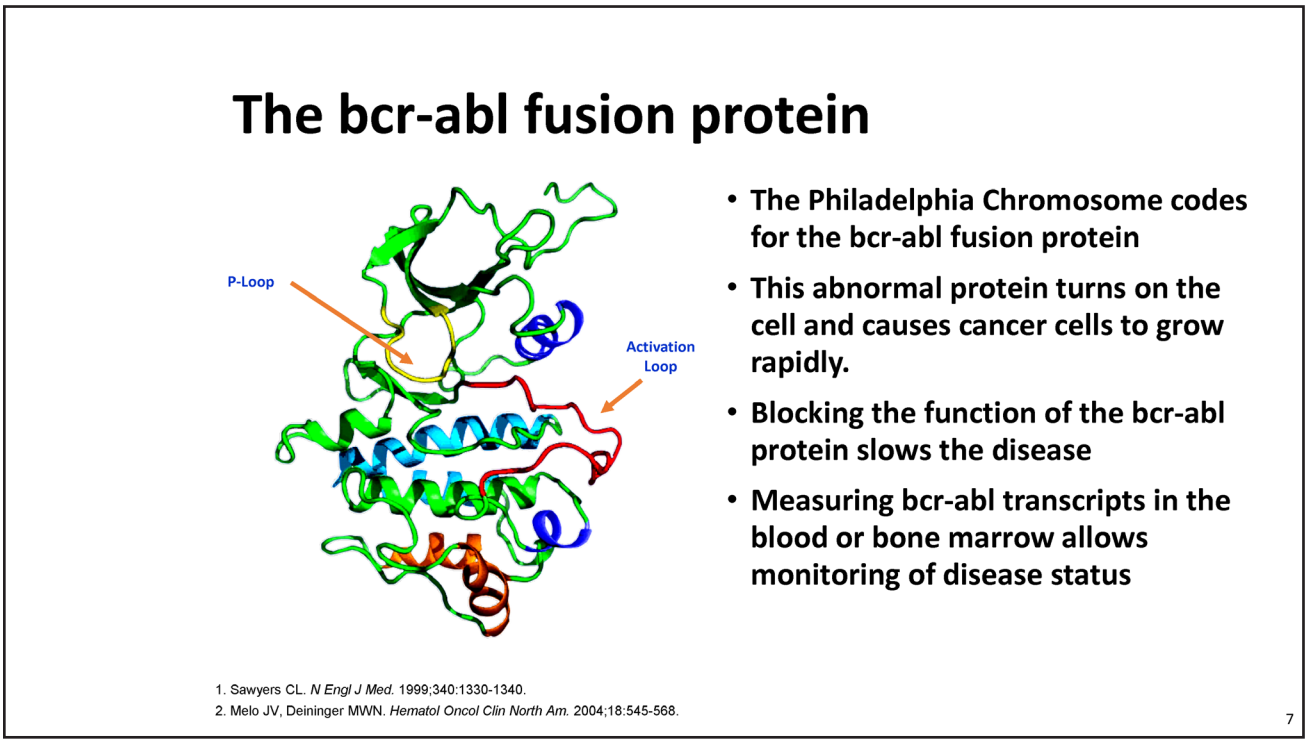
Slide 6: The Philadelphia Chromosome

So, in every cell of your body there are chromosomes, there are genes that tell the cell what to do. Actually, even to become the cell and what kind of cell to become. We call those the chromosomes. So, these chromosomes actually tell the body, tell each cell what their job is to be.

Well, back in the late 1950s, early 1960s, investigators were starting to learn all about genetics. Looking inside the cell and seeing these pictures of what these cells look like. And, on the right-hand of the slide you can actually see a whole gene pattern for a male. The reason I know it's a male, the last 2 cells in the bottom right-hand corner, one is big and one is little. The big one is an X and the little one's a Y, and that would tell me that this is going to be blood from a male person. But, what you also see is those 2 little arrows, which is blown up on the left-hand side, those are chromosomes number 9 and 22. And so, what happened in the early '60s is investigators in the city of Philadelphia were looking at the blood and at the bone marrow in cells from patients with chronic myeloid leukemia. And, what they noticed was that chromosome number 22 had gotten very short and they called that the Philadelphia chromosome because of the people with chronic myeloid leukemia had this very, very short chromosome number 22 that was abnormal.

Over the next several years, we actually learned that chromosome number 9 had actually gotten a little bit bigger, and what had actually happened was a piece of number 9 had broken off and gone onto chromosome 22 and a piece of 22 had broken off and gone onto number 9, they swapped their ends. But, they didn't get an even swap and number 22 got the short end and became a little bit tinier and that's what they saw is the Philadelphia chromosome.

Now, what do chromosomes do? Chromosomes tell your body to make proteins and basically do things. And so, what happened was that a brand new gene was formed because that new piece of number 9 and number 22 fused together and formed a new sentence that told the body to make a protein that normally doesn't exist in man. And that protein is called the BCR-ABL or BCR-dash-ABL protein, which you see on this next slide.

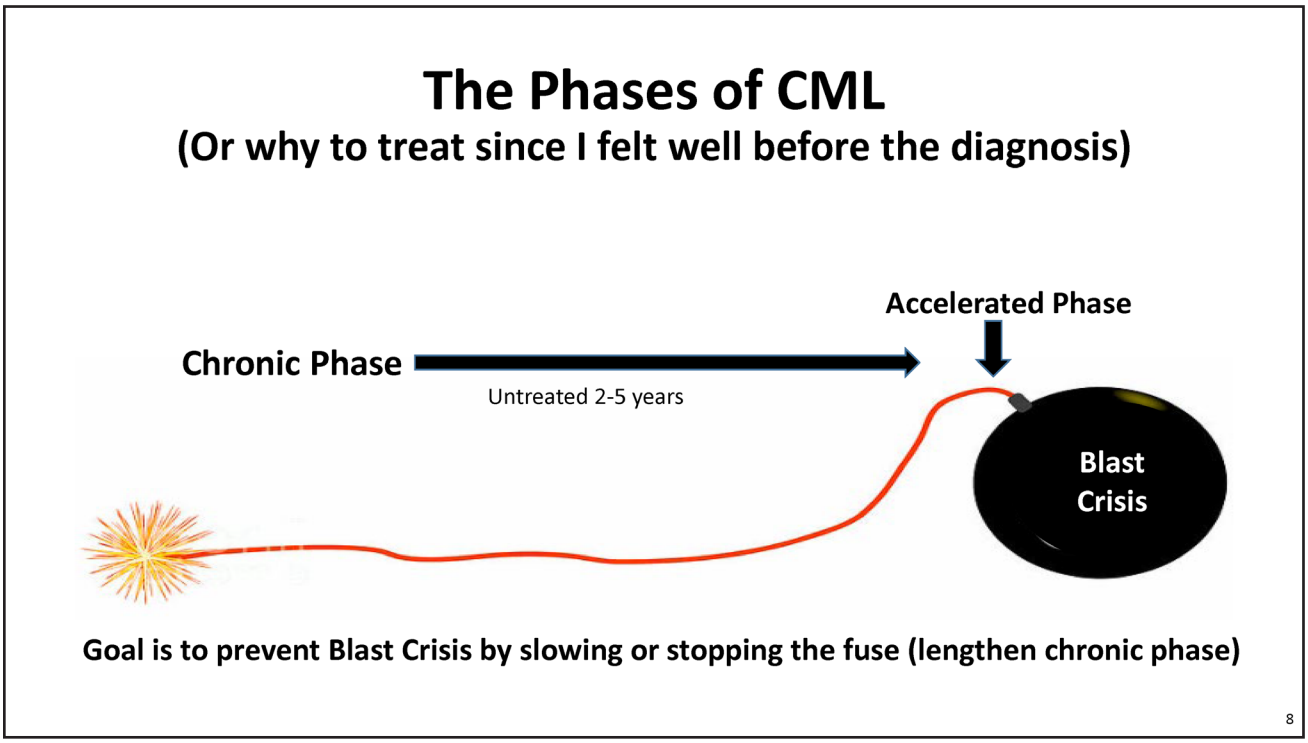


Slide 7: The bcr-abl fusion protein

And, that's actually the structure of it on the left-hand side and knowing that structure actually becomes very important to the discovery of how to stop it. But basically, just think of at this point that the Philadelphia chromosome, something has caused those genes to break, swap pieces, and now that new little 22, the Philadelphia chromosome, is now telling the body to make a protein that it normally wouldn't make. And that protein, what you're seeing here, tells the cell to turn on. So, the gene makes a protein, that protein then tells the cell to turn on and grow out of control.

So, when we have a patient who's newly diagnosed, we want to look to see does this patient have CML. Well, the way we can find it is either to find the gene or to find the protein. And, if we can find either the chromosome itself, the Philadelphia chromosome, or we can find the BCR-ABL fusion protein, then we know that this patient really does have CML. And so, that's one of the first tests that your doctors would do, to confirm the diagnosis.

Okay, so if CML is just a disease, as I said, of too many white cells, but the white cells work, why should we even care about it? Why should we care if somebody has too much of something that's working? Well, if you were to run a factory too fast for too long, over time it's going to start making mistakes, and as it makes those mistakes new genes will start to break, new problems will start to develop, and that's what happens in CML.

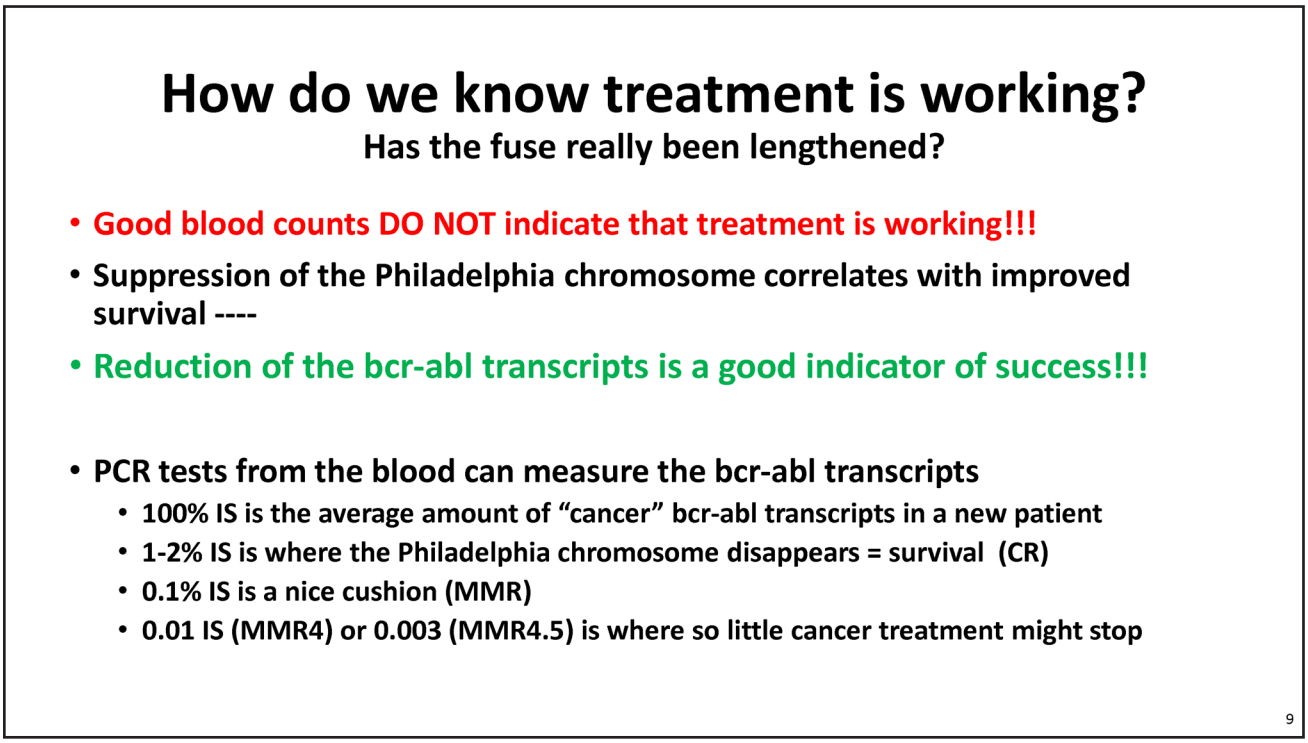


Slide 8: The Phases of CML

Another way to think of what CML is, is a time bomb with a 5 or so year fuse. While that fuse is burning, not much looks like it is happening, and we call that, during that time frame when the fuse is burning, the chronic phase. So, many of you may have been diagnosed with high white counts when you just went to the doctor for a routine visit and may not have had any symptoms at all. Or, sometimes a doctor will have followed you for a couple of months, say, hey, the white count's a little elevated, let's just keep following you, and then finally they said let's examine a little more deeper.

But, during that initial phase, for the most part, other than having a high white count, which shows up on a piece of paper, most patients are feeling quite good. Some individuals will have a big spleen, which is an organ that sits on the left-hand side, because the spleen can actually make blood also, and that may enlarge and you may have some pressure on the left-hand side. Maybe a little fever or sweats. But essentially, while the fuse is burning, while you're in the chronic phase, most patients don't even know that they have the disease. But then, over a period of time, somewhere between 2 and 5 years, if no treatment is offered, we see all of a sudden the white count starts to go up and down, up and down, we see platelets start to change, we see other numbers start to not look so good, we see therapies that were working, stop working. That's like the spark right before a bomb goes off. We call that the accelerated phase. And, if we look in the inside of the cell, we might see not only just the Philadelphia chromosome broken, but we may see other genes that are starting to break. And now, when we look under the microscope, we may start to see not just healthy-looking bacteria fighting the cells, healthy neutrophils, we may start to see a few of those ugly blasts. And, if we don't do anything at that point, shortly thereafter, within a couple of months, the whole bomb explodes and we call that blast crisis. And, in blast crisis if I didn't know the person's history and they just came to see me for the first time, I would think that they have acute leukemia, because now their bone marrow doesn't look normal, it's all these big ugly cells that don't work, and they don't make red cells, so they don't have energy, and they don't make platelets, so they start to bleed. That's a medical emergency.

So, our goal in CML is to catch people while the fuse is burning, while they're in that chronic phase, and then to stop the fuse from burning, to stop that process from continuing on.



Slide 9: How do we know treatment is working?

