Slide 1: CHRONIC MYELOID LEUKEMIA: KNOW YOUR OPTIONS

Lizette Figueroa-Rivera:

Hello, everyone. On behalf of The Leukemia & Lymphoma Society, I'd like to welcome all of you. We have over 1000 people participating from across the United States, as well as other countries including Afghanistan, Australia, Bermuda, Canada, Egypt, Germany, Greece, India, Indonesia, Ireland, Macedonia, Mexico, New Zealand, Singapore, Spain, and Taiwan. I want to welcome all of you.

And, special thanks to Dr. Kendra Sweet for volunteering her time and expertise with us today.

Before we begin, I'd like to introduce Dr. Louis DeGennaro, The Leukemia & Lymphoma Society's President and Chief Executive Officer, who will share a few words.

Dr. Louis DeGennaro:

I'm Dr. Louis DeGennaro, President and CEO of The Leukemia & Lymphoma Society. I'd like to welcome all of the patients, caregivers, and healthcare professionals attending the program today.

At The Leukemia & Lymphoma Society our vision is a world without blood cancers. Since we started in 1949, LLS has invested more than $1.2 billion in breakthrough research to advance lifesaving treatments and cures. We've played a pioneering role in funding many of today's most promising advances including targeted therapies and immunotherapies that have led to increased survival rates and improved the quality of life for many blood cancer patients.

Though LLS is known for funding groundbreaking research, we do so much more. As this program demonstrates, we are the leading source of free blood cancer information, education, and support for patients, survivors, caregivers, families, and healthcare professionals. We also support blood cancer patients in their local communities through our chapters across the country, and we advocate at the state and federal level for policies to ensure that patients have access to quality, affordable, and coordinated care. We're committed to working tirelessly toward our mission every single day.

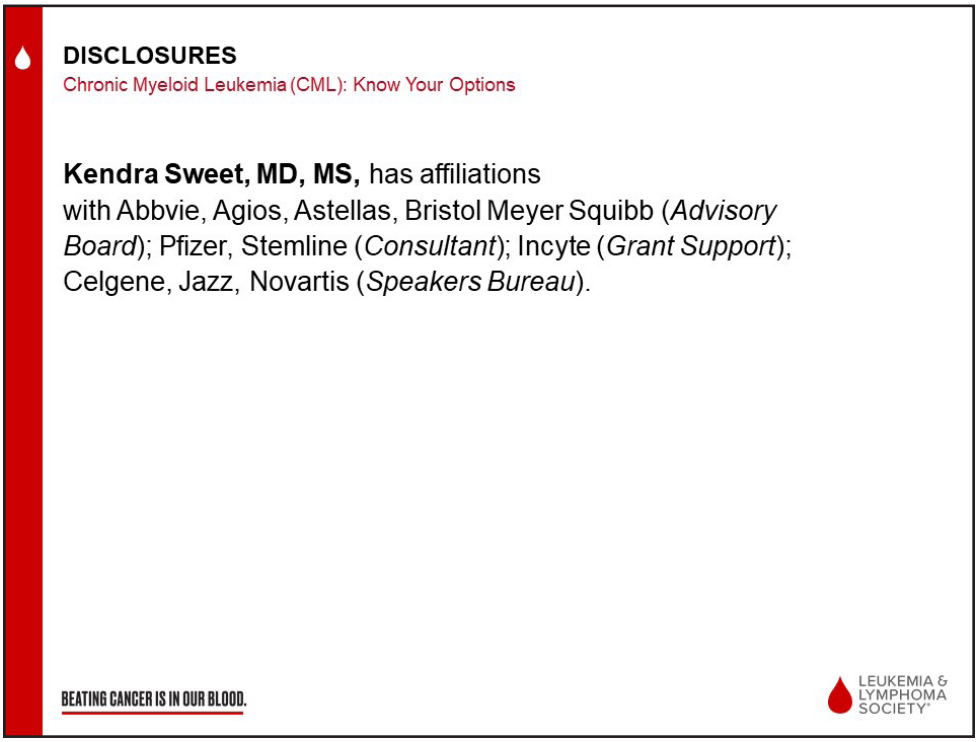
Today you'll have the opportunity to learn from esteemed key opinion leaders. They each have volunteered their time and we appreciate their dedication to supporting our mission, their commitment to caring for patients living with blood cancers.

Thank you for joining us.

Lizette Figueroa-Rivera:

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

I am now pleased to introduce Dr. Kendra Sweet, who is an Assistant Member in the Department of Malignant Hematology at the Moffitt Cancer Center in Tampa, Florida. Dr. Sweet, I'm privileged to turn the program over to you.



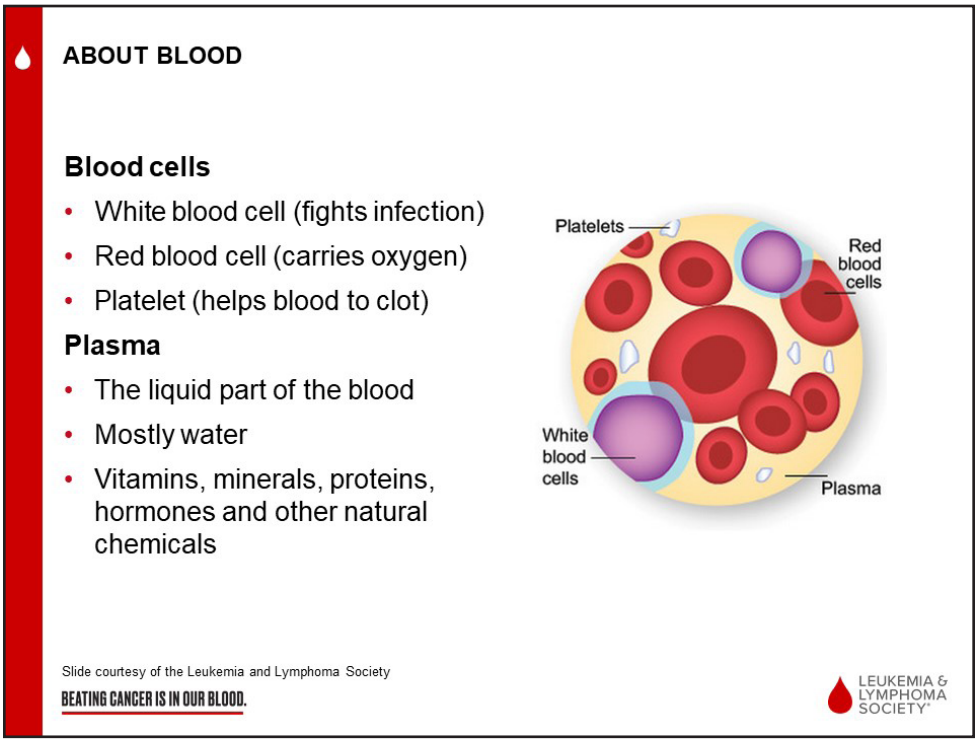
Slide 2: DISCLOSURES

Dr. Kendra Sweet:

Thanks so much. And, I apologize in advance for my voice. I have this cold that's apparently been going around, so please forgive me.

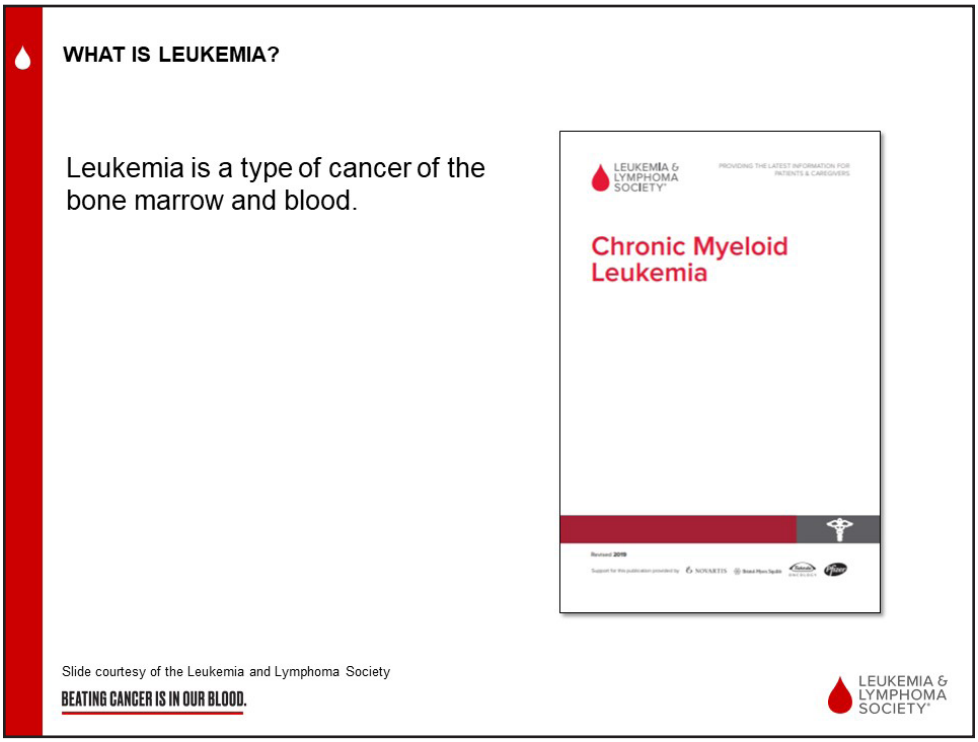
I'm Kendra Sweet. I am part of the Malignant Hematology Department at Moffitt Cancer Center, specializing in treatment of chronic myeloid leukemia (CML) and acute myeloid leukemia (AML).

These are my disclosures here.



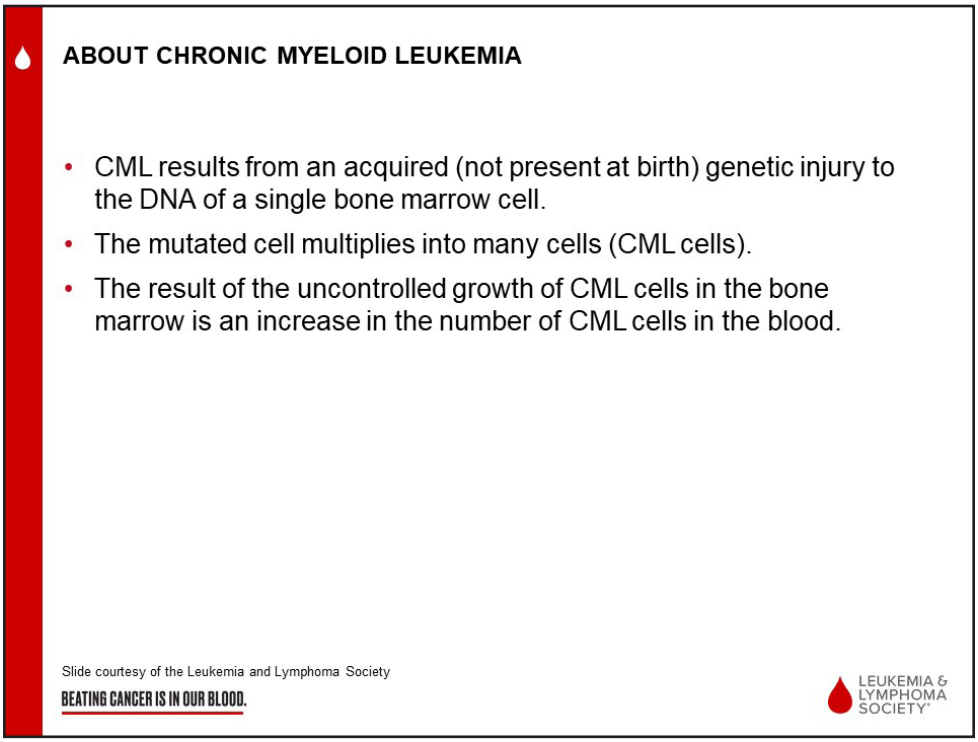
Slide 3: ABOUT BLOOD

We're going to start with just a brief overview on blood. So, as most of you probably are aware, your blood is made up of millions of cells including white blood cells, which are the cells that are important for helping you fight infection; red blood cells, which are the cells that help carry oxygen to all of the tissues in your body; and platelets, which are the cells that help your blood clot. The liquid part of your blood is called the plasma and that's comprised primarily of water.



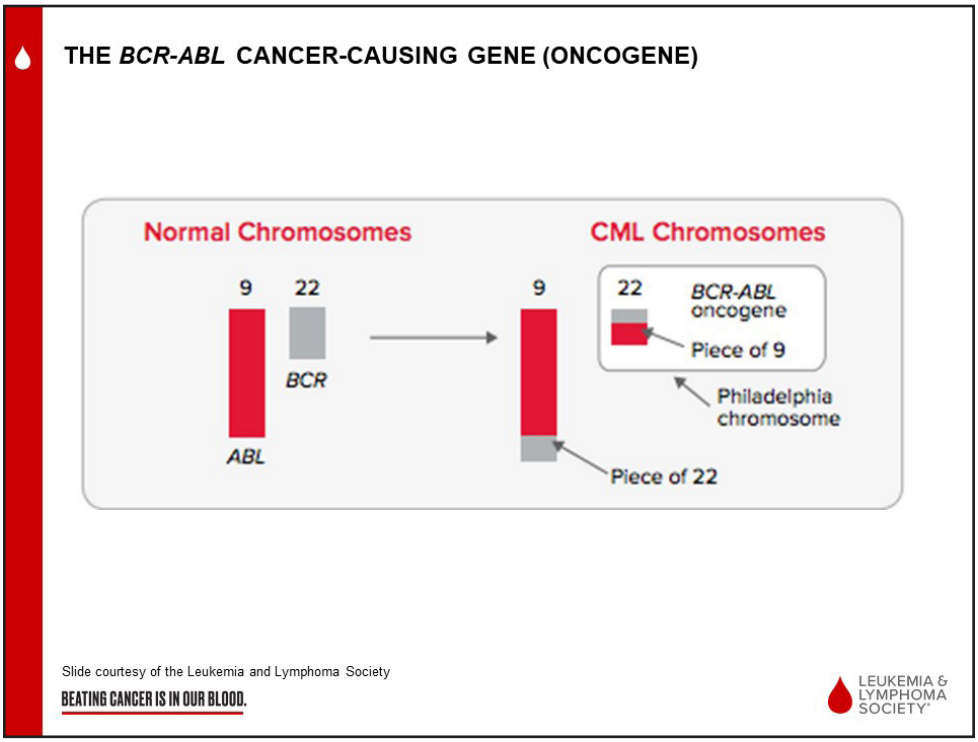
Slide 4: WHAT IS LEUKEMIA?

Leukemia is a cancer of the bone marrow and the blood. The bone marrow is the factory that makes all of these blood cells and there's multiple types of leukemia that rise in different types of blood cells. And, they all have different disease courses and treatments and prognoses. So, not all leukemia is treated equally.



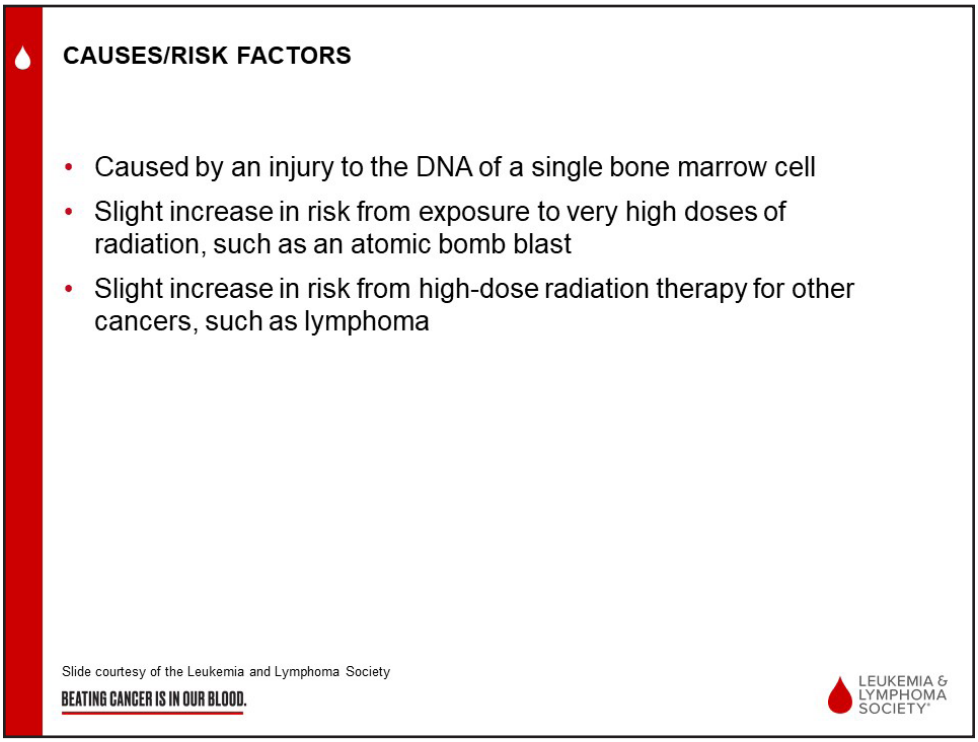
Slide 5: ABOUT CHRONIC MYELOID LEUKEMIA

So, CML is the result of an acquired genetic change that ultimately leads to an uncontrolled production of abnormal white blood cells. It's actually the result of a change between 2 chromosomes. If I can take you back to your high school biology class, you probably learned at one point that you received 23 chromosomes from your mom and 23 from your dad, so a normal chromosome make-up in a female is 46 XX and in a male is 46 XY.



