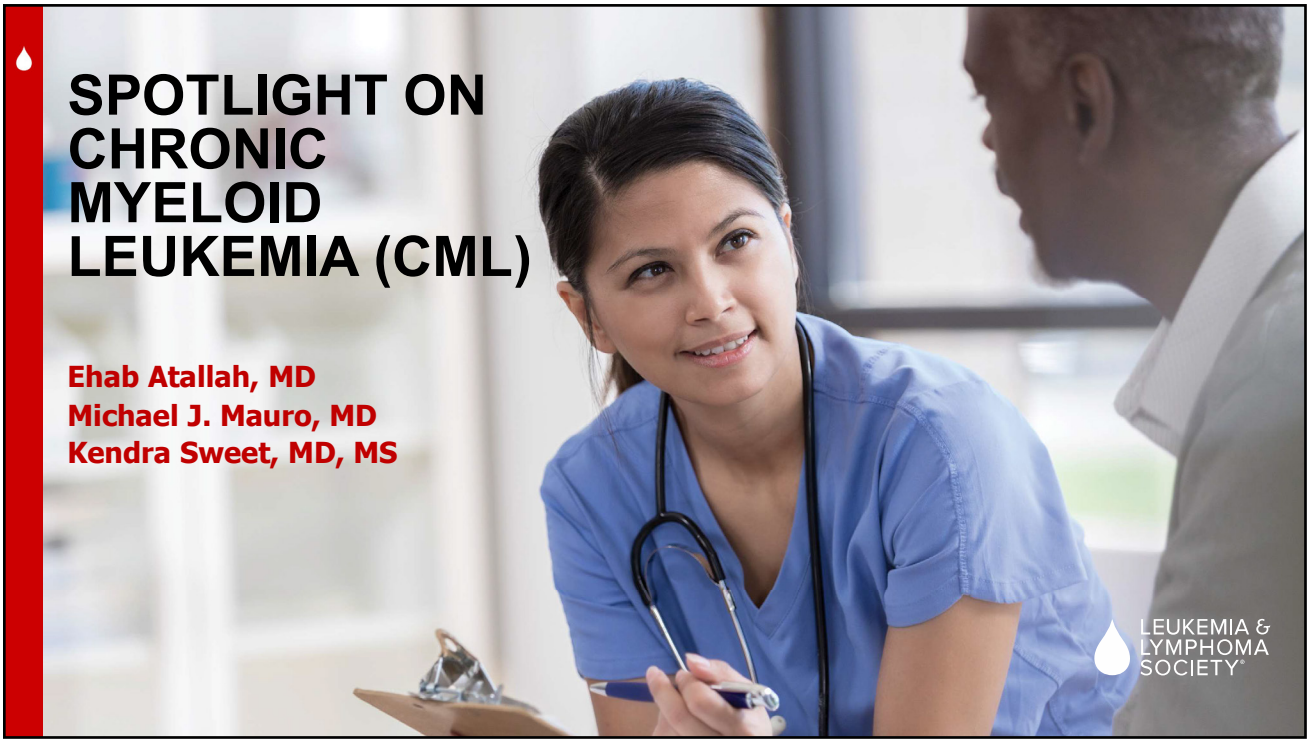



**Slide 1: SPOTLIGHT ON CHRONIC MYELOID LEUKEMIA (CML)**

**Operator:**

Greetings and welcome to Spotlight on Chronic Myeloid Leukemia telephone and web education program. It is now my pleasure to introduce your moderator, Lizette Figueroa-Rivera. Thank you, Lizette, please begin.


**Slide 2: WELCOMING REMARKS**

**Lizette Figueroa-Rivera:**

Thank you. 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 other countries including Australia, Canada, India, Ireland, Israel, Kuwait, Mexico, Nepal, Nigeria, the Philippines, Romania, Trinidad, and the United Kingdom. Thank you all for joining us today, especially since part of the United States is experiencing hurricane conditions. I do want to let you know that Dr. Sweet is on the line with us, she is in the path of the hurricane, so we wanted to thank you for being with us today and understand at any point if you do have to leave the program.

Today our admired CML experts, our key opinion leaders in the field, have volunteered their time to discuss how far we've come with CML treatments and how they are working together to find a cure for CML.

Dr. Atallah from the Medical College of Wisconsin will speak about the history of CML treatment and frontline and advanced phase treatments for CML, as well as introduce the CML Consortium, followed by Dr. Mauro from Memorial Sloan Kettering Cancer Center in New York, who will discuss clinical trials and treatment-free remission, followed by Dr. Sweet from Moffitt Cancer Center in Florida, who will finish the presentation with her insights on emerging therapies, as well as improving quality of life with CML.

LLS helps you navigate cancer treatments and ensures that you or your loved ones have access to quality, affordable, and coordinated care. Research will help us achieve an end to cancer. In the meantime, patients and caregivers need help before, during, and after a cancer diagnosis. LLS is the leading nonprofit that does just that. Please continue to inform us of what you need during this time and please continue to let us be here for you.

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

I'm now pleased to introduce Dr. Atallah who will start the program.


**Slide 3: FACULTY**

**Dr. Ehab Atallah:**

Hello, everyone and thank you Lizette for organizing this program. I'll jump into it right away because we have limited time with lots of information.

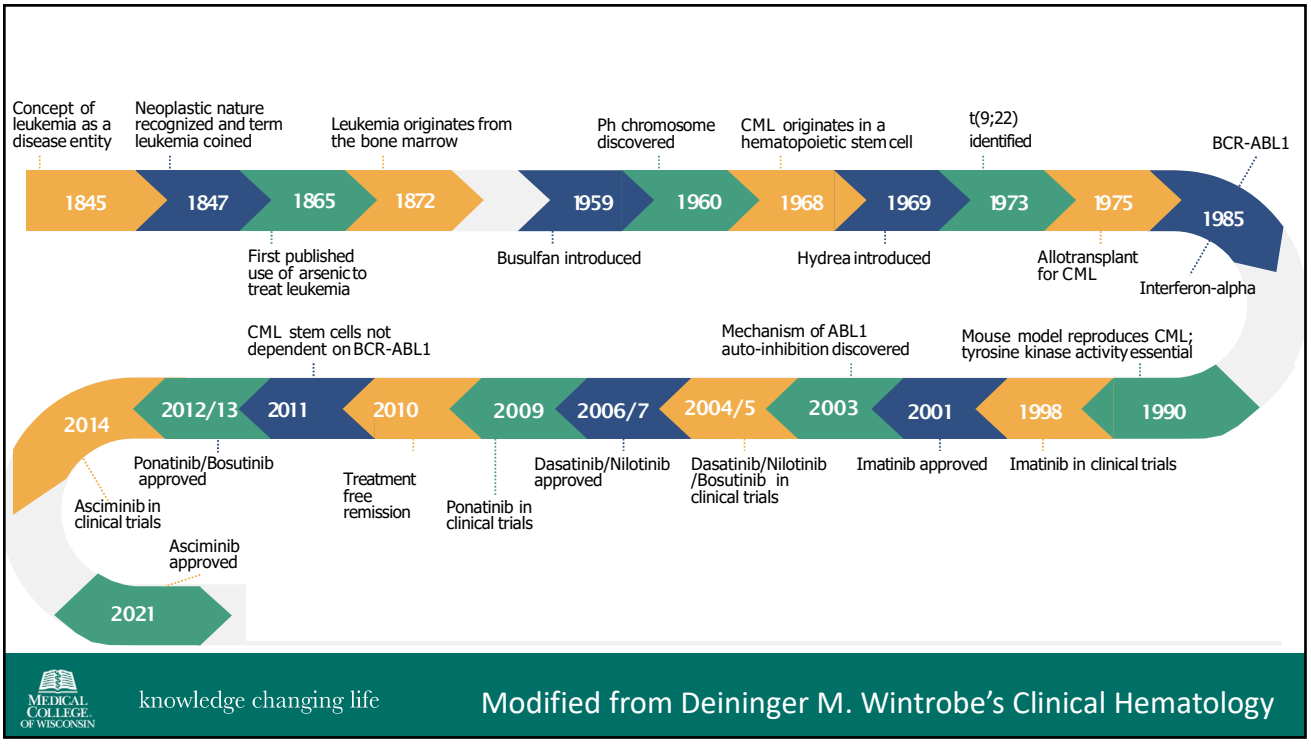

**Slide 4: DISCLOSURE SLIDE**

These are our disclosures. Dr. Mauro will list his disclosures when it's his time to give his presentation.


**Slide 5: OVERVIEW**

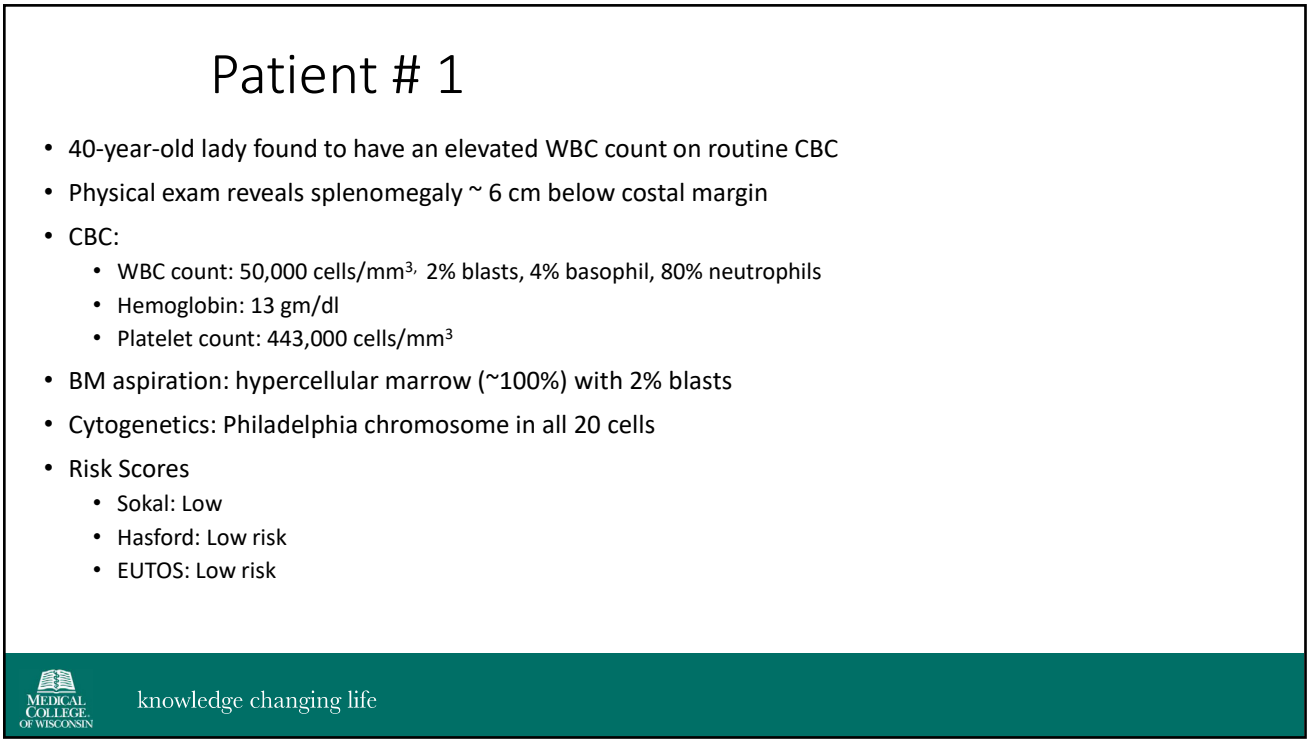
So what I'll talk about is the history of CML, and then I'll talk about the choice of first-line therapy, second-line therapy, and future directions and where we're going.

This is a nice t-shirt from one of my patients showing the CML World Day 9/22.



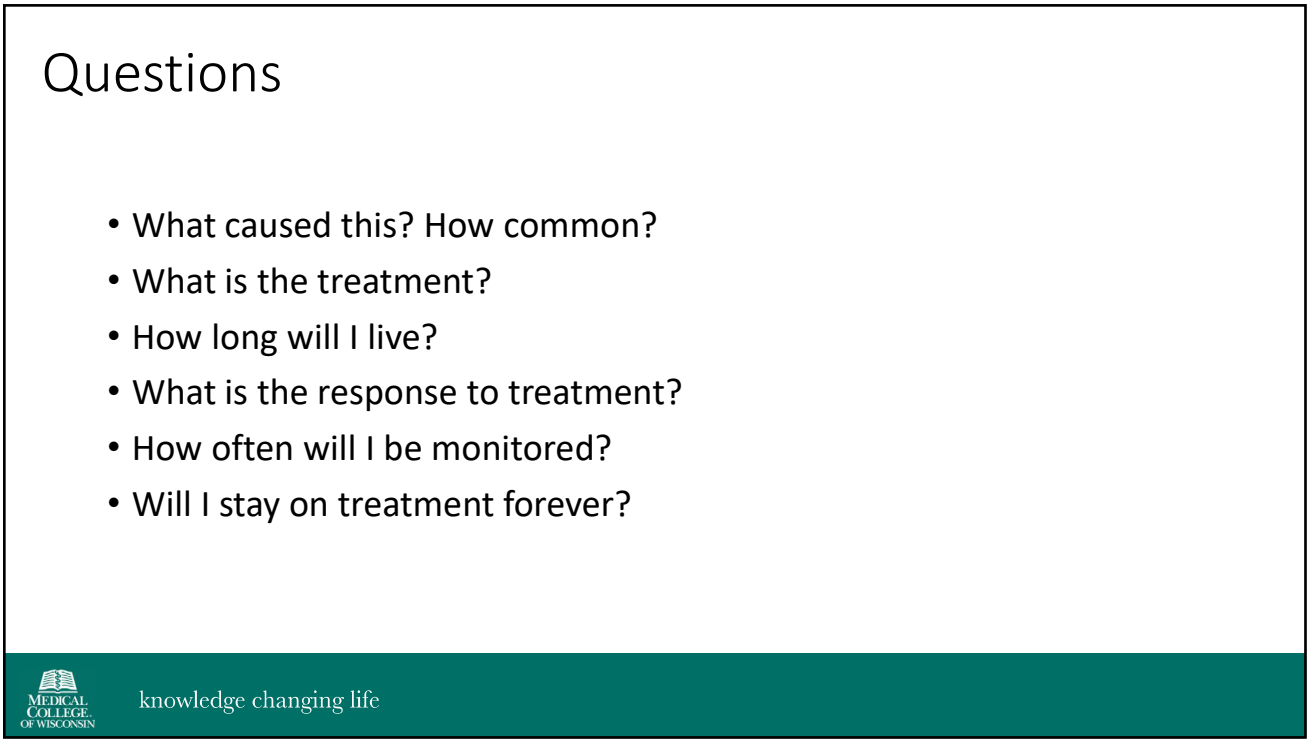

**Slide 6: HISTORY OF CML**

So, for those of you who don't really know the history of CML and how far we've come, I thought just a little reminder of how much things have changed over the last 20 years, I'll jump into right here. It was in 1973 when the Philadelphia chromosome was first identified, which is here. Following that, from 1975 all the way to 2001, just 25 years, if someone had CML the only option for treatment or the only cure really was a stem cell transplant. Obviously, stem cell transplant is still something that's done for patients with CML, but it also is associated with significant side effects and morbidity. Other than transplant, interferon was also there, interferon did put a small percentage of patients into remission but was also associated with significant side effects. Starting in 1998, clinical trials for imatinib (Gleevec®) started and then 2001 imatinib was approved. From there on, then we have approvals for the second-generation TKIs (tyrosine kinase inhibitors), which are dasatinib (Sprycel®), nilotinib (Tasigna®), and bosutinib (Bosulif®). And then 2012, 2013, we have approval for ponatinib (Iclusig®), which is identified as a third-line TKI, and most recently we have another approval, asciminib (Scemblix®). So, we went from a treatment of the only choice for treatment was stem cell transplant or interferon, to having 6 different drugs that we could use for this disease and adjust according to response, side effects, and tolerance overall. So pretty amazing progress over maybe 20 to 30 years.



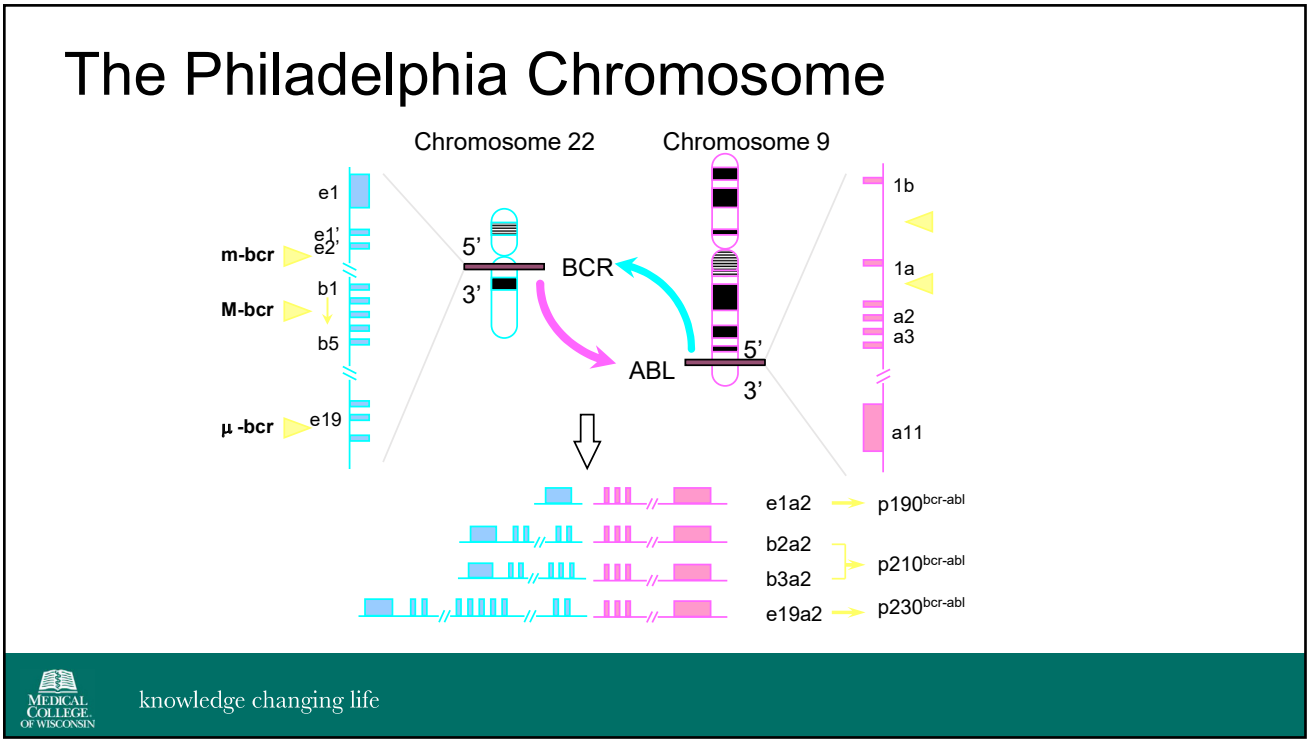

**Slide 7: PATIENT #1**

I'll start out with a presentation. Patients present with different symptoms different ways. Commonly, patients now could present with just an elevated white count without any symptoms, where they were undergoing labs for any other reason. Some patients present with hip pain, bone pain, pain in the left side of the abdomen of the belly from an enlarged spleen. And these are the different presentations for patients with CML.