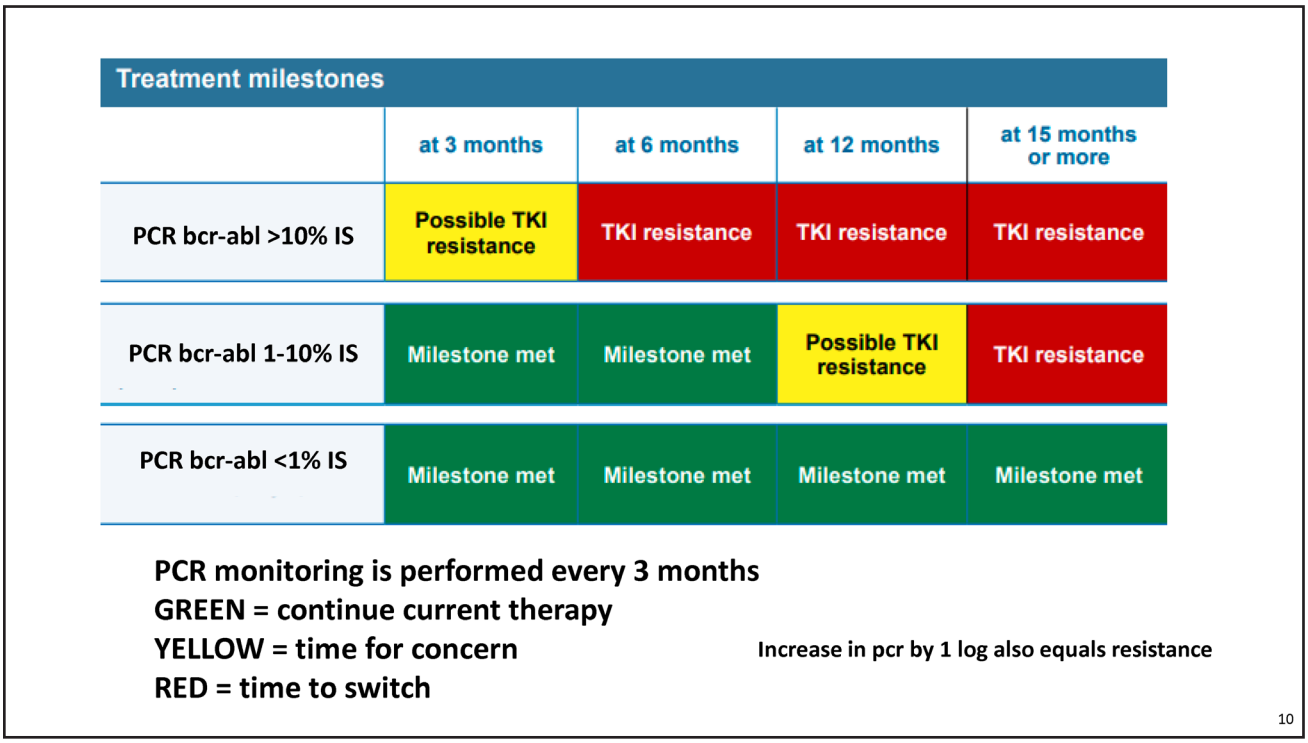
So, how do we do that? Well, how do we know that we have stopped the fuse from burning? Because all we can see is high white counts. Well, if we put somebody on a treatment that's working, we may see obviously the white cells start to come down and we might see the blood counts look normal and we might be very happy when you go to see the doctor and the doctor says, oh, your blood counts are fine. Well, that's a good start, but it doesn't tell us for sure that the fuse isn't burning.

So, one of the most common misconceptions with patients, and sometimes even doctors who don't deal with leukemia, get confused with is they may see that a normal blood count does not mean that the disease is not moving along, that the fuse isn't burning. So yes, you need normal blood counts, but that doesn't mean that we stopped the disease.

What it does mean is that the disease has stopped suppressing the Philadelphia chromosome. If we're killing the cells that have that bad chromosome, then that chromosome's not making that bad protein, that bad protein is not telling the cell to grow out of control, and then the disease is going to stop in its tracks, is not going to move on towards that blast crisis. So, what that means is what we really need to do is, when we have a person with CML and we put them on treatment, we want to make sure that the Philadelphia chromosome is disappearing or that that BCR-ABL fusion protein is disappearing. And luckily, we can look for that BCR-ABL fusion protein in the blood, so we don't have to keep sticking needles in people's hips. We can measure that BCR-ABL transcript with something called a PCR test or polymerase chain reaction test. So, this is the test, the PCR test, that many of you may have being done every 3 months or so, sometimes down the road maybe twice a year, to keep looking to see is the fuse being turned off.

So, the PCR test can be done from the blood. Usually about a couple hundred dollars, so you'll see when you look at your doctor bills, that every once in a while there's a bigger test of, you know, called a PCR, that's a couple hundred dollars, and that's one way to tell that your doctor is doing the test. Hopefully, they're also telling you what the results are.

And so, in the beginning when a person's brand new diagnosed and they haven't had any therapy, the values on that PCR test are usually around 100. In fact, that's how it was defined back in the turn of the century, around 2000, we actually took samples from brand new patients with CML and we said this is how much cancer these people have, we found out the average amount and we call that 100%. Some of you, when you were diagnosed, may have waited until the white count was really, really, really high and therefore you may have a number that's above 100% at the beginning, and some patients were maybe diagnosed when they just had a little bit of elevation of white count, and they may have less PCR. But, doesn't really matter what your number was at the beginning, it's where you want to end up when you're all finished.



Slide 10: Treatment milestones

So, a normal new patient, untreated, has a value of about 100. If we drop that by one-tenth, that's 10%. We drop it another log, we get down to 1% or basically 2-log reduction, which we call around 1%. If we were to start sticking needles in people's hips and they only had 1% on the PCR test, all of a sudden we wouldn't be seeing the Philadelphia chromosome any more. So, we define a value of about 1% on the PCR test as being a complete cytogenetic remission. That's the one number you want to remember. When the doctor does a PCR test, you want to hear that your PCR, which was high before, is now down to 1% or less. Why? Because, if you only have 1% or less that means that there's very few Philadelphia chromosomes, not a lot of protein, of that bad protein, and the fuse has stopped. And, that's when people start to live longer and longer and longer.

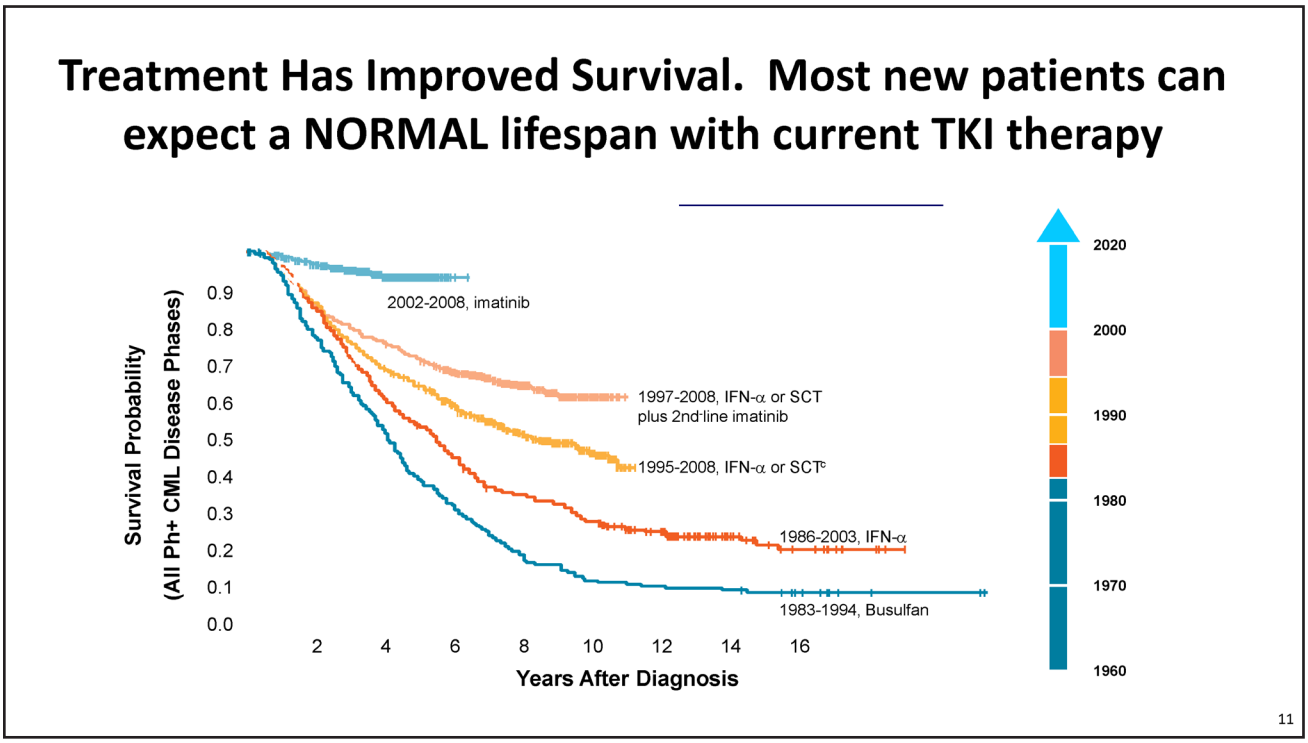
Now, we don't want to be right on the border where the fuse could start over again, so we like to get a little greedy and we like to see a number of 0.1%, so-called 3-log reduction. And the 3-log reduction, that's called an MMR or major molecular response. That gives us a nice cushion. So, if your doctor says that you're in a major molecular response, 3-log reduction or a value of 0.1%, you can feel very comfortable that the fuse has really stopped and that there's a good chance for a long, long time of survival. And then, some of us want to get even greedier and push it down to a 4-log reduction or 4 and a half-log reduction, and why would we want to even be pushing farther and farther, because if we can push it down very low, maybe we don't even need medications any more. We'll talk about it in a few seconds.

So, if you understand what the PCR is, now we can see how doctors are monitoring you, because what they'll do is when you first are diagnosed they'll do that PCR test, they'll put you on a medication, and then they'll watch to see is that Philadelphia chromosome or is that fusion protein disappearing.

And, just like a runner who wants to run a 4-minute mile, he knows that at 2 minutes he better be halfway there. Well, what you're seeing on this grid is what the doctors are using. This is from the National Comprehensive Cancer Network (NCCN). They're the people who write the guidelines that write the textbooks that tell us how to be watching people.

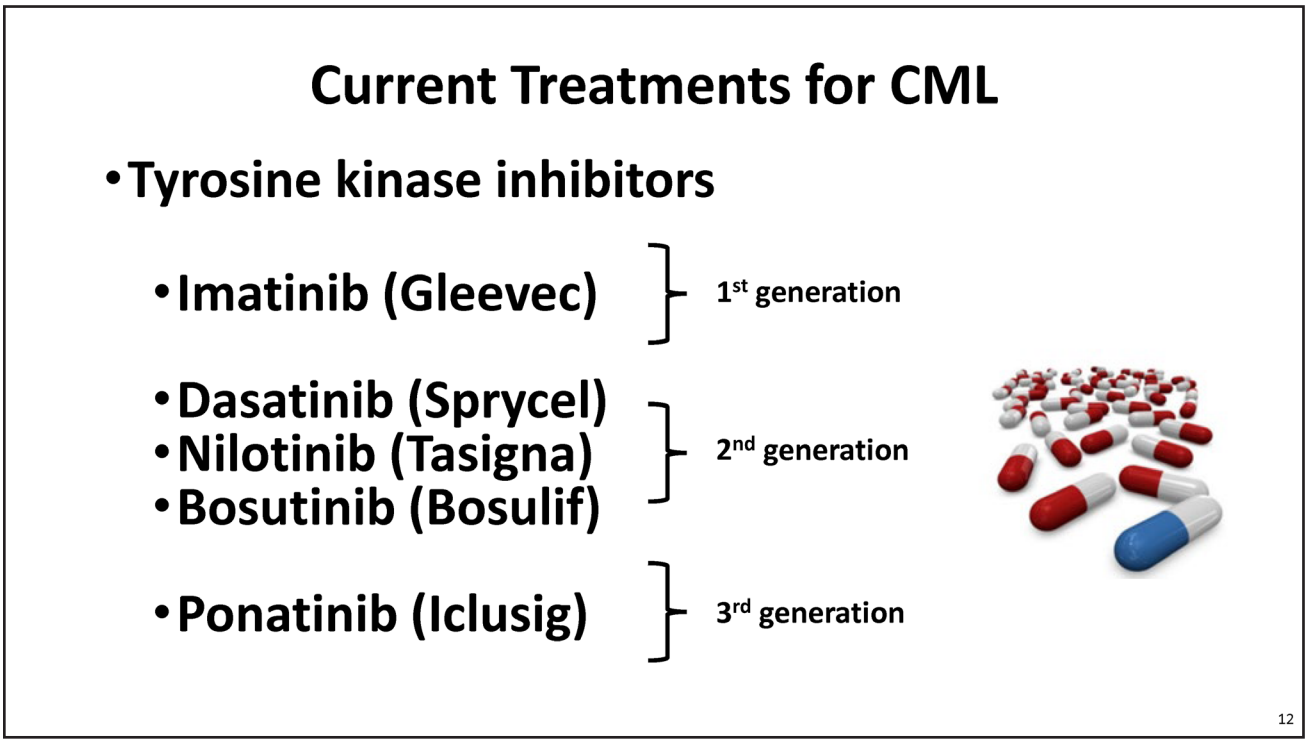
And, what they said is that if you put somebody on a brand-new medicine, by 3 months you want to see that number go from 100% down to 10%. And certainly, by 6 months you want to be below 10%. And by the time that you get to one year, you want to be below 1%. And, if you hit those so-called milestones, you're winning the race, you're getting there deep enough, fast enough, that the odds are that the fuse has stopped and the people are going to have long-term outcomes, good outcomes.

But, if you're sort of dilly-dallying and you're not going down, it's not dropping very quickly, not getting below those milestones, well, then the disease is still moving and has a chance to change its character and become angry. And, those are things that we don't want and that would tell us maybe it's time to start changing treatment.



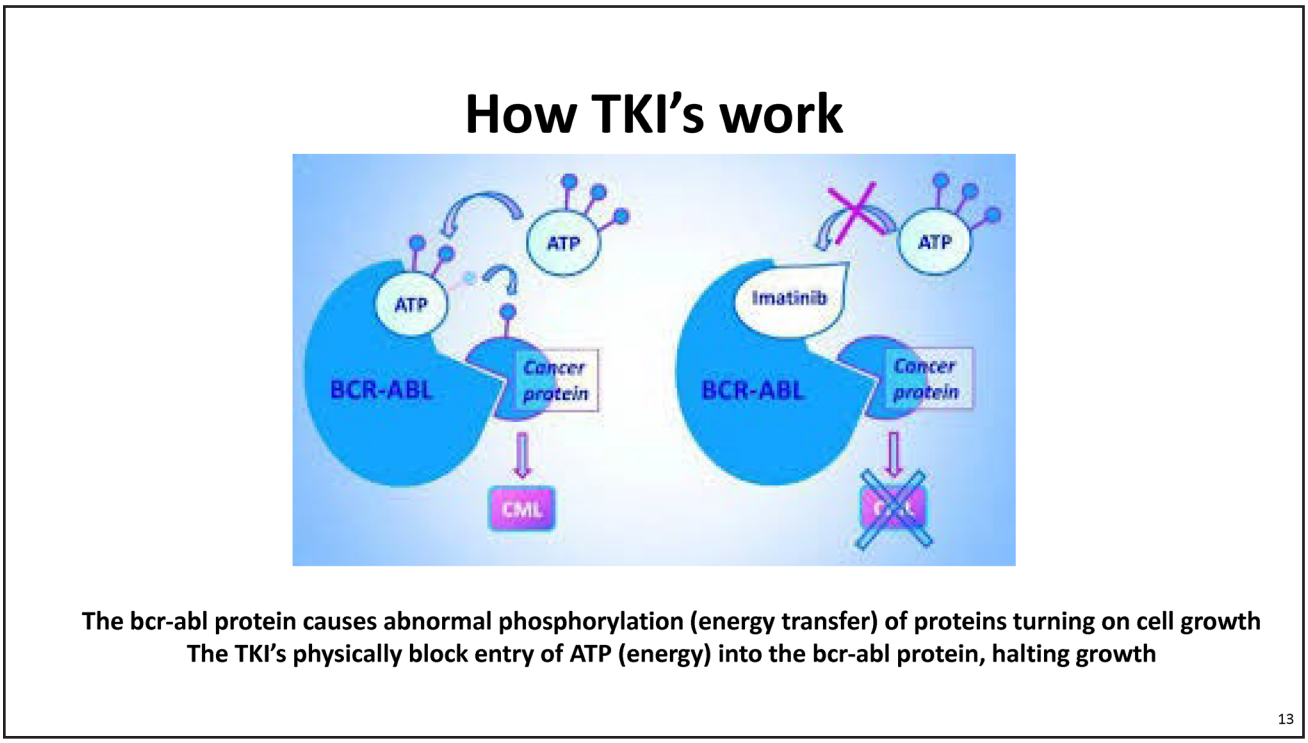
Slide 11: Treatment Has Improved Survival. Most new patients can expect a NORMAL lifespan with current TKI therapy

So, how do we have therapies that work? And, the answer is we can stop that fuse. And so, what you see on this slide is over the last decades, how the outcomes have gotten better and better. And, you can see that top line is almost all the people doing well, that's at the turn of the century when we developed the tyrosine kinase inhibitors (TKIs), when the first real therapies that could really work started to put people into remission all the time.