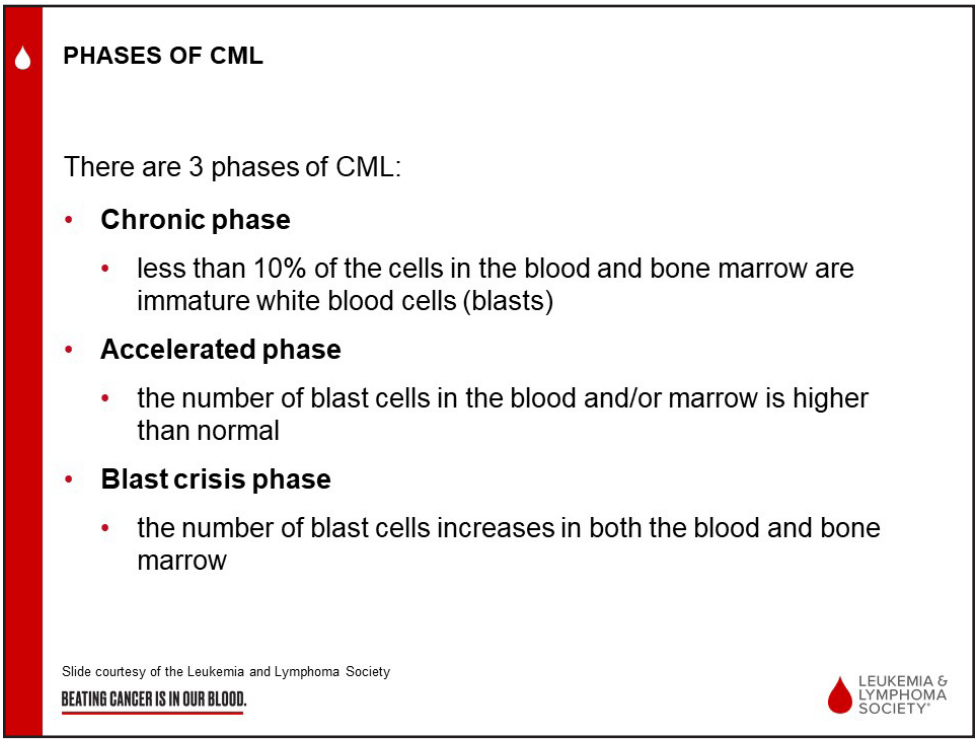
Slide 6: THE BCR-ABL CANCER-CAUSING GENE (ONCOGENE)

So, when someone develops CML, it's caused by this change between chromosome 9 and chromosome 22. So, part of each chromosome breaks and they swap, and they form this new chromosome that we now call the Philadelphia chromosome. And, where these 2 come together forms a new gene that's called BCR-ABL and BCR-ABL is ultimately what causes CML.



Slide 7: CAUSES/RISK FACTORS

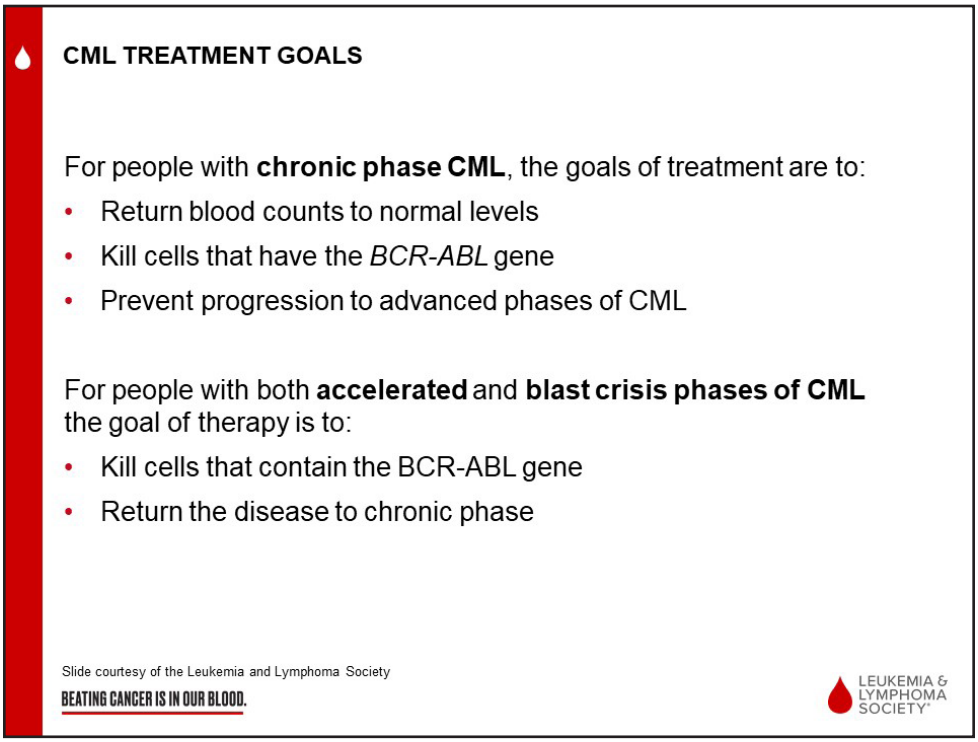
No one really understands why this change takes place. It's not something that you're born with, but rather something that happens later on in life. There's a slight increased risk of developing CML in someone who's been exposed to high doses of radiation, but the truth is the majority of people with CML have never been exposed to radiation and the majority of people with radiation exposure don't go on to develop CML. So, at the end of the day we still don't really know what causes CML in the vast majority of people.



Slide 8: PHASES OF CML

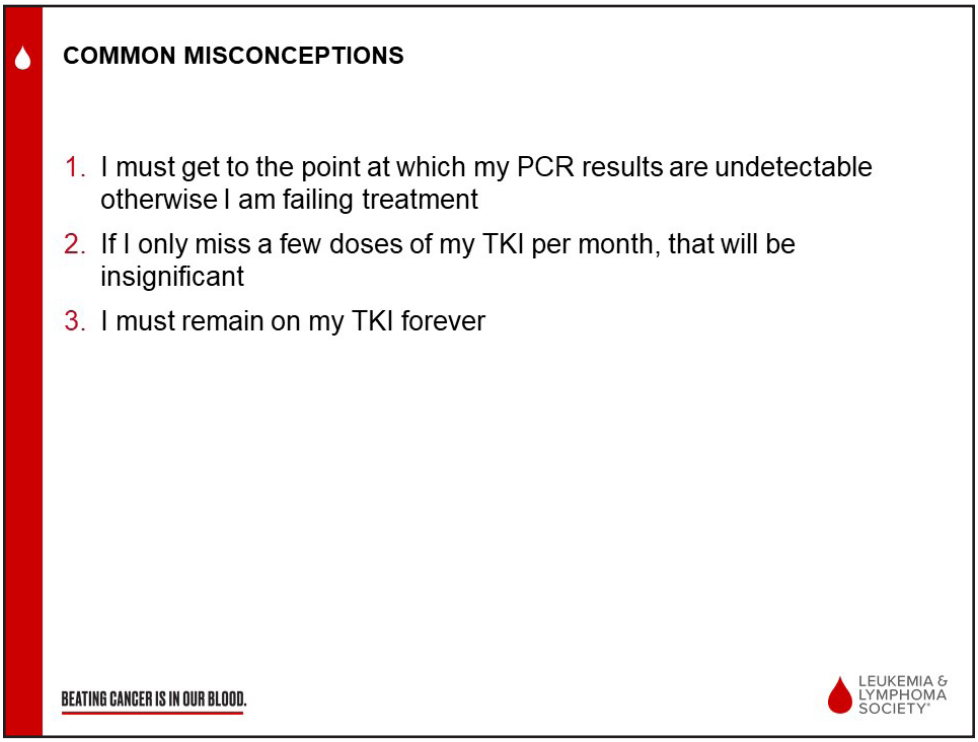
There's 3 distinct phases of CML. The first is chronic phase and that's the earliest phase of the disease. Middle of the road phase is called the accelerated phase and the most advanced phase of CML is blast phase. The distinction between these 3 phases is really determined based on the number of immature cells that we call blasts in the bone marrow. The vast majority of people are diagnosed in the chronic phase and when all is said and done our primary goal in treating anybody with chronic phase CML is to keep them in chronic phase and prevent the progression to an advanced phase of CML.

So again, the majority of people are diagnosed in the chronic phase. And, about 50% of those people, it's an incidental diagnosis, meaning they don't have any symptoms of their disease at the time they're diagnosed. They just happened to get routine blood work done for one reason or another and the white blood cell count was high and that led to this whole work-up that ultimately led to a diagnosis of CML. The other half may be experiencing symptoms like fatigue, unintentional weight loss, night sweats, abdominal pain, and those can be of varying severities.



Slide 9: CML TREATMENT GOALS

So, as I just mentioned, the primary goal of treating somebody with chronic phase CML is to prevent the progression to an advanced phase of CML. In addition to this, we're trying to kill the cells that harbor this BCR-ABL gene and restore the normal function of the bone marrow and return the blood counts to normal. For someone with an accelerated or blast phase CML, our goals are to kill as many of these BCR-ABL-containing cells as possible and hopefully return these patients back to the chronic phase.

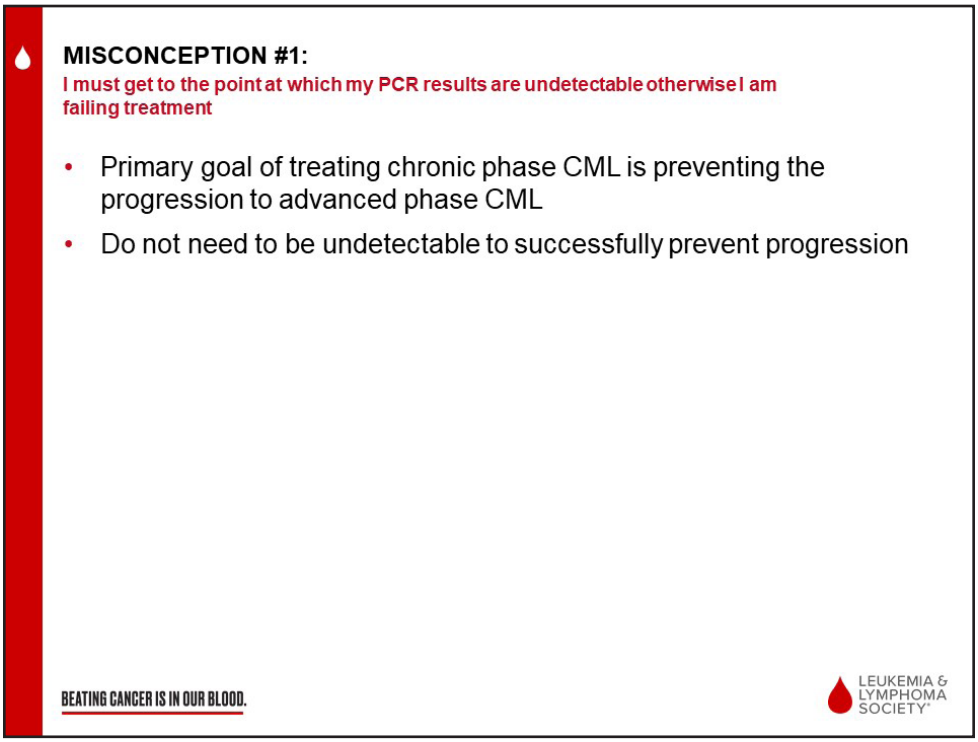


Slide 10: COMMON MISCONCEPTIONS

So, moving forward I want to address a few misconceptions about CML and the treatment for this disease. And, I've listed 3 statements here that I hear quite frequently that I'd like to discuss in more detail because I think this could answer a lot of questions, at least questions that I hear on a regular basis.

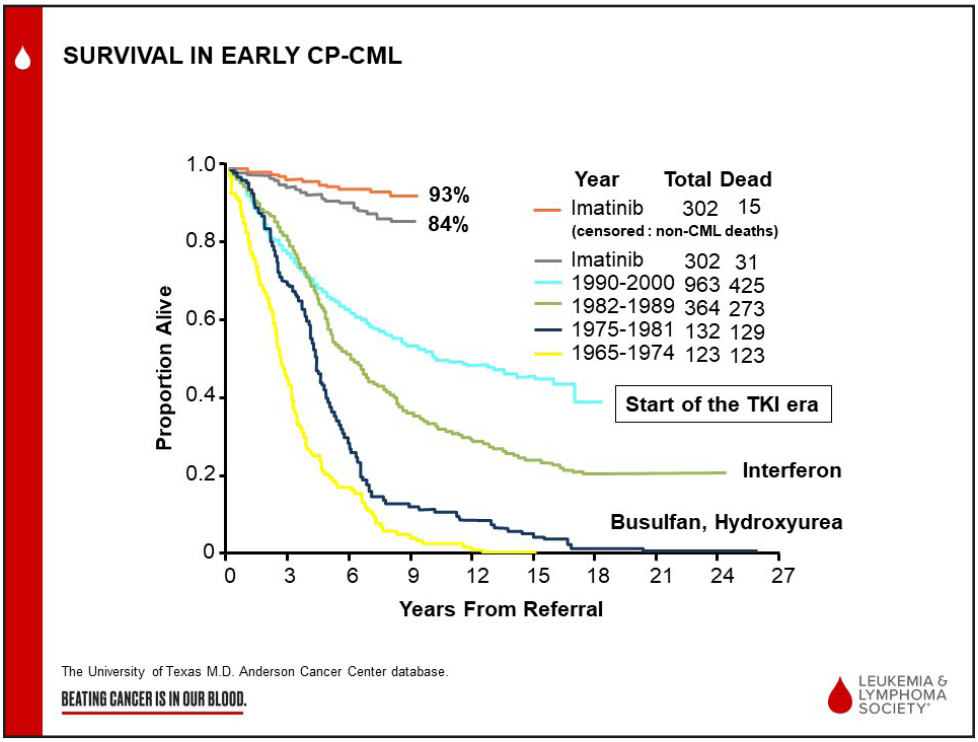
So, the first statement I hear, not infrequently, is: I must get to the point where my PCR (polymerase chain reaction) is undetectable, otherwise I'm failing treatment. The second is: If I miss just a few doses of my TKI (tyrosine kinase inhibitor) per month, that will be insignificant. And lastly: I must remain on my TKI forever.

So, we'll go over each of these in a lot of detail and explain why in reality none of these statements are actually accurate.



Slide 11: MISCONCEPTION #1:

So, the first statement I made in regard to needing to have undetectable BCR-ABL levels, again I want to go back to what I mentioned a few minutes ago, which is, if we have to choose one singular goal for treating CML, it actually has nothing to do with our PCR results. It's truly to prevent the progression to accelerated or blast phase CML, and it's not necessary to have undetectable BCR-ABL in order to prevent progression. The truth is that the majority of people never become undetectable and they do extremely well long-term.

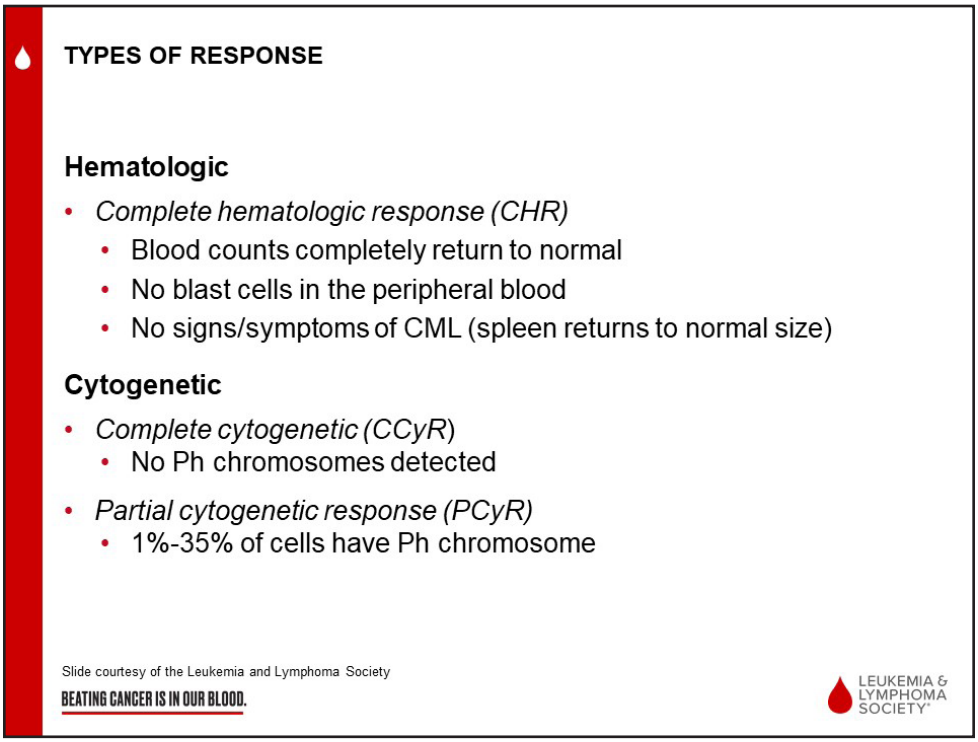


Slide 12: SURVIVAL IN EARLY CP-CML

I think this is illustrated nicely in this slide. This is a survival curve for people with chronic phase CML and, it illustrates the difference in survival over the last 45 years or so. And, you can see the significant improvements that occurred when imatinib or Gleevec® was developed and approved in 2001. And since that time, we've honestly changed CML from a disease that was once a leading indication for a bone marrow transplant, and now have turned it into a chronic disease that we can manage much like hypertension or diabetes, where it requires daily medication and frequent monitoring, but with proper treatment people can do very, very well.