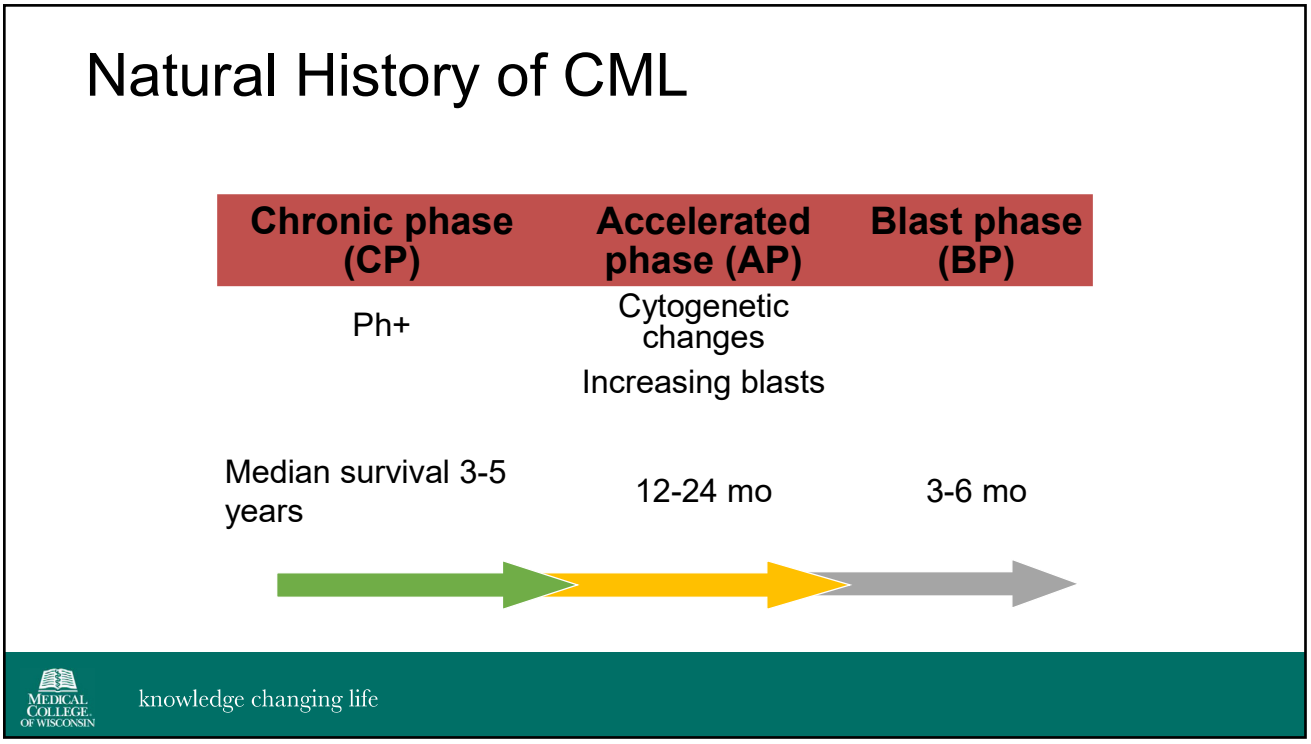

**Slide 8: QUESTIONS**

And usually the questions that go through anyone's mind when anyone hears that they have an illness of any sort, I think revolves around: what causes this and how common? what's the treatment? how long will I live with this disease? what's the response? how will I be monitored? and will I need to stay on treatment forever? I'll address some of those but I leave the treatment forever for Dr. Mauro with the next presentation.



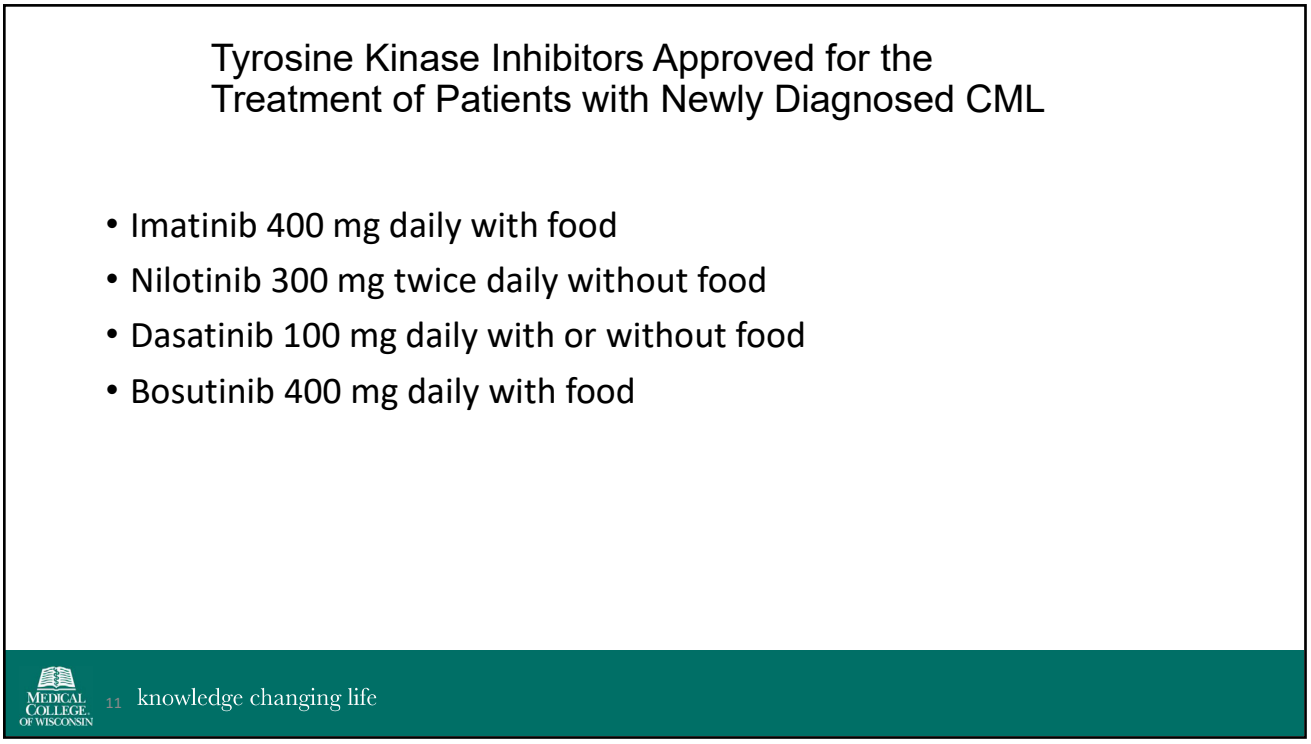

**Slide 9: THE PHILADELPHIA CHROMOSOME**

So, you all know that CML is really caused by the Philadelphia chromosome and the Philadelphia chromosome is a translocation between chromosome 9 and 22. Chromosomes are essentially the computer system of our cells, so in the computer system of the cell, you have 2 pieces or 2 little computers sitting next to each other, that they're not supposed to be sitting next to each other, these 2 little computers send messed up signaling to the cell and they tell the cell you need to divide, divide, divide, don't stop, without regular control that we have. So that's what that Philadelphia chromosome is.



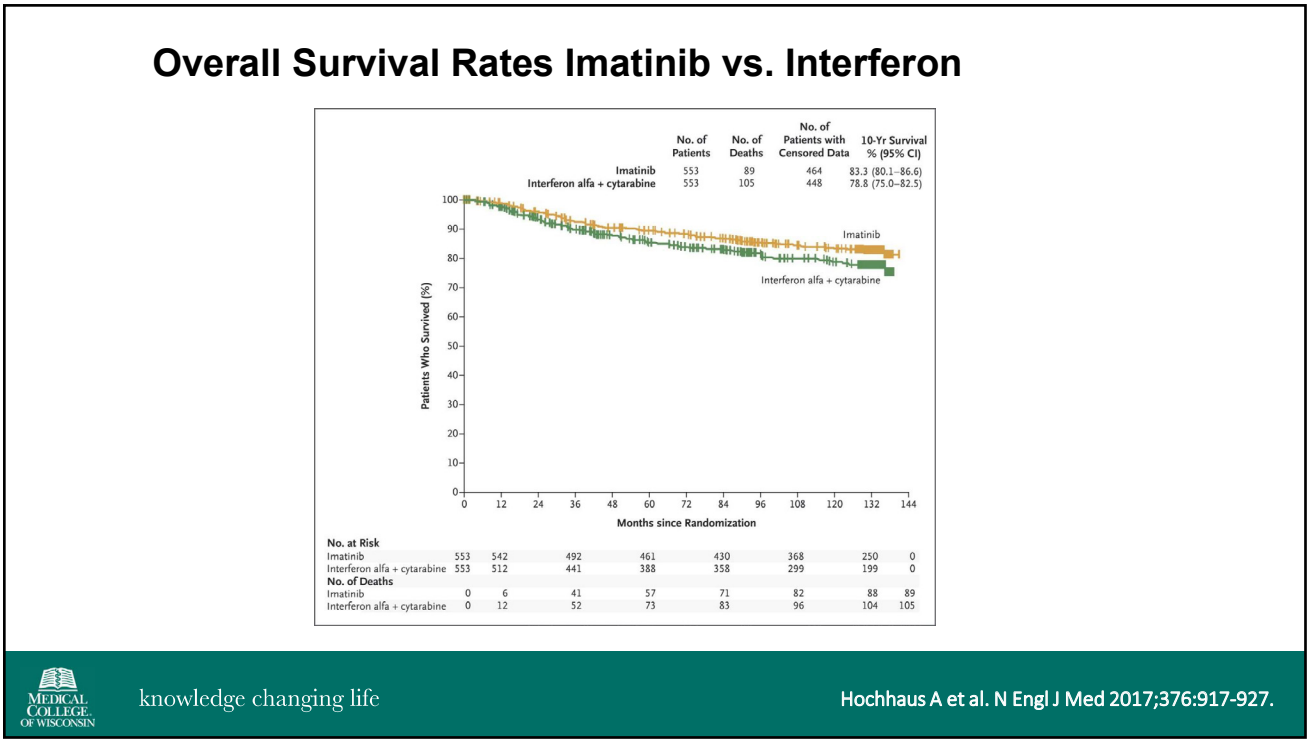

**Slide 10: NATURAL HISTORY OF CML**

And CML is also characterized by 3 different phases: chronic phase, accelerated phase, and blast phase. And before we had these treatments, before we had the TKIs without any treatment, patients would progress through these 3 different phases and unfortunately most patients would have died in about 7 years, and that's again without treatment, emphasizing without treatment, and things are very different now, of course, with the treatments that we have.



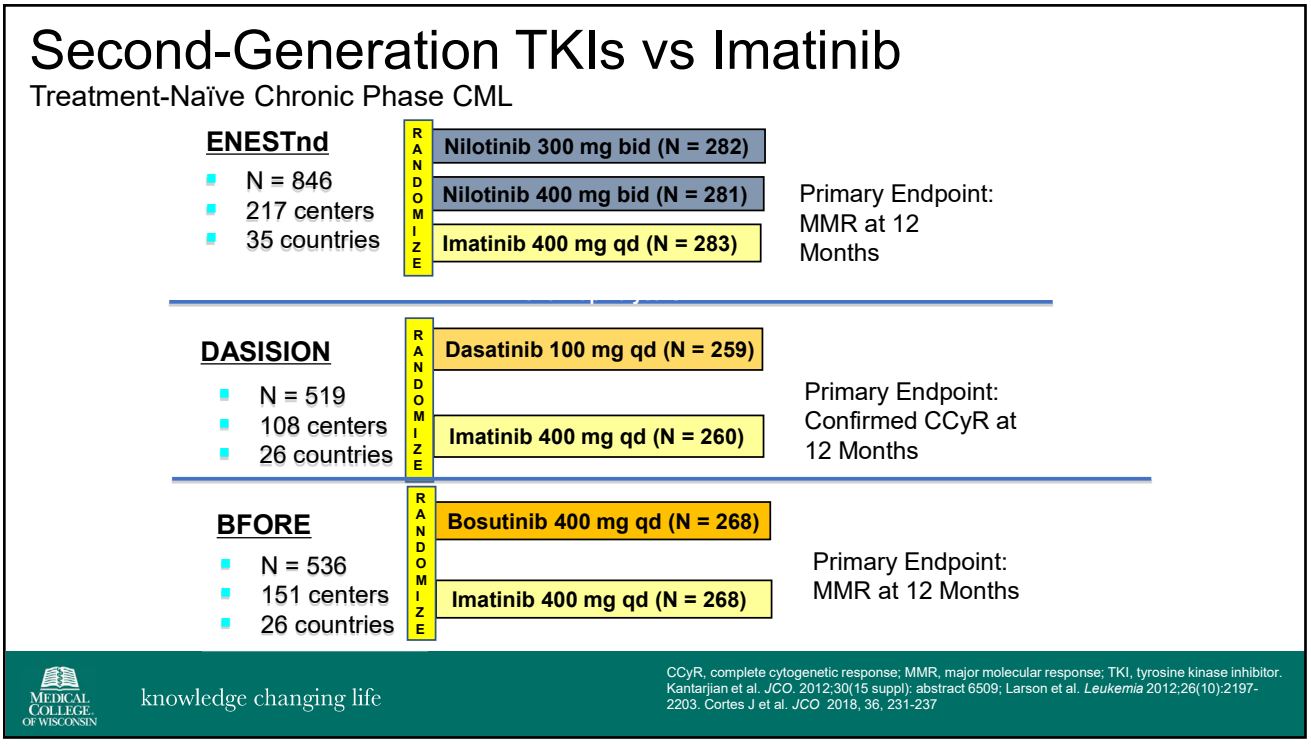

**Slide 11: TYROSINE KINASE INHIBITORS APPROVED FOR THE TREATMENT OF PATIENTS WITH NEWLY DIAGNOSED CML**

We currently have 4 drugs (“nibs”) that are FDA approved for frontline treatment of patients with CML: imatinib, nilotinib, dasatinib, and bosutinib. It’s like a tongue-twister.



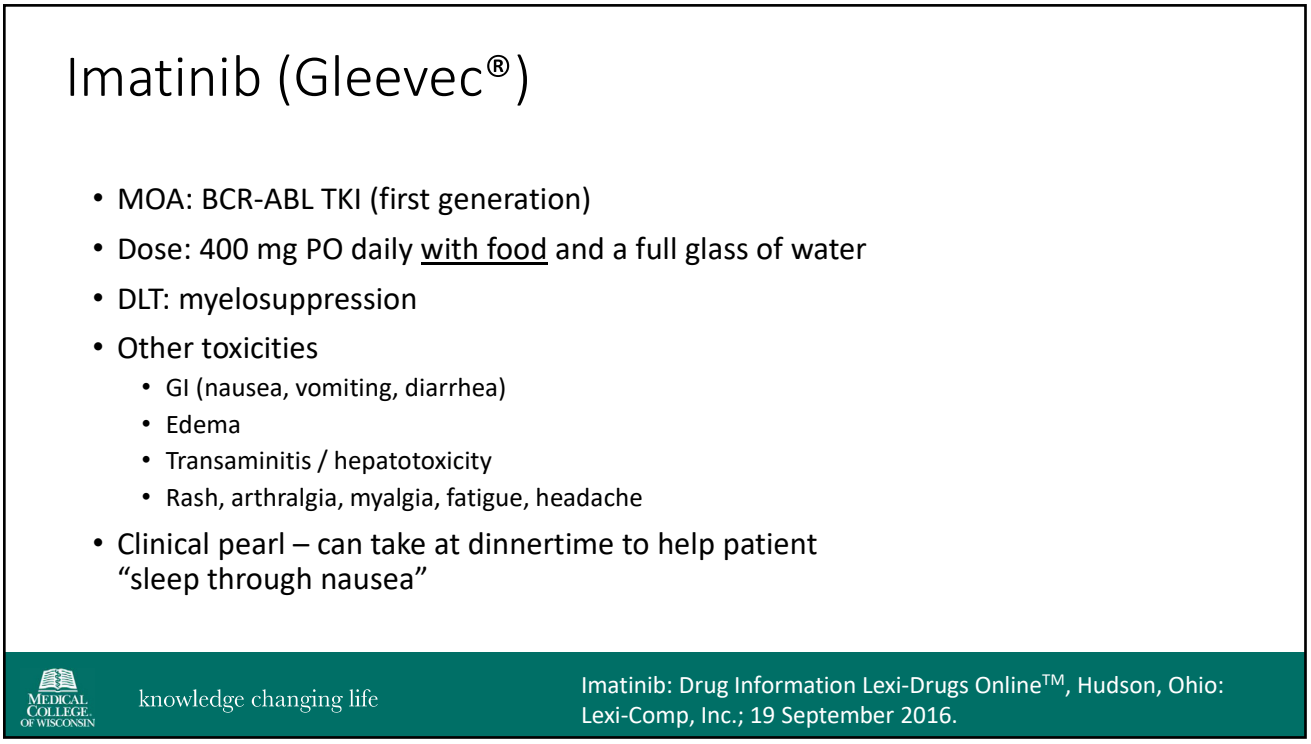

**Slide 12: OVERALL SURVIVAL RATES IMATINIB VS. INTERFERON**

They're very effective and imatinib was the first one that was approved and looking at the survival of patients on that study for imatinib, now we have 10 years of follow-up, and the 10-year survival is more than 80% of patients are alive and remain in remission with imatinib. Pretty impressive results again compared to transplant.