Slide 12: Current Treatments for CML

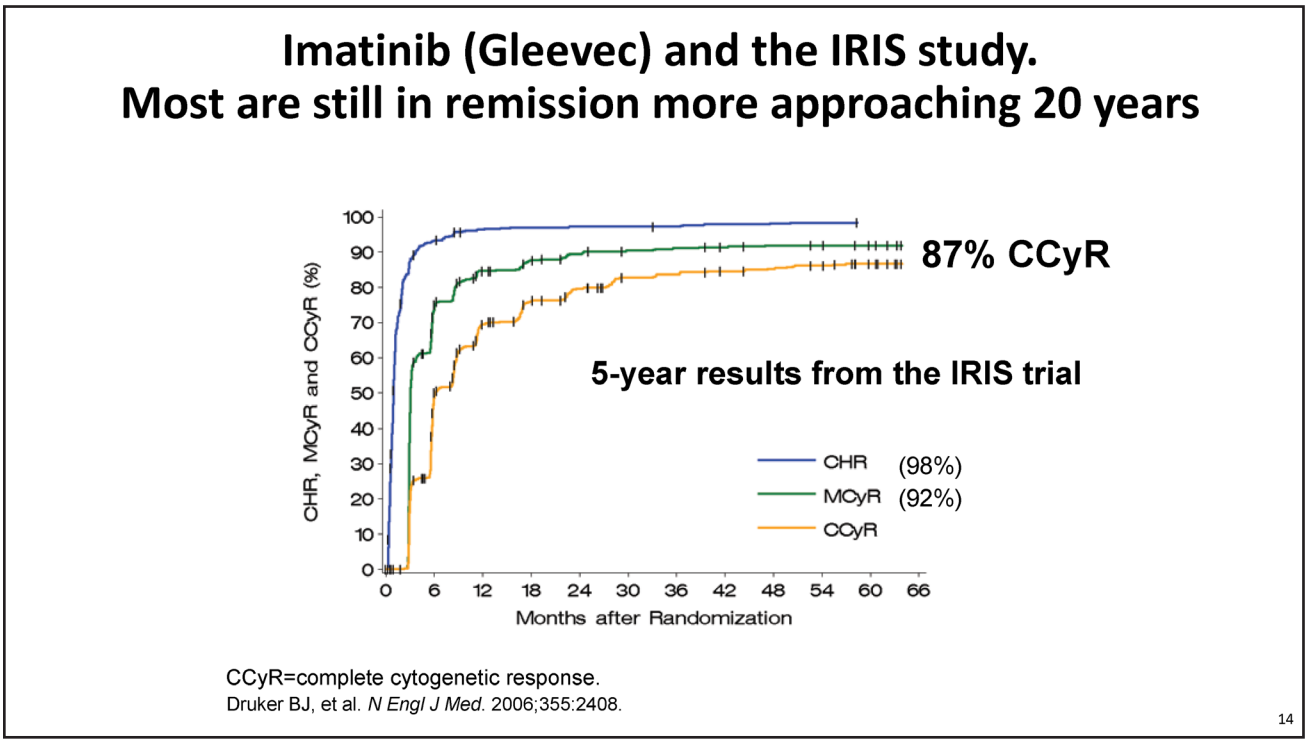
So, what are the treatments we currently will use? The most common therapies for chronic myeloid leukemia are a group of medicines known as the tyrosine kinase inhibitors or TKIs for short. We've had our first medication, was a drug called imatinib with a brand name of Gleevec, came out around 2000. And then, we have the second group of medicines called the second generation TKIs, dasatinib, brand name Sprycel®, nilotinib, brand name Tasigna®, and bosutinib, brand name Bosulif®, that were developed a few years later, mostly to help treat people that the first generation, first generation imatinib, wasn't working on. And then, a third-generation drug, ponatinib or brand name Iclusig®, once again a more potent drug that works when the other drugs stop working.



Slide 13: How TKI's work

Well, to give you a little more history, how do these TKIs work? Well, I told you that the Philadelphia chromosome makes that funny-looking protein, that I showed you the structure of, and the reason knowing that structure was so important is that what that structure shows us is that there's a groove, there's a little hole in that protein, in that BCR-ABL protein. And, what happens is that other proteins come into that groove in the off-position, they pick up energy in the form of a phosphorus from ATP – and then they leave in the on-position. So, the BCR-ABL fusion protein acts sort of like a place for things to come in, meet with energy, and then cells leave all charged up.

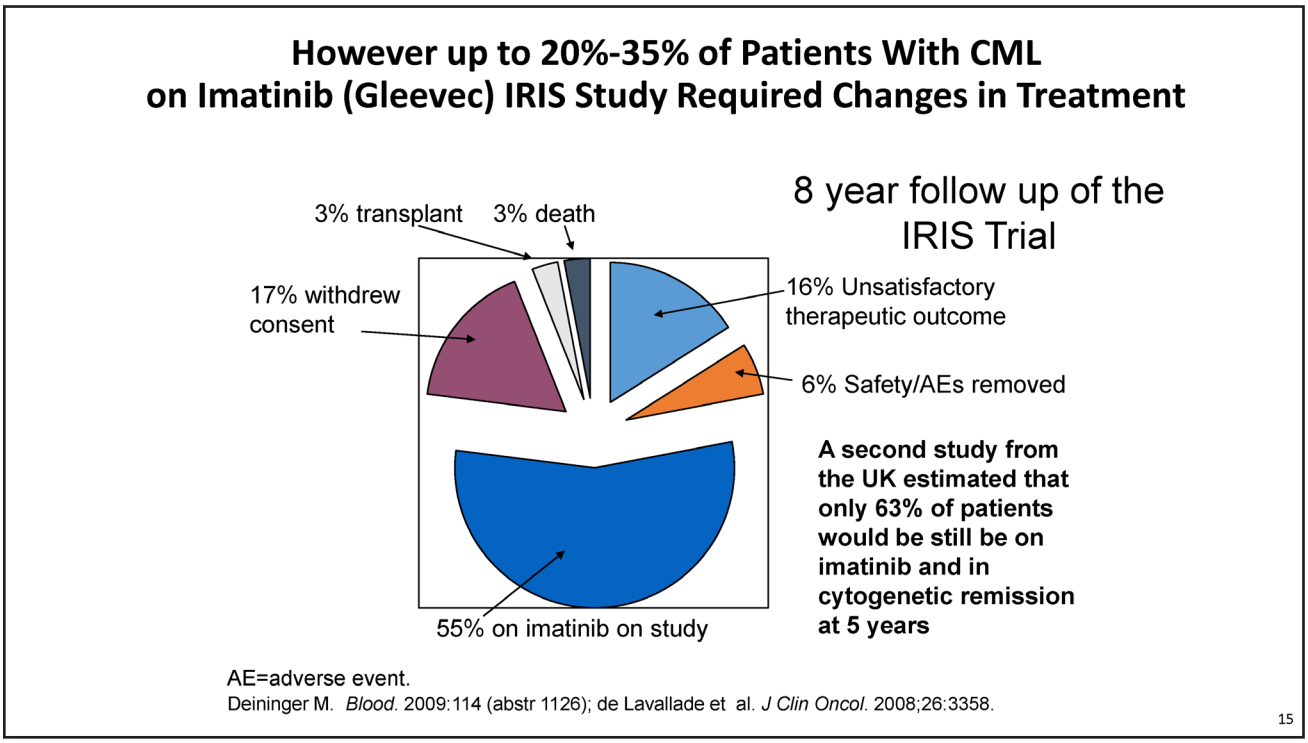
And so, what the idea was, if you put something of putty in the middle of that lock, the key can't fit in anymore. And so, now other proteins would try to get into that BCR-ABL fusion protein, but there would be something blocking it, therefore they wouldn't get turned on, those cells wouldn't want to grow faster, and the cells would eventually die. So, it's really like the idea of putting putty into a lock and preventing anything from getting inside.



Slide 14: Imatinib (Gleevec) and the IRIS study. Most are still in remission more approaching 20 years

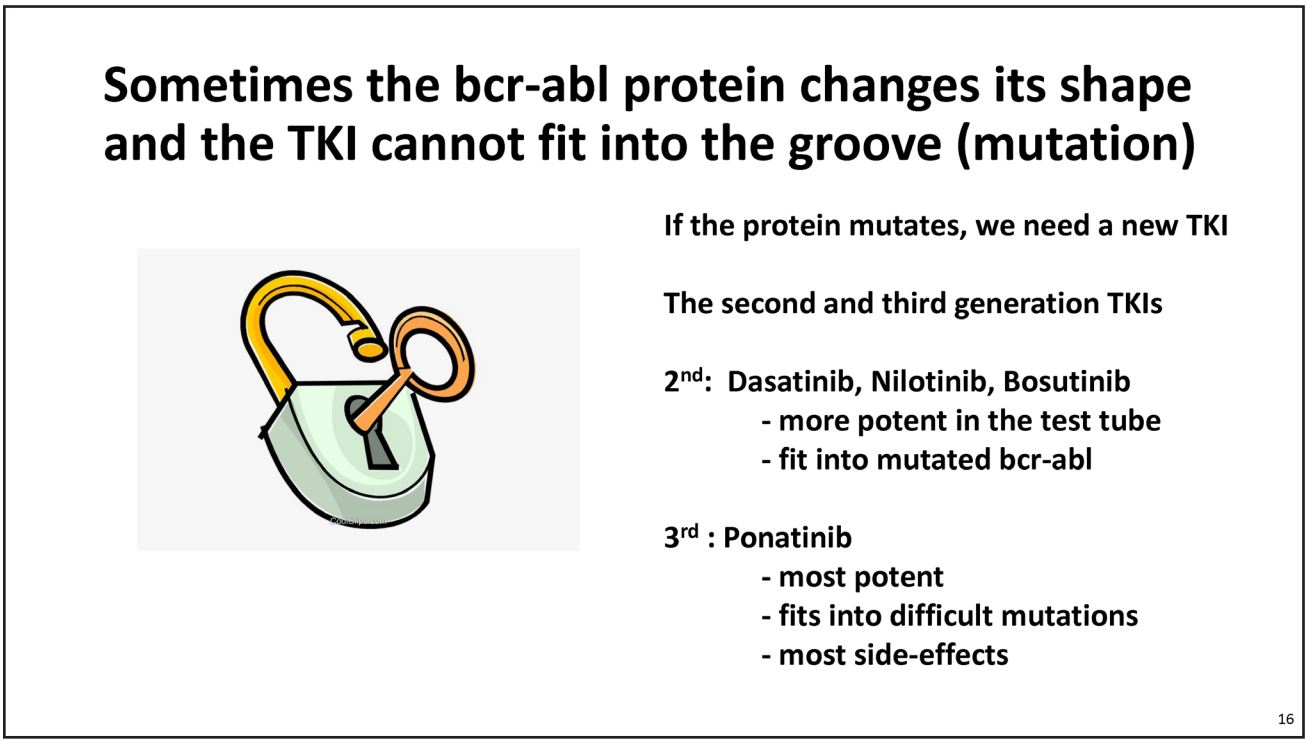
And so, at the turn of the century, what we saw was a medicine called imatinib or Gleevec came out. And, it was based on a study called the IRIS study. This is one of those medical classic studies. And, what you can see here is we took about 550 patients, gave them imatinib, and watched to see how many of them could have the Philadelphia chromosome disappear, how many of them could have the BCR-ABL protein disappear, using those modern techniques I just showed you.

And, what you can see is almost 9 out of every 10 patients benefitted, that their Philadelphia chromosome would disappear, and many of those patients, in fact most of those patients, are still alive 15 to 20 years later. So, this therapy clearly showed, for the first time, a remarkable ability to put people into remissions and to keep people in remissions and really change the outcome. Most people now have what we project to be a normal life-span with this disease.



Slide 15: However up to 20%-35% of Patients With CML on Imatinib (Gleevec) IRIS Study Required Changes in Treatment

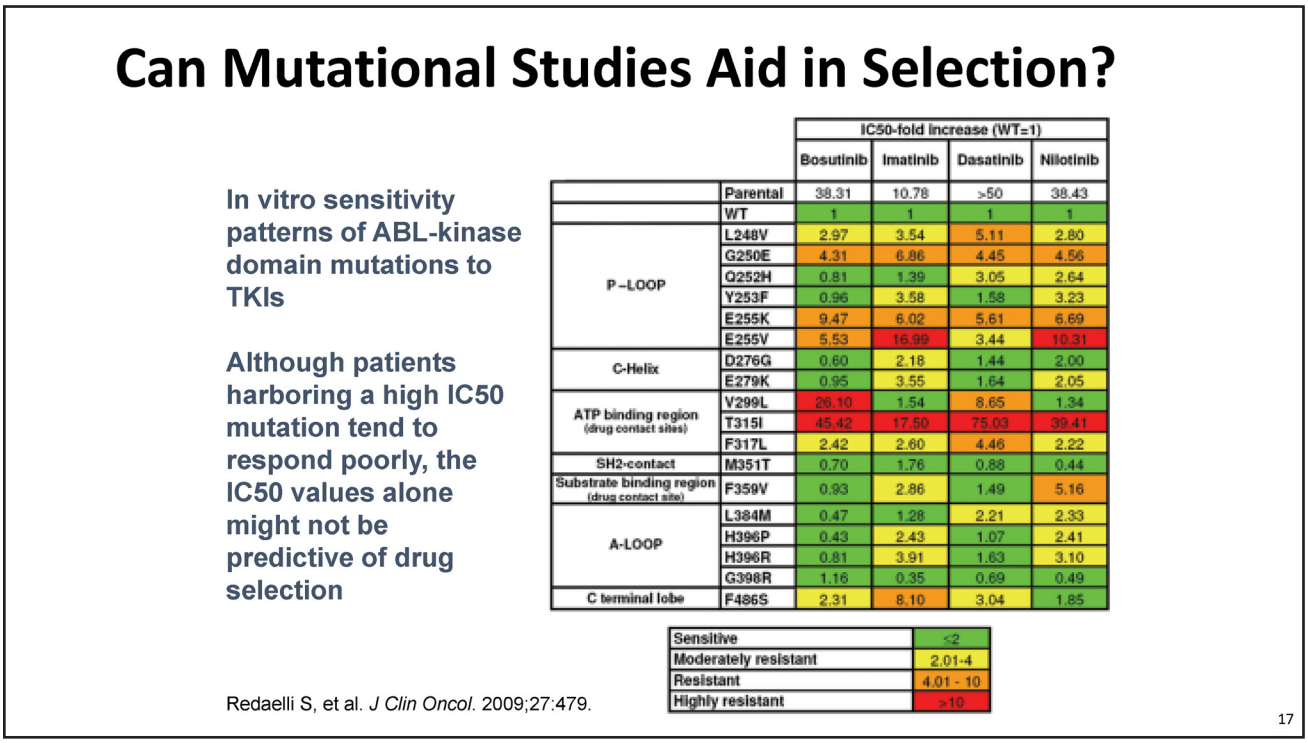
Well, 9 out of 10 looks great, but it's not everybody. And so, we did have some more work to be done to get that last 10%. And unfortunately, some people on the IRIS study who got into remission a couple of years later started to fail. The treatment was no longer working. And then, there were other people who were on the drug and they started to get side effects and had to come off the medicine. So, we still had some work to do and that's where the second-generation drugs came in.