So, looking at this curve you can see that in the imatinib era, 84% of patients are still alive 10 years after being diagnosed with CML. And, if you look only at patients or only considering deaths related to CML, 93% of patients are still alive at 10 years, which is absolutely remarkable. And, one thing I can absolutely assure you is that not all 93% of these patients had undetectable BCR-ABL. And, they still have done extremely well.

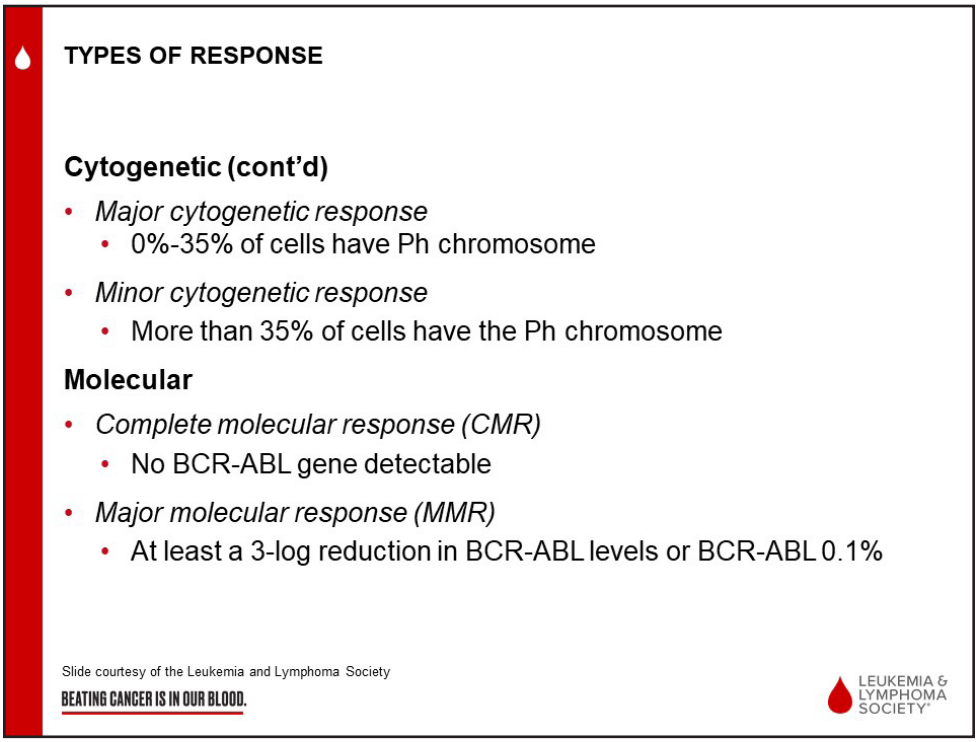
So, once someone's started on treatment for CML, it's critical that they're monitored closely in order to assess response to treatment as well as assessing tolerance to treatment.



Slide 13: TYPES OF RESPONSE

In regard to response, there are 3 different types of responses that we follow. The first is called a hematologic response and this is really the least sensitive way to monitor CML. So, a complete hematologic response means that the blood counts in your CBC (complete blood count) have normalized and the spleen has returned to a normal size. This is expected to happen within the first month after starting treatment and once this happens, if we're just monitoring blood counts, we're getting very little information about the response to treatment.

So, for this reason we then start looking at the next, more sensitive way of monitoring CML, which is looking for cytogenetic responses. This means monitoring for the presence of the Philadelphia chromosome in the bone marrow. A complete cytogenetic response means that we're no longer able to detect the Philadelphia chromosome when we look at the cytogenetics in the bone marrow. The expectation is that this should occur by the end of the first year on treatment. And, there are various types of cytogenetic responses that we look for during that first year on treatment, but at the end of the day, it's this complete cytogenetic response that's really the most important.

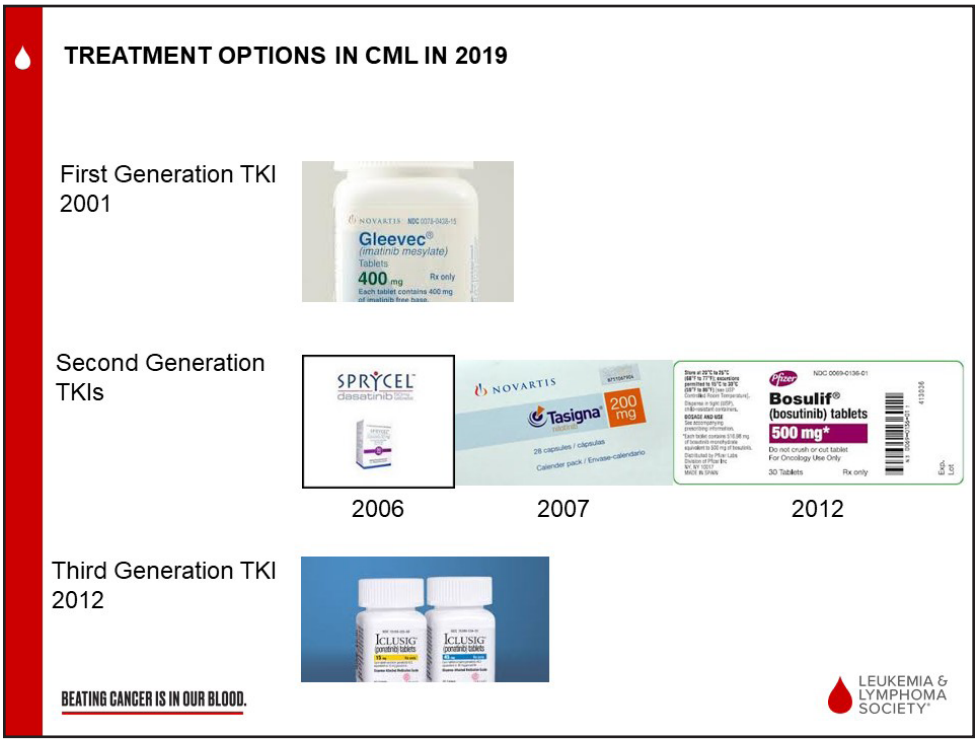


Slide 14: TYPES OF RESPONSE

So, once we're no longer able to detect the Philadelphia chromosome in the bone marrow, there's really no reason to continue doing bone marrow biopsies unless we're concerned that someone is progressing. At this stage when someone has a complete cytogenetic response, the bone marrow is going to look normal and it's not going to give us any additional information about how well a patient is responding to treatment. So, from that point forward the only way to monitor CML is on a molecular level, using a test that we call PCR. And, what PCR does is it measures the amount of BCR-ABL that's present in the blood and there are various levels of molecular responses that we can assess.

So, the first molecular response that we can assess for is something called a major molecular response, which is a 3-log reduction in the amount of BCR-ABL, since the time that a patient is diagnosed. And, you can see, and I'll explain this more in a few slides, is major molecular response is equivalent to a value of 0.1% on the scale that we use to monitor response.

The deepest level of molecular response is referred to as a complete molecular response, which means that we're no longer able to detect BCR-ABL in the blood. What's really important to point out here, though, is that just because we can't detect BCR-ABL at this point, it does not mean that it's not there. It just means that the amount of BCR-ABL is so low that our tests are not sensitive enough to pick it up anymore.



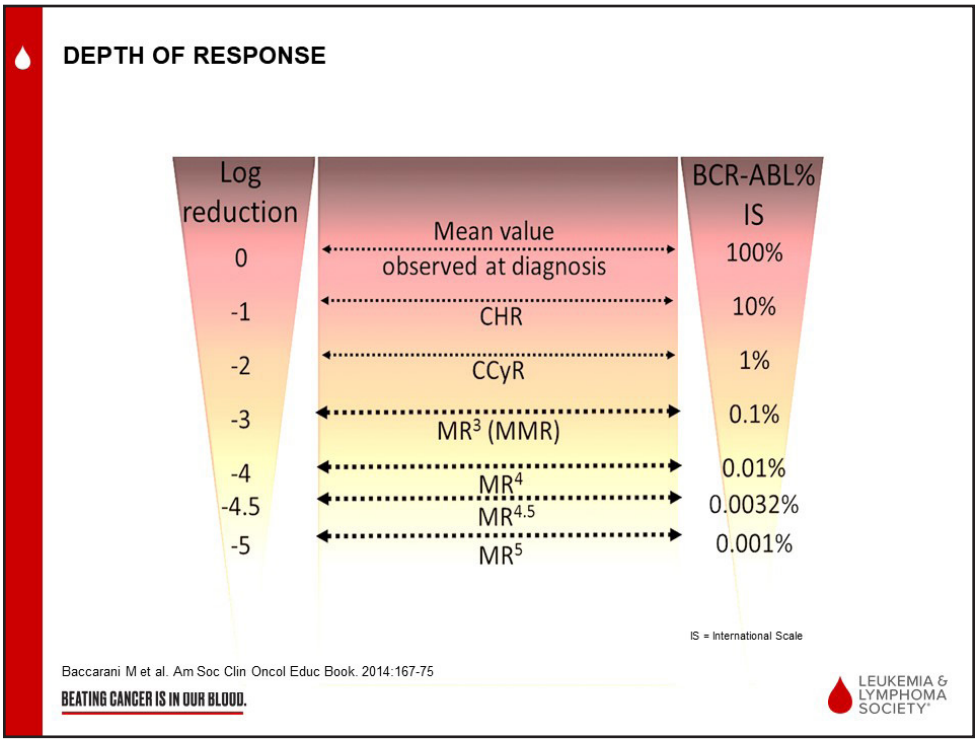
Slide 15: TREATMENT OPTIONS IN CML IN 2019

As most of you already know, we have quite a few very effective treatment options for CML these days. So, the drugs that we use to treat CML are called tyrosine kinase inhibitors or TKIs. And, these drugs directly target BCR-ABL and kill any of the cells with this genetic change.

So, the first TKI that was approved for CML was imatinib, which was approved in 2001. It's also called Gleevec. Since then we've had 3 second generation TKIs approved, first being dasatinib or Sprycel® in 2006, then nilotinib or Tasigna® in 2007, and then bosutinib or Bosulif® in 2012. And, now we also have a third generation TKI called ponatinib or Iclusig®, which was also approved in 2012.

So, once someone's diagnosed with CML, the doctor will look at the specific features of their disease, as well as looking at other medications that someone's taking and other medical conditions, and then compare all of that information with the potential side effects of each TKI in order to determine what the most appropriate first-line drug is for each individual patient.

Once someone's started on treatment, they need to be monitored very closely in order to assess for the different response types that I mentioned earlier, as well as monitoring for possible side effects of the TKI. So typically, in my practice anyways, I'll see somebody once a week during the first month on treatment, every other week during the second month on treatment, and if someone's doing well after 2 months I'll bring them back at 3 months in order to do their first molecular assessment. That's really the first time that we're monitoring molecular response to treatment.

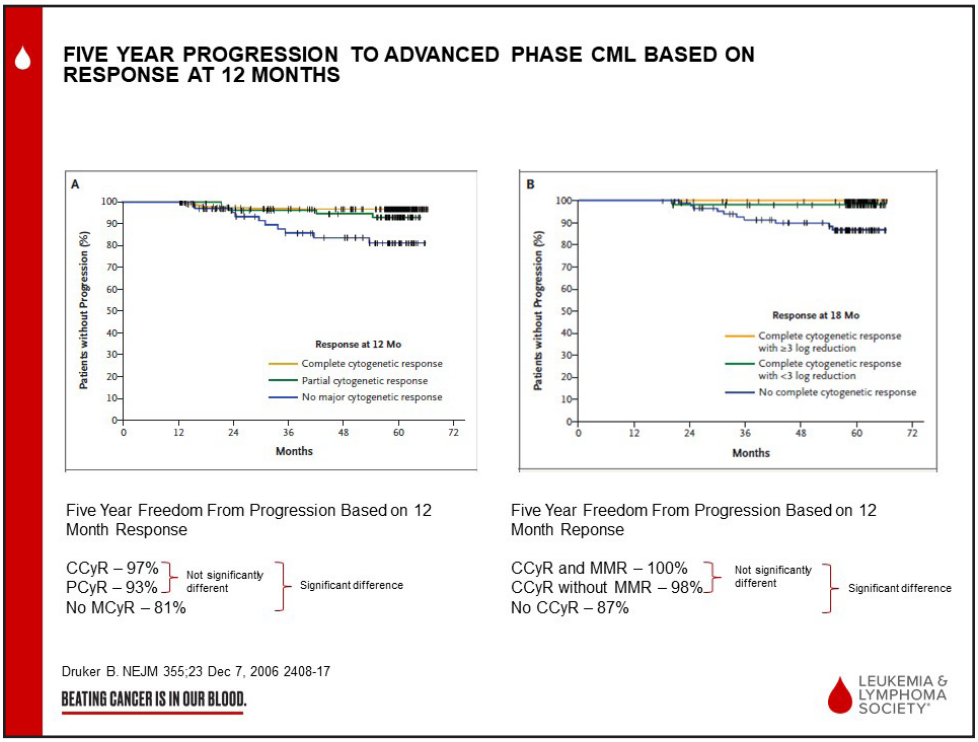


Slide 16: DEPTH OF RESPONSE

So, after 3 months, if someone's doing well, there's really no need for them to be seeing their physician any more frequently than every 3 months for molecular testing. And again, this molecular testing is measuring the amount of BCR-ABL that's present in the blood. So, as the number of leukemic cells decreases on treatment, so does the number on that scale that we're using to measure BCR-ABL. So, this scale is called the International Scale and it's abbreviated as IS. So, if you ever see your PCR reports, you'll see BCR-ABL percent IS and you know that that's really the number that's being monitored very closely.

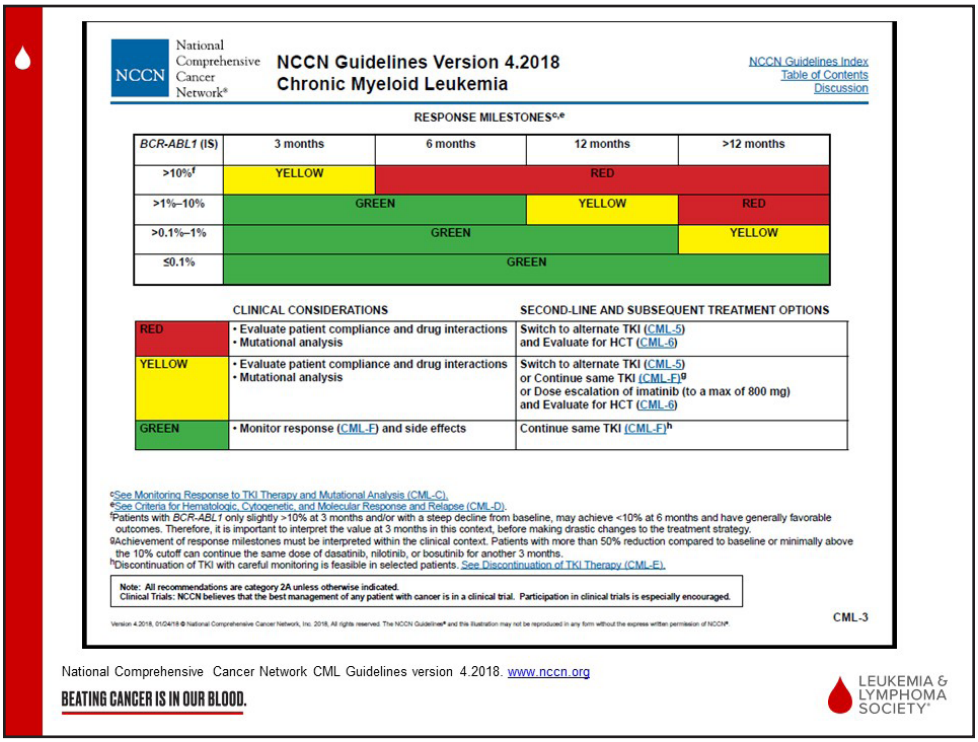
So, this scale was designed so that we could compare results between labs, so that someone can get labs at LabCorp one day, at Quest another time, at their local cancer center another time, and we're still able to compare the results between the 2 labs.

Looking at this slide, you'll see that even though this BCR or this International Scale gets to very, very small numbers with the depth of response it really doesn't become zero. And again, that's not the expectation for the vast majority of people with CML.