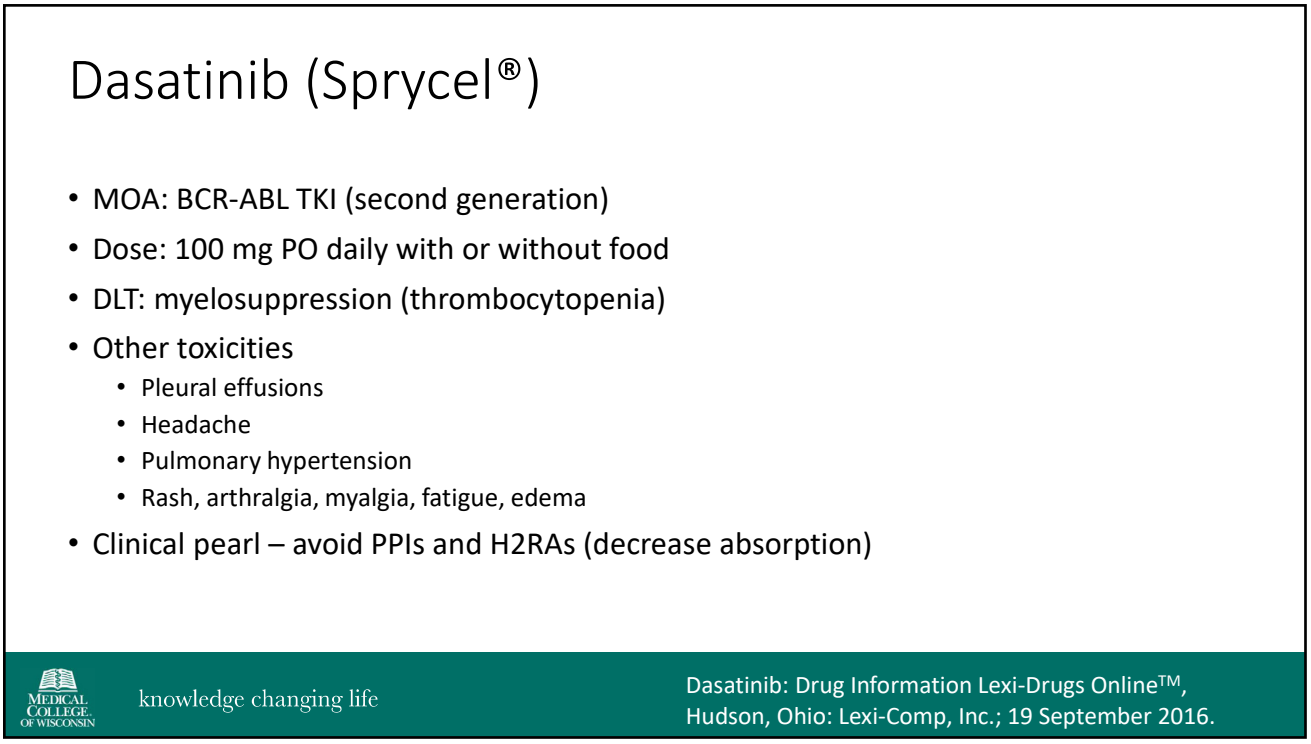

**Slide 13: SECOND-GENERATION TKIS VS IMATINIB**

However, we know that only 60% of patients really stay on the drug that they start with and there are patients whose disease is resistant to the treatment. So for that the second-generation TKIs were developed, which are nilotinib, dasatinib, and bosutinib. And they were compared head-to-head with imatinib in 3 different trials and they're not compared to each other, each one was compared to imatinib separately, and they all have different toxicities.



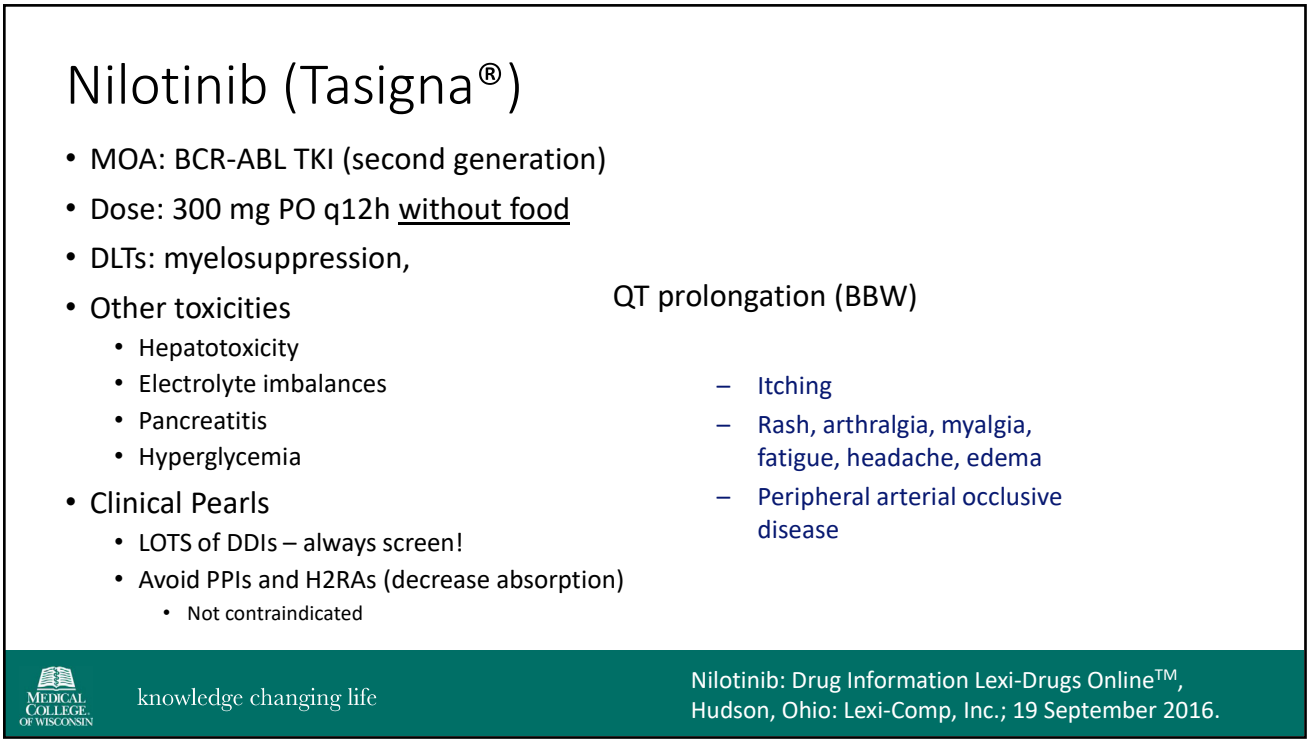

**Slide 14: IMATINIB (GLEEVEC®)**

For example, imatinib, mostly is known for causing GI upset, nausea, vomiting, diarrhea, swelling of the legs, swelling under the eyes, it can affect the liver, muscle cramps is sometimes quite significant, and fatigue.



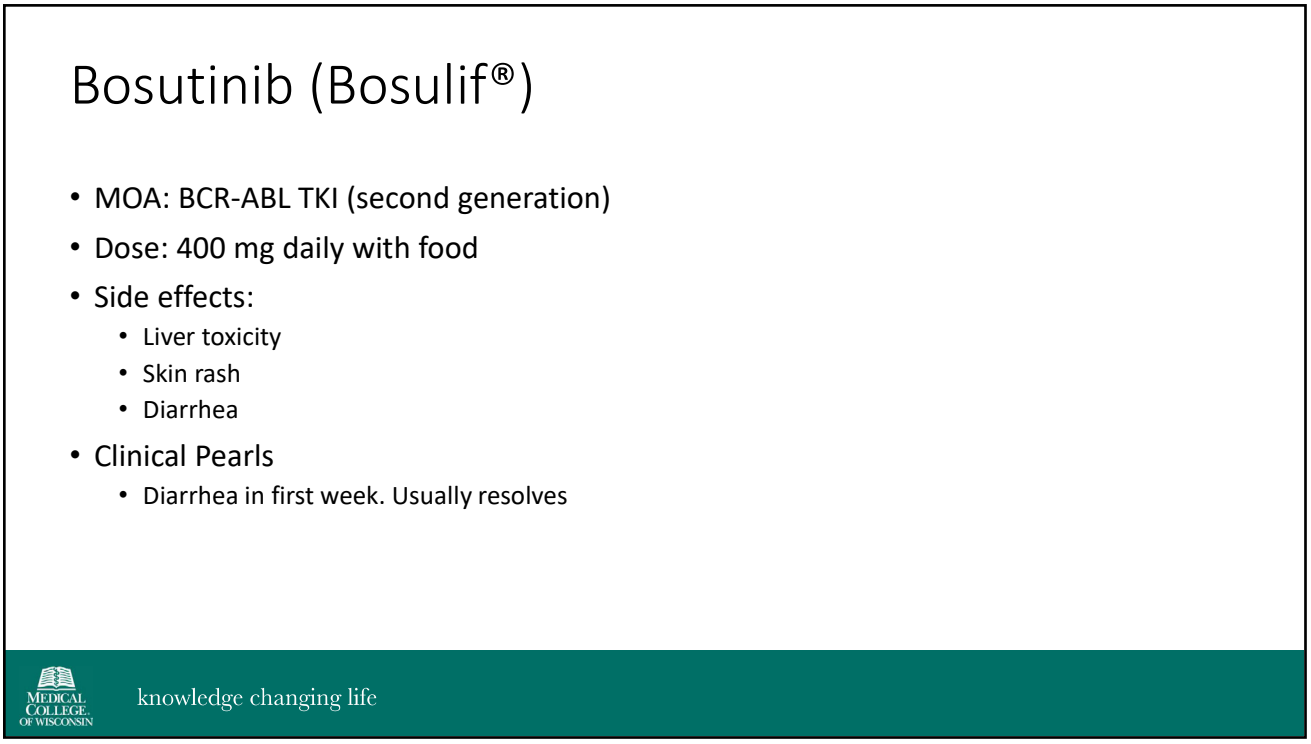

**Slide 15: DASATINIB (SPRYCEL®)**

Dasatinib on the other hand, in about 20% of patients, can develop a pleural effusion, which is fluid buildup around the lung. This is not life-threatening; this is more annoying than life-threatening. And of course very inconvenient, inconvenient is probably a very mild word because sometimes it requires a needle to drain out the fluid. It can also cause high blood pressure in the lung and can cause headaches.



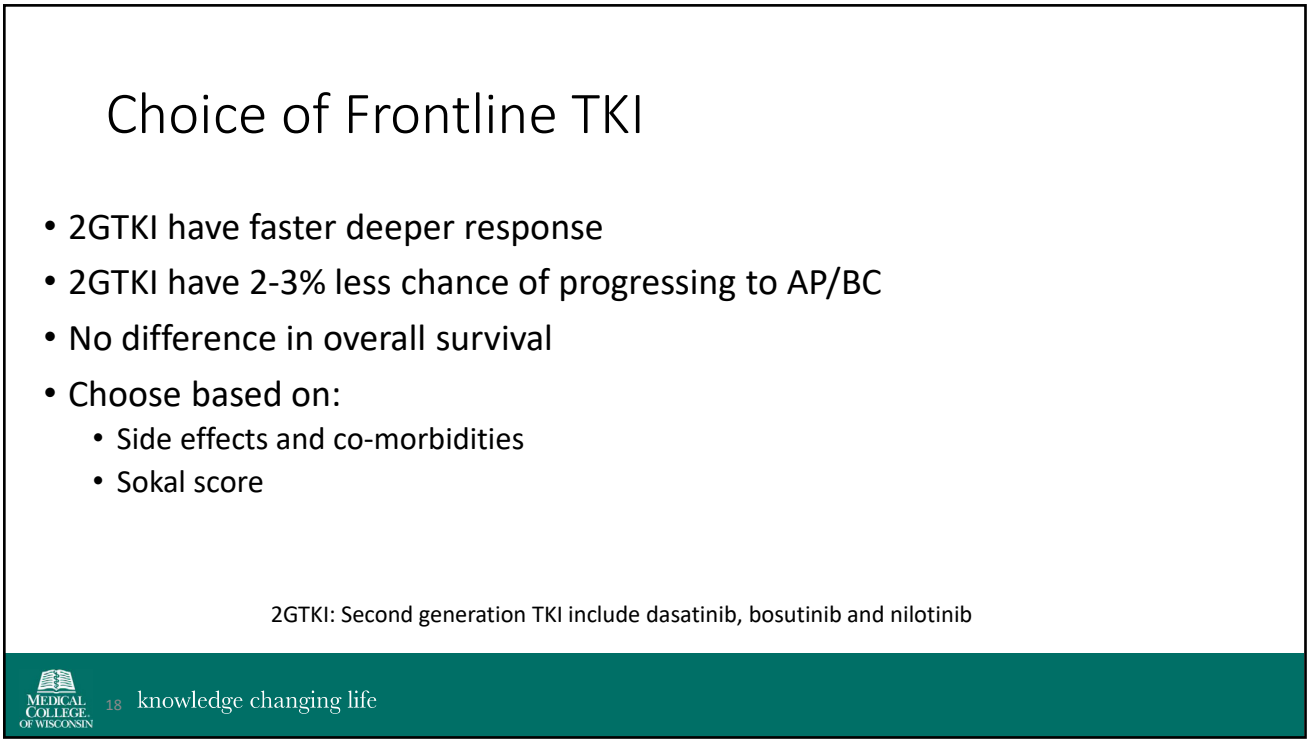

**Slide 16: NILOTINIB (TASIGNA®)**

Nilotinib is given twice a day. It can affect the liver. And also has the side effect which happens in about 10% of patients, of affecting the blood vessels of the body. So that's been a concern with nilotinib, especially upfront.




**Slide 17: BOSUTINIB (BOSULIF®)**

Bosutinib was the last one that was FDA approved as first-line and common side effects for it include complications with the liver (which we can monitor for), skin rash, and diarrhea.



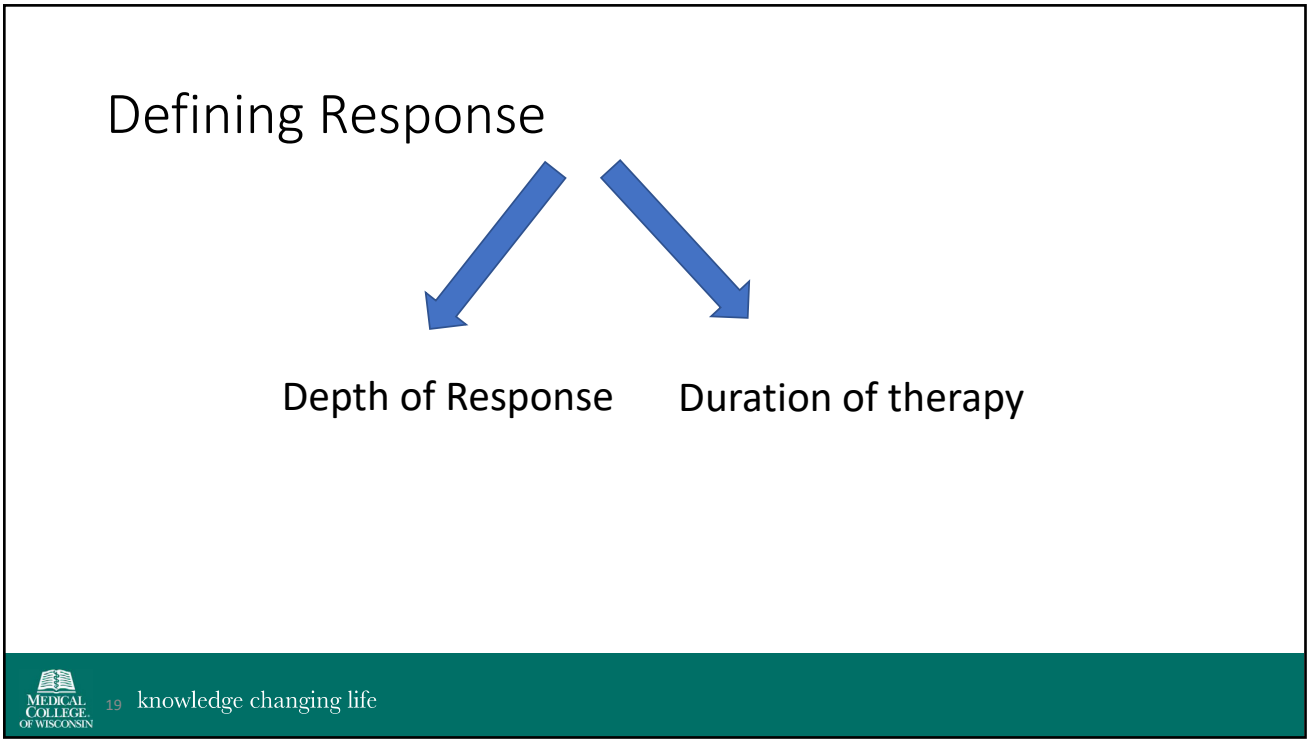

**Slide 18: CHOICE OF FRONTLINE TKI**

So. we have these 4 drugs; how do we pick for our patients and how do you as a patient also pick which one is best for you? It really depends on several things.

First, we know that the second-generation TKIs, which are dasatinib, nilotinib, and bosutinib lead to a deeper response. Those 3 drugs also compared to imatinib, there's a small difference in the progression to accelerated phase or blast crisis, about a 3% to 5%, depending on the study, but that progression to accelerated phase or blast crisis is pretty serious and significant, requiring a transplant. Across all the trials, there was no difference in survival when the patient started on imatinib or any of the second-generation TKIs.