Slide 16: Sometimes the bcr-abl protein changes its shape and the TKI cannot fit into the groove (mutation)

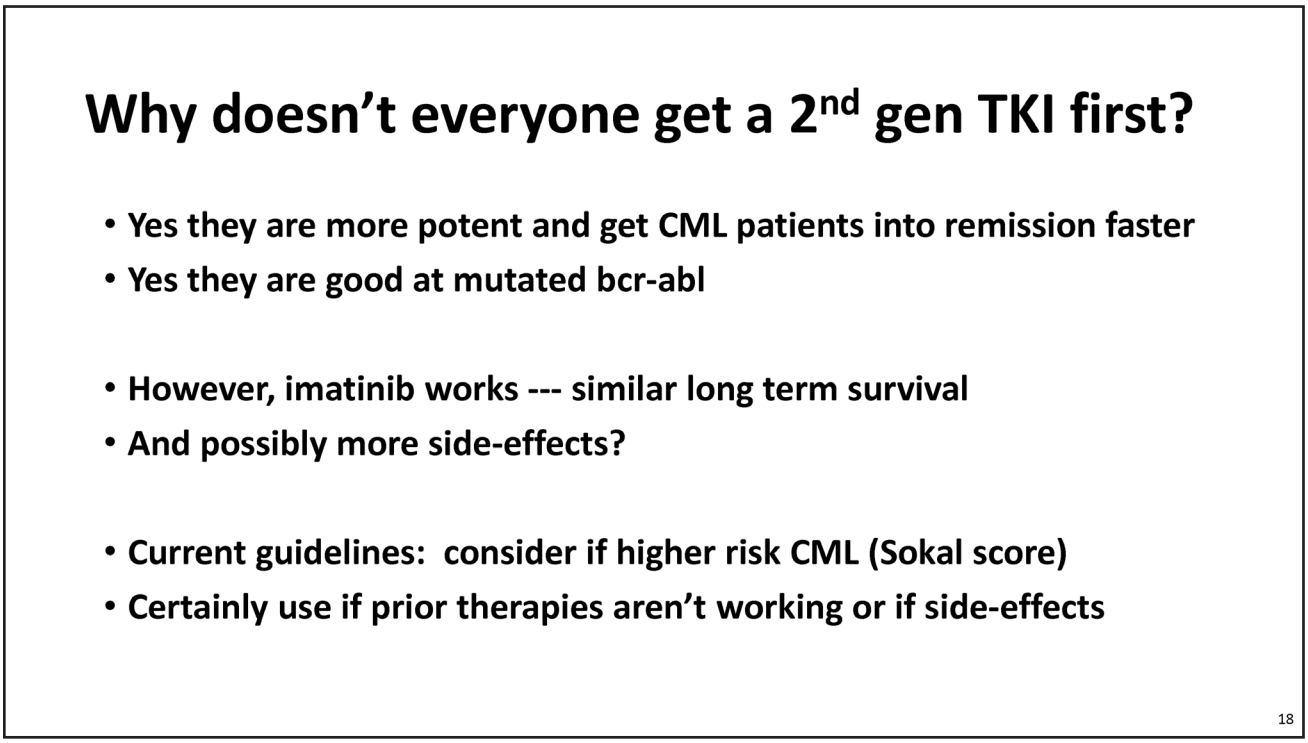
Now, there are a number of reasons why the drug may not have worked. The first I will tell you is not taking the medicine, so adherence we will sort of, as physicians and healthcare teams, we always tell our patients, take the medicine, take the medicine, doesn't work if you don't take it. But, among those patients who are taking it, sometimes that lock doesn't fit in the key any more, that new TKI, the pill, won't get into the cell and protein. And, the reason is because the cancer cell gets sneaky and changes the shape of the lock. If it changes the shape of the lock, the key may not fit in and that's why we need to develop second- and third-generation medications that would fit into those new grooves.

So, the second generation is dasatinib, nilotinib, and bosutinib. They're more potent than imatinib and they fit into the groove if the groove starts to change its shape. And the ponatinib, even more intense drug with a lot more side effects unfortunately, but also fits into the grooves that even the other drugs don't fit into.



Slide 17: Can Mutational Studies Aid in Selection?

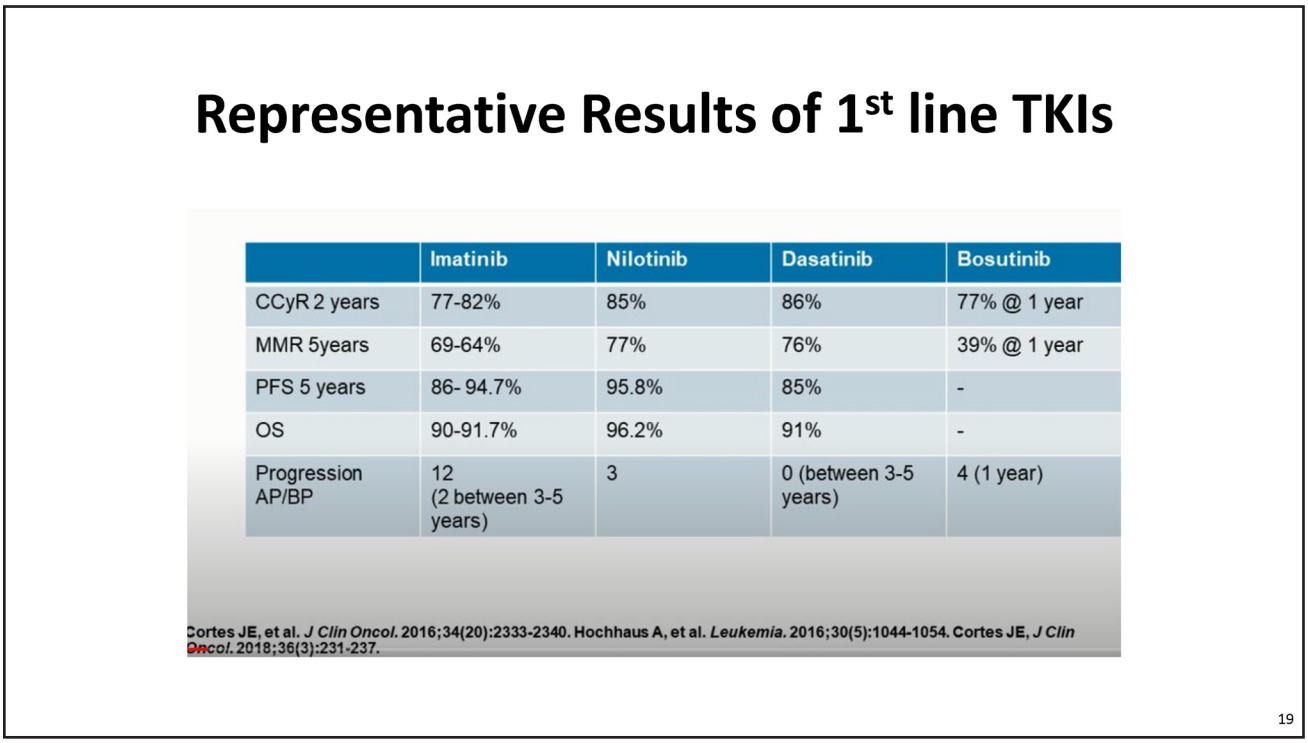
So, how we as physicians can pick if something's not working, how do we pick which of those other drugs to use? Well, if you know the shape of the lock, you know which key to use. And so, what you see here on the right-hand side is a table that we have and the tables keep changing, so I don't even bother memorizing them, I just pull out the book. If somebody has disease that's not listening and the BCR-ABL fusion protein's not disappearing, they're not getting below 1%, or they were low and all of a sudden disease starts to come back and that PCR is rising, I send what's called an ABL kinase mutation study. I can ask the laboratory, tell me the shape of the lock. And the test, they can run this blood test, and from that they can tell me now the shape of the Philadelphia chromosome fusion protein, what that BCR-ABL fusion protein looks like, and then I can say, okay, well, for that particular lock this might be the best key. And, so I can pick my next drug based on the shape of the Philadelphia chromosome fusion protein.



Slide 18: Why doesn't everyone get a 2nd gen TKI first?

So how have we done? What you can see on this slide is why doesn't everybody get these more potent drugs? Well, it's because the first drug works. Many times yes, the second generations are more potent, they do get more people into remission faster, and they are good for patients who have had mutated disease, but the first-generation drug imatinib also works. It may take a little longer to get there, but most patients who get imatinib, as you saw, do quite well. And so therefore, at this time we can't really use that to determine which kind of drug to use first.

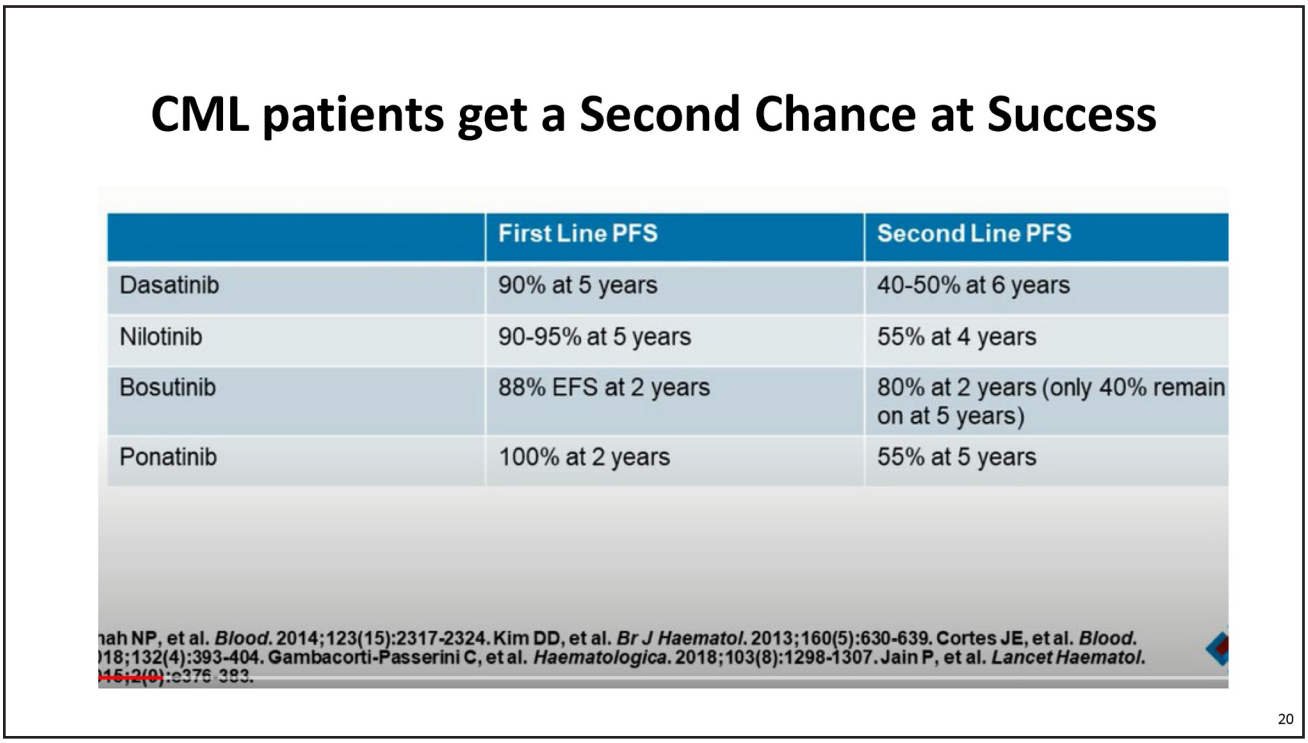
Now certainly I will tell you as a physician, there are people that I'm more worried about when I first diagnose. There are so-called risk scores. And so, I can say that this person has a higher disease risk and I might want to use the more potent drug up front, and so the National Comprehensive Cancer Network (NCCN), the people who write the textbooks, they do give us some guidance when it might be more important to use a more aggressive drug up front, but for the most part we can pick between any of those 4 drugs, the 4 top. We don't typically use ponatinib and actually it's not FDA approved to use the bottom one, the ponatinib, the third drug, the one at the bottom, because that does have more side effects. But, among the other ones we can use any of them we feel best for our patient.



Slide 19: Representative Results of 1st line TKIs

Well, do these drugs work? And, as you can see on this slide, that we can see that about 80% of the patients who were given any of the drugs will enter what's called a complete cytogenetic remission by the first 2 years. That means that we can't see any Philadelphia chromosomes with the standard old-fashioned chromosome test, or that the PCR now is down to 1% or less.