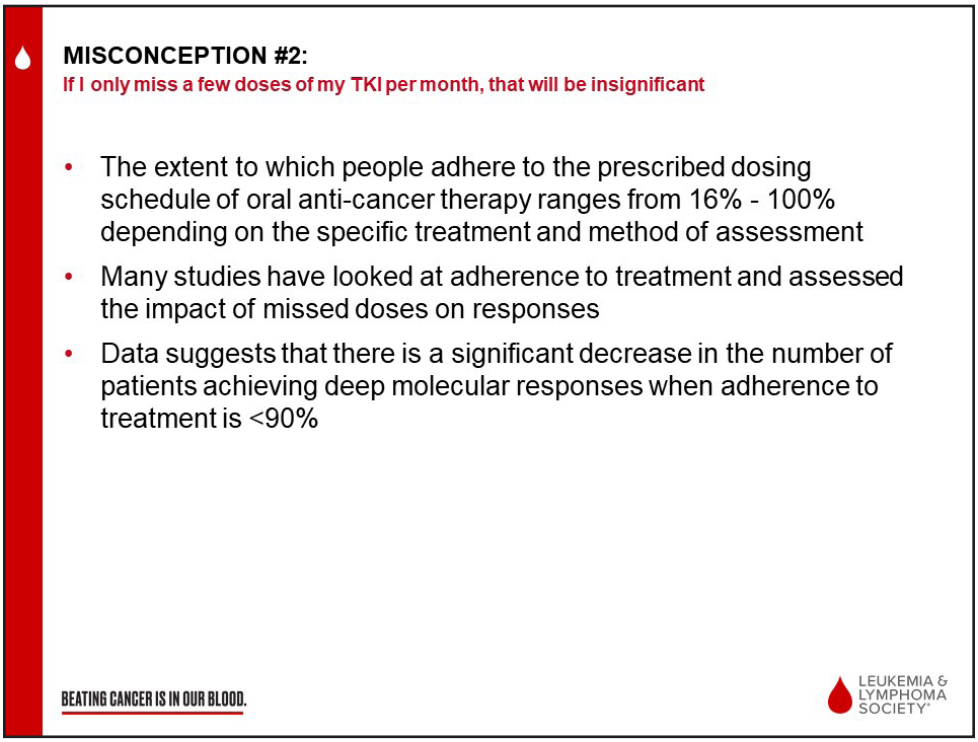
Slide 17: FIVE YEAR PROGRESSION TO ADVANCED PHASE CML BASED ON RESPONSE AT 12 MONTHS

So, what this slide is showing, and it may be a little bit hard to understand if you're not used to looking at curves like this, but what this is looking at is the impact of certain levels of response on long-term outcomes. And it's really showing us the risk of progressing with various levels of response. So again, the cytogenetic response or complete cytogenetic response is not quite as deep as a major molecular response. But, if you look at this curve here on the left you can see that in patients who achieved a complete cytogenetic response by 12 months on treatment, only 3% of those patients ultimately progressed in their CML. Now, if patients developed a major molecular response by 12 months on treatment, none of those patients progressed. And, none of these responses are anywhere near undetectable levels of BCR-ABL but looking at this you can tell that these people do extremely well. So, I'm just trying to illustrate the point again that although it's really nice to see undetectable BCR-ABL, it's certainly not a requirement in order to have excellent long-term outcomes. People can do very, very well without them.



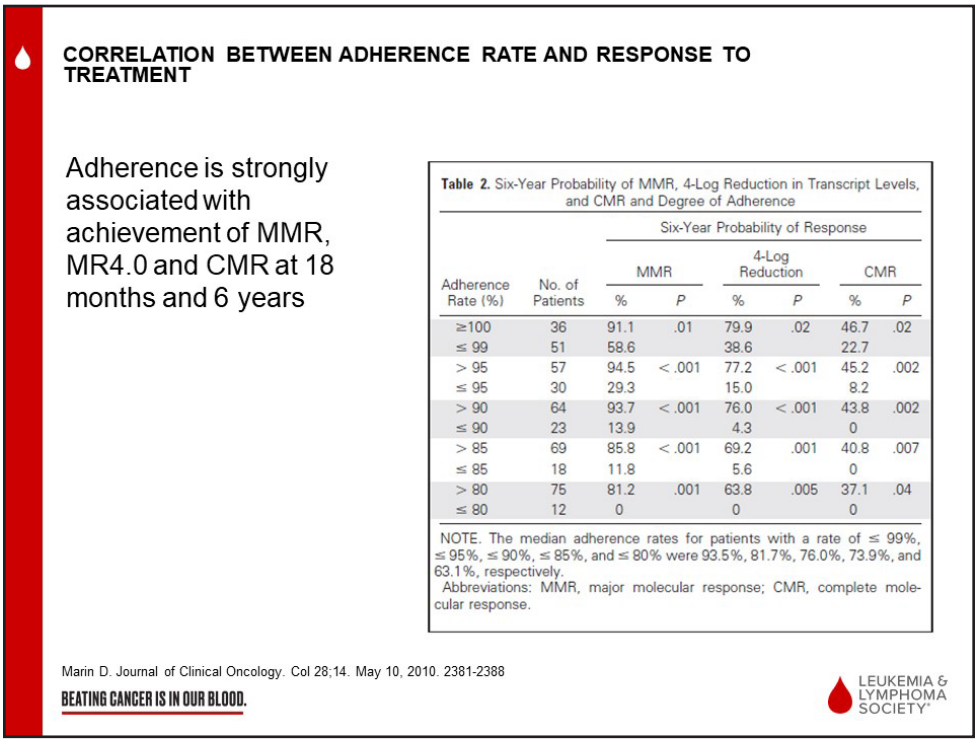
Slide 18: NCCN GUIDELINES VERSION 4.2018 CHRONIC MYELOID LEUKEMIA

And, the National Comprehensive Cancer Network or the NCCN is the national committee that develops guidelines for treating CML. And, this table was taken from the NCCN guidelines and it's color-coded for the desired response milestones at various time points in treatment. So, you can see if someone falls into a green category that indicates they're doing very well. If they fall into a yellow category, they still could be doing very well, but it may require some additional testing or some questions about missed doses or possible drug interactions. If someone falls into a red category, that would be an indication to change treatment. But, at no point in these guidelines do they suggest that someone is expected to be undetectable. In fact, looking at this, you can see as long as the PCR is less than 0.1%, that's considered to be an ideal response to treatment. And, anything beyond that is just really extra benefit.



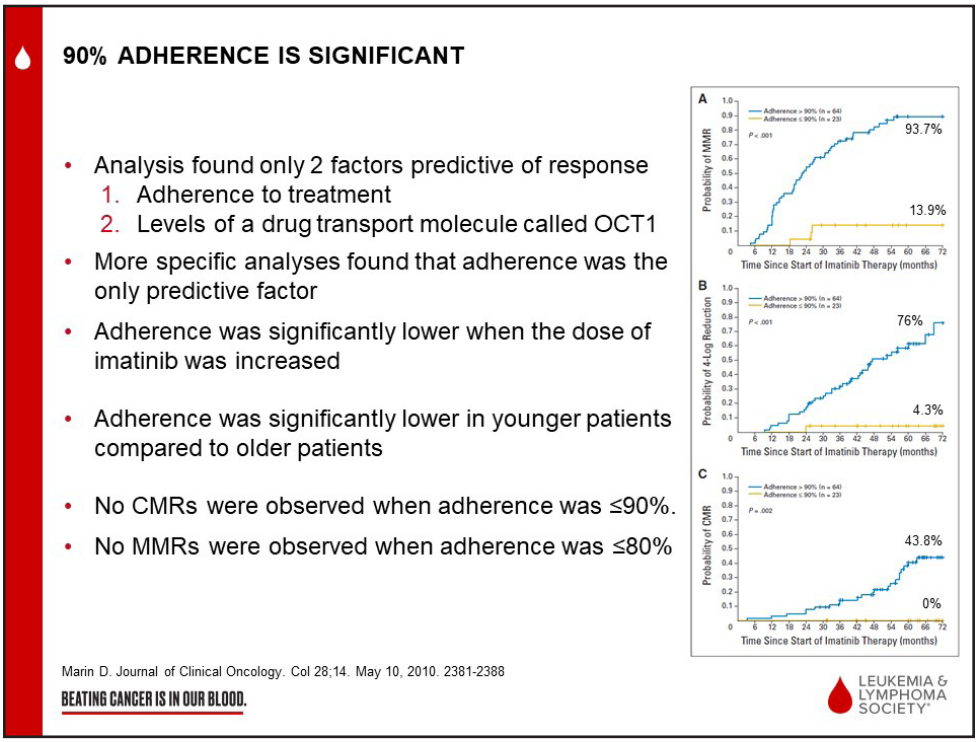
Slide 19: MISCONCEPTION #2

So, the second misconception I wanted to talk about, and I hear frequently, it relates to the necessity of taking medication daily without missing any doses. And, there's no question that it's hard to take these drugs on a daily basis. It's hard to remember to take them once or twice a day, things come up and people miss doses, they go on a vacation, they accidentally leave the drug at home. If someone's experiencing side effects from their TKI they may choose to skip a few doses in order to minimize those side effects. But unfortunately, even missing just a few doses a month can have detrimental effects on your response to treatment. So, a number of studies have looked at the correlation between adherence to treatment and depth of response and suggested that a significant decrease in the number of people who achieve deep molecular responses occur in patients who are taking less than 90% of the prescribed dose of the medication.



Slide 20: CORRELATION BETWEEN ADHERENCE RATE AND RESPONSE TO TREATMENT

So, hopefully this is not too hard to read but, this study looked at differences in achievement of various levels of molecular response, and adherence to treatment, and found that there are very strong achievement of deep molecular responses at 18 months and again at 6 years. So, just as an example, you can see over on the right column they found that nearly 44% of patients who took at least 90% of their prescribed TKI dose had undetectable BCR-ABL by 6 years. In comparison, none of the patients who took less than 90% of the prescribed dose had undetectable BCR-ABL at 6 years.

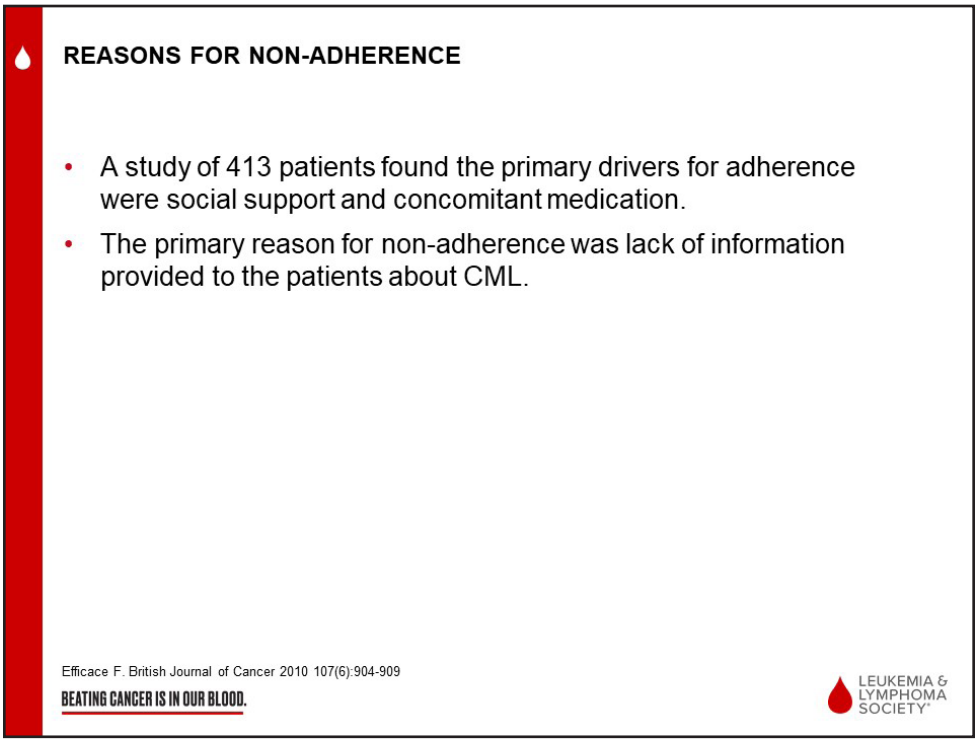


Slide 21: 90% ADHERENCE IS SIGNIFICANT

So, another specific analysis looked at factors that could possibly predict response, this is to imatinib, and they found that adherence to treatment was really the only predictive factor to achieving certain responses. They also found that adherence was much lower in patients who were on higher doses of imatinib. To me this makes a lot of sense because high-dose imatinib, or Gleevec, can cause a lot of side effects. So, if someone's experiencing a lot of side effects, they're probably not going to be taking their drug all the time because it makes them feel bad, it's very hard to do that.

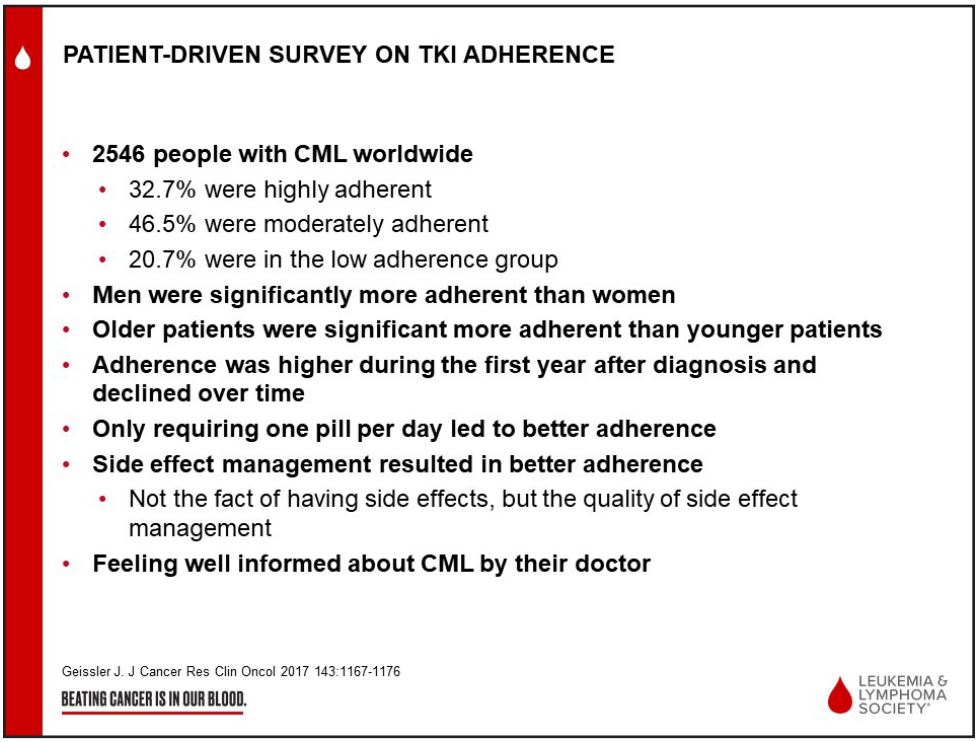
In addition to that, adherence is a lot lower in younger patients compared to older patients. And, that I think is a whole separate talk, but it has been shown repeatedly in many of these different studies looking at reasons for adherence versus non-adherence to treatment.

So, there's another study that looked at factors that were associated with adherence versus non-adherence, and they found the 2 most significant drivers for adherence were social support and the addition of supportive care medications to help aid with some of the side effects.



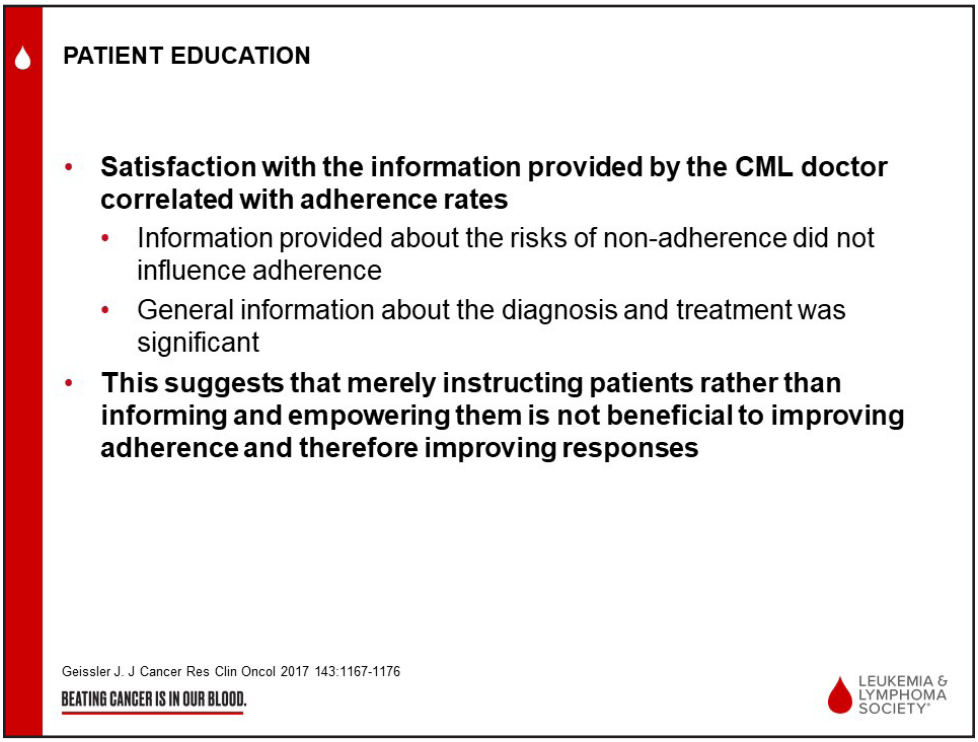
Slide 22: REASONS FOR NON-ADHERENCE

Interestingly, and probably one of the most important facts for any doctor who treats CML to remember is that the primary reason for non-adherence was the lack of information provided to a patient about CML. To me this makes a lot of sense, because if you're asked to take a drug every day, that drug has side effects that can be challenging to deal with, most people want to understand why they need to take it and what type of response they should expect with and without the drug, and that's what's going to motivate them to take it. So, people tend to be much more motivated to do things if they understand why it's important to do so. And, this study illustrated that very nicely.