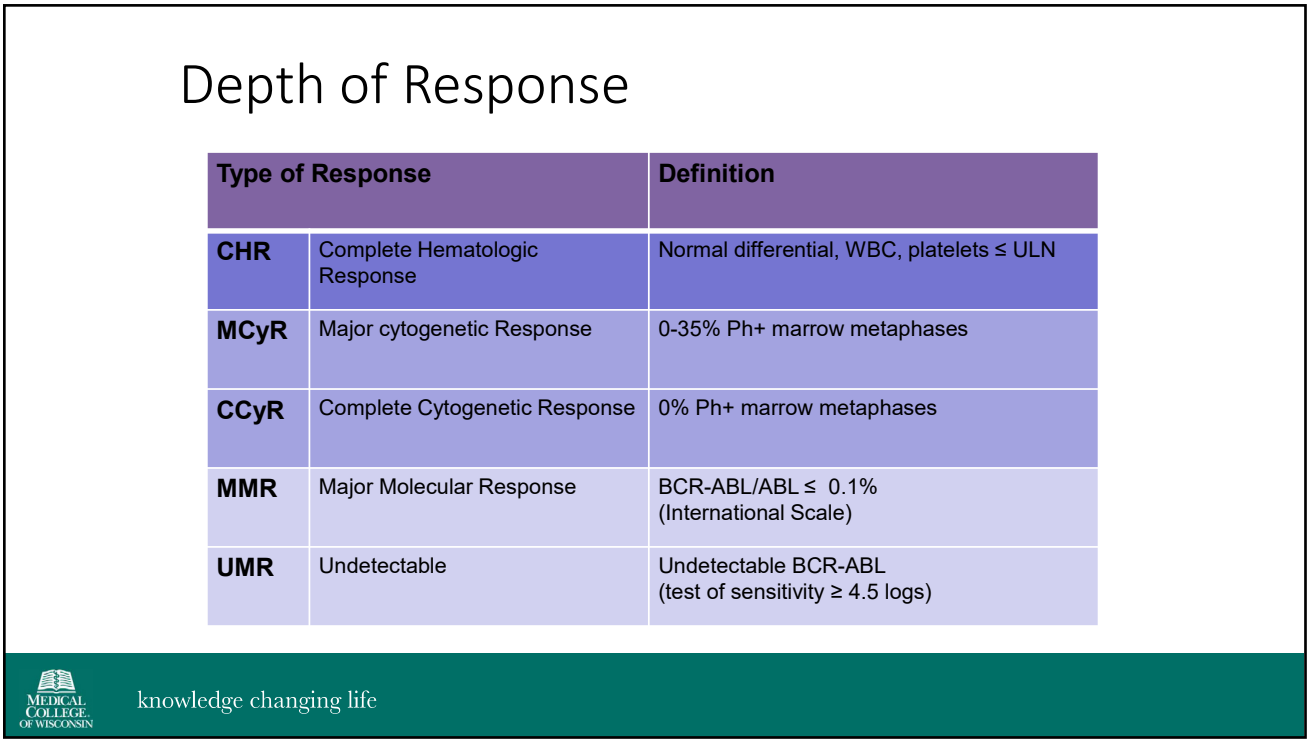
So, we really choose based on a conversation with the patient, we choose based on side effects, other medical problems, and also a Sokal score, which I didn't talk about earlier. The Sokal score is a score of the risk of the disease, and we make patients who receive a second-generation TKI, who have a high-risk Sokal, do better than if they receive imatinib.

So many factors go into choosing the first-line TKI. There's really no wrong answer, it's just what's best for you, what's best for that specific patient.



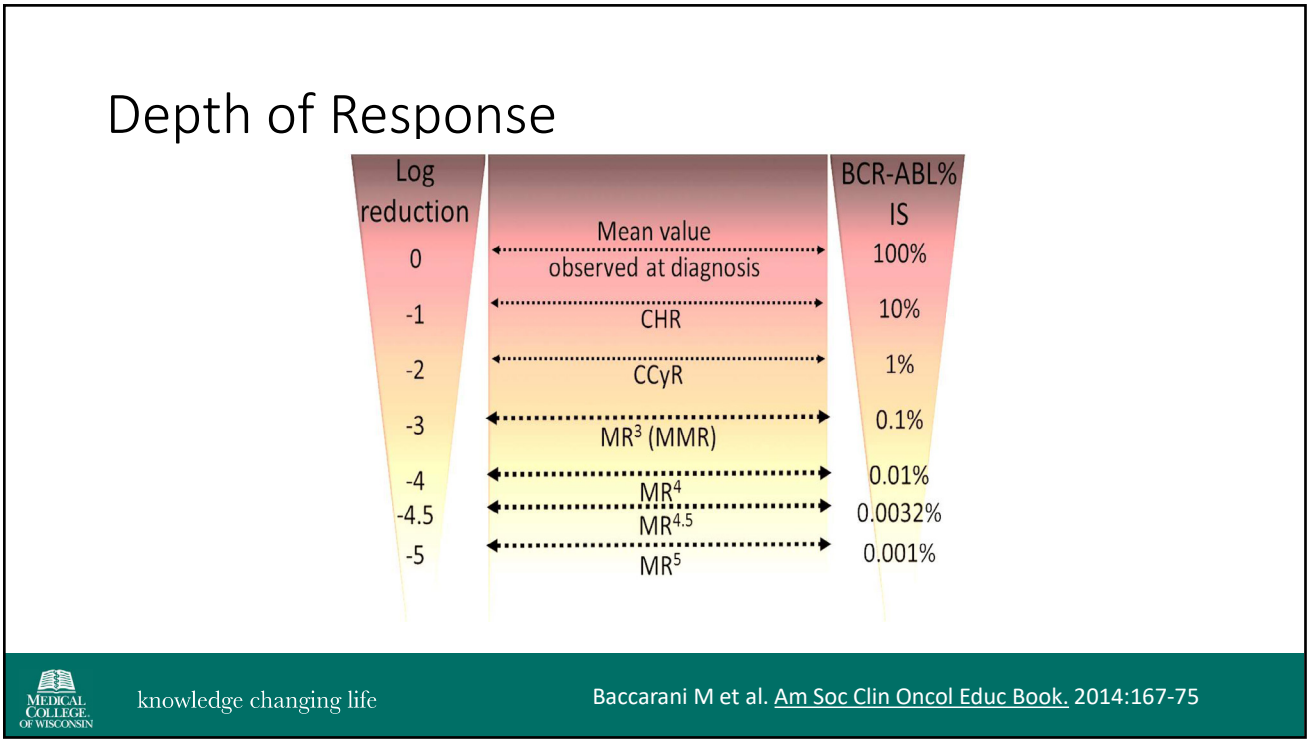

**Slide 19: DEFINING RESPONSE**

Once someone starts treatment, then we start looking at response and the way response is assessed in CML is by following that Philadelphia chromosome mostly by PCR (polymerase chain reaction) test. And it depends on how long someone's been on the drug and how deep is the response.



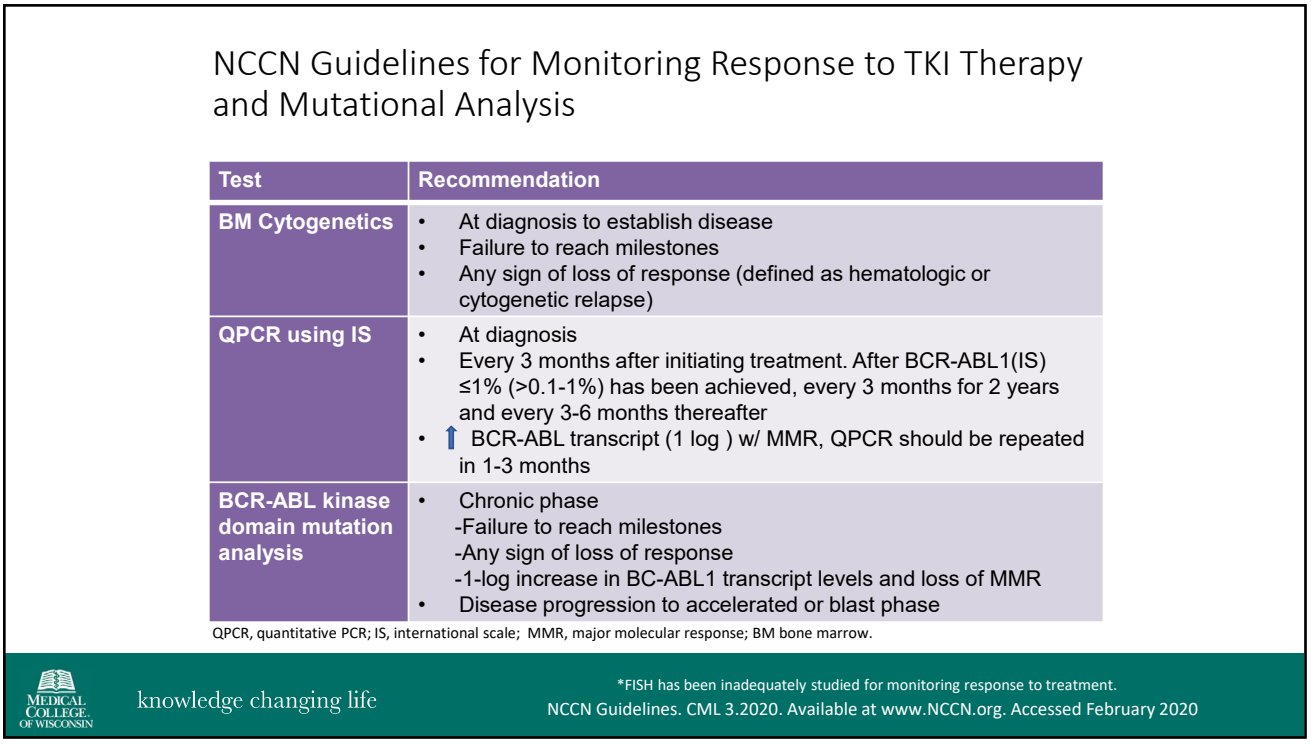

**Slide 20: DEPTH OF RESPONSE**

These are the different levels of response and some of them are based on doing a bone marrow biopsy, which we rarely do in following up patients, and the 2 lower ones, which is major molecular response (MMR) and undetectable, is based on looking at the Philadelphia chromosome by a sensitive test, PCR, in the blood.



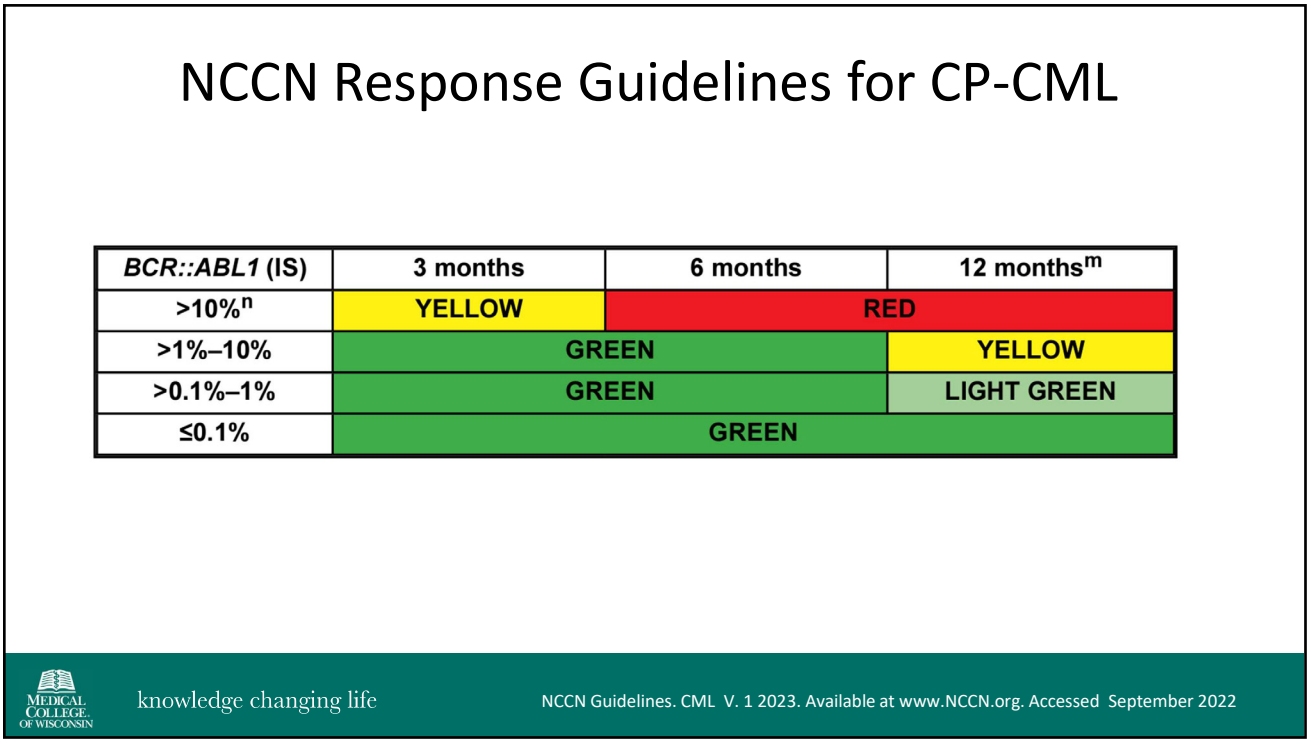

**Slide 21: DEPTH OF RESPONSE**

These are the different levels of response. What they are is log reduction, it's a level, a log reduction compared to a standard value. What you really need to know, what I really need to know, is that the 0.1% is the level called MMR, and then $MR^4$ is 0.01%, and $MR^{4.5}$ is 0.0032%. Some patients come and ask me and say $MR^3$, $MR^4$, I really think it's so much easier to think of it in terms of just the numbers, 0.1, 0.01, and just sort of don't get confused with $MR^3$, $MR^4$, $MR^{4.5}$, just follow the numbers.




**Slide 22: NCCN GUIDELINES FOR MONITORING RESPONSE TO TKI THERAPY AND MUTATIONAL ANALYSIS**

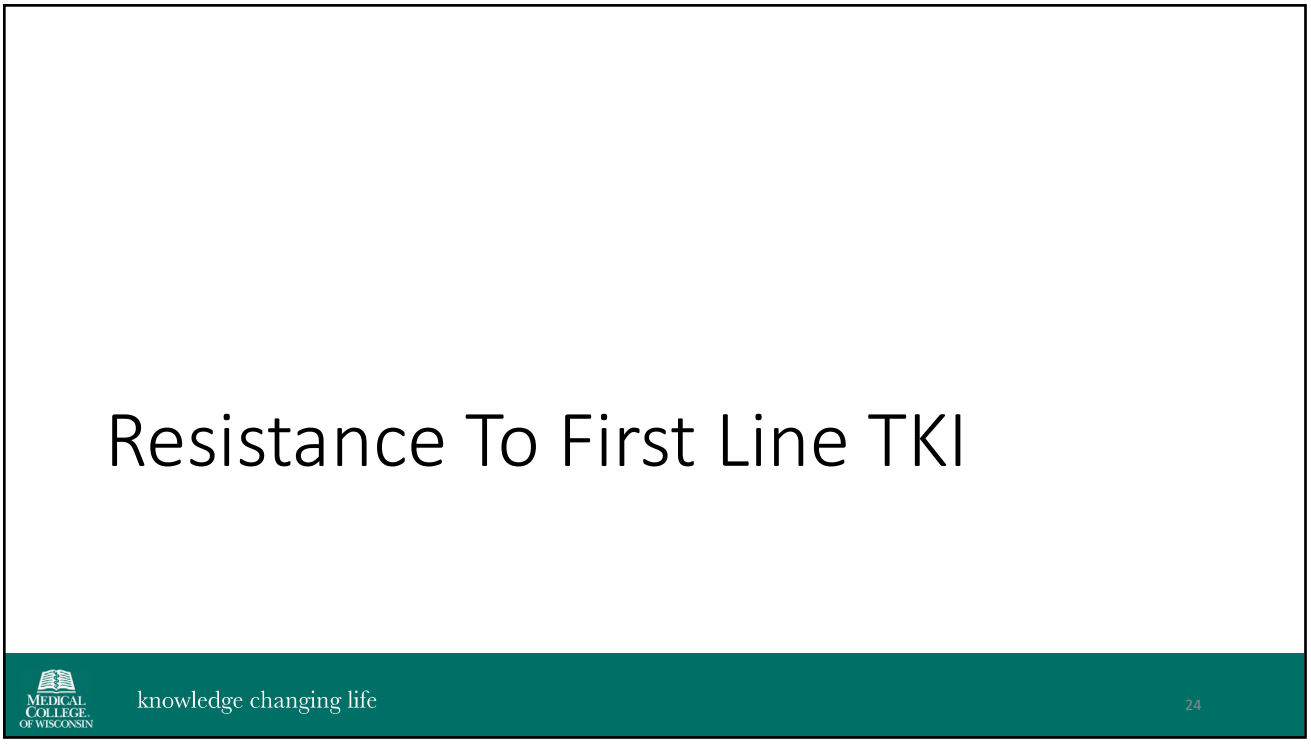
It's recommended that we follow the PCR every 3 to 6 months in general. And we also have guidelines, one is NCCN (National Comprehensive Cancer Network) guidelines and the other is ELN (European Leukemia Net) guidelines. These are the 2 big guidelines that we have for CML. And based on how long someone has been on the treatment and how deep the response is, you could look at this chart and see, is this response is adequate or not.