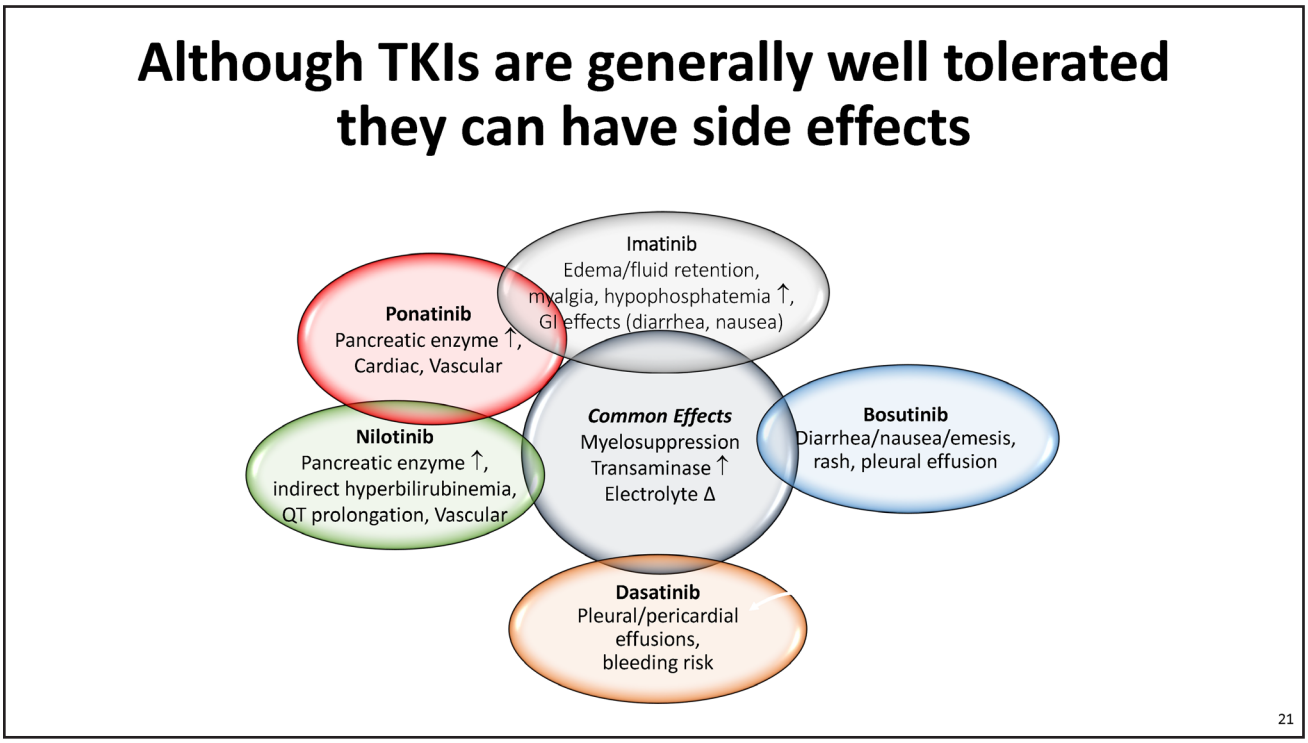
And then. if we want to go really deep, we can see that maybe up to 70% of those patients will get down to even 3- and 4-log reductions with these type of medications, where they're very deep, where they have that cushion.



Slide 20: CML patients get a Second Chance at Success

If the first drug doesn't work, we do get a second chance. We can switch to one of those other more potent drugs. And the second time, we can get people back into remission.

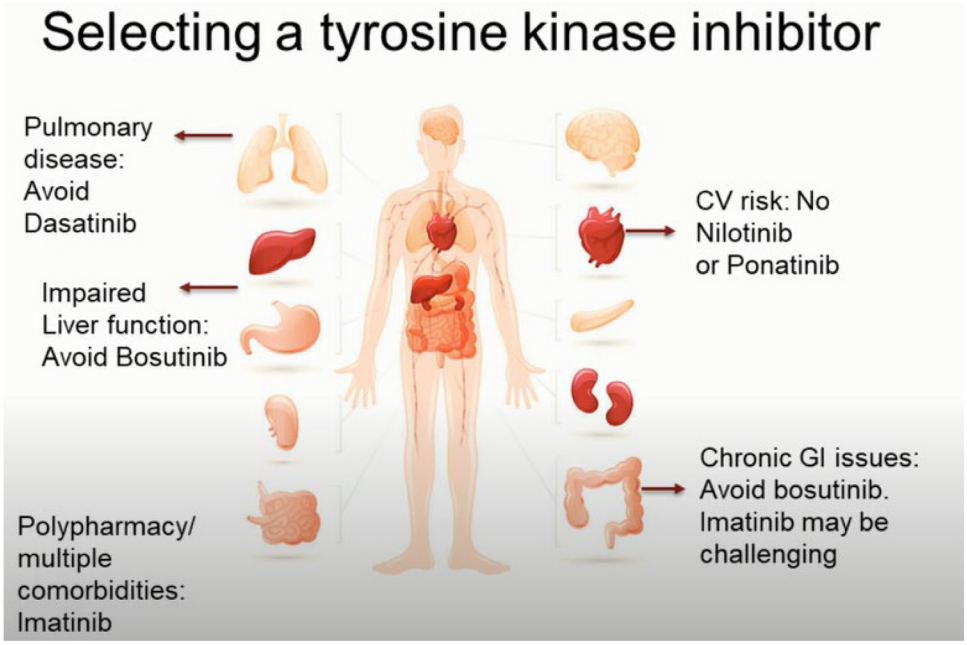
Now, the remission rates for second chances do change as to why you're changing. If the person's changing because they have a side effect, well, then good chance that they're going back into remission with a change. If they didn't go into remission or they lost remission because of a mutation, the chance of going back into remission goes down a little bit. But in general, we do get a second chance. So, the drugs really do work.



Slide 21: Although TKIs are generally well tolerated they can have side effects

But, the next part is that nothing comes without a price and that despite the fact that the drugs work, they do have some side effects.

Now compared to old-fashioned chemotherapy, compared to bone marrow transplant, compared to a lot of other things that cancer doctors are used to, we consider these to be very safe drugs. So, sometimes I know patients come in and they feel that I'm a little blasé when I see them because they feel that they're being blown off by their doctor, that their doctor's not appreciating their side effects. Well, as cancer doctors who take care of people with a lot of different types of leukemia, you know, we see patients who have bad types of leukemia, where the chemotherapy drugs are causing all kinds of side effects. And, we sort of are relieved when we see a patient with CML because for the most part they do well and they don't really have a lot of side effects. But, that's certainly different when you're on your side of the table because any side effect is too much. And so, we need to be thinking about what can we do to minimize the side effects, especially in a chronic disease where you're going to be on medications for years and years and years.



Slide 22: Selecting a tyrosine kinase inhibitor

So, what you can see on this table is some of the common side effects that we see. Most of the TKIs, almost all of the TKIs I should say, will cause some suppression of the good blood counts as well as the bad blood counts. And so, this sometimes is one of the bigger problems of picking a medication, or using a medication, is adjusting the dosing, trying to be able to get the medicine in without causing a lot of suppression of the red cells, so people don't feel tired, or suppression of the platelet counts so that people aren't bleeding.

Fortunately, compared to other chemotherapy drugs, the TKIs don't cause a lot of suppression of the blood counts, but it can still sometimes be a problem.

But then, each of the other drugs have different side effects. And, we're going to use that to help us pick which medicine to pick.

So, for example, imatinib or Gleevec causes a lot of fluid retention. People get a little puffy around the eyes, they get puffy in the legs, they get muscle cramps. Very common. There are things we can do. We can give them things to make them pee a little bit more, so-called diuretics. For muscle cramps, we can give them tonic water, what says quinine on the bottle, or Tums, old-fashioned calcium pills or sports drinks like Gatorade. Those will help the muscle cramps.

But you know, these are things we have to work with patients with. For example, dasatinib or Sprycel, known to cause fluid around the lung, not in the lung, but around the lung, some called pleural effusion. So, we're talking to our patients all the time, are you having shortness of breath, if you're on that medication. And if they do, not a big deal, we give a little bit of prednisone, give a little diuretic to make them pee the water out, we drop the dose of the dasatinib and most people will do quite well. But, we want to be watching for that.

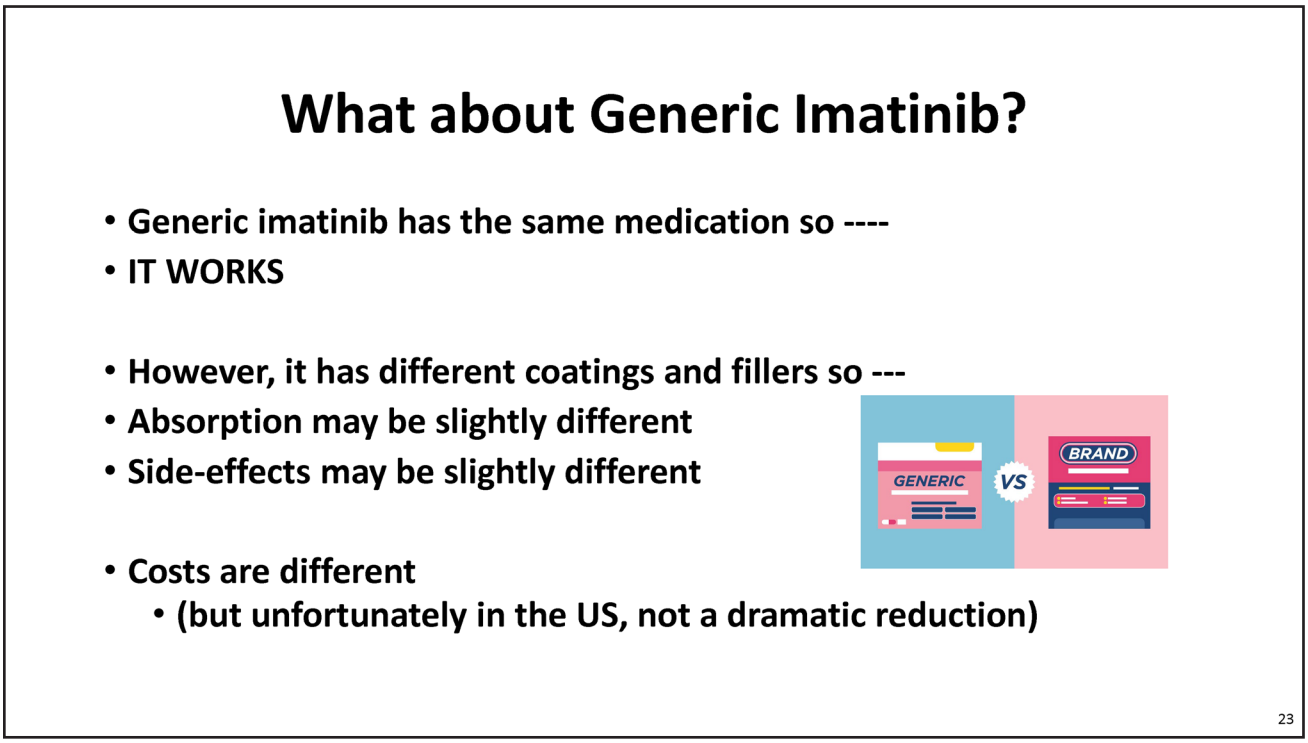
With nilotinib or brand name is Tasigna, but we're watching for pancreas problems, abdominal pain, we want to look for rhythm problems in the heart, make sure that the calcium is okay, make sure that the salts are all in check.

Bosutinib or Bosulif, when you first start that medication, often causes a lot of diarrhea during the first week or so, but then that tends to go away. So, we warn our patients, have Imodium at home, be able to watch for the diarrhea up-front.

And then ponatinib, like I said, that's the more dangerous one, the third generation. We tend to use that only more as a last resort or when other drugs haven't worked. It can cause more significant cardiovascular problems. So, we do usually get people to see their cardiologist, to do a little cardiac work-up and to really talk to them about what things we need to be watching for with heart problems.

So, we can use that information though, of what the side effects could be for each of the drugs, to pick the best drug. So for example, if I have a patient who has lung disease, I don't want to pick a drug that has a side effect of having lung problems. So, I probably would not be taking dasatinib. If I have a person who has diabetes, I probably don't want to be talking to them about a drug that they have to fast for or that has problems with the pancreas, so I wouldn't be probably using nilotinib.

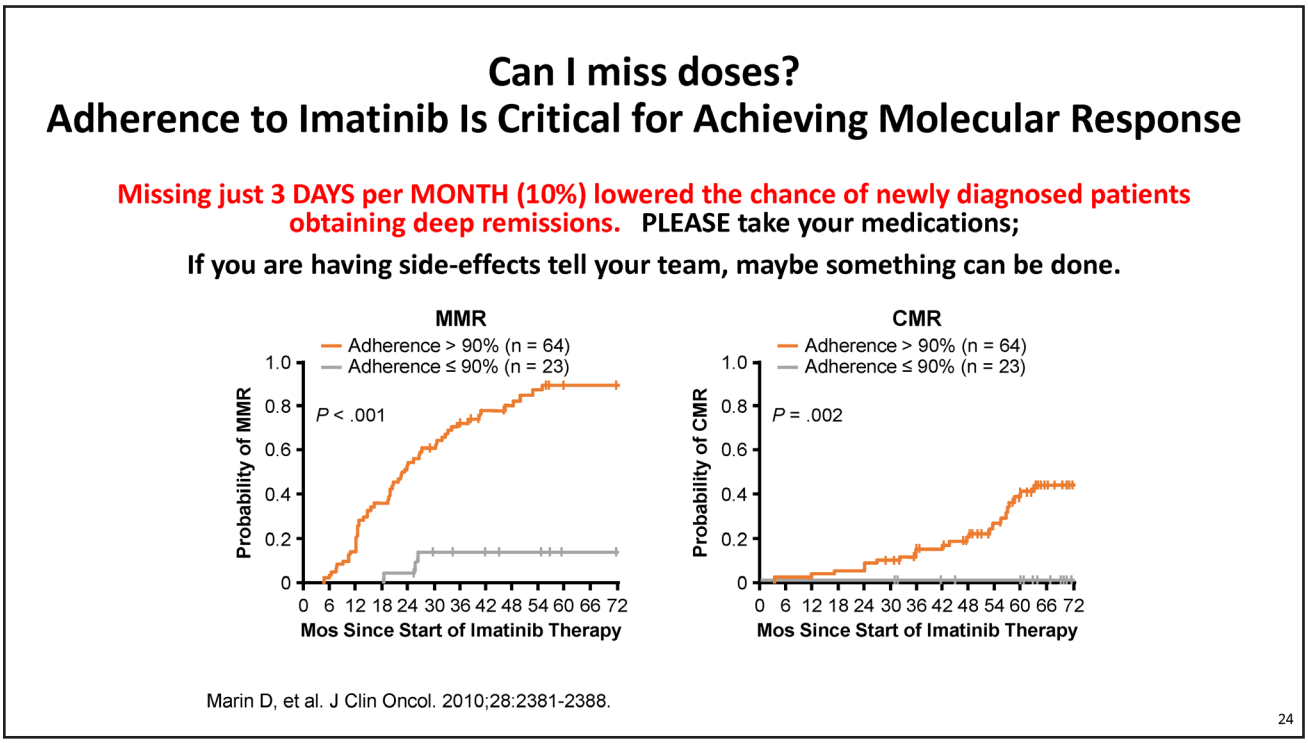
So, these are things that we sort of use to sort of pick, that doesn't mean it's wrong to pick those drugs, it just means we have to watch those particular side effects.



Slide 23: What about Generic Imatinib?

So, in the last couple of years we have another player and that is the cost. We have to start worrying about the cost. And, imatinib or Gleevec now has a generic version. And, I have had some patients, their insurance companies are asking them to switch from Gleevec to the generic version imatinib, and they get all concerned. And I say don't worry, don't worry, it's the same drug, it's the exact same drug. And, we know from other studies that have been done that generic imatinib works. So, you shouldn't be overly concerned that, oh, the drug that was working is no longer going to work for me, or my insurance company is going to kill me because they're making me take it, you know, a cheaper knock-off. The answer is generic imatinib does work.