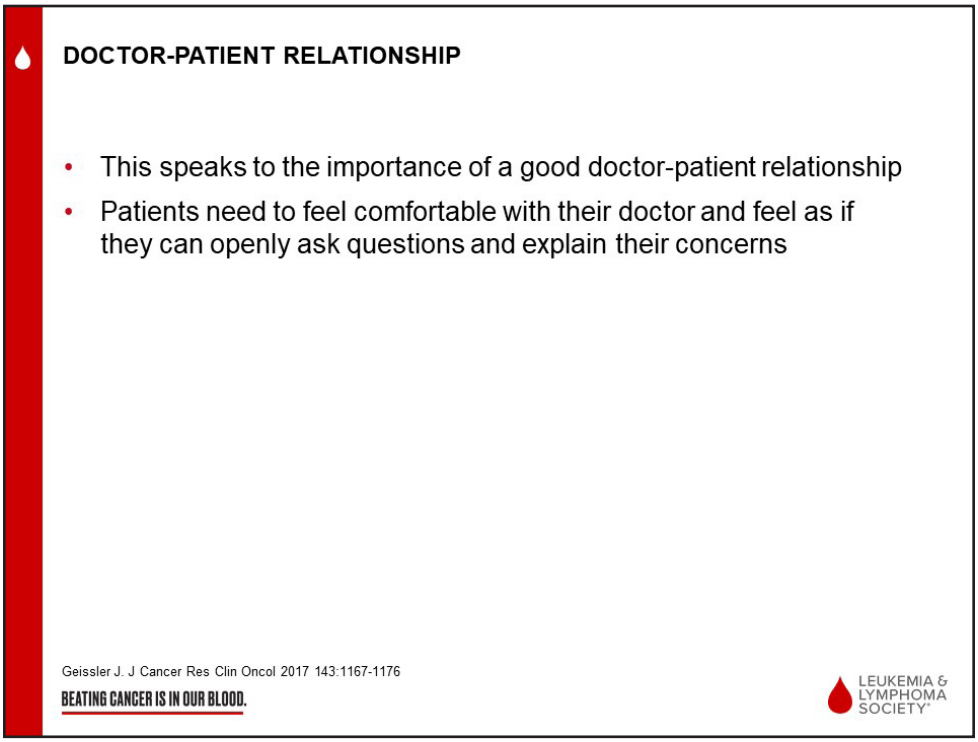
Slide 23: PATIENT-DRIVEN SURVEY ON TKI ADHERENCE

There's another study, a large study, 2500 people, looked at adherence in TKIs and found that only a third of CML patients were considered highly adherent to treatment. They also noted that in general, men were more adherent than women, older patients again more adherent than younger patients in general – these are all generalities here, adherence was higher during the first year of treatment and tended to decline over time, and those patients taking one pill a day were more adherent than those who had to take more than one. In addition to that, feeling well informed about CML by their doctor was also a significant factor. And finally, effective side effect management was critical. Importantly, it wasn't the fact of having side effects or not having side effects was important, it was really whether or not those side effects were being taken seriously and were being addressed. And, that's what seems to play a big role. So, I really think this illustrates the point that it's critical for anyone with CML to be able to talk openly with their doctor about how they're feeling and any side effects they may be having, so they can be adequately addressed. Most side effects from TKIs can be addressed if we're aware that they're going on. We can't always make them go away 100%, but certainly can do something to make them better. And, it's critical to have that open dialogue between the patient and their physician if we're hoping to have success with treatment.



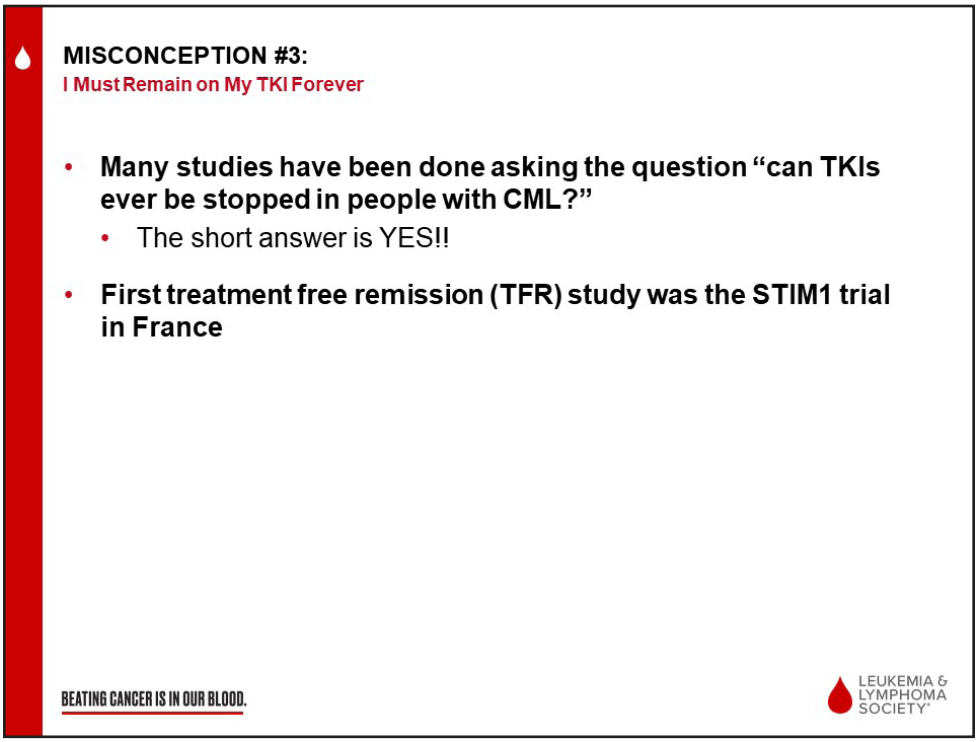
Slide 24: PATIENT EDUCATION

When it came to providing information about CML, they found simply stating that it's important to take your medication did not impact adherence to treatment. And, I think that's probably pretty obvious. What they found again was providing general information about CML and treatment made a big difference. So, what this suggests is that merely instructing patients, rather than informing and empowering them, is not beneficial to improve adherence and therefore to improve responses. What's really important I think in the beginning to educate someone about their disease, educate them about what the drug is supposed to be doing, and why it's important to be taking it and what kind of response we're expecting. And, important for patients to find resources to educate themselves as well.



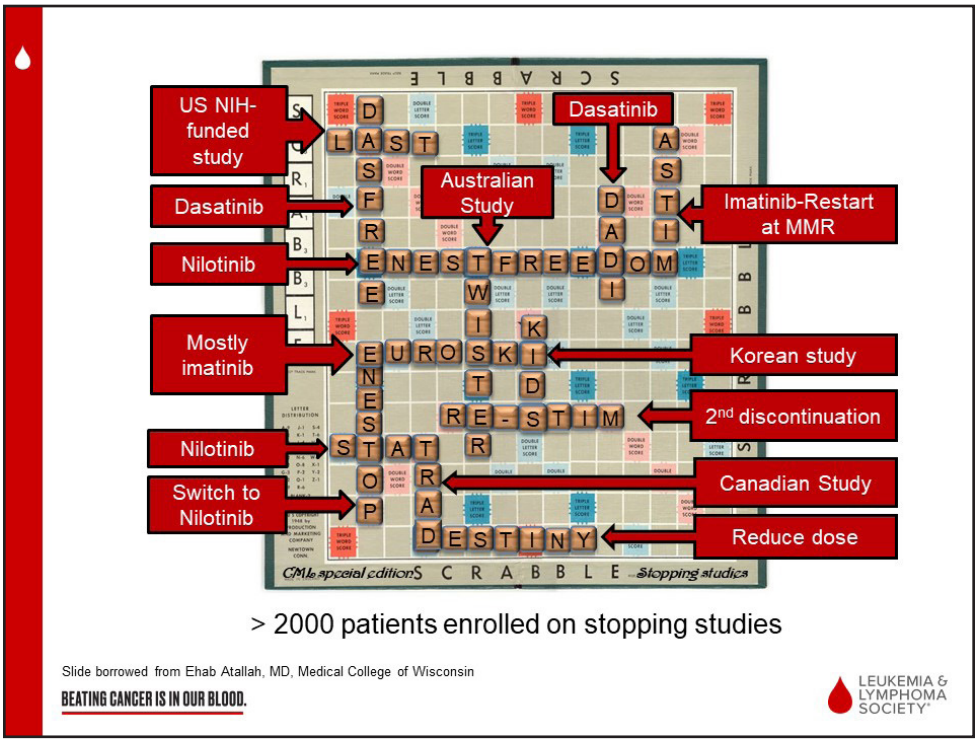
Slide 25: DOCTOR-PATIENT RELATIONSHIP

So again, I've said this a couple of times now, right, this speaks to the importance of a good doctor-patient relationship. The patient needs to feel comfortable with their doctor and needs to know that they can openly ask questions and discuss concerns in order to have the highest chance of success on treatment.



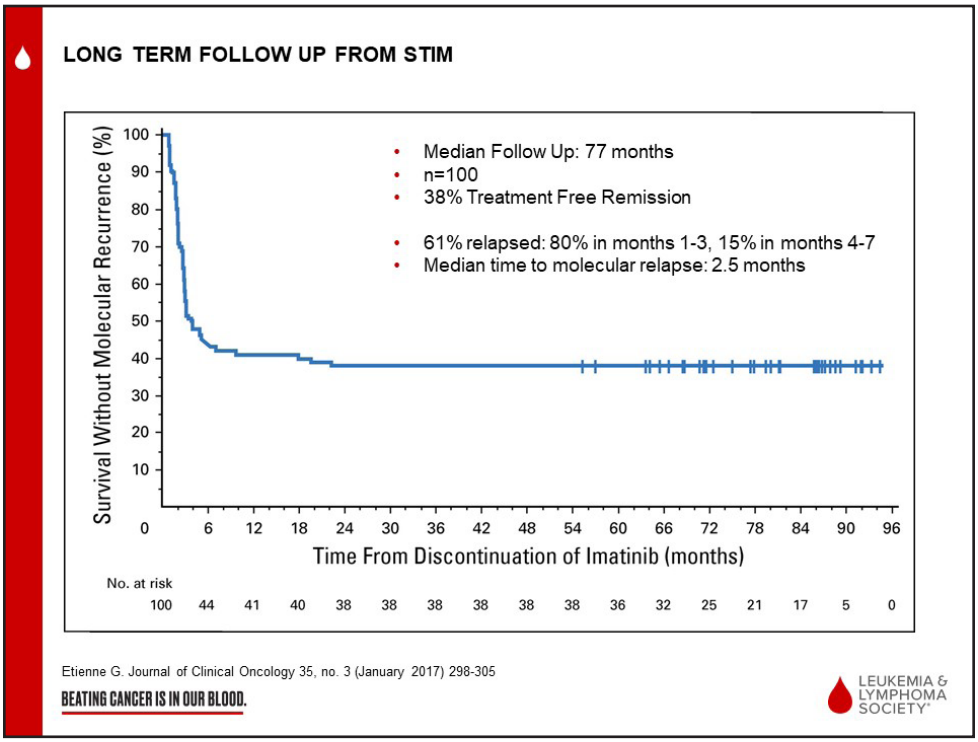
Slide 26: MISCONCEPTION #3

So, the third topic I wanted to address is the potential for stopping treatment. And, this is a huge question in the field, this is a huge question we get all the time. Is it really possible to stop TKIs in someone with CML? The textbook answer to this question may be no, but the real answer to this question is yes. It's not 100% of people who are going to be able to stop treatment, but there are a fair number of people who are eligible to try.



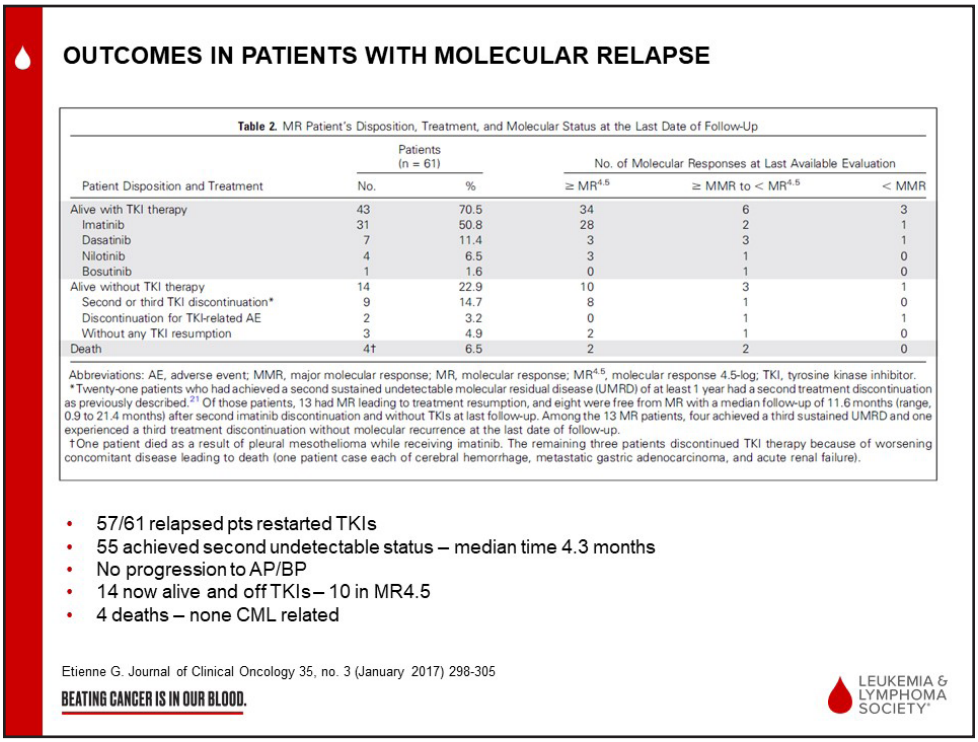
Slide 27: STIM TRIAL

So, the first study that looked at this question was the STIM trial, which was done in France. Since the STIM trial, we've had many other TKI discontinuation trials that have been completed and have enrolled over 2000 patients on these studies over the past 10 or 12 years now. So, we have fairly robust data telling us about the safety of attempting to stop treatment.



Slide 28: LONG TERM FOLLOW UP FROM STIM

The longest-term data we have available on discontinuation is from the STIM trial. So, this trial enrolled 100 patients who were being treated with imatinib, who had undetectable BCR-ABL for a minimum of 2 years, and then these patients discontinued treatment. There was a median follow-up time of 77 months, 38% of the patients remained in a treatment-free remission, their TFR, which means they remained off-treatment without any detectable BCR-ABL. You can see looking at this curve, of those patients who relapsed the majority of them did so in the first 6 months after stopping treatment. So, what this data suggests is that when we stop TKIs in someone, then they relapse, the relapse is likely to happen very quickly. If it doesn't happen in the first 6 months the likelihood of relapse decreases significantly. It's not zero, but certainly it's far lower than it was at the time that they actually stopped treatment.



OUTCOMES IN PATIENTS WITH MOLECULAR RELAPSE

Table 2. MR Patient's Disposition, Treatment, and Molecular Status at the Last Date of Follow-Up

Patient Disposition and Treatment	Patients (n = 61) No.	Patients (n = 61) %	No. of Molecular Responses at Last Available Evaluation ≥ $MR^{4.5}$	≥ MMR to < $MR^{4.5}$	< MMR
Alive with TKI therapy	43	70.5	34	6	3
Imatinib	31	50.8	28	2	1
Dasatinib	7	11.4	3	3	1
Nilotinib	4	6.5	3	1	0
Bosutinib	1	1.6	0	1	0
Alive without TKI therapy	14	22.9	10	3	1
Second or third TKI discontinuation*	9	14.7	8	1	0
Discontinuation for TKI-related AE	2	3.2	0	1	1
Without any TKI resumption	3	4.9	2	1	0
Death	4†	6.5	2	2	0

Abbreviations: AE, adverse event; MMR, major molecular response; MR, molecular response; $MR^{4.5}$, molecular response 4.5-log; TKI, tyrosine kinase inhibitor.
*Twenty-one patients who had achieved a second sustained undetectable molecular residual disease (UMRD) of at least 1 year had a second treatment discontinuation as previously described.[23] Of those patients, 13 had MR leading to treatment resumption, and eight were free from MR with a median follow-up of 11.6 months (range, 0.9 to 21.4 months) after second imatinib discontinuation and without TKIs at last follow-up. Among the 13 MR patients, four achieved a third sustained UMRD and one experienced a third treatment discontinuation without molecular recurrence at the last date of follow-up.
†One patient died as a result of pleural mesothelioma while receiving imatinib. The remaining three patients discontinued TKI therapy because of worsening concomitant disease leading to death (one patient case each of cerebral hemorrhage, metastatic gastric adenocarcinoma, and acute renal failure).