**Slide 23: NCCN RESPONSE GUIDELINES FOR CP-CML (CHRONIC PHASE-CML)**

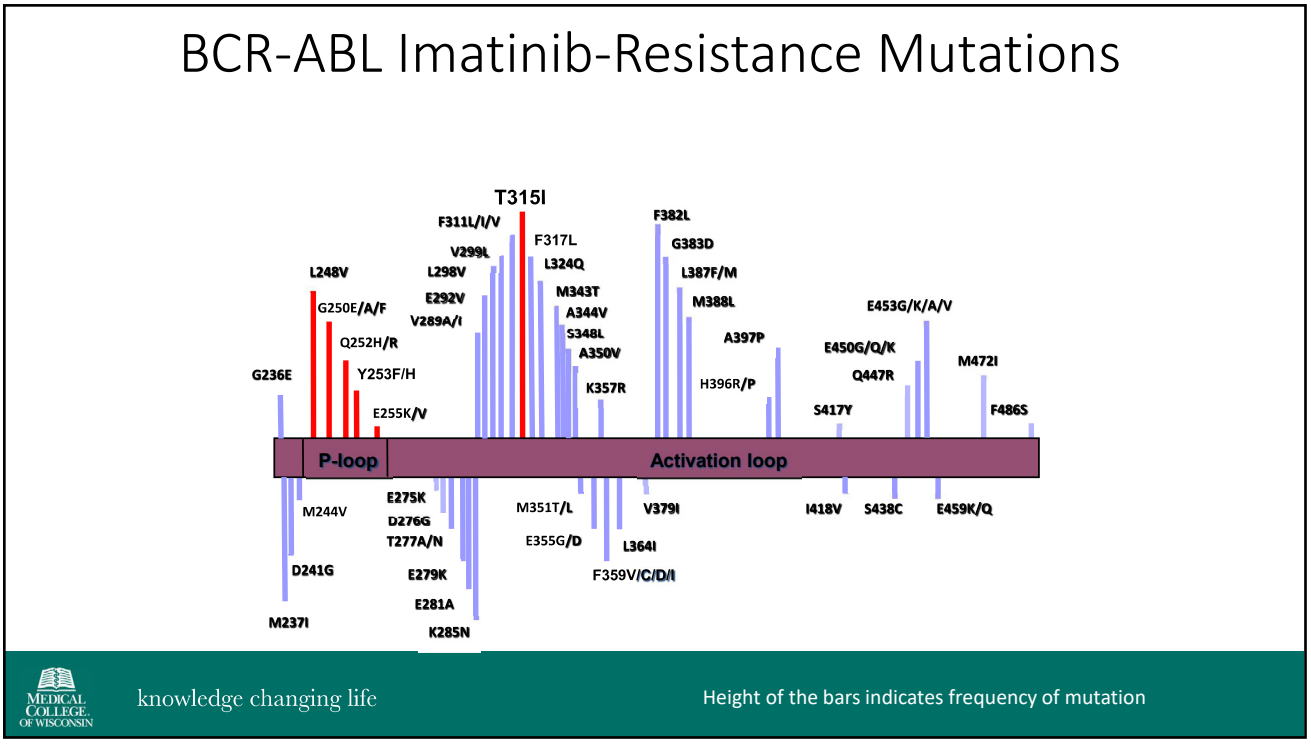
So for example, if someone's PCR is more than 10% at 12 months, that's red, that's not good. But if someone is more than 1% at 12 months, that's yellow, that's okay. We need to follow as long as the numbers continue to get better, we can follow and stay there.

So, it's straightforward in terms of looking at this table, but also, we need to take into account, are the numbers going down: is it a continuous downward trend? How fast is the halfing time? What's the dose that the patient is on? It's pretty straightforward with some nuances, if someone is not following the milestones exactly like you're seeing here in this table.



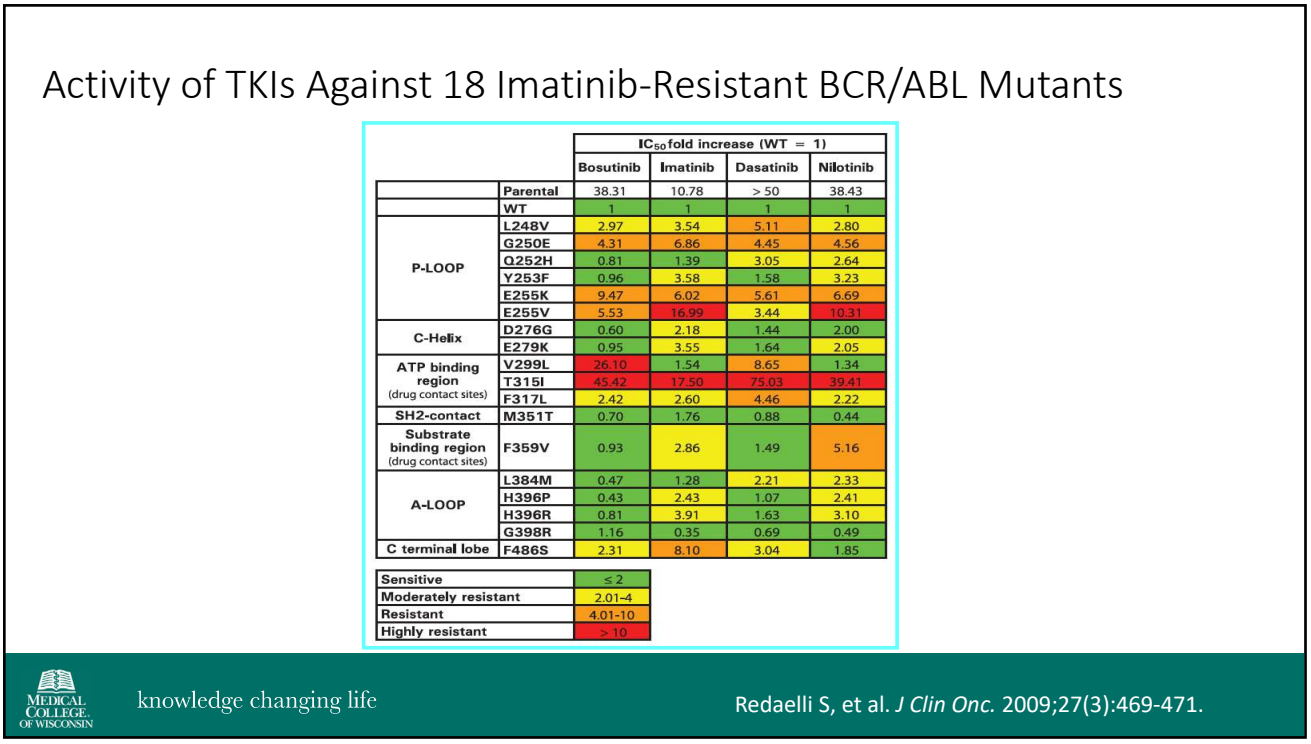

**Slide 24: RESISTANCE TO FIRST LINE TKI**

So, if someone's not following these milestones, one of the common causes for not responding appropriately, is not taking the drug. Because it's a drug that needs to be taken every day and if I'm having side effects from the drug, if I wake up every morning, I have to take the pill and I feel tired, I'll try to avoid taking the pill or forget. So, not taking the drug is one of the main reasons we see why someone is not responding appropriately.



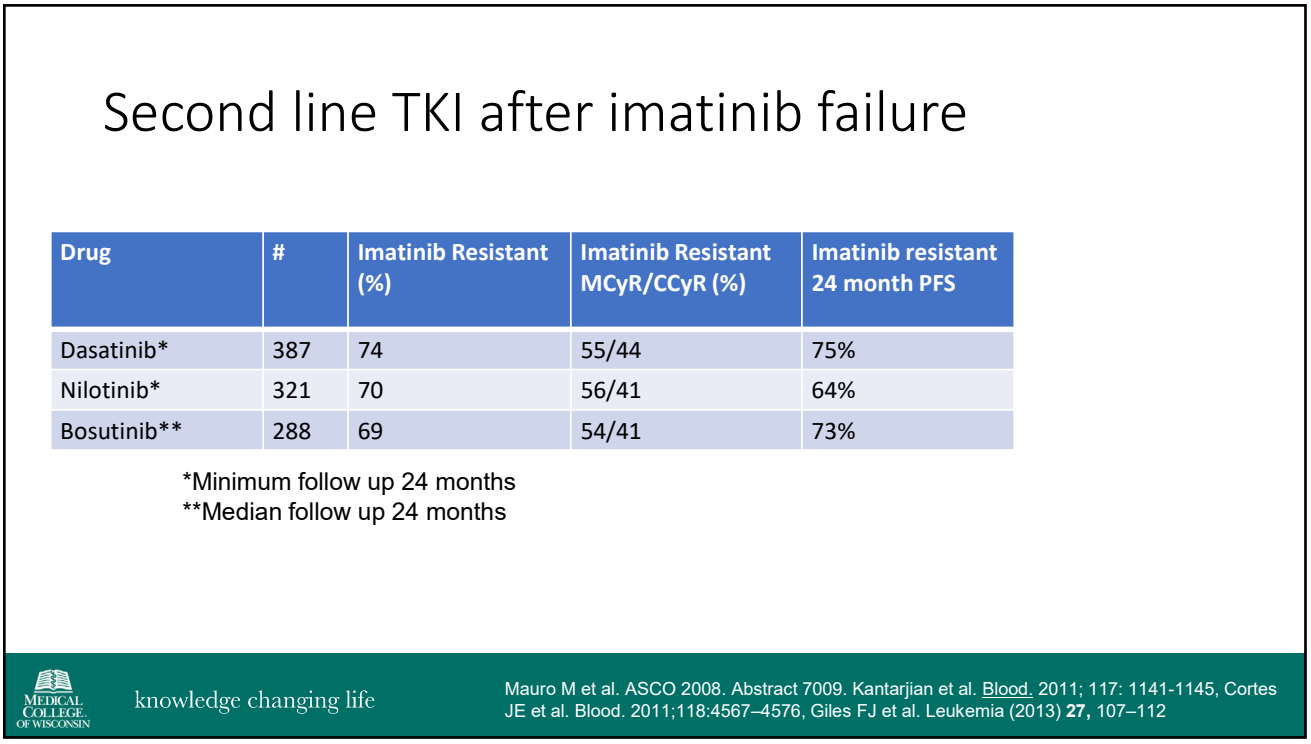

**Slide 25: BCR-ABL IMATINIB-RESISTANCE MUTATIONS**

Outside of that, resistance could happen because the way these drugs work is they bind to the protein that's made by this abnormal chromosome. Protein is the messaging system in the cell. So they bind to that protein and some leukemias become smarter and modify that protein so the drugs can bind, which is the BCR-ABL mutation. Perhaps the most famous is the T315I mutation and that one, only 2 drugs are effective if someone has a T315I mutation.




**Slide 26: ACTIVITY OF TKIS AGAINST 18 IMATINIB-RESISTANT BCR/ABL MUTANTS**

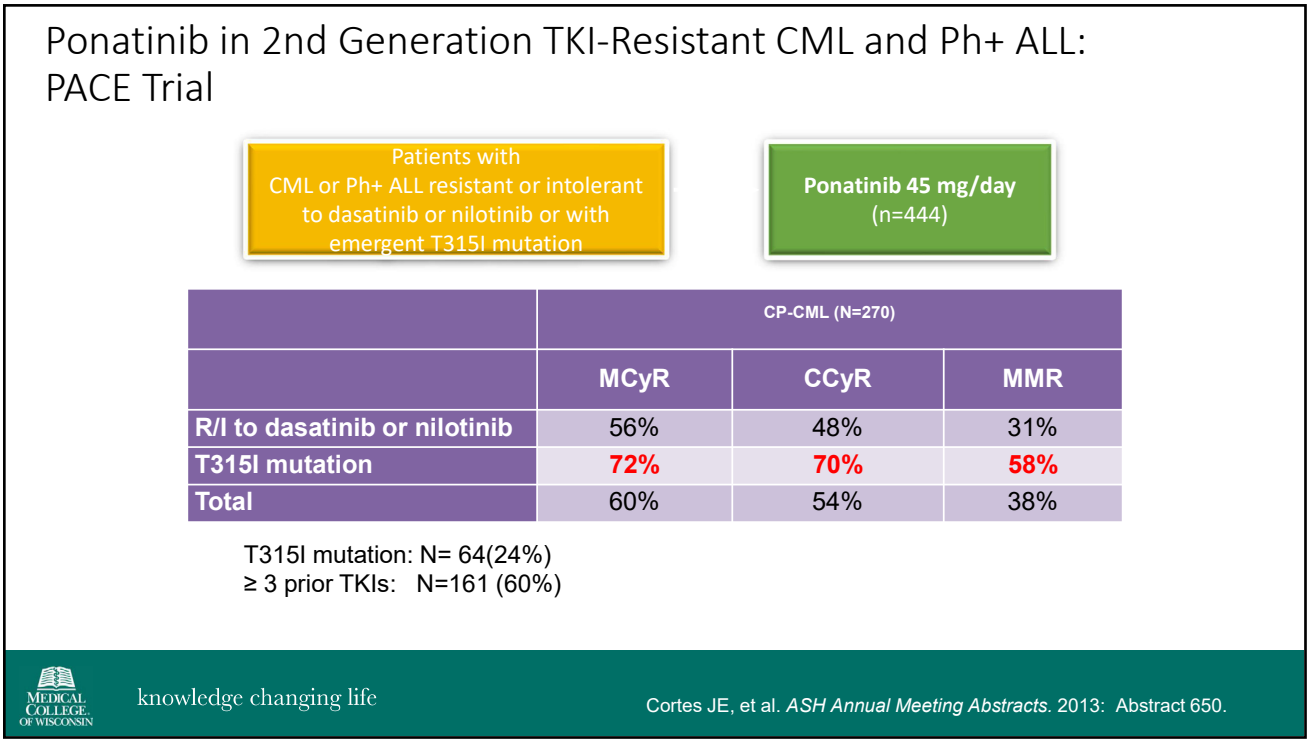
What's interesting about these mutations, or the knowledge about these mutations, is now with each drug we know which mutations are more sensitive to. So when we get a mutation analysis, we can look at the type of mutation and say, okay, so bosutinib is better for you, nilotinib is better for you, or dasatinib is better for you. And like I mentioned earlier for the T315I only ponatinib and asciminib work.




**Slide 27: SECOND LINE TKI AFTER IMATINIB FAILURE**

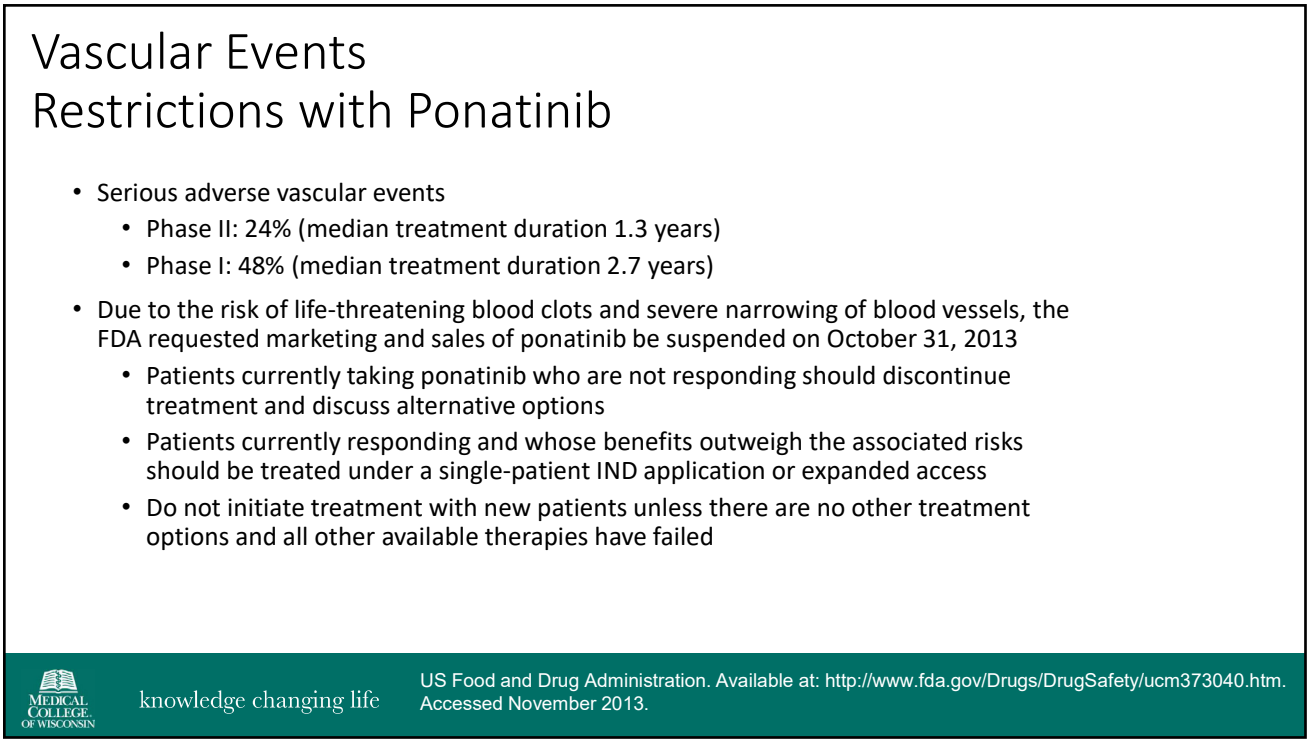
So what about if someone is taking imatinib, taking it like they should, but is not achieving the milestones and not responding appropriately? On average, if someone switches to dasatinib, nilotinib, or bosutinib – about half the patients respond and about three-quarters of those patients continue to respond 2 years out.

This is pretty old data. We don't have follow-up data for second-line or for third-line.



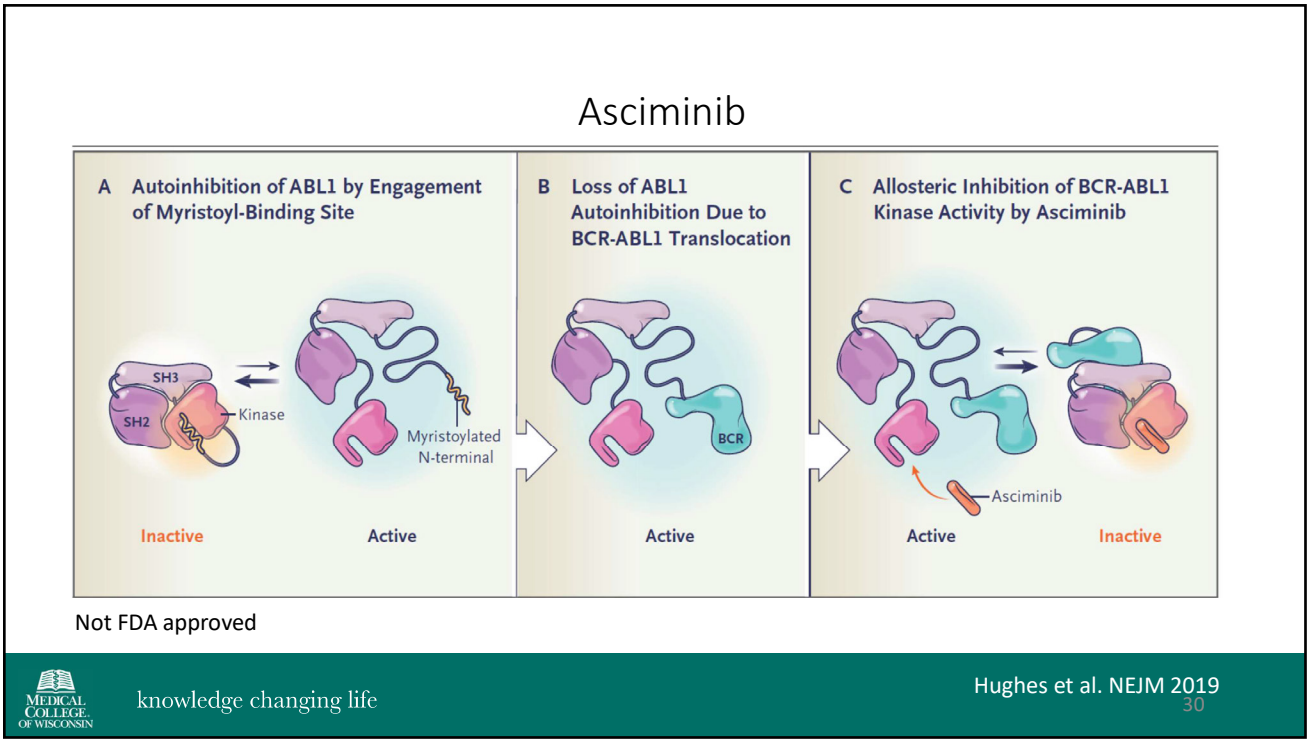

**Slide 28: PONATINIB IN 2ND GENERATION TKI-RESISTANT CML AND PH+ ALL: PACE TRIAL**

Then we come to what's known as the third-generation TKI, which is ponatinib. And, in patients who are resistant or intolerant to dasatinib or nilotinib, about half of those patients respond and specifically in patients who have a T315I mutation, about 70% have a complete cytogenetic remission with ponatinib.