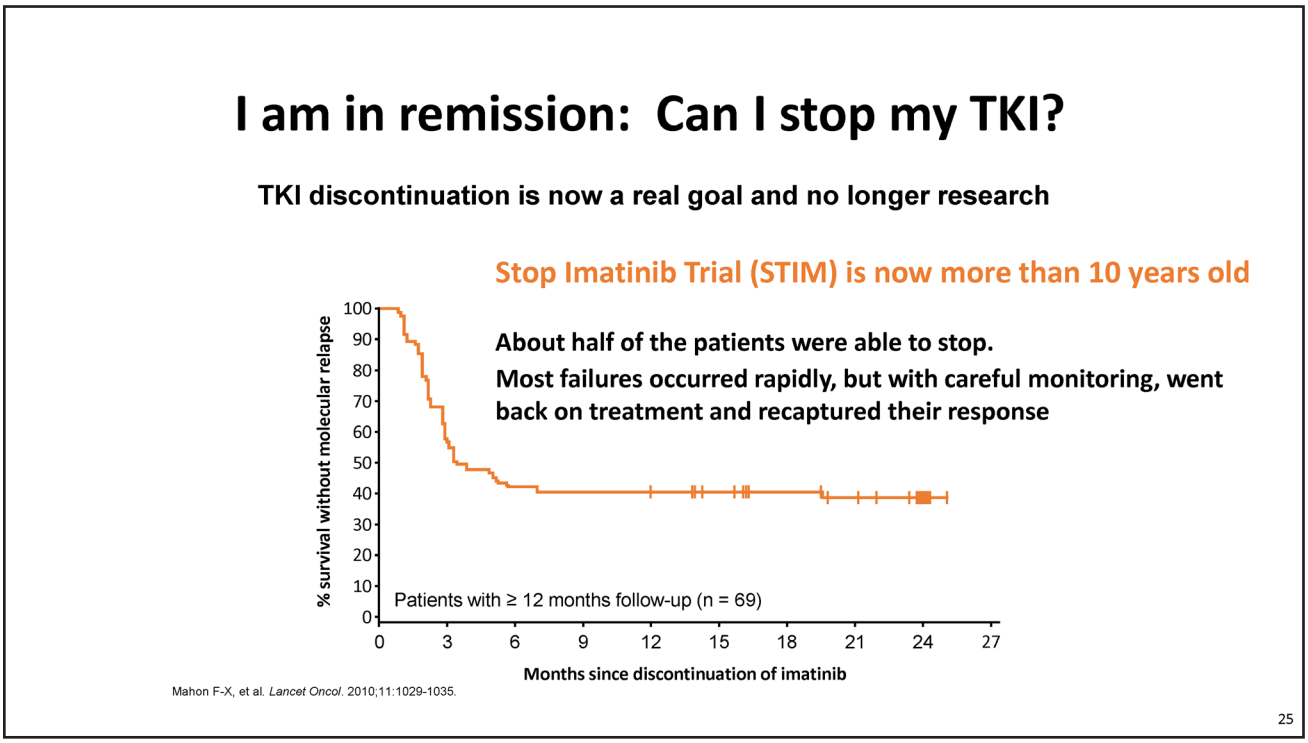
But, I will tell you that the coatings on the pills are different. That's what's different in generics, is the coatings, the fillers that they put in. The actual medicine is exactly the same. But, the coatings do affect how it gets absorbed and may affect some of the side effects. So, I've had patients who were doing quite well on brand Gleevec, they get switched to generic imatinib, and now all of a sudden they start to get muscle aches and muscle cramps. Not uncommon, we can work through that, often with calcium with that, but I've seen just the opposite. Patients who were doing poorly on brand Gleevec, get better when they get switched to imatinib, have less muscle cramps. So, we do have to watch for these side effects, but don't be worried that it's not going to work.



Slider 24: Can I miss doses? Adherence to Imatinib Is Critical for Achieving Molecular Response

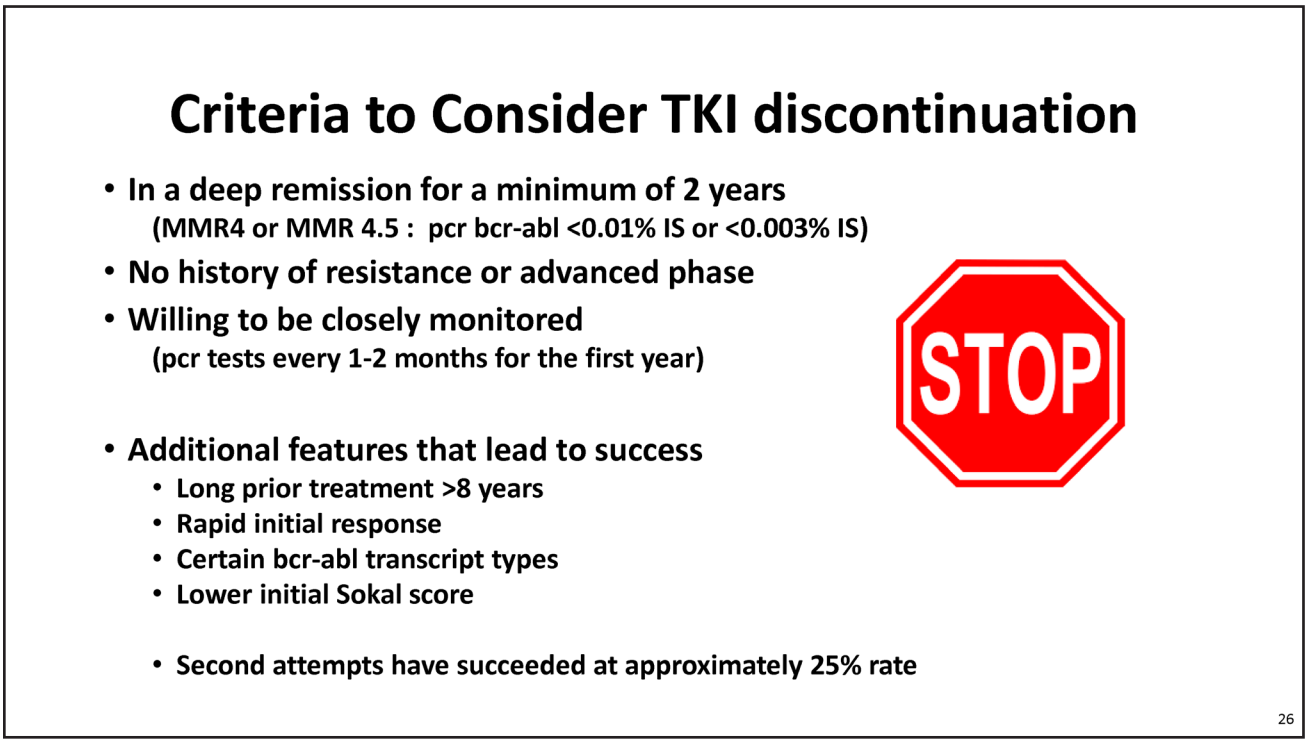
The next thing to say is, can you start missing doses? Another question I often get. Is that I'm doing okay, can I start missing doses? And the answer is, definitely not. This is a study that was a sneaky study, done by investigators in Europe, where they actually put little caps in the bottles and they monitored how many times the patient was taking the pills, unbeknownst to them. And, what they found was that if you missed 3 pills per month, that's not very many, just 10%, the chances of getting into a deep remission went down dramatically.

You can see in the red lines, the chance of getting 3-log reduction, getting really deep, was like almost 90%, if a person took all their pills during the first couple of months. But, if they missed 10% of pills, it's the black line, less than 20%. So, you definitely want to take your pills, especially in the beginning, until you push those PCR values well below 1%. Get into remission, then start talking to your doctor.



Slide 25: I am in remission: Can I stop my TKI?

And, what can you talk to your doctor about once you're in a deep remission? Well, the question is can I stop my medicine? And, the answer to that question is maybe. We now have data, out 15 years from the French, something called the Stop trial or STIM trials, and there's many more studies like this, they have taken people who have been in deep remission for a couple of years, and then go ahead and stop the drug and see what happens. Now, the key there is they have to be monitored, they have to watch them very carefully. But, what you can see from the slide is about half the people who stopped medications continued to do well more than 10 years later, off medications. So, stopping medications, which we now call TFR, treatment-free remission, is really a new goal.

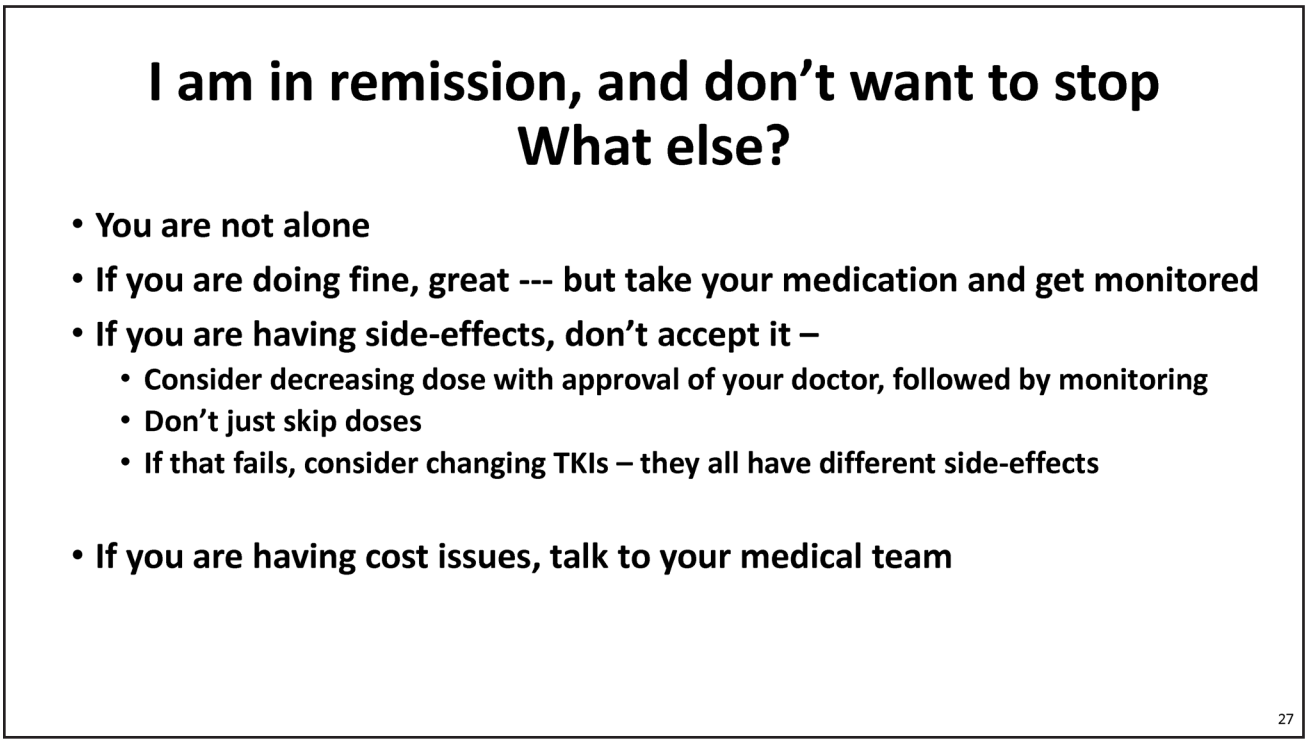


Slide 26: Criteria to Consider TKI discontinuation

And so, we will try to talk to our patients now and there are some criteria. First is, you have to be on a medication that works. It has to be working for a long time. So, you want to see people who are in a deep remission and that is an MMR of 4, basically 4-log reduction or .01 on that PCR or even lower than that. You want to get down to that very deep level and stay there for a couple of years before you try taking off the medication.

And then, you have to be willing to be monitored monthly for the first several months. And if the numbers start to come back, you go back on the medication, and if they stay away, everything's good, you could be monitored less frequently, but you still need to be monitored.

So, we know that treatment-free remission is now a possibility and something that some patients will want to try to get there, by pushing the disease with very deep dose.



Slide 27: I am in remission, and don't want to stop...What else?

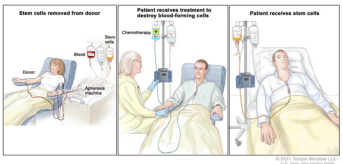
Well, what about if you don't get deep enough to be able to stop or, as many of patients said, ain't broke, don't fix it, I don't want to try gambling with stopping medication. Well, that's okay. In fact, the majority of patients don't stop medications today. And, if you're doing fine and everything's good, great, stay on the medication, be monitored, and have a nice life.

But, if you're not doing great, if the doctor says everything's good, you're in remission, your PCR is less than 1%, I'm real happy, but you're not happy because you're having muscle cramping, you're having pains, you're having nausea, having diarrhea, don't accept that. Because there are lots of things we can do. You can reduce the dose, you can then talk to your doctor, whether or not the dose can be lowered, so that you don't have as many side effects, and sometimes even switch the medications to see if that will help. So, some patients who are doing really well, but in the doctor's standpoint, if you're not feeling well, we haven't done our job.

And then, there's the cost issue. Talk to your doctor about cost. Because there are things that the medical teams can do. There are support programs for a lot of patients. I've had patients who think that they have great insurance, but still have a copay, even to say I'm not going to qualify for any support, surprised when they find out that there are support programs, even for people who are in the more well-off categories.