- 57/61 relapsed pts restarted TKIs
- 55 achieved second undetectable status – median time 4.3 months
- No progression to AP/BP
- 14 now alive and off TKIs – 10 in MR4.5
- 4 deaths – none CML related

Etienne G. Journal of Clinical Oncology 35, no. 3 (January 2017) 298-305

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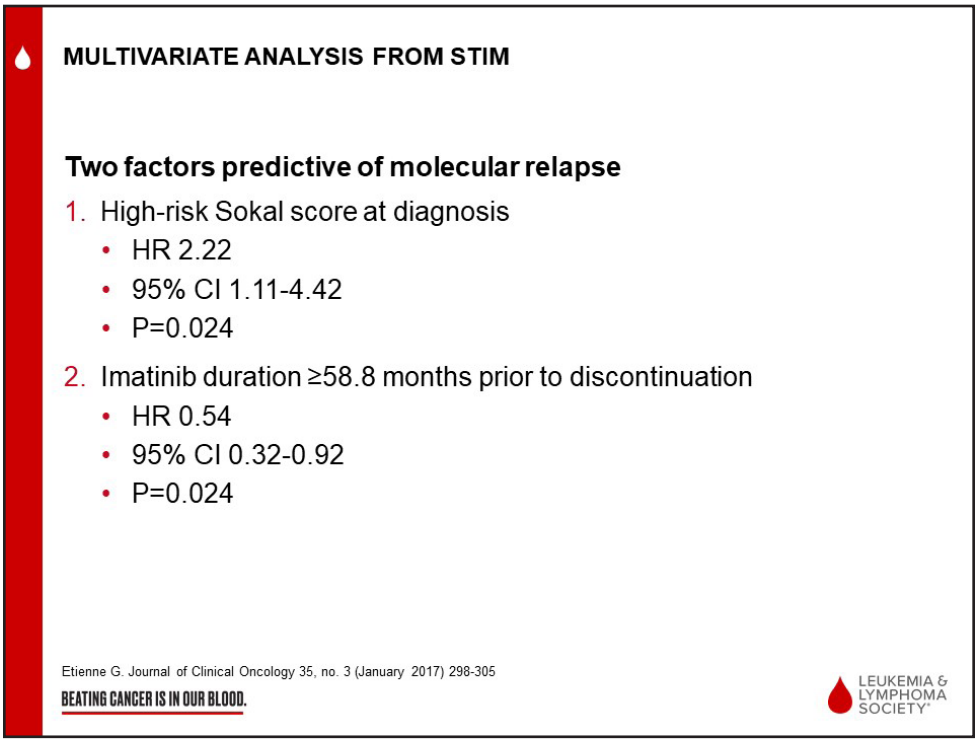
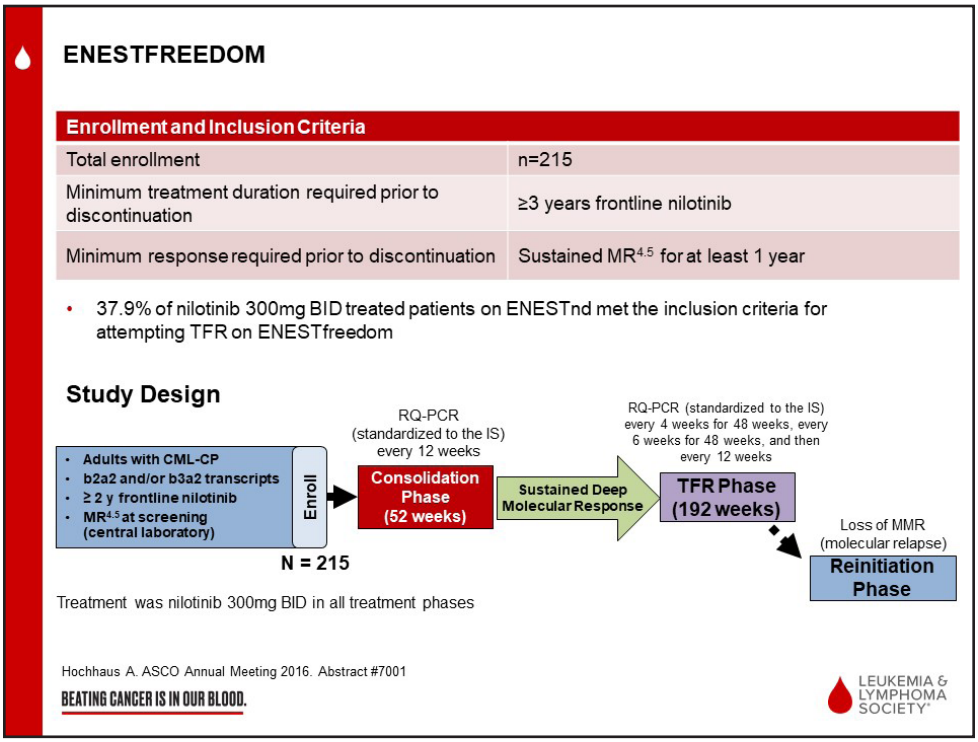
Slide 29: OUTCOMES IN PATIENTS WITH MOLECULAR RELAPSE

In my opinion, what's perhaps more important than the fact that we can stop some people's treatment is the fact that in those patients who did relapse, nearly all of them regained their prior response within a matter of months after restarting therapy. Nobody progressed to accelerated or blast phase CML. And, what this tells us is that if we select patients appropriately to attempt TKI discontinuation, and if we monitor them closely, it doesn't appear that we're causing any harm by trying to stop treatment.



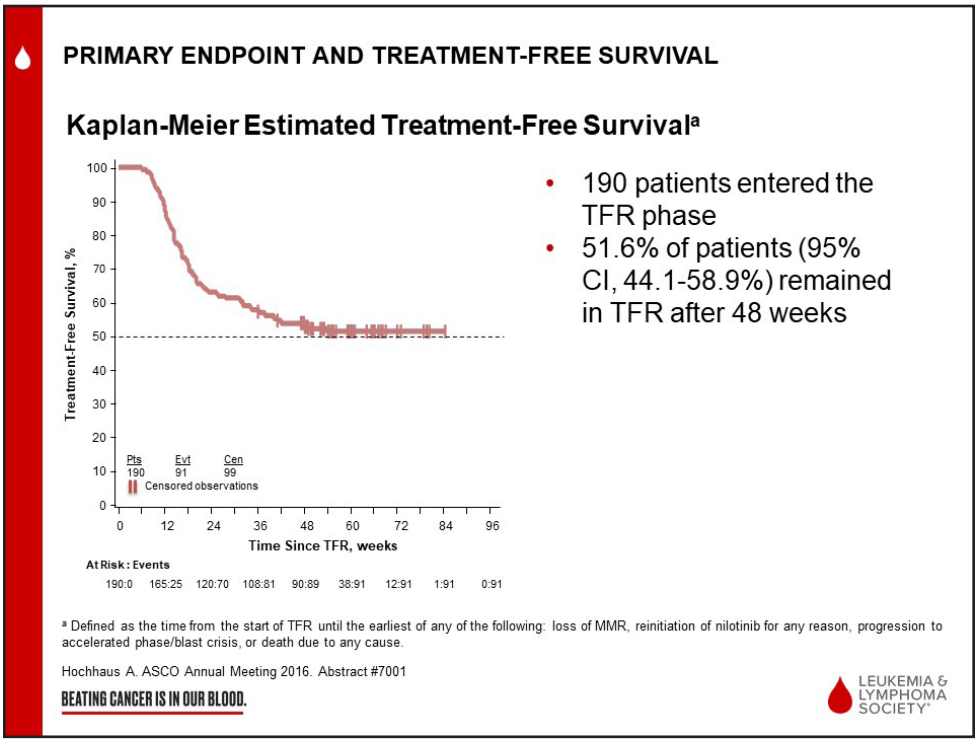
Slide 30: MULTIVARIATE ANALYSIS FROM STIM

The investigators on the STIM trial then tried to identify some factors that were predictive of molecular relapse. And, they found 2 factors that they think are predictive. One being a higher risk Sokal score at the time that their CML is diagnosed, and if someone has a higher risk Sokal score that increases the likelihood that they could relapse after TKI cessation. The other is duration of time on treatment. So those with a shorter duration of time on treatment had a higher likelihood of relapse. Some of these factors have held true in other discontinuation trials and others have not. And, we're still trying to really nail down the predictive factors here.



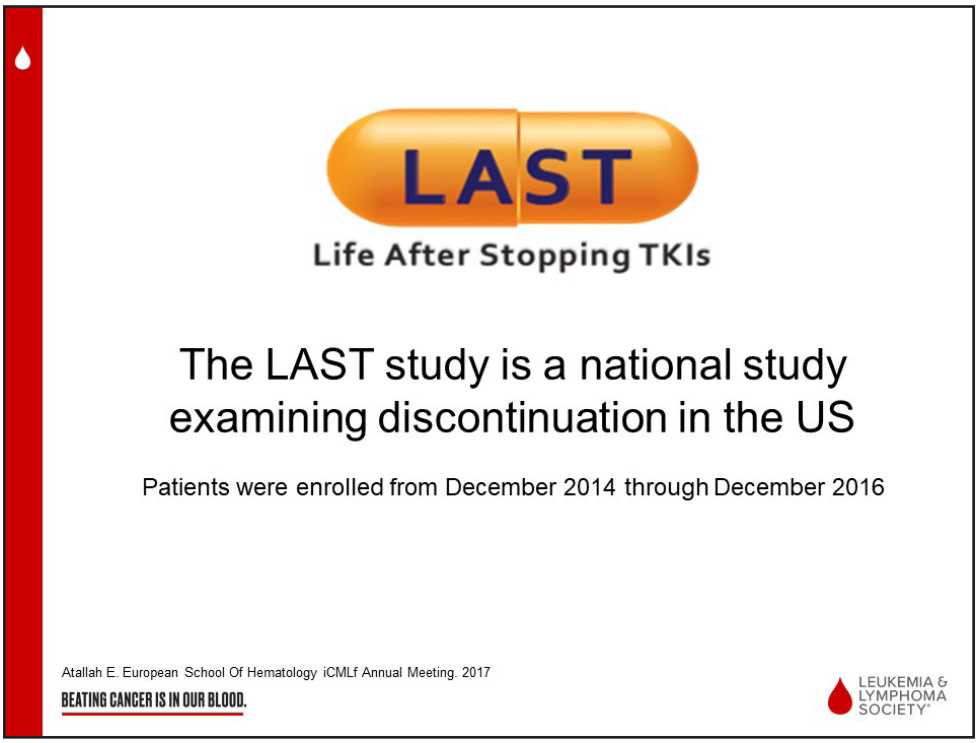
Slide 31: ENESTFREEDOM

So, the ENESTfreedom study was another TKI discontinuation trial, but this study looked at stopping nilotinib, or Tasigna. So, in this trial they enrolled patients who'd been on nilotinib for a minimum of 2 years and had undetectable BCR-ABL or a 4½ log reduction in BCR-ABL for at least 1 year. Patients then continued nilotinib for an additional year, so they were on for a minimum of 3 years at the time that they discontinued treatment. And, as long as they had maintained that 4½ log reduction in BCR-ABL, they were eligible to stop treatment.



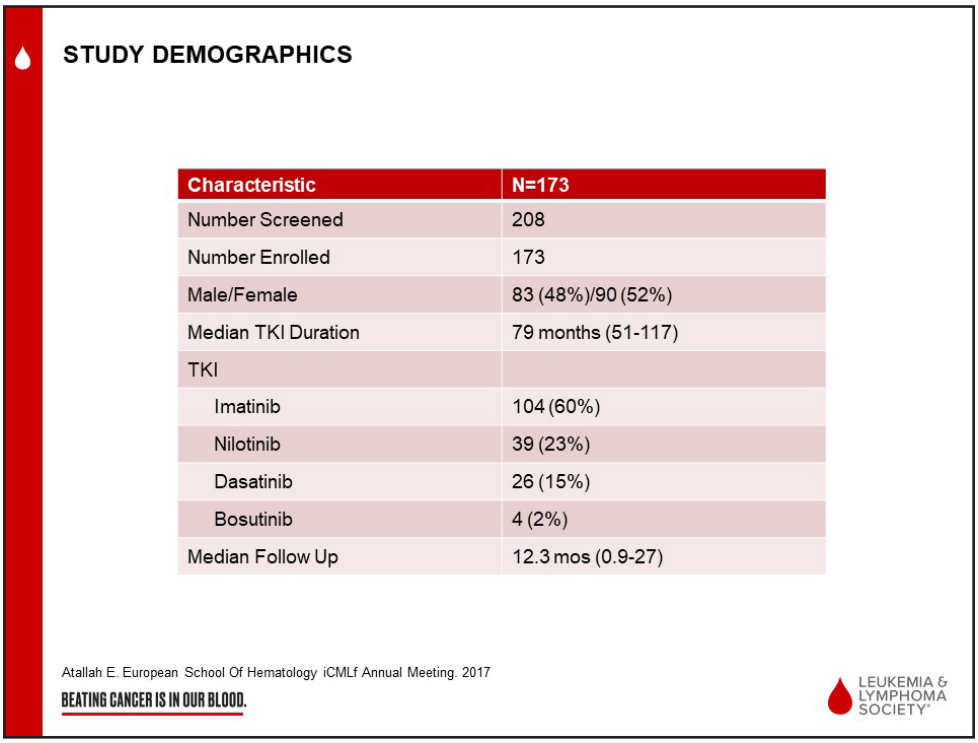
Slide 32: PRIMARY ENDPOINT AND TREATMENT-FREE SURVIVAL

So, what this study found was that at 48 weeks, 52% of the patients remained off treatment without a molecular relapse. What's really important to point out here, though, is that in the ENESTfreedom and the STIM trial they had different definitions for molecular relapse, and this partially explains the different numbers that we're seeing in regard to the number of patients remaining off treatment. While in the STIM trial, any detectable BCR-ABL that was confirmed by the second test was considered relapse and patients were required to restart treatment. In ENESTfreedom, molecular relapse was defined as loss of major molecular response. So, patients could have detectable BCR-ABL, but as long as it stayed below 0.1% they could remain off treatment. So, a lot of these discontinuation trials have different criteria or different definitions for relapse, so we need to take that into account when looking at the different studies.



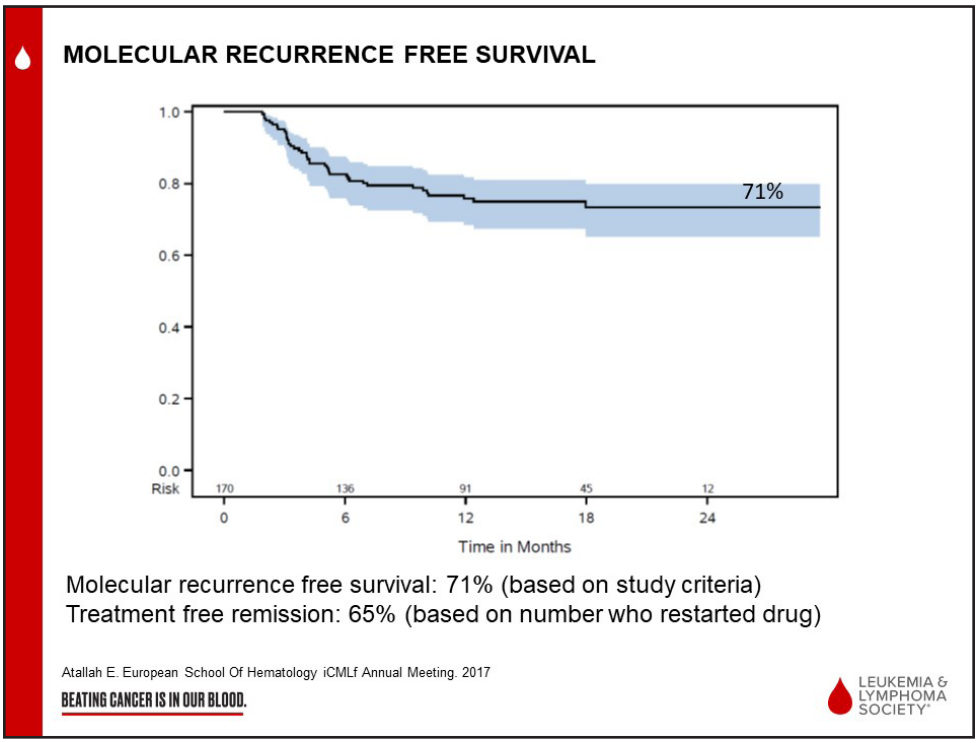
Slide 33: LAST STUDY

The LAST study of the TKI discontinuation trial was done here in the United States, and some of you actually may have participated in this trial.