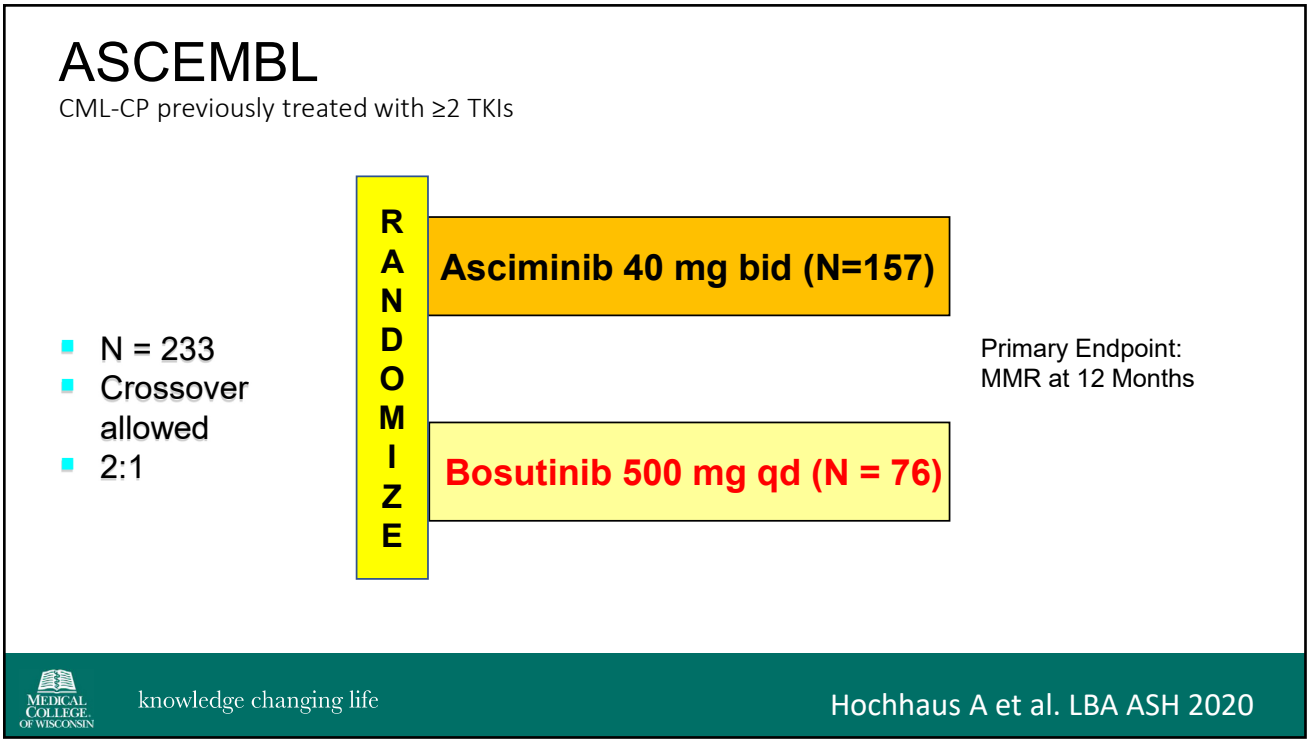

**Slide 29: VASCULAR EVENTS – RESTRICTIONS WITH PONATINIB**

Ponatinib, however, does have a black box warning of also affecting the blood vessels of the body. This is an important side effect; however, we have to balance that with how effective the drug is and if someone needs to take it, we know now that with some adjustments to the dose and adjusting the other cardiovascular risks or the other, medical problems of the patient, that could really help in reducing that risk.



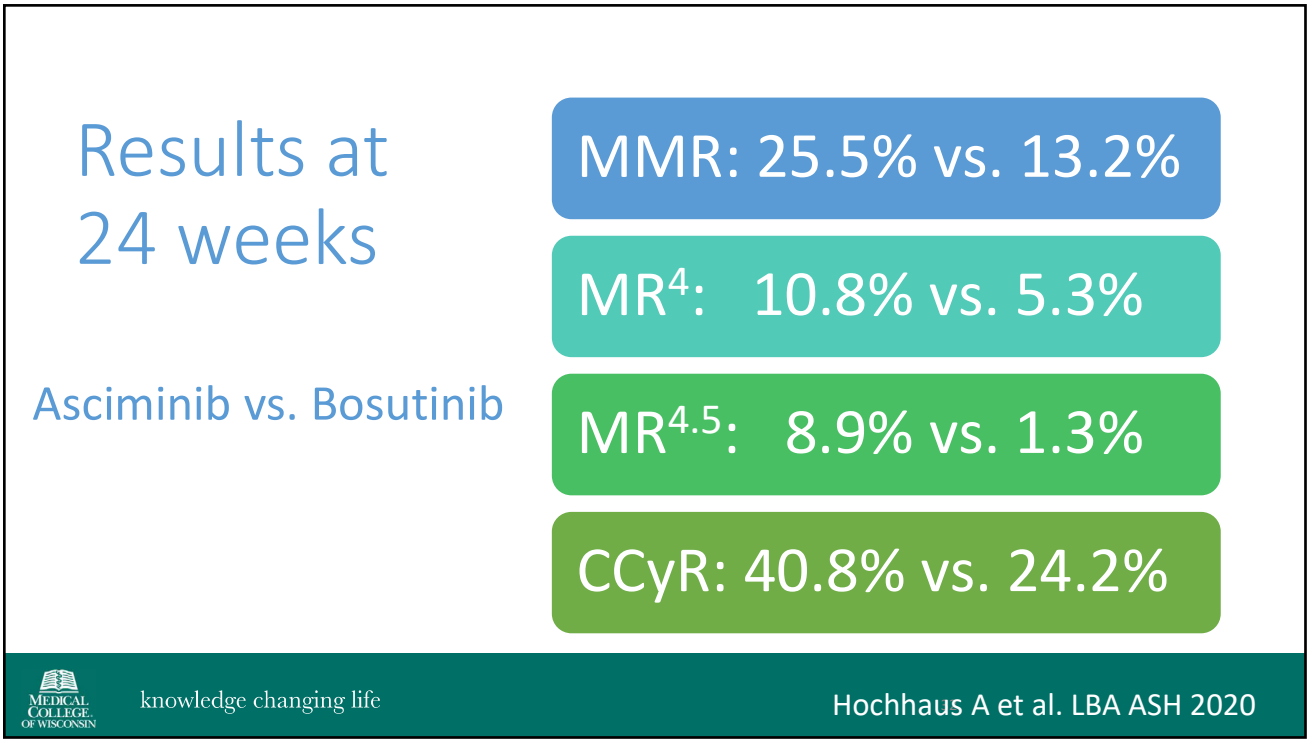

**Slide 30: ASCIMINIB**

And finally, most recently asciminib was FDA approved for patients who've been on 2 prior TKIs and not responding. Asciminib is really a drug that just binds to a completely different spot than the other 5 drugs. So, it works in patients who have been on a TKI and not responding.



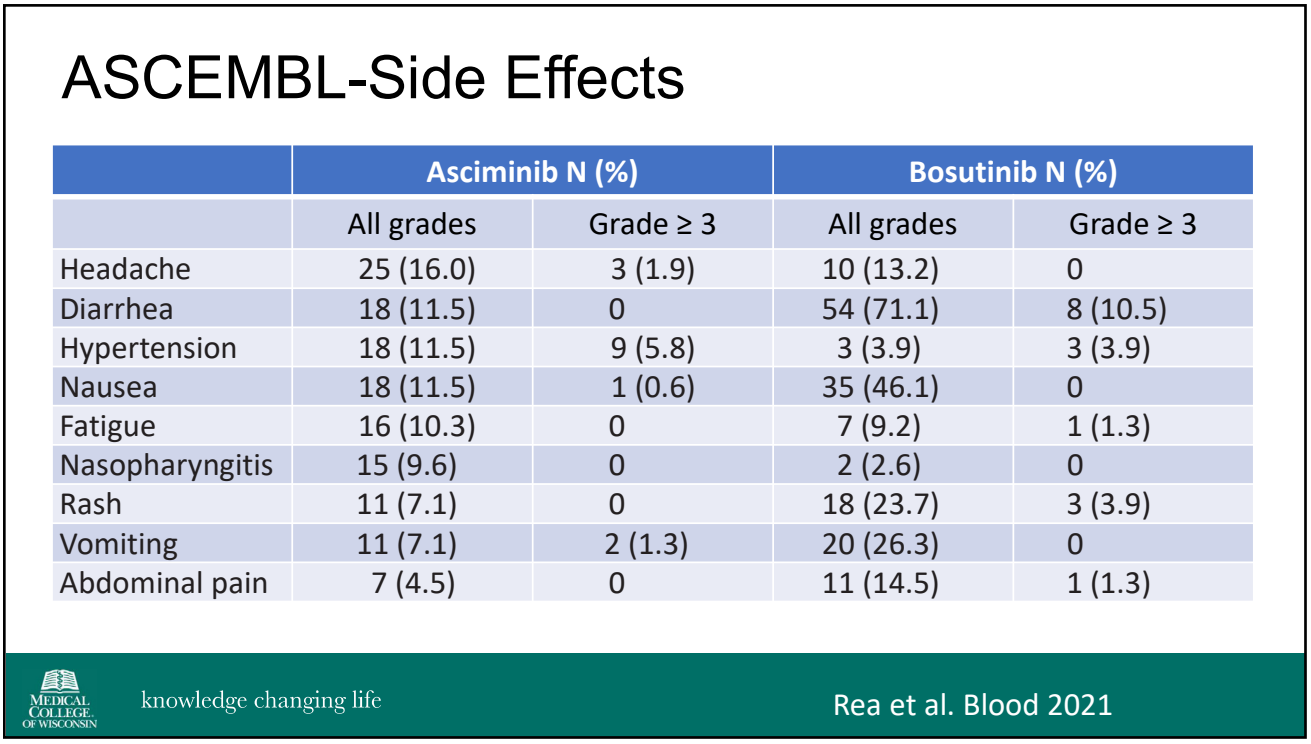

**Slide 31: ASCEMBL**

And in a study, the way we figure these things out, which I think you all know, is we have a large study, flip a coin, someone takes asciminib and someone takes another drug, in this case in the study was bosutinib.




**Slide 32: RESULTS AT 24 WEEKS**

With 24 weeks of follow-up and this data has held out to 96 weeks, the percentage of patients hitting MMR, which is 0.1%, about a quarter of the patients hit that and at 96% (96 weeks) that number even went up to more than 30%.



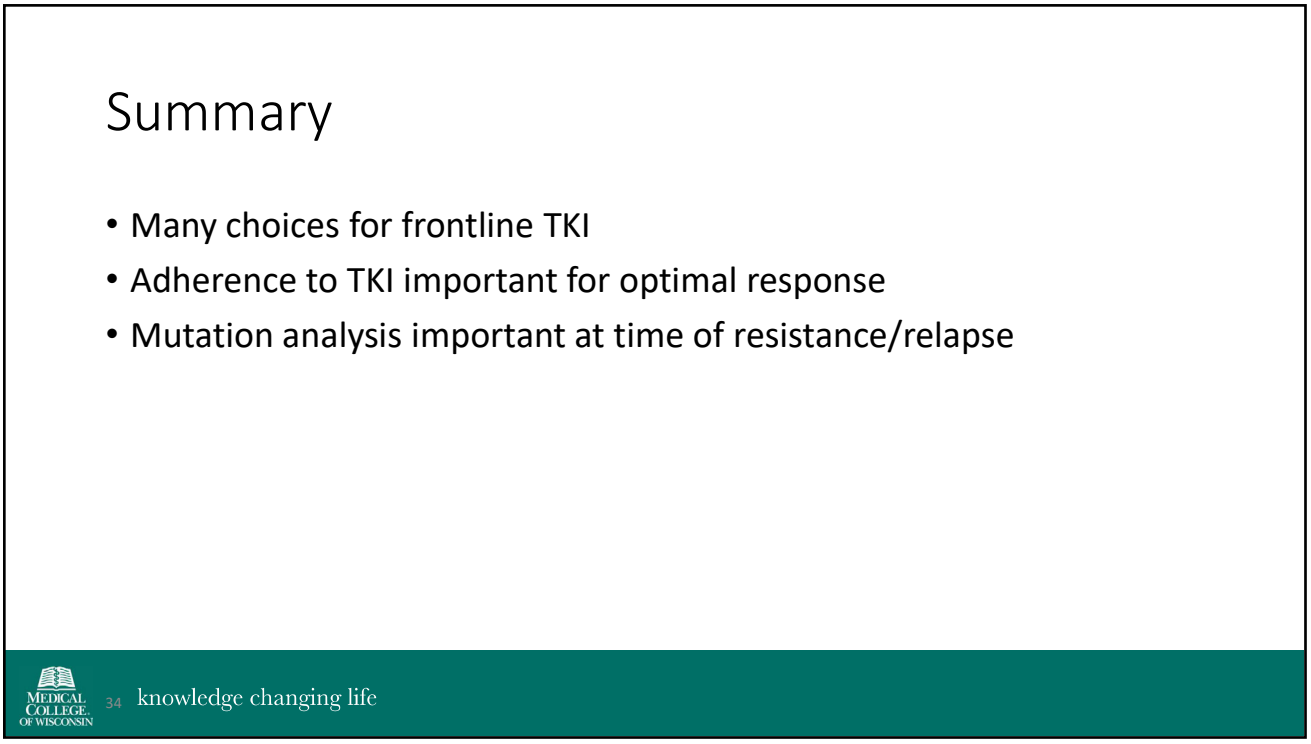
# ASCEMBL-Side Effects

| | Asciminib N (%) | | Bosutinib N (%) | |
|---|---|---|---|---|
| | All grades | Grade ≥ 3 | All grades | Grade ≥ 3 |
| Headache | 25 (16.0) | 3 (1.9) | 10 (13.2) | 0 |
| Diarrhea | 18 (11.5) | 0 | 54 (71.1) | 8 (10.5) |
| Hypertension | 18 (11.5) | 9 (5.8) | 3 (3.9) | 3 (3.9) |
| Nausea | 18 (11.5) | 1 (0.6) | 35 (46.1) | 0 |
| Fatigue | 16 (10.3) | 0 | 7 (9.2) | 1 (1.3) |
| Nasopharyngitis | 15 (9.6) | 0 | 2 (2.6) | 0 |
| Rash | 11 (7.1) | 0 | 18 (23.7) | 3 (3.9) |
| Vomiting | 11 (7.1) | 2 (1.3) | 20 (26.3) | 0 |
| Abdominal pain | 7 (4.5) | 0 | 11 (14.5) | 1 (1.3) |



**Slide 33: ASCEMBL-SIDE EFFECTS**

Asciminib is overall well tolerated, does have a side effect of some GI upset, headaches, high blood pressure, does cause changes/inflammation in the pancreas, so it does have its own set of side effects.




**Slide 34: SUMMARY**

So, in summary, there's been significant progress over the last few years for CML. Patients need to take the drug, go into remission, however, we don't think that that's enough, we need to do more, we need to get people to an actual cure where not taking a drug and not having any detectable disease.


**Slide 35: THE H. JEAN KHOURY *CURE CML CONSORTIUM (HJKC3)***

And with that, we started a CML Consortium which is in the United States, which includes 19 academic centers, it's named after our good friend, our late good friend Dr. Jean Khoury, who encouraged this and unfortunately died in 2017. So we named the Consortium after him. And our goal really is to keep moving the field forward and keep working on trying to find a cure for CML by collaborating all together, clinicians, basic scientists, and hopefully we can get to a point of not just take a pill every day, now we actually get to a point where we can cure more patients, they don't need to take their pill and they can completely forget about CML.