Other Treatments for CML

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



- **Interferon**
  - **Used mostly during pregnancy**

- **Omacetaxine (Synribo)**
  - **Used in resistant disease**

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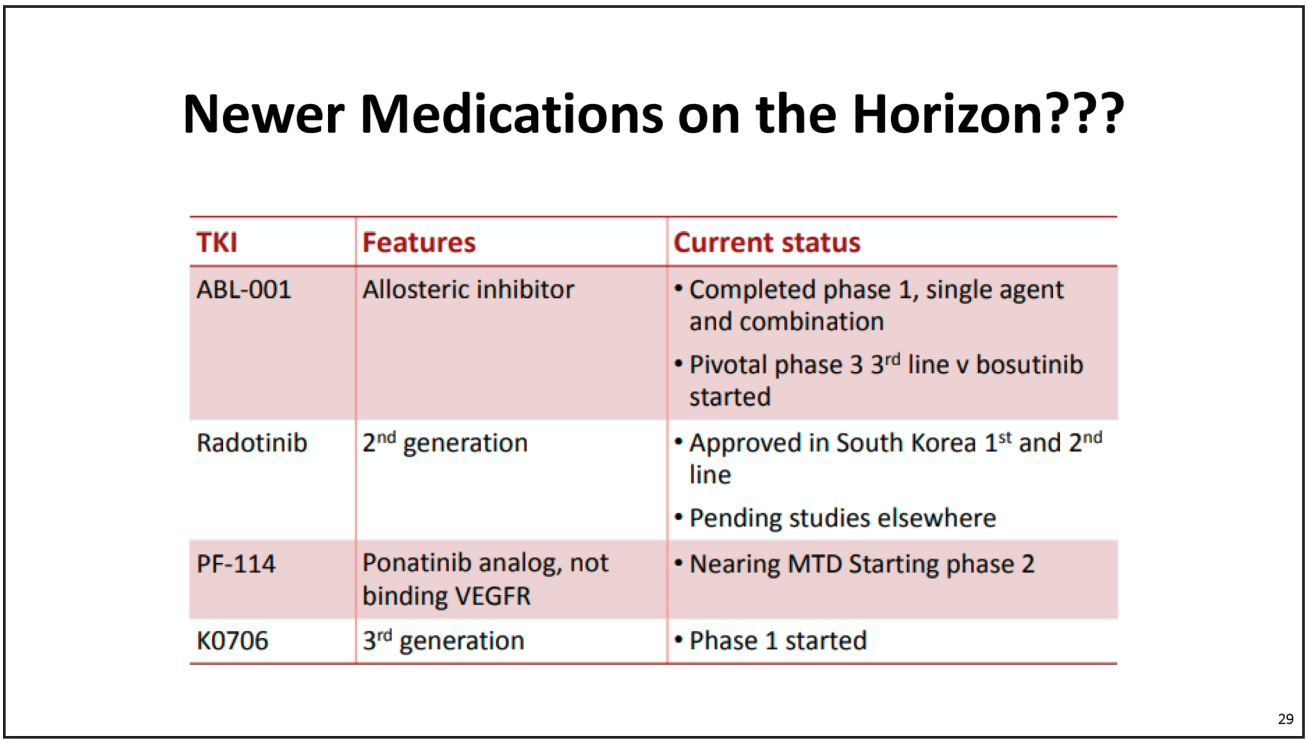
Slide 28: Other Treatments for CML

Finally, are there other treatments for CML? Well, we do have our bone marrow transplants. We have this aggressive therapy that requires hospitalization, that can cure people, but typically limited to those patients where the other medicines aren't working or are in very special circumstances.

Interferon, the treatment we used to use before TKIs came out, still used occasionally in pregnancy. And then, we have a drug called omacetaxine, brand name of Synribo®, which is an injection, used also for patients who have more advanced disease. Not very common in the United States, but we do use these medications when we have people that aren't responding to TKIs.



Slide 29: Newer Medications on the Horizon???

And, there also are obviously newer medicines that are being explored. The top drug ABL-001, shown a lot of activity, we're very excited about this drug, but it's been very slow to come to market, in part because not many people need it. But, there are clinical trials that are available for people who aren't responding to the treatments. Fortunately, that's not many people.

Remaining Challenges?

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

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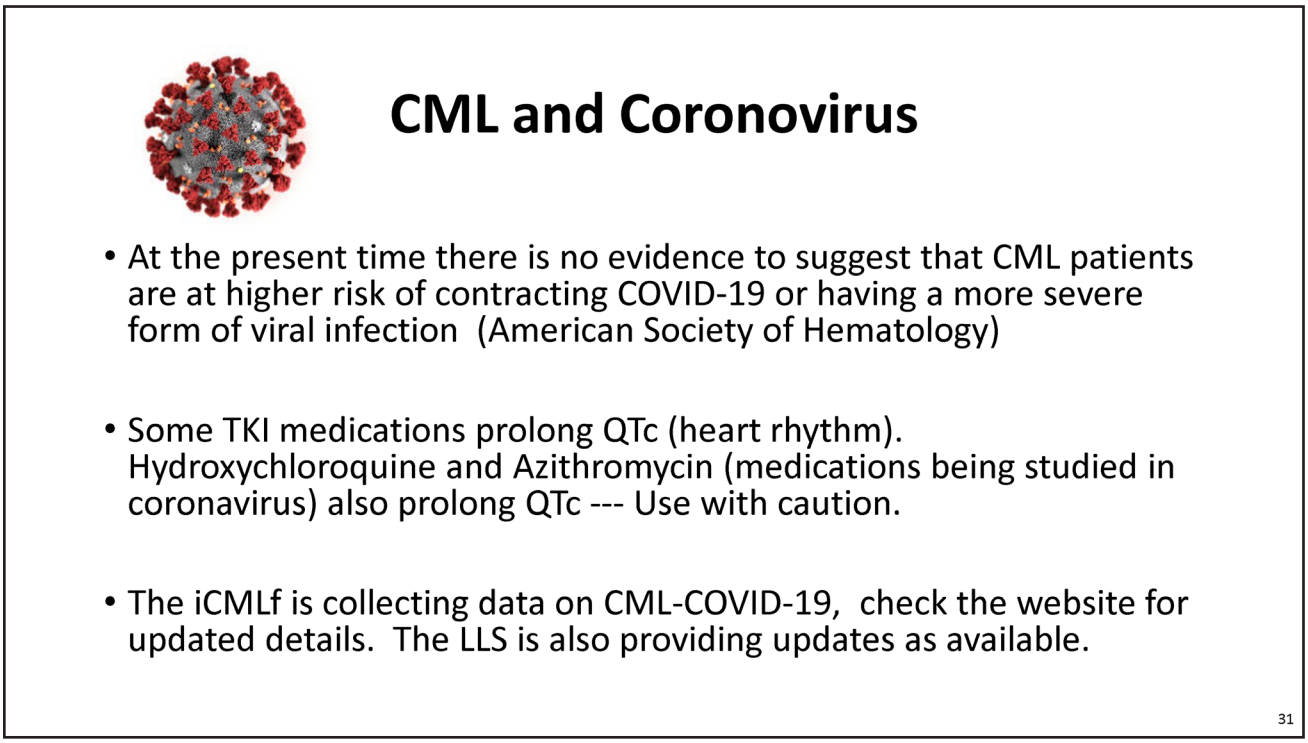
Slide 30: Remaining Challenges?

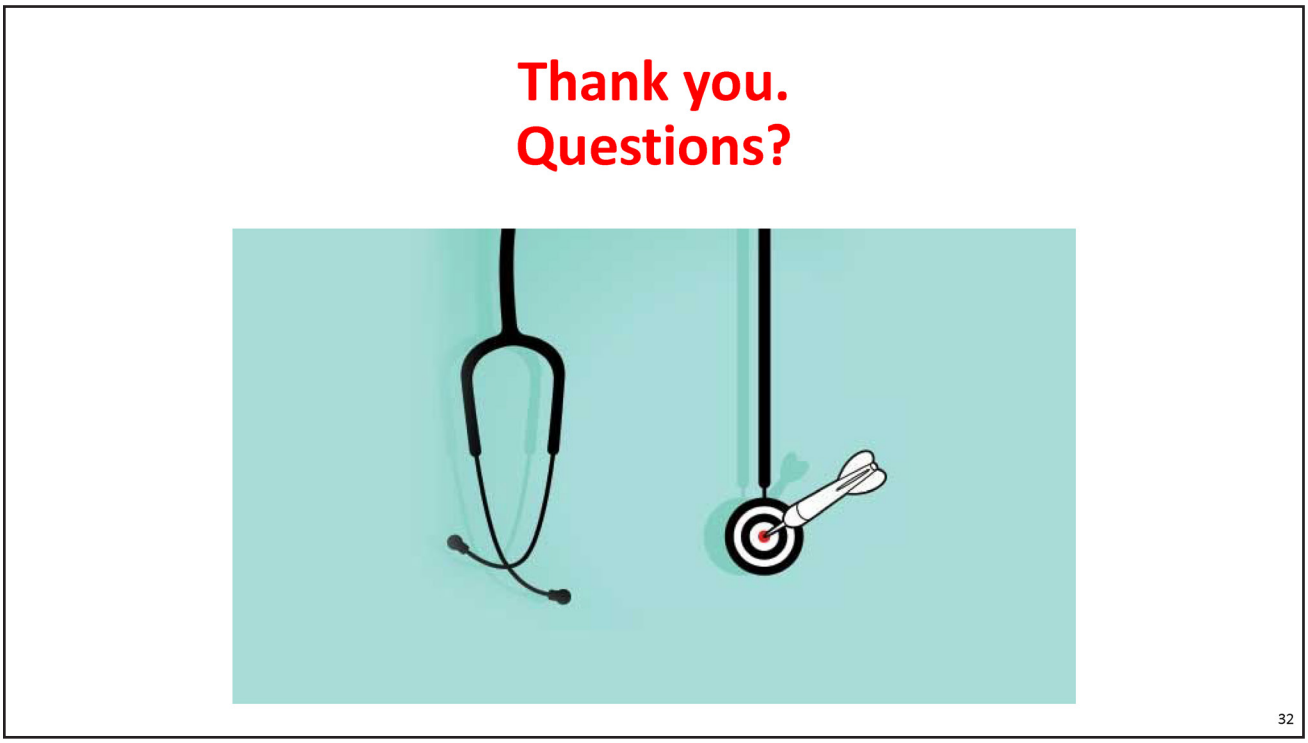
So, what are the remaining challenges? Well fortunately, most patients with CML do quite well and can expect a normal lifespan. We want to, however, in trying to increase the number of people that can try TFR, but maybe being a little more aggressive upfront, want to try to improve our ability to select those patients who need second attempts to TKIs or those with resistance. And then, we want to try to grapple with some of the medical costs.



Slide 31: CML and Coronavirus

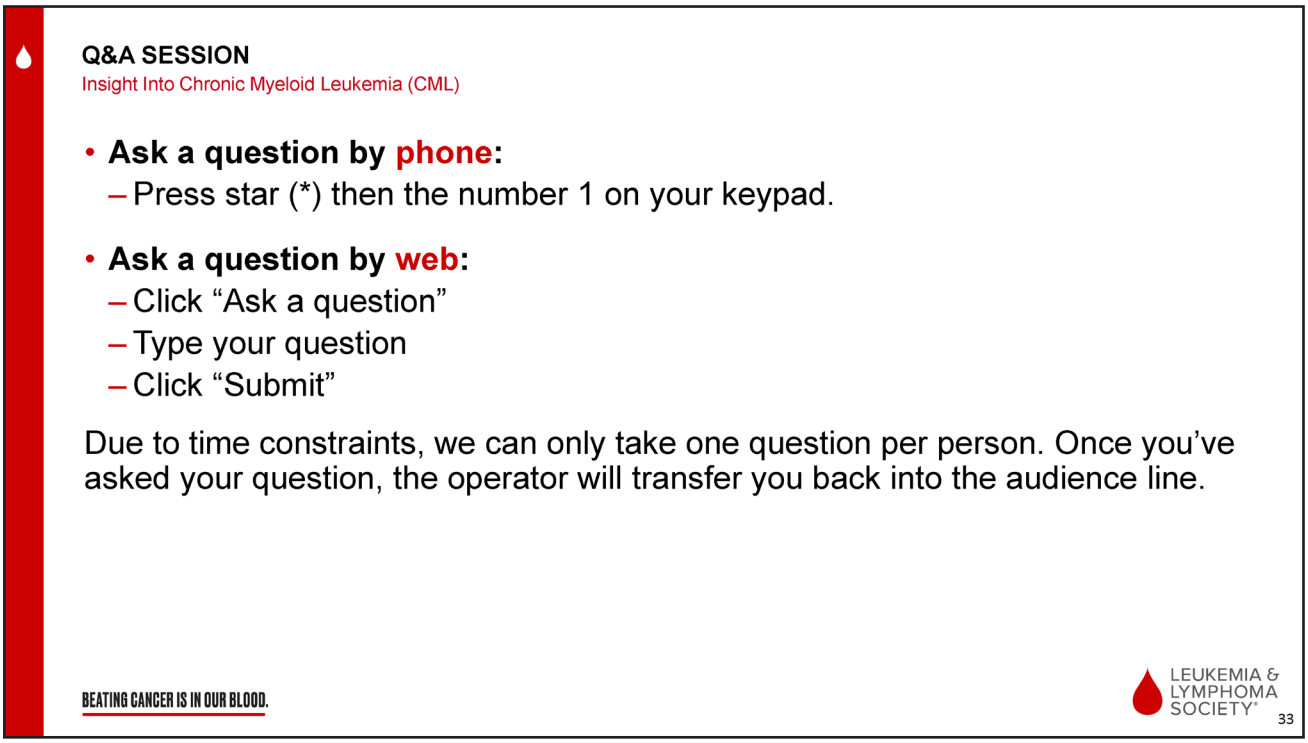
And finally, my last slide, deals with coronavirus. It's on our mind all the time obviously. What do we know about CML and coronavirus? Not much right now. We're still learning a lot about coronavirus. But, at the present time, there's no evidence to suggest that patients with CML are more at risk of getting coronavirus, and if they do unfortunately get coronavirus, fortunately right now it looks like patients with CML do just as well as the general population. It's not a very big immune-suppressive type disease, so it doesn't seem to be hitting our CML population more. However, I should caution you that some of the CML drugs prolong one of the heart rhythms, called a QTc, and some of the drugs that are being used to study in coronavirus, like hydroxychloroquine, like zithromax, these drugs that you've heard a lot in the news, they also prolong the QTc, so your doctor should be aware of your disease and what medicines you're on.

There are now efforts to try to learn more about CML and coronavirus and I suggest The Leukemia & Lymphoma Society to get more information.



Slide 32: Thank you. Questions?

So, with that, I'm going to turn the program back over to our moderator. Hopefully, I've hit the mark and answered many of your questions, but I'll be glad to take some more of your questions. Thank you.



Slide 33: Q&A SESSION

Ms. Figueroa-Rivera:

Thank you so much, Dr. Goldberg.

Doctor, our first question from the web. Can CML at some point during or after remission change to AML?

Dr. Stuart Goldberg:

So, CML and AML are different diseases, so they don’t really change from one to the other, but that’s more a name problem. As I showed you in an earlier slide, what happens with CML if it’s not treated, it moves into what’s called a blast crisis. And, under the microscope in blast crisis the bone marrow looks just like AML. There’s lots of big ugly blasts, they don’t function, they don’t fight infections, and for all intents and purposes, it is AML. It’s more of a name game.

So, in some ways the answer is yes, that CML turns into AML, but it’s actually more technically called CML turning to blast crisis.

Patients in blast crisis are treated with aggressive hospital-based chemotherapy and often will then be referred for bone marrow transplant.

So, that’s what we’re trying to avoid, we’re trying to avoid the transformation of CML from a quiet disease to a blast crisis that looks like AML.

Ms. Figueroa-Rivera:

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

Operator:

Thank you, Lizette. We’ll hear from a caller in Texas. Jessica, please go ahead, your line is open.

Jessica:

Hi there. My doctor has me taking a TKI just Monday through Friday and I don't take it on the weekend. So, first of all, is that okay? And then, right now my platelets are low and so she has me holding off on my TKI for 10 days. But you had said never to miss a pill, so I want to make sure I'm doing the right thing.

Dr. Stuart Goldberg:

Okay, thanks for your question. And so, I showed you on the slide where some of the side effects of the TKIs can be suppression of the blood counts, one of the more common side effects and one of the more troubling for us as physicians and patients, because we then have to start to adjust the therapy.

So, what your doctor is doing is actually quite appropriate. He or she, is trying to give you the medication, but then adjust it to be able to make sure that the platelet counts or the blood counts are holding. So, sometimes we have to reduce the dose, sometimes we do have to miss a dose, but that's under the doctor's guidance.