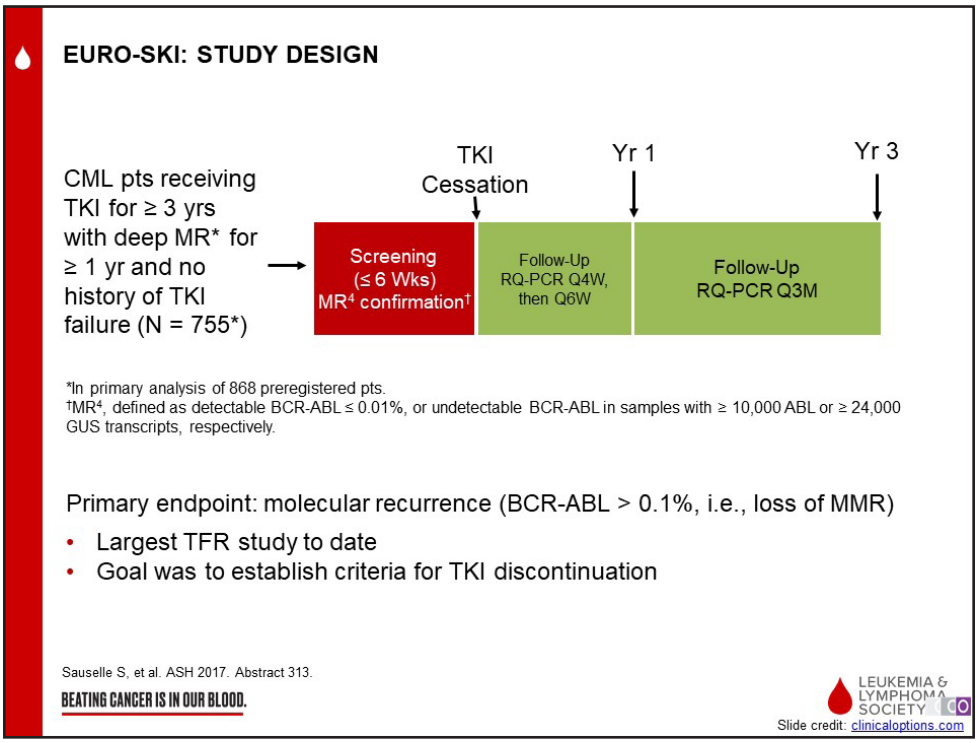
Slide 34: STUDY DEMOGRAPHICS

It looked at discontinuation of any TKI, other than ponatinib, and in this trial the definition of molecular relapse was the same as the ENESTfreedom, but the criteria to enroll was a little bit looser. So, patients were eligible even if they had detectable BCR-ABL, as long as the value was below 0.01% on that International Scale that I mentioned previously. The median follow-up time was 12 months when this data was presented and 71% of patients were free of a molecular recurrence.



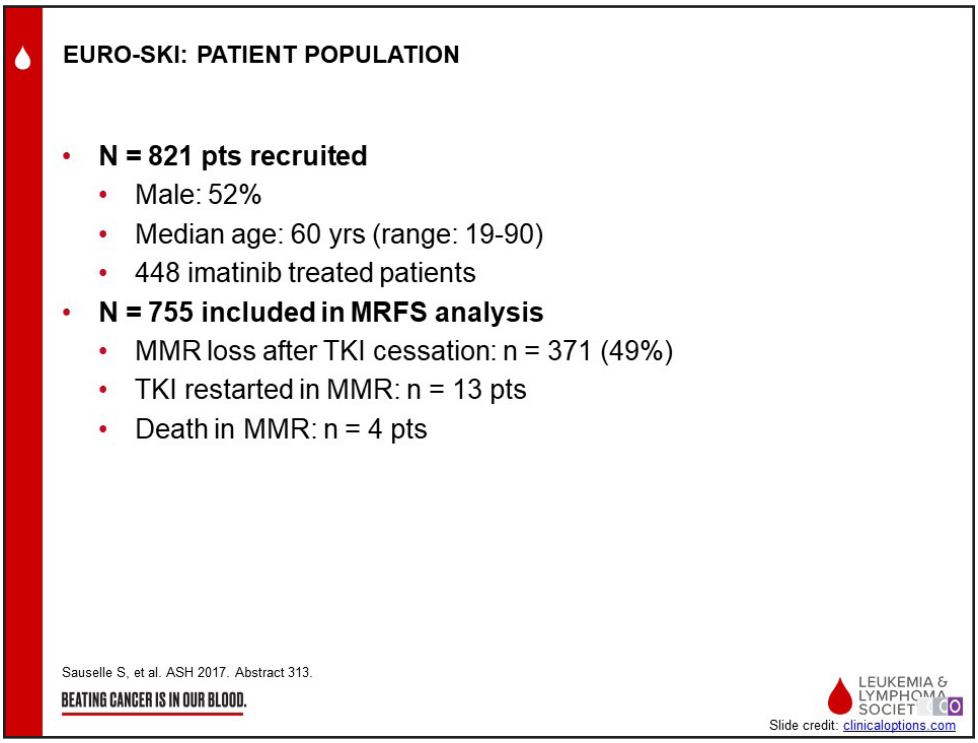
Slide 35: MOLECULAR RECURRENCE FREE SURVIVAL

In spite of this, only 65% remained in a treatment-free remission because there were a few patients who restarted treatment even without meeting the criteria for relapse and there's a lot of reasons for that, that we don't need to necessarily delve into right now.



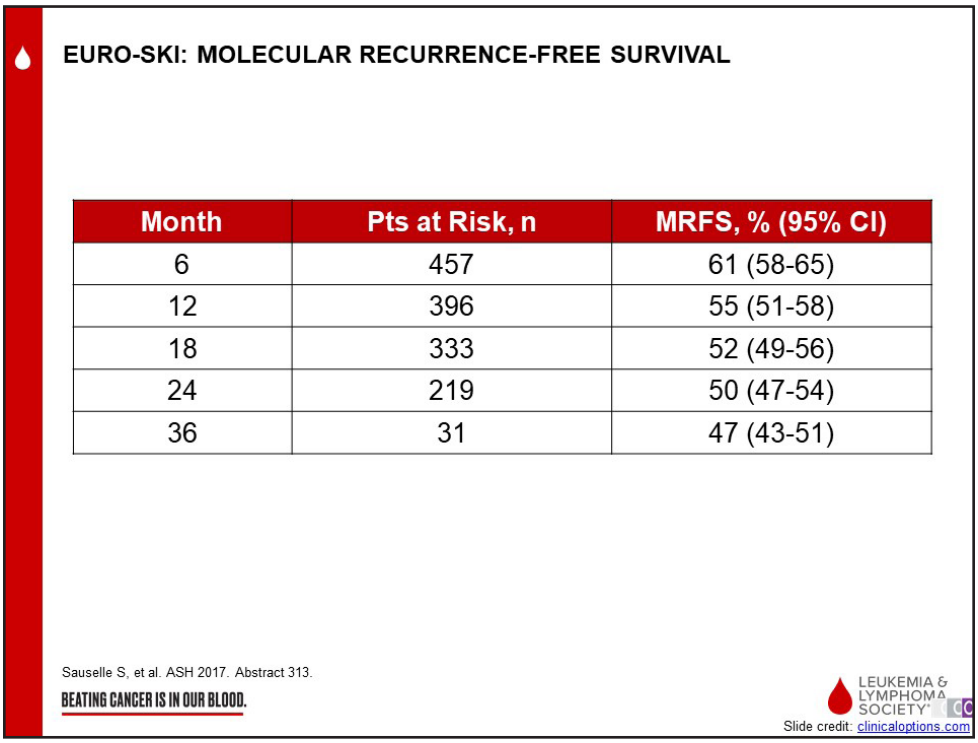
Slide 36: EURO-SKI: STUDY DESIGN

The EURO-SKI trial was the largest discontinuation trial that's been done so far. This was done in Europe. They enrolled 755 eligible patients and really the goal of this trial was to try and develop criteria or establish criteria for safe TKI discontinuation.



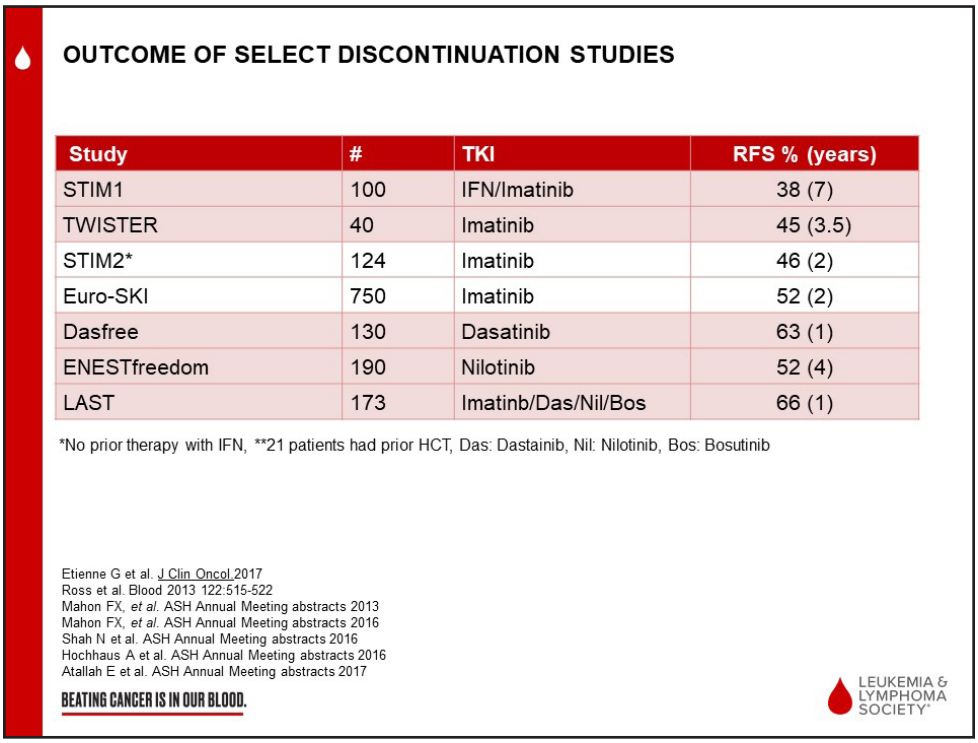
Slide 37: EURO-SKI: PATIENT POPULATION

Of the 755 eligible patients, 49% lost their molecular response after stopping treatment, meaning that those patients met the criteria for relapsed disease.



Slide 38: EURO-SKI: MOLECULAR RECURRENCE-FREE SURVIVAL

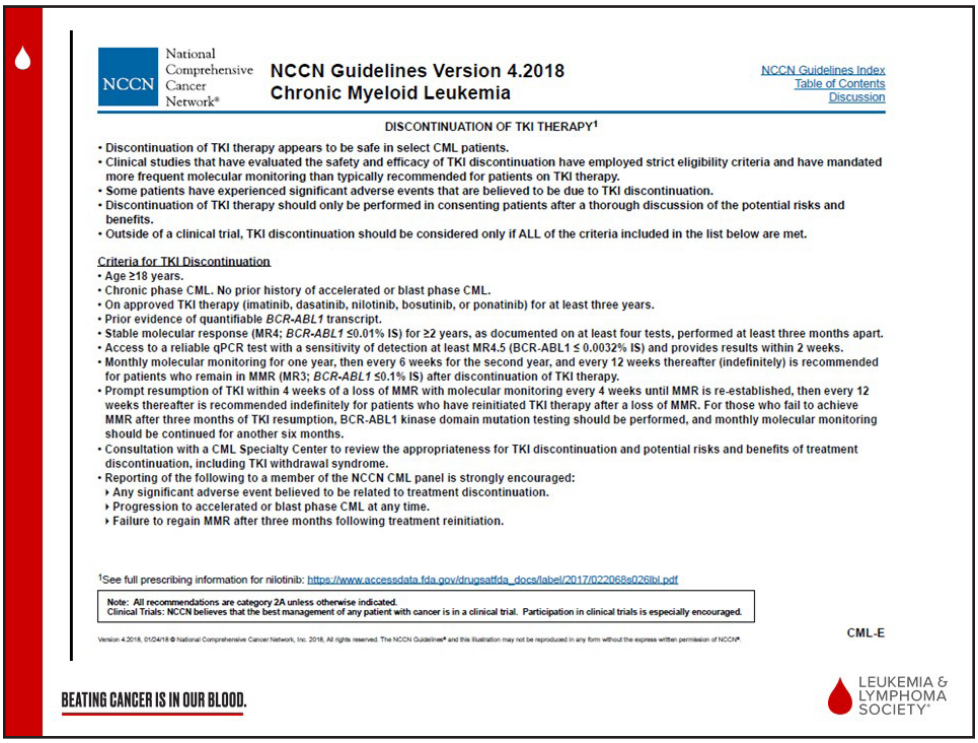
As you can see here in this table, most of the patients who relapsed did so in the first 6 months, which is what we've seen on all these other discontinuation trials as well, but there were still some patients who relapsed at later time points, so this really speaks to the importance of continued monitoring, even in patients who've been off treatment for many years.



Slide 39: OUTCOME OF SELECT DISCONTINUATION STUDIES

So, this table sums up many of the large discontinuation trials and you can see the results are strikingly similar across the board. And, what this is really telling us by looking at all this data together, is that there is a select group of patients who are able to achieve deep enough molecular responses, be able to attempt stopping treatment. Of those patients, approximately 50% will relapse and the other 50% are able to stay off-treatment for a prolonged period of time. What isn't clear is why some people relapse while others don't, and that's a question we're all still trying to find the answer to.

Again, it's important to point out that in those patients who did relapse, once they restarted their treatment they were able to regain their prior level of response, typically within a matter of months, and no one has progressed to advanced phase CML when they've been monitored appropriately and restarted on treatment at the time that they lose MMR.



Slide 40: NCCN GUIDELINES VERSION 4.2018 CHRONIC MYELOID LEUKEMIA

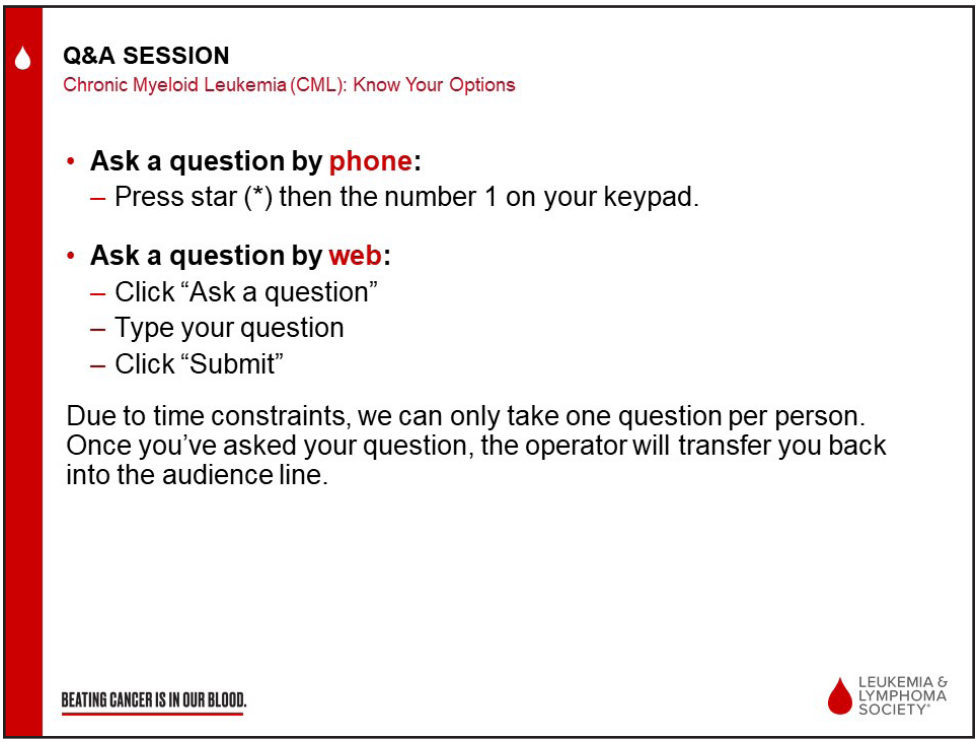
So, this is my final slide. This is NCCN guidelines again. The NCCN has now incorporated TKI discontinuation into the national guidelines for the treatment of CML, so this is something we're now doing routinely off-study, outside the setting of a clinical trial. There are very strict criteria that need to be met in order for someone to be eligible for an attempt at stopping treatment. And, frequent monitoring is absolutely essential when someone has stopped their TKI. So, the NCCN actually recommends doing PCR monthly for the first year after stopping, every 6 weeks for the second year, and then you can go back to every 3 months beginning in the third year after stopping treatment.