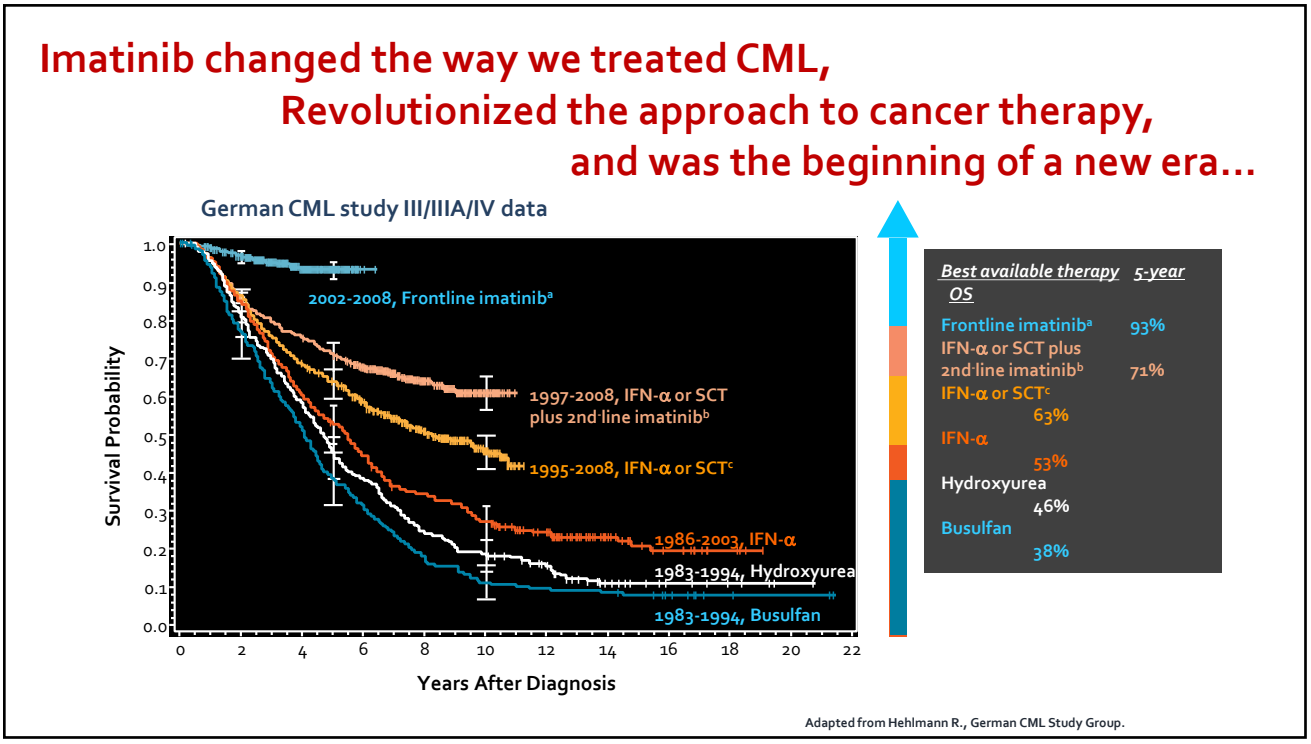
So, I know I talk very fast and we'll have more time for questions at the end. Thank you all very much. Next, I'll introduce Dr. Mauro. Dr. Mauro of course is part of the Consortium. He's a Professor of Medicine at Memorial Sloan. So thank you very much, Dr. Mauro for being with us. So go ahead.


**Slide 36: CML CLINICAL TRIALS, TREATMENT FREE REMISSION, FUNCTIONAL CURE!**

**Dr. Michael Mauro:**

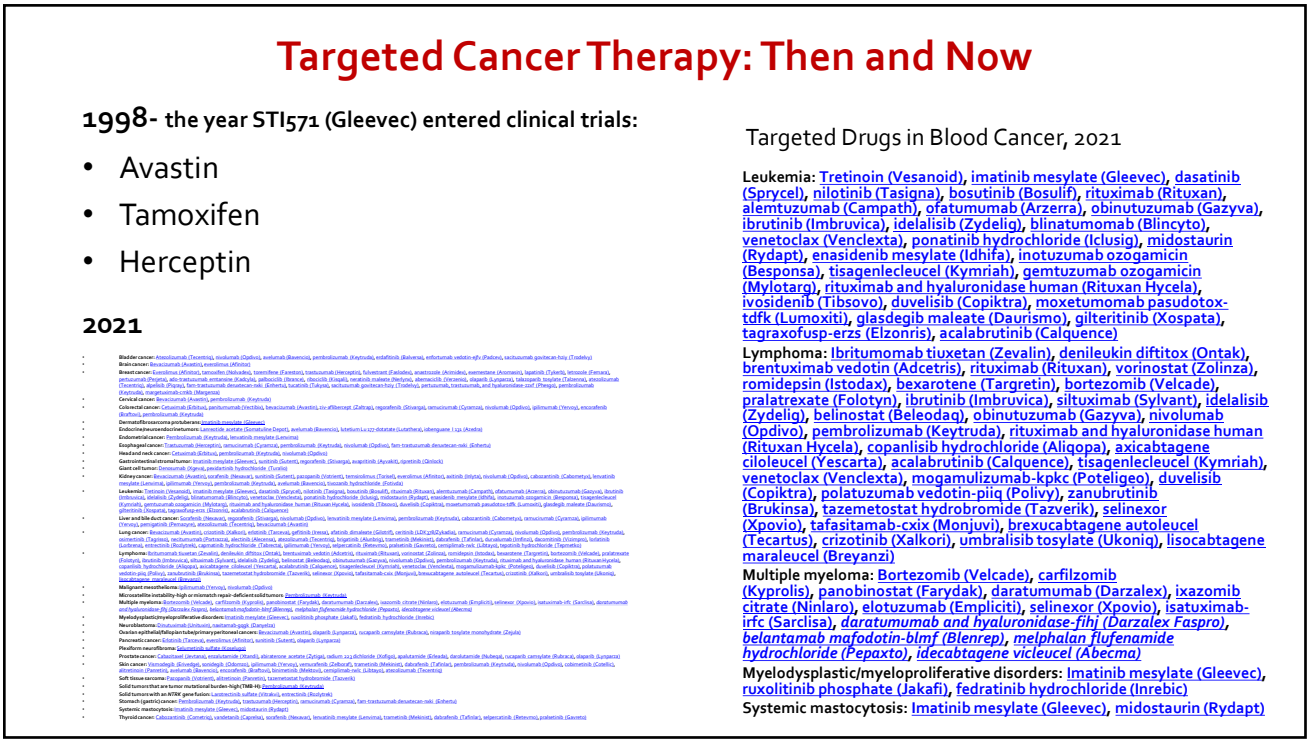
Thanks, Dr. Atallah. That was a great overview of CML and the nuts and bolts about our tools and our treatments. So I kind of get to talk about the icing on the cake now. I'd also like to thank LLS for organizing this and hosting us and can't underestimate the dedication of my colleagues and the terrific Consortium that we've been able to develop in the U.S., the CML Consortium, really with a goal to cure CML. So, in the next few minutes I'll speak to you about CML clinical trials, talk to you about this new era we're in and this new term of treatment-free remission and functional cure for CML.

My disclosures, just to verbally state them, would be that I do partner with the main manufacturers of TKIs, that would be Novartis, Bristol Myers Squibb, Takeda, Pfizer, and some other smaller companies, such as Sun Pharma, where they give research support to our institution, to Memorial Sloan Kettering Cancer Center to run clinical trials, and I have consulted with those companies as we develop clinical trials.



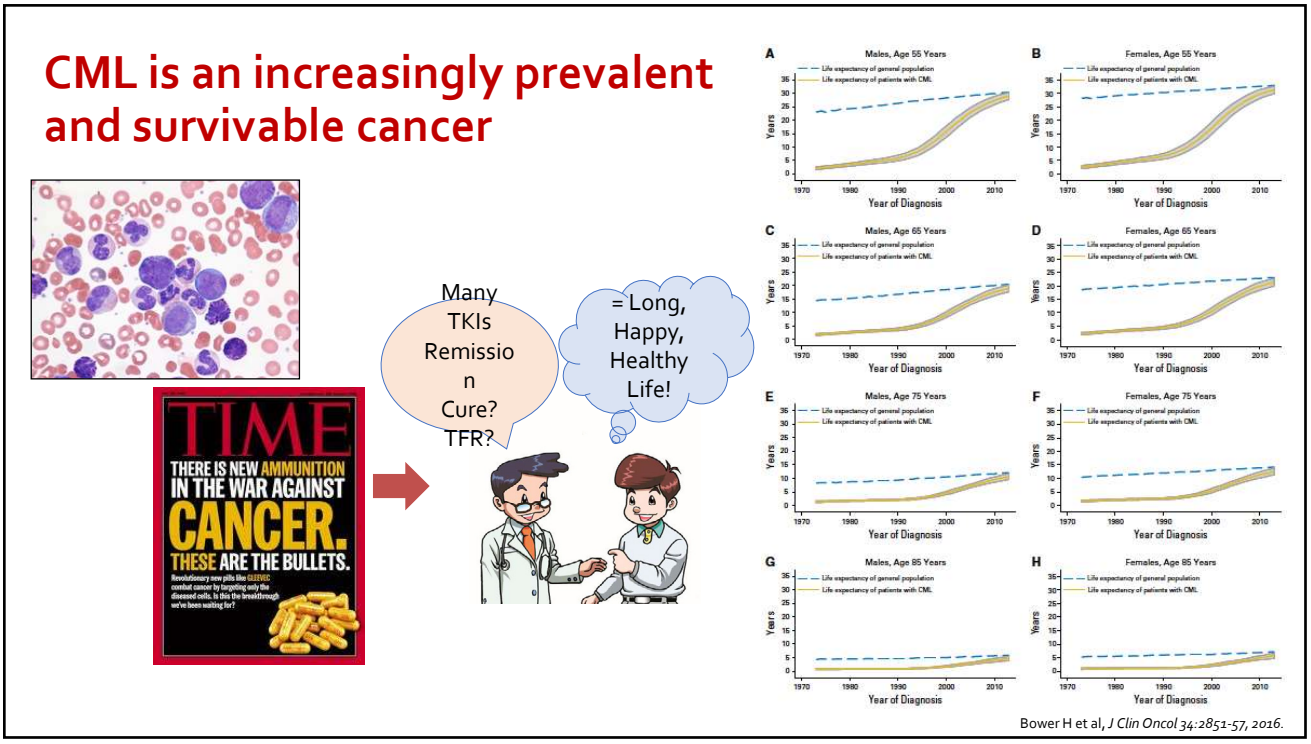

**Slide 37: IMATINIB CHANGED THE WAY WE TREATED CML, REVOLUTIONIZED THE APPROACH TO CANCER THERAPY, AND WAS THE BEGINNING OF A NEW ERA…**

So imatinib, it's the first TKI we had approved, and this was back more than 20 years ago now, really changed the way we treat CML. To be frank, I think it revolutionized the approach to cancer therapy and was the beginning of a new era. This figure on this slide shows you how unfortunately the trajectory of CML used to look. And thank goodness this is not the case anymore. On the bottom where the way statistically, things went with CML in the 80s when we really just had medical therapy, then again interferon and more use of stem cell transplant, we were able to help more patients survive and beat CML. But you can see the stark difference with the introduction of imatinib, how when that was available and the drugs that came after it, now instead of most people unfortunately having difficulties and succumbing to CML over a few years, now the exact opposite was the case and nearly all patients were surviving CML. And that is unprecedented. We really don't have that kind of change in any other disease.



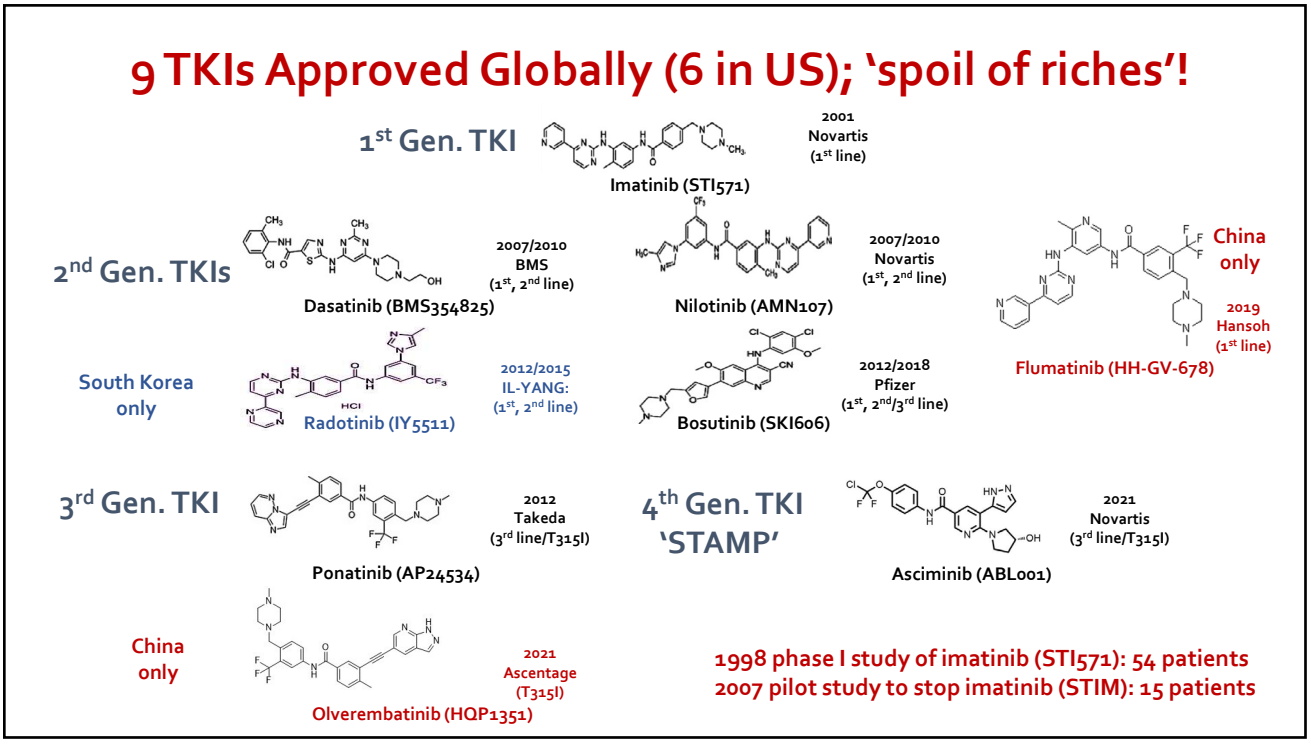

**Slide 38: TARGETED CANCER THERAPY: THEN AND NOW**

And targeted cancer therapy really was in its infancy. In 1998 when imatinib was in clinical trials, then known as STI571, there were 3 targeted drugs: Avastin® (bevacizumab), which was a global sort of vascular growth inhibitor drug, and the anti-estrogen drug tamoxifen (Nolvadex®, Soltamox®), and Herceptin® (trastuzumab), which was an antibody, was the first really targeted drug approved, that was 1998. In 2021, I purposely put this figure small so you can't read it because it lists the targeted drugs, actually it's just a partial list in solid tumors, and on the right is a now outdated list from 2021 of targeted drugs just in blood cancers alone. So Gleevec® really set the stage and this was not that long a history, so we've really come a long way in targeted cancer therapy.




**Slide 39: CML IS AN INCREASINGLY PREVALENT AND SURVIVABLE CANCER**

What we've seen in change with CML, and this was so aptly put on the cover of Time Magazine back in 2001 when imatinib was going through FDA approval, what we saw was that we now had an increasingly survivable for cancer. These figures on the right show the life expectancy of patients with CML in their 40s, 50s, 60s, and 70s, and what happened was it used to be inferior to or lower than the general population, and in the year of targeted therapy it is now not inferior, it matches, so peoples' life spans are not affected with a diagnosis of CML any longer.




**Slide 40: 9 TKIs APPROVED GLOBALLY (6 IN US); 'SPOIL OF RICHES'!**

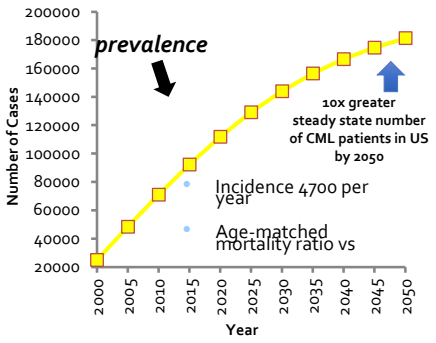
Dr. Atallah went through the therapies in the United States. I think if we'd take a step back, we recognize it globally, there's actually 9 TKIs now approved. And, to give a nod to our colleagues outside of the U.S. in South Korea, in China, there are second-generation TKIs that are approved. One called flumatinib (Hansoh Xinfu®), another one radotinib (IY5511). And also in China a third-generation TKI, olverembatinib (HQP1351), which is active against the T315I mutation.

This is really, as many people say, a spoil of riches. We have a palette of drugs we can now use. And if you look at other diseases, CLL and other diseases as well, the same paradigm is followed, where we have one very good medication and maybe another class of medication also may develop, but we build on that and we just essentially develop 2.0 and 3.0 and 4.0 versions of the drugs we had to make them even better.

Sorry, just want to move back one slide (slide 39) and just make a comment on the importance of clinical trials. All of this development of TKIs is on the shoulders and due to the generous and brave and heroic volunteerism of patients willing to enter clinical trials. You know, clinical trials are designed of course to serve patients, but they come in different phases. Phase I trials may be just exploring the dose and the side effects of a drug with a hope of benefit. Phase II studies are looking to see perhaps how strong a signal and how good a medication is. And a Phase III study is proving should this be our new standard of treatment. In 1998 was when imatinib started in clinical trials. The Phase I study with that agent had 54 patients. Those are some pretty brave patients who at the time there was no such thing as targeted therapy, were taking essentially a pill with a chemical in it that was believed to be a small molecule, kind of smart drug, to inhibit leukemia. And believe me, confidence was not necessarily high. I'll have to acknowledge that the support for that clinical trial came from The Leukemia & Lymphoma Society, so without that type of support, without that type of volunteerism and willingness and trust of patients, that trial wouldn't have got off the ground. The good news, I can tell you, is that 53 out of 54 patients went into remission in that trial.

## The Unmet Need: Increasing the CURE Fraction– *Treatment Free Remission*

- Number of people living with CML– CML survivors continues on increase (prevalence)
- Number of people achieving safe and stable remissions is very high
- Increasing guidelines and potential to plan ***deliberate, carefully monitored treatment cessation ('TFR')***




Huang et al, *Cancer* 118:3123-3127, 2012
Hochhaus A, et al, *Leukemia* 34(4):966-984, 2020

**Table 7** Cumulative incidence of deep molecular response ($MR^4$ and $MR^{4.5}$) with imatinib, nilotinib, and dasatinib by 5 and 10 years.

| Study | | 5 years (%) | 10 years (%) |
|---|---|---|---|
| CML-Study IV[a], [36, 37] | Imatinib $MR^4$ | 68 | 81 |
| | Imatinib $MR^{4.5}$ | 53 | 72 |
| ENESTnd[b], [41, 52] | Nilotinib $MR^4$ | 66 | 73 |
| | Nilotinib $MR^{4.5}$ | 54 | 64 |
| | Imatinib $MR^4$ | 42 | 56 |
| | Imatinib $MR^{4.5}$ | 35 | 45 |
| Dasision[c], [40] | Dasatinib $MR^{4.5}$ | 42 | NA |
| | Imatinib $MR^{4.5}$ | 33 | NA |

DMR rates of these trials cannot be directly compared owing to different methods of trial evaluation.