In addition to watching the blood counts, your doctor will continue to watch the PCR. So, they'll make sure that the side effects are being controlled by the lower dose, but make sure that the efficacy continues to be there, that the drug is working, by watching the PCR.

So, when I said not to miss doses, that's when people do it just on their own. Under the guidance of a physician who's watching and telling you to do it because they want to make sure that you get being able to tolerate the medication, that's a whole different story and is very appropriate, what your doctor's doing.

Jessica:

Okay, thank you very much.

Ms. Figueroa-Rivera:

And, thank you for the question.

Doctor, our next question. More and more young adults are being diagnosed with CML, just like Roman Reigns, who was diagnosed in his 20s. Because patients so young may have to be taking TKIs for the rest of their lives, how do doctors decide which medications or what treatments they start younger patients with?

Dr. Stuart Goldberg:

That's an excellent question and something that we do have to grapple with. We know that CML, usually the average age to develop this is in the late 50s and early 60s, and it's been consistent in that for many, many years. But, there are younger patients who develop this, especially people who want to have children down the road. And so, when we have a young patient, you want to be talking a lot about what is your goals. There're some patients who don't mind taking a pill for the rest of their lives and some patients who really do want to think about stopping drugs.

So, if I have a patient who might be willing in the future to stop drugs, I might pick a more aggressive drug, like a second generation, either dasatinib, nilotinib, or bosutinib, one of those more aggressive drugs, in the hopes that I can drive them really deep, so that in the future they can come off therapy down the road.

This is especially important for younger women, where they may want to become pregnant down the road, and when you're pregnant, you can't be on the TKIs. So, when a woman is telling me I might be wanting to get pregnant, I want to make sure that her PCR is as low as possible before she gets pregnant, so I may want to be more aggressive with the TKIs. And so, the second generations often are favored for younger patients, to try to get them that deep, so that they have a chance both at treatment-free remission and also if they need to take a gap, so they can have pregnancy, that we can get through safely.

Ms. Figueroa-Rivera:

Thank you, Doctor. We had so many questions about pregnancy and CML and I just want to thank Courtney for her comment. She said, I recently gave birth to my son after going through a discontinuation protocol and having a normal pregnancy without medication. I would love for others to know it might be an option for them. So, thank you Courtney and congratulations.

We'll take our next question from the telephone audience, please.

Operator:

Lizette, thanks. We'll hear from Anne in New York. Please go ahead, your line is open.

Anne:

Okay, hi. Hi, Doctor, that was a really excellent talk, I appreciate it. I have a question for you about Ph-like ALL. Recently, there has been a lot of literature about the TKIs working for these patients who don't have CML, but they have ALL, acute lymphoblastic leukemia, with a Ph-like phenotype. Do you know how effective the drugs are to work on these patients, to help them through their therapy?

Dr. Stuart Goldberg:

Thank you for your question. So, acute lymphocytic leukemia, ALL, is one of those acute, aggressive type of leukemias. So, as we talked about in the beginning, this is a disease – so leukemia, cancer of the white cell, lymphocytic, this is not the myeloid cell, but actually the lymphocytes that became cancerous, and the acute being the ugly blasts. So, these patients are usually quite ill, quite suddenly, because these cells come on very quickly and they destroy the bone marrow fairly quickly, so in a matter of weeks somebody goes from being quite healthy to quite sick.

In these patients we need to be fairly aggressive, we're often talking about combinations of chemotherapy, of real old-fashioned chemotherapies, the type that put people in the hospital, the type that we need to be very careful watching.

Now a fraction of patients with ALL, when we look on the inside of the cell we can see that the chromosome is broken. In fact, as in adults over the age of 50, ALL with the Philadelphia chromosome, is actually fairly common. In children for some reason the ALLs typically don't have the Philadelphia chromosome, although they can.

The Philadelphia chromosome is shaped slightly differently in ALL, but the TKIs can work for Philadelphia chromosome positive ALL, given in conjunction with chemotherapy. So, we don't use them by themselves, but we combine them with it. And most patients can go into remission with a combination of the TKI plus chemotherapy, and then many of these patients will be referred for transplantation.

There's also now something called Ph-like, where we can't find the Philadelphia chromosome, but they have some changes in the other genes, and whether the TKIs will work in those patients is much more questionable. So, many physicians will not use the TKIs if they can't find the Philadelphia chromosome or the BCR-ABL fusion protein in the Ph-like, but these patients once again will be referred for aggressive combination chemotherapy.

Ms. Figueroa-Rivera:

Thank you, Doctor.

And the next question. Can you please address reduced dosage treatment of CML? Many patients seem to be on 200 milligrams of imatinib, occasionally 300, but there does not seem to be a widespread clinician support of this or peer-reviewed studies to support it.

Dr. Stuart Goldberg:

Sure. So when I have a patient who's newly diagnosed, I want to make sure that they get into remission, I want to make sure that I can push them down into that Philadelphia chromosome, undetectable by the chromosomes or the PCR value of less than 1. So early on, I do try to give patients as much chemotherapy, as much of the TKIs as they can. So, a full dose of imatinib is 400 milligrams or a full dose of dasatinib at 100 milligrams or a full dose of nilotinib at 300 milligrams or a full dose of bosutinib at 250, 500 milligrams. Because you want to get people into remission.

But, once somebody's in remission and they're doing better, then the question is does a full dose start to have more side effects. So then, there is a movement in the field to start lowering the dose, especially for the second generations where we think that the drugs are actually more potent than they need to be. So, there's a lot of literature now for reducing the second-generation drugs in patients who are in remission and maybe even starting in older patients.

With imatinib, with Gleevec, the dose of 400 has been the traditional, we do see that in the test tube 300 will work and we actually know that patients will do well with 300. But once you get below 300 that, in the test tube at least, it's not enough to really stop the Philadelphia chromosome from continuing to grow. So, in general, we try not to use doses of imatinib of 200 or less, however, I do have some patients who've done well and they have reduced and we watch the PCR. I think at the end of the day, monitoring, monitoring, monitoring. If you're going to make a change in drug, make sure you monitor. So, you can try something, 3 months later do a PCR, and if it's working, you'll know, and if it's not working then you know that that was the wrong thing to do.

So, we have the ability to try things and then monitor. So, I won't argue with a patient who's on 200 of Gleevec all the time and is continuously PCR negative or PCR 0.11 or something like that. You know because they're proving that that's enough for them.

Ms. Figueroa-Rivera:

Thank you.

And, our last question today. I've been on treatment-free remission for 3 years. During that time, my test results have been stable. I have one concern, though. There's a significant difference between my results from the PCR blood test and the bone marrow aspiration sampling. Which is correct? Are they both just information and is one result more important than the other?

Dr. Stuart Goldberg:

The bone marrow typically will look at the correlation or the agreement between the bone marrow and the blood, when it comes to looking at PCR tests, is quite high. The correlation between a bone marrow and blood tests when you look at Philadelphia chromosomes is measured by FISH or by cytogenetics, is not so good. So, we typically will use the PCR studies because the correlation is so good between the 2. And if a patient who's on drug and they're below 1%, we're quite happy they're in remission if they're below .1%, they're in a deep remission.

Now, for TFR, for stopping treatment completely and being on nothing, the current recommendations are that you should always be below .1. So, if you start to go above .1 on the PCR test, that's a person that maybe TFR isn't holding them deep, that being on nothing is appropriate. So, that's the cutoff on when you would restart therapy. But typically, it should be pretty well correlated between the PCR and the marrow.

The other reason why they may not be correlated if the PCR is volume. You need a lot of blood or a lot of marrow in order to get the test accurately, and sometimes I've seen physicians send just a little tiny drop of bone marrow and thinking that they're going to get an accurate PCR, and that may not be accurate. You need a bigger quantity because if you only have a little bit, a little sample from the bone marrow, it may make the result not as reliable.

Slide 34: LLS EDUCATION & SUPPORT RESOURCES

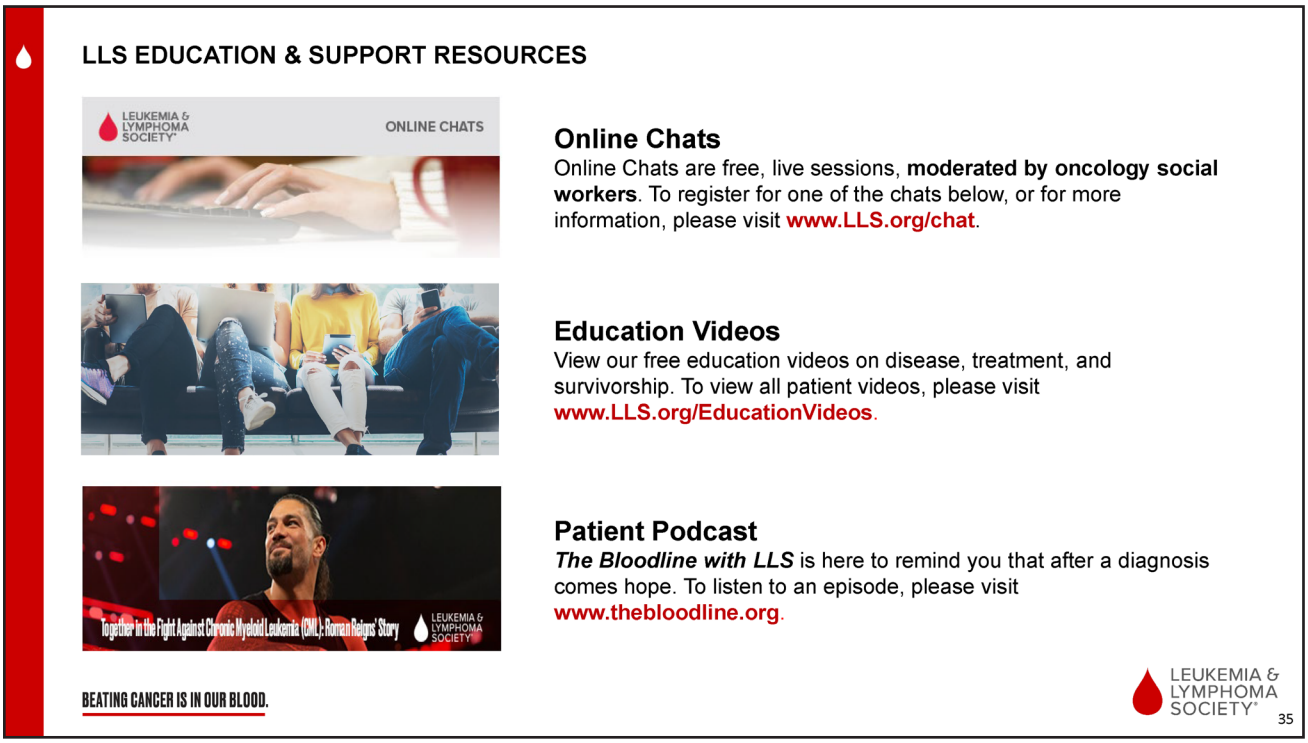
Ms. Figueroa-Rivera:

Well, thank you for all of your questions. And, thank you so much Dr. Goldberg for your continued dedication to patients.

And, 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.

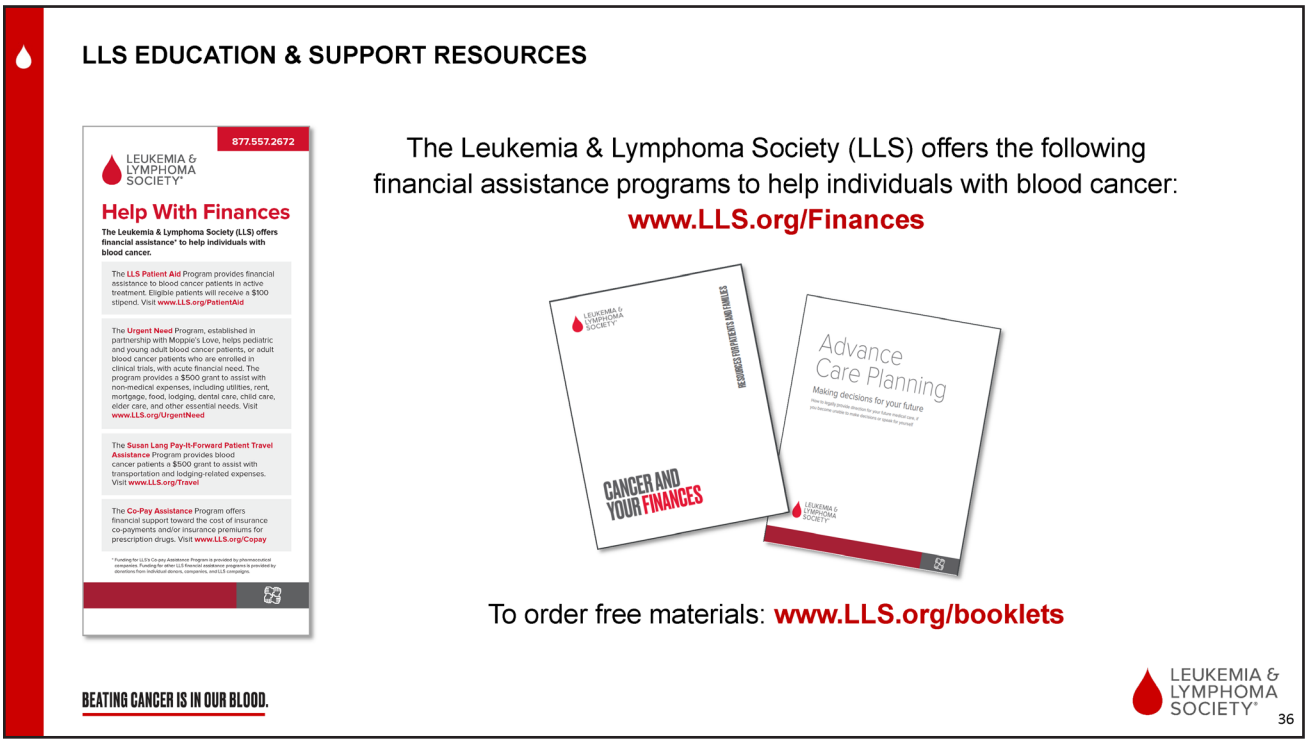
If we weren't able to get to your question today or you want more information, you may speak to an LLS Information Specialist at 1-800-955-4572 from 9 AM to 9 PM Eastern Time or reach us by e-mail at **infocenter@LLS.org**.

Information Specialists are available to answer your question about treatment, including clinical trials, and answer other questions you may have about support, including financial assistance for treatment.



Slide 35: LLS EDUCATION & SUPPORT RESOURCES

We also have a Clinical Trial Support Center (CTSC), where Clinical Trial Nurse Navigators, who are registered nurses with expertise in blood cancers, can assist you with finding out if a clinical trial is right for you. And, they can be found at www.LLS.org/Navigation.



Slide 36: LLS EDUCATION & SUPPORT RESOURCES

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

Again, we'd like to acknowledge and thank Bristol-Myers Squibb, Pfizer, Novartis, and Takeda Oncology for support for this program.

Slide 37: THANK YOU

Dr. Goldberg, again thank you 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.

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