Taking all CML patients together, it's approximately 20% who are likely going to be successful with stopping treatment at some point during their disease course. But, for that remaining 80% who aren't so lucky, we do have clinical trials that are ongoing, looking for ways to deepen molecular responses, to allow more patients to be eligible for attempting stopping treatment, and other trials that are ongoing for patients who have stopped and then relapsed, trying to find ways to increase the chances of success if they make a second attempt at stopping treatment in the future.

These trials are being done at many sites around the United States and honestly most of us that specialize in CML are really hopeful that in the coming years we're going to eventually find an effective way to cure this disease.

Slide 41: Thank you!

So, with that I'd like to thank you for your time and I'm happy to take any questions.



Slide 42: Q&A SESSION

Ms. Figueroa-Rivera:

Thank you so much, Dr. Sweet. It's now time for the question and answer portion of our program.

We'll take the first question from our web audience. Doctor, Ahmed is asking do I need a CML specialist or will any oncologist be knowledgeable about CML?

Dr. Sweet:

So, I may be a little biased in answering that question, seeing that I am a CML specialist. What I can say is CML is not a common disease. It's becoming more common because people are living a normal life expectancy, so oncologists, general oncologists, are seeing more and more CML patients for longer periods of time. And, some feel very comfortable treating CML. Others may not.

So, I think my recommendation would be if you feel like you have a good relationship with your oncologist, you feel like your questions are being answered adequately, you feel confident in the information that you're being given, then you're probably fine to stay with your general oncologist. But, if you have questions that you're having doubts about or if you just want additional information, I think it's always a good idea to see a specialist, at least once, just to make sure you're on the right track and make sure that you really understand what's going on with your treatment.

Ms. Figueroa-Rivera:

Thank you. And, we also always encourage second opinions. I know, Doctor, you encourage second opinions for your patients also. And, you can always contact us as well as your doctor for further information about obtaining a second opinion. And, I'll give you the number to our LLS Information Specialists later in the program.

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

Operator:

Certainly. Thank you, Lizette. Edward in Maryland, please go ahead, your line is open.

Edward:

Yes, hi. Thank you very much. Excellent presentation, Dr. Sweet. My question relates to imatinib and excipients. Many of us are on imatinib. And, there're different manufacturers of that drug, Sun, Teva, others. And, there's been recent discussion on the LLS chat room about whether the difference in excipients can explain some of the adverse side effects that patients get from the drug. And, I'm wondering if you have thoughts on that? And, then secondly, any thoughts on the difference between the branded Gleevec and the generic imatinib?

Dr. Sweet:

So, there's a lot of conflicting data I guess with the difference between branded Gleevec and generic imatinib. I think it's safe to say in general responses are equivalent. But, I do think, and I've seen this firsthand, I do think that side effects may be different and everyone is different. And, I've had people come to the clinic and tell me I know that I got switched to a different generic brand because I suddenly started developing horrible acid reflux. Or, my nausea got significantly worse. You know, whatever it may be. But, I don't think that we can say one brand is necessarily better or worse than the other. It's just person-dependent really. Some people do absolutely fine on generic. I have a couple of people where we still have to get them brand name Gleevec because they haven't been able to tolerate generic. But, I really do think that it's dependent from one person to the next in regard to toxicity from specific generic brands.

Ms. Figueroa-Rivera:

Thank you, Doctor. And, our next question from the web is from James. He's asking what problems can arise from an accidental double-dose?

Dr. Sweet:

Well, it would depend on what drug. If it happened one time, probably nothing. Maybe some increased fatigue or nausea or something, you know, for the next 24 hours or so, but long-term toxicity, probably nothing. It also depends on what dose of the drug that someone's on. If they're already on a reduced dose of their TKI and they've accidentally doubled it, they're probably just fine. And truthfully again, I think if it happens just once it's probably okay, but definitely we want to make sure people have pill boxes and are really keeping good track. Because, it could be dangerous if that was happening repeatedly.

Ms. Figueroa-Rivera:

Thank you, Doctor. And we'll take the next question from the phone audience, Robert in Florida.

Robert:

I'm 54, got diagnosed in 12/17. Been on Sprycel 100 milligrams ever since. Achieved MMR in the first 6 months. However, in the last year I seem to have plateaued, 0.064, 0.044, 0.022, and now we are at 0.033. And, my doctor wants to switch me to Bosulif. And, I'm kind of worried about doing that. Wonder if you have any thoughts on switching?

Dr. Sweet:

I actually do have a lot of thoughts on that. So, anything that's deeper than MMR I wouldn't worry about it. Again, we don't need you to be undetectable. Your response is fabulous. You're doing excellent on treatment. So, as long as someone achieved MMR, we don't need it to be any deeper than that. And, if someone's tolerating a TKI, I would not change treatment just to try to get a deeper response, if they have achieved major molecular response.

With that being said, we do have a clinical trial that is open specifically for people like yourself, who are on nilotinib,

dasatinib, or bosutinib, so Tasigna, Sprycel, or Bosulif, people who have detectable BCR-ABL, but have good responses, but have detectable BCR-ABL, and it's using a combination of therapies that we're trying to deepen molecular responses to see if we can get more people to a point where they could potentially be eligible to stop.

So, my honest opinion is, I would try something like that prior to switching if someone's tolerating treatment well, because that response is fine. So, I think either try a clinical trial or stay on the Sprycel and don't rock the boat.

Ms. Figueroa-Rivera:

Thank you, Doctor.

Ms. Figueroa-Rivera:

And our next question today is from Anne. Anne is asking what's the protocol for a male CML patient who wishes to have children and what are the risks?

Dr. Sweet:

The risks, I mean, so obviously never been studied firsthand, nobody wants to do studies on getting pregnant and people taking TKIs. But, in the past we used to recommend that men hold their treatment. You'll get them to a good enough response, hold their treatment, and then try to conceive and then go back on treatment. More recently there's been some data that suggests there's really no harm to the fetus if a man is on TKIs or on imatinib at the time of conception. But I would take that again on kind of a patient-by-patient basis. If the response is really good and we feel comfortable holding for a couple of months, I don't see anything wrong with that. But if, you know, someone's response isn't great, then I think there is some data that suggests that it's okay for men to stay on treatment.

Ms. Figueroa-Rivera:

Thank you. I'll take the next question from the telephone audience, please.

Operator:

Thank you. Carol, in Kansas, do you have a question for Dr. Sweet? Your line is open.

Carol:

Thank you. I do have a question. Could you address for patients who are in treatment-free remission, withdrawal side effects? My oncologist doesn't think there should be such a thing since the drug is out of our system, but I'm on a Facebook group and I see that many other people are having specifically bone pain. And, it goes on for quite, you know, a period, some of them are a period of a year or more. What are your thoughts?

Dr. Sweet:

You're absolutely right. So, TKI withdrawal syndrome is absolutely a real thing. Why does it happen? I don't really know. It may have something to do with something called KIT expression, but at the end of the day whatever causes it, it is real. And, it happens in about 25 to 30% of people when they discontinue their TKI. Usually it starts in, you know, maybe month or two. And, on average lasts 6 months or so. Some people it's much less, some people it's longer. And usually, it's just kind of this low grade musculoskeletal pain, that's kind of diffuse. And usually, it's not something that prohibits people from their daily activities, but it's just there and it's frustrating. Can often be treated with ibuprofen or, you know, other anti-inflammatories. Some people find benefit in taking Claritin®, the allergy medication. Very infrequently do we need to give somebody steroids for a short period of time, but it does go away. And, what we don't want to do is restart a TKI just because of TKI withdrawal. Because it will go away. And again, it's usually fairly low grade. But, definitely don't let anyone tell you it's not real, because it's definitely a real thing.

Ms. Figueroa-Rivera:

And, the next question comes from the web audience. Barbara is saying that her brother as well as herself have both been diagnosed with CML and have you seen this in others? They've been told that it's neither genetic nor hereditary, but they both have been diagnosed.

Dr. Sweet:

That's interesting. I mean again the textbook answer is CML is not a hereditary disease. It occurs by chance and we don't know why. I do have one patient with chronic phase CML whose sister also has chronic phase CML. They were diagnosed maybe 2 years apart. I don't know how to explain that because again it's not, to be a hereditary thing. Whether it's something to do with environmental exposures, maybe where you grew up, if there is some, you know, radiation exposure or some pesticide exposure or something, maybe that's more what it is. But, it's hard to argue when you have siblings with the same rare disease, it's hard to argue that there's no correlation there. But the reality is we don't see any sort of hereditary component to CML.

Ms. Figueroa-Rivera:

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

Operator:

Jeannette in California, your line is open. The doctor is listening.

Jeannette:

Have you heard of any instances where there's a diagnosis of early onset monoclonal gammopathy?

Dr. Sweet:

In people with CML? I mean MGUS is not uncommon. It's a pretty common phenomenon that occurs as people age. It usually is a very benign condition. It doesn't transform into multiple myeloma. And, it's maybe 1% per year that will transform. So, it's not really thought to correlate with CML. I've seen people with both, but again I think that's because MGUS is actually fairly common, but definitely not correlated to CML.

Ms. Figueroa-Rivera:

Thank you. And, we'll take the next question from the web audience. Actually, I have many people asking about fatigue, if there's any treatment they can take for their fatigue. And I have questions from people that are on different TKIs.

Dr. Sweet:

Fatigue is far and away the most common side effect of TKIs. There are some studies that show over 80% of people have fatigue from TKIs. and that's challenging. And, it can be low grade, it can be more, you know, an annoyance, or it can be really severe. We did a study here at Moffitt actually with our behavioral health and outcomes group for patients with chronic phase CML who have fatigue related to their TKI. And, it sounds so simple it's almost annoying, but really the study involved cognitive behavioral therapy and then daily activities, daily exercise, and good sleep hygiene. So, people were starting out with, you know, walking maybe 5 minutes a day and after a week they increased it to 6 and then 7 and then 8. And truthfully, we saw a significant improvement in fatigue in the people who were on that interventional arm who were increasing their exercise, making changes in their sleep habits. Those people had significant improvement in their fatigue.

So, I actually had a patient who, the first time I met her, came in, she's young, telling me she needed to go on disability because her fatigue was so severe. And, I put her on that trial and within a matter of months she's walking 5 to 7 miles a day, she's probably the most energetic person I see ever. I mean she gets me riled up when I see her because she's so

happy and energetic all the time, just from those interventions.

Another guy, same thing in the beginning, severe fatigue, went on that study, was increasing his exercise, making sure he was going to sleep at the same time every night, waking up at the same time every day. Within a matter of months was training for Spartan races and feeling amazing.

So, fatigue is super common. It's really discouraging for people. But, the best thing to do for fatigue is to stay active, make sure you're sleeping at the same time every night, waking up at the same time every day, and talking to your support system about how you're feeling and getting some encouragement from the people around you, to keep doing these things.

Ms. Figueroa-Rivera:

Thank you. I know that's been a great concern for most of our patients.

Dr. Sweet:

It's a very real concern, no question about it.

Ms. Figueroa-Rivera:

And, Michael is asking, how do I go about discussing dose reduction with an oncologist that is reluctant to do so?

Dr. Sweet:

I think the question would be, well, 2 questions. One, why does someone want the dose reduction and, 2, why is the doctor reluctant to do so? If it's because of side effects, but the response is okay, then it's probably a reasonable thing to do. But, I also think that if someone has a question like that, is it reasonable to reduce my dose, that's the time when getting a second opinion makes a lot of sense. Because, if you see a specialist, they may be able to give you a little more information about when it's safe or why it's safe or if it's safe and what to reduce the dose to. But certainly, I have a large number of patients on dose-reduced TKIs because of side effects and they still do extremely well. So, in the right person at the right time it is reasonable. So, I would say ask for a second opinion if it's something that you feel strongly about and see if someone else can maybe help answer those questions.

Ms. Figueroa-Rivera:

Thank you. And, our next question is from the telephone audience.

Operator:

Hello, Bruce, calling from Minnesota, your line is open.

Bruce:

I'm just kind of wondering about why it's so expensive and how can we ever get on that reduced thing, it's costing an arm and a leg for me?

Dr. Sweet:

So, these drugs are incredibly expensive and that's a whole different talk in and of itself about cost of pharmaceuticals, especially anti-cancer drugs. What I can tell you is there are programs available to help cover the cost of these drugs. It takes effort on the part of the physician and the pharmacist, but in truth, I have not had a single patient who I have not been

able to get on treatment because of the cost of the drug. Most all of these companies have copay assistance programs that people can apply for. There's also, if they're not eligible for whatever reason, there's usually foundation funding. Some people get funding through The Leukemia & Lymphoma Society, there's other foundations as well that can provide financial support so that you can afford your drug.

But, as far as I'm concerned, it's not something that should break the bank. The expense should not be yours to burden, or it shouldn't be a burden to you. And, if it is, then we need to have the pharmacy and your physician looking for programs to help offset some of that cost.

Ms. Figueroa-Rivera:

Exactly. And, I will be providing the number to our Information Resource Center, you can call them, and they will try to find you some financial assistance through LLS or another organization that's providing assistance at this time for CML.

Our next question comes from Tom. Tom is asking is there a higher incidence of secondary cancers for CML patients?

Dr. Sweet:

It's a good question. I don't know. We actually looked at that ourselves and, in looking at all the data it's really kind of conflicting. Some data suggests that there is a higher incidence of secondary cancer, some suggests that maybe, you know, drugs like imatinib are actually protective. So, at the end of the day it's not entirely clear. I think that, you know, when someone's diagnosed with CML, even if there is a slightly increased risk of secondary cancers, obviously it makes sense to treat someone with CML because when it's treated appropriately the life expectancy for that person is the same as the general population. So, we need to be treating people with CML. And then, just continue with age-appropriate cancer screening like colonoscopies and mammograms and things like that, skin checks and things like that, to try and catch cancer early, if it does in fact pop up.

Ms. Figueroa-Rivera:

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

Operator:

Hello and welcome, Christie in Texas.

Christie:

Yes. I wanted to know does CML mimic any other disease?

Dr. Sweet:

That's an interesting question. I mean CML is in the family of myeloproliferative neoplasms, so there are other bone marrow malignancies that are in the same family, things like myelofibrosis, polycythemia vera, essential thrombocytosis. They're all in the same family. But, typically no. I mean CML is characterized by that Philadelphia chromosome, so once you see that you have a diagnosis of CML.

I've seen one person who presented with blood counts that looked like CML and actually ended up having lung cancer, which was really odd. But, they did not have the Philadelphia chromosome. So, it's just their CBC that looked kind of classic for CML, but it wasn't. But, really no, it doesn't usually mimic other cancers.

Ms. Figueroa-Rivera:

Thank you for the question. And, we're also getting questions, as Mary is asking, about transplant. So, when is transplant an option for a CML patient for treatment?

Dr. Sweet:

Transplant is only appropriate for CML, in someone who has progressed to advanced phases of the disease, so accelerated or blast phase CML, that's when we would consider transplant. Or, when someone has failed to respond to multiple lines of therapy in the chronic phase. It's very uncommon to transplant CML nowadays. The side effects and the risks of transplant are far greater than the side effects and the risks of taking a TKI life-long. So, we definitely don't recommend transplant unless someone has progressed to advanced phase disease or has failed to respond to multiple TKIs.

Ms. Figueroa-Rivera:

Thank you. And, we'll take the next question from the web audience. David is asking about the effect of Tasigna on the liver and what can you do if the bilirubin goes too high?

Dr. Sweet:

So, Tasigna can cause in some people, a benign elevation in the bilirubin. It's usually not something that we're overly concerned about. If it gets too high, I mean if you see a bilirubin of 7 or 8, I'd probably stop Tasigna and switch to a different TKI. All TKIs can irritate the liver, not necessarily increasing the bilirubin, like Tasigna does, but can irritate the liver and cause elevation of liver enzymes. But, most of the time when we see an elevation in the bilirubin it's a benign thing that we don't get too worried about, we just know that it can happen with Tasigna.

Ms. Figueroa-Rivera:

Thank you. And, I've also gotten a lot of questions about nutrition in general as well as if people should be taking any type of multivitamins or any supplements while on treatment.

Dr. Sweet:

Nutrition is something, I mean, there's no nutritional advice that I can give you that would really affect response to treatment for CML. As far as supplements are concerned, I generally recommend a multivitamin daily and in women calcium supplement daily, but nothing beyond that. There's nothing really to prove that high doses of any other vitamins or supplements are beneficial. We just don't know. It hasn't been studied, and we don't know how certain things will interact with the TKIs, so I would always stick with just a multivitamin and a calcium supplement in a woman.

Slide 43: FREE LLS EDUCATION & SUPPORT RESOURCES

Ms. Figueroa-Rivera:

First, I really wanted to thank Dr. Sweet 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.

Slide 44: LLS EDUCATION & SUPPORT RESOURCES

You can call an LLS Information Specialist at 1-800-955-4572 from 9 AM to 9 PM Eastern Time or you can reach us by email at infocenter@LLS.org and Information Specialists are available to answer your questions about treatment, including clinical trials, and answer other questions you may have about support, including financial assistance for treatment. And of course, international participants, please feel free to email us or call us.

Slide 45: THANK YOU

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

Dr. Sweet, thank you again for volunteering your time with us today. Goodbye and we wish you well.

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