*NA* not available.

[a]Imatinib ($n = 1442$).

[b]Nilotinib 300 mg twice daily ($n = 282$), imatinib 400 mg daily ($n = 283$).

[c]Dasatinib 100 mg once daily ($n = 259$), imatinib 400 mg daily ($n = 260$).

**'Functional Cure' Fraction**

- ~75% Deep Remission
- ~35-40% successful TFR
- majority of patients thus remain on TKI…for now… but not for long?!

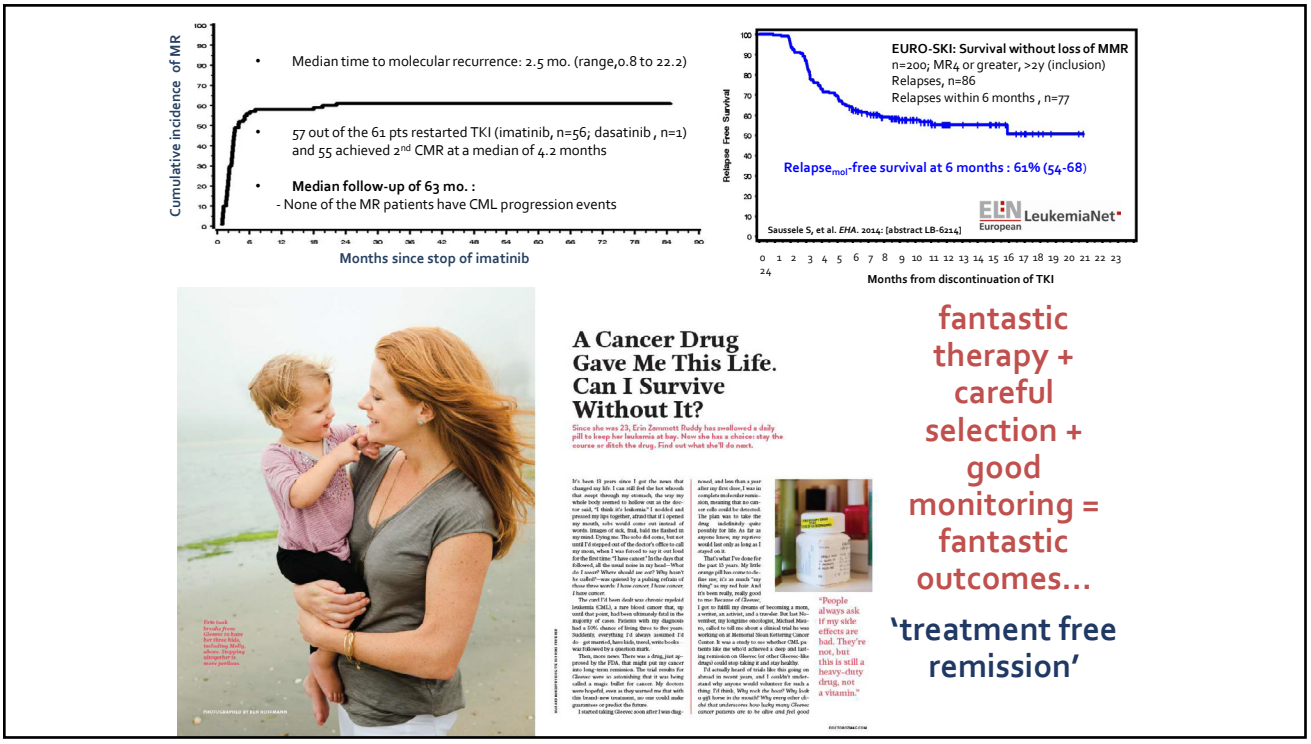

**Slide 41: THE UNMET NEED: INCREASING THE CURE FRACTION–*TREATMENT FREE REMISSION***

In 2007, the first studies began for treatment-free remission, which I'm going to describe in a moment, that was only 15 patients. Now that was even braver a group of patients, who now just 9 years later, after imatinib really was first in development, these patients hadn't had that long on treatment, their doctors had proposed: you're in a very good remission and we believe it may be possible for you to interrupt your treatment or stop your treatment and be monitored, will you be willing to do it? And these patients stepped up to try that. I'm glad to say that exactly 50% of those patients remained in remission off-treatment and really pioneered what is now our goal at our CML Consortium and one of our main themes for today, which is treatment-free remission.

It's a very good story and it's based in really what I would say is an unmet need. We have an increasing number of people surviving CML, which means the prevalence of CML is increasing, not that it's happening more often, just that more people around are living with CML. The number of people who have a safe and stable remission is very high and there are now guidelines and essentially it's approved and able to be the case, where people can have deliberate and careful monitored treatment cessation, as long as they meet certain criteria and are followed very carefully for something called a treatment-free remission or a TFR.

Some of the wrinkles are that we don't have the ability to get everyone to that finish line. We have about three-quarters over long periods of time where patients were able to get a deep remission, so there's already a fraction of people who aren't able to have that opportunity. That doesn't mean they can't do quite well, but they're not able to.

From that about half of patients are successful. So that's not what we'd like to say. We'd like to say that nearly all patients are able to achieve the remission and makes them possible to potentially stop treatment, and that not just 50% or slightly less of patients are successful. So, we want to do more.




**Slide 42: FANTASTIC THERAPY + CAREFUL SELECTION + GOOD MONITORING = FANTASTIC OUTCOMES…**

The successes are sweet I can tell you, but sometimes the failures are bitter as well. On the top are just some of the figures on just how stable the population looks once they make it past the initial period when they may need to be retreated. And in a word, that is not a turbulent time and people are able to regain remissions at extremely high or near perfect rates with very little change in side effects, but again this is not always successful.

On the bottom is a photo of one of my patients who I've followed for more than 2 decades. A very brave woman who actually went on some of the first imatinib trials, went into a very deep remission, was doing very well, had stopped treatment not once, not twice, but 3 times to have children, and did so successfully, but wasn't able to successfully stop treatment as part of a cessation trial. So, it's very good and we're looking to do better and it can really be summed up in one woman's story.

## One Woman's Story Says it All.....

**Slide 43: ONE WOMAN'S STORY SAYS IT ALL.....**

This woman's name, just because she's quite public about her CML, is Erin Zammett Ruddy, who's also a strong supporter of The Leukemia & Lymphoma Society and has raised a large number of dollars and awareness. And here's me as a young hematologist, starting to care for her when we were both a bit younger, and here's her 3 children, her 3 beautiful children, who are now growing older with her and she's doing quite well.

## The Balance: TKIs have low (but not *NO*) toxicity…

| Issue | Imatinib | Nilotinib | Dasatinib | Bosutinib | Ponatinib | Asciminib |
|---|---|---|---|---|---|---|
| **Dosing** | QD/BID, with food | BID, without food (2h) | QD, w/ or w/o food | QD, with food | QD, w/ or w/o food | QD or BID, w/o food; dosing varies (T315I or not) |
| **Long term safety** | Most extensive | Extensive; Emerging toxicity | Extensive; Emerging toxicity | Extensive, No emerging toxicity | More limited but increasing; Emerging toxicity | Emerging; long phase I data (8y) |
| **Heme toxicity** | Intermediate | Least | Most severe; ASA-like effect; Lymphocytosis | ~dasatinb in 2nd, 3rd line; ~nilotinib in 1st line | Thrombocytopenia ASA-like effect | Thrombocytopenia Neutropenia |
| **Non-Heme toxicity** | Edema, GI effects (diarrhea, nausea), Muscle cramps, ↓Phos | ↑Lipase, ↑Bili, ↑Chol, ↑Glu, Fatigue, Musculo-skeletal symptoms Black box: QT prolongation | Headache (early/transient) Pleural / pericardial effusions | Diarrhea; Transaminitis | ↑Lipase, Pancreatitis, Rash, Hypertension Black box: vascular occlusion, heart failure, and hepatotoxicity | ↑Lipase, Pancreatitis, Hypertension, Hypersensitivity reaction, Possible cardiovascular adverse events |
| **Special concern issues** | **Early question re: CHF ?late renal effects** | **Vascular events (ICVE, IHD, PAD)** | **?PAH (pulmonary arterial hypertension)** | **? Mild renal effects** | **Vascular events (ICVE, IHD, PAD, VTE)** | **Longer follow-up needed re: cardiovascular AEs** |

**Slide 44: The Balance: TKIs have low (but not *NO*) toxicity…**

The reason why we're pursuing treatment-free remission is that it's a balancing act. As Dr. Atallah nicely summarized, the TKIs we use, they don't have a lot of side effects, but they certainly aren't side-effect free and some of them are somewhat concerning. He touched on several of these in describing each drug, where we have some specific side effects of special concern, vascular side effects, or cardio, or cardiopulmonary side effects, again which can be identified and managed, but are somewhat more risky. Not a bad reason to think about coming off-treatment.

## Financial Toxicity of Current TKI Therapy Paradigm

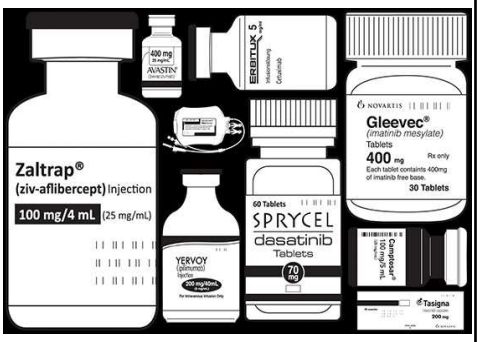

- Global access to care and TKI therapy *varies very widely*
- Limited generic options (imatinib (global), dasatinib (ex-US))
- Paradigm shift between 'lifelong' and defined duration therapy would be remarkably less

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

Experts in Chronic Myeloid Leukemia

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

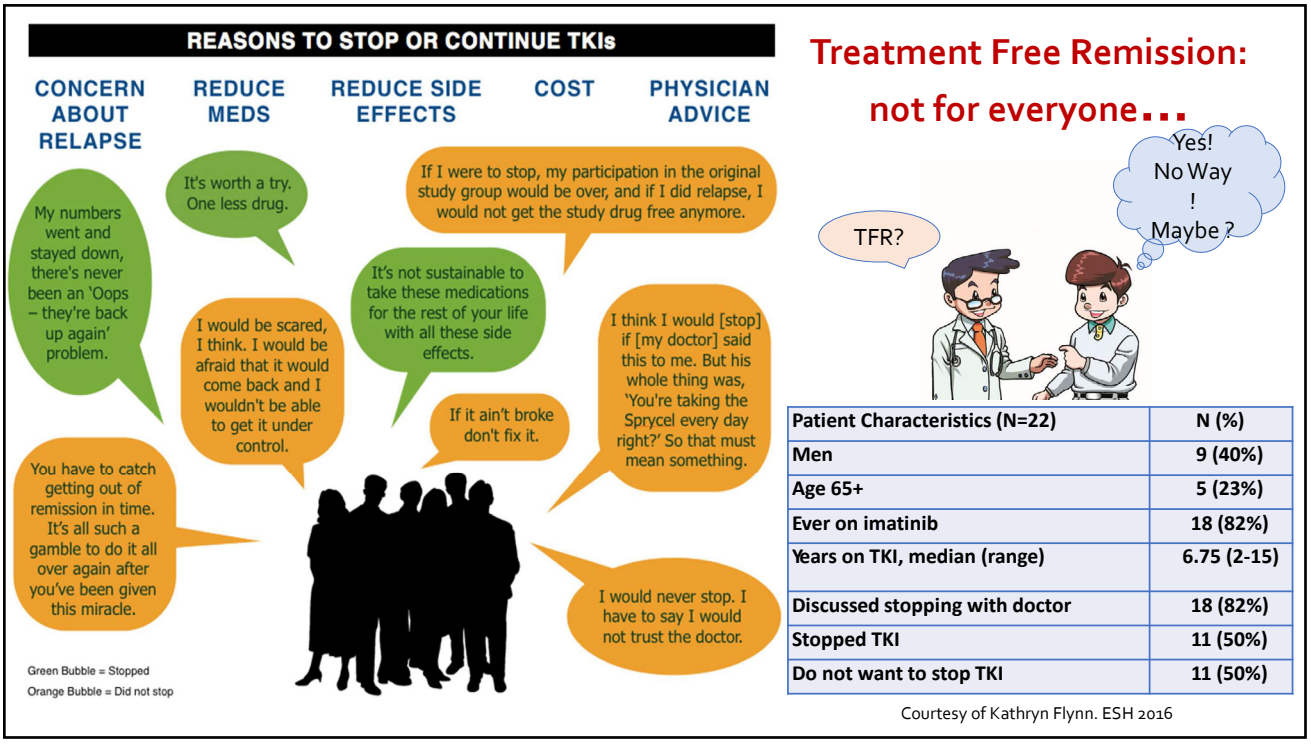
As a group of more than 100 experts in chronic myeloid leukemia (CML), we draw attention to the high prices of cancer drugs, with the particular focus on the prices of approved tyrosine kinase inhibitors for the treatment of CML. This editorial addresses the multiple factors involved in cancer drug pricing and their impact on individual patients and health care policies, and argues for the need to (1) lower the prices of cancer drugs to allow more patients to afford them and (2) maintain sound long-term health care policies. (*Blood.* 2013;121(22):4439-4442)




Kantarjian H. *Blood* 121: 4439-4442, 2013
Hall S, *New York Magazine,* Published 10/20/13

**Slide 45: FINANCIAL TOXICITY OF CURRENT TKI THERAPY PARADIGM**

Another good reason from a global perspective or maybe from a more societal perspective is that there of course is financial toxicity. We'd love to say that patients have an easy time getting medications and having them covered, and that's definitely not the case. Global access, even in U.S. access is variable, and sometimes there's hardship and excessive costs. Generic therapy isn't always as cheap as we'd like it. And we'd love to see a paradigm shift where we don't have to think about life-long therapy, but we can think about a defined duration of therapy, which would change the economic equation and allow us to minimize this financial toxicity. And CML is not the only disease in which this question has come up.

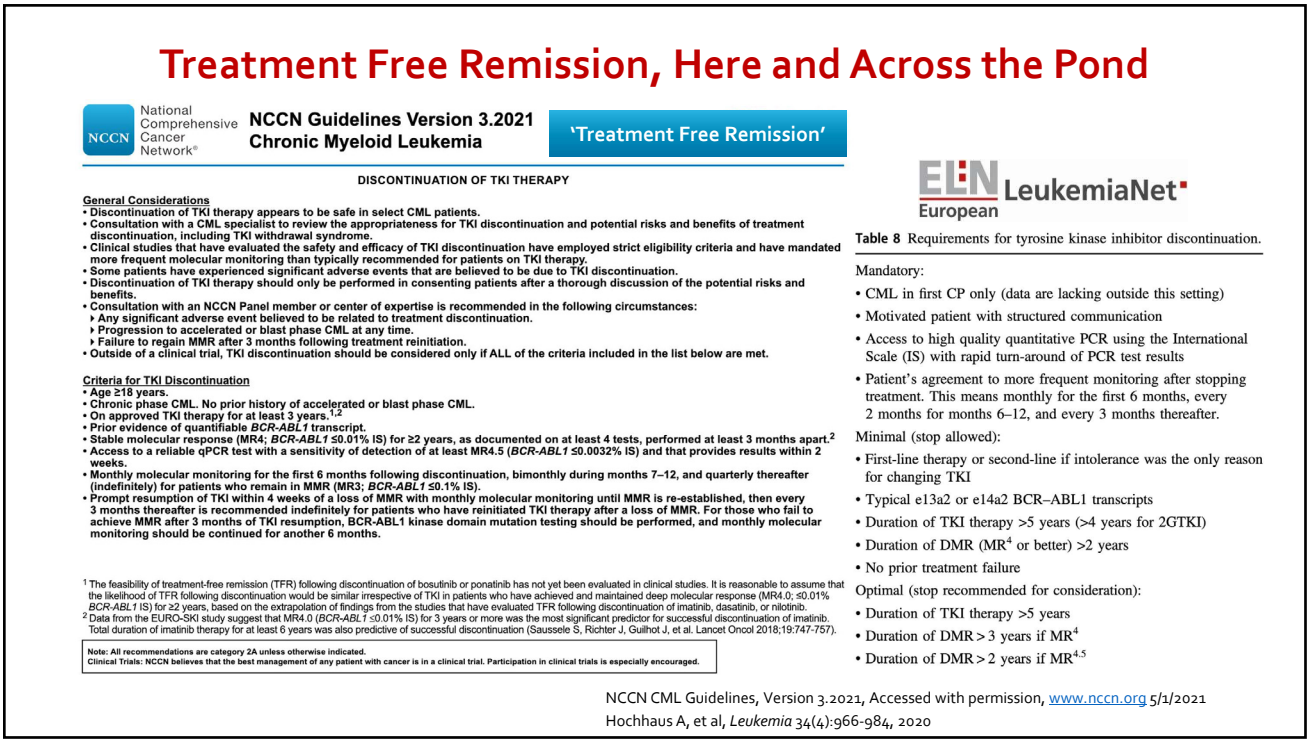



| Patient Characteristics (N=22) | N (%) |
|---|---|
| Men | 9 (40%) |
| Age 65+ | 5 (23%) |
| Ever on imatinib | 18 (82%) |
| Years on TKI, median (range) | 6.75 (2-15) |
| Discussed stopping with doctor | 18 (82%) |
| Stopped TKI | 11 (50%) |
| Do not want to stop TKI | 11 (50%) |

Courtesy of Kathryn Flynn. ESH 2016

**Slide 46: TREATMENT FREE REMISSION: NOT FOR EVERYONE…**

So it seems like it would be a no-brainer if you're eligible and you could, you'd want to stop treatment, but that's not always the case. Some nice work by Kathryn Flynn, one of Dr. Atallah's partners at Medical College of Wisconsin, in preparation for our treatment-free remission trial done through the Consortium with executed patient surveys. And treatment-free remission really wasn't for everyone. There were some patients who were both on the positive side and some on the hesitant side or the negative side and that's quite normal, expected and reasonable. It's not for everyone. But we'd like to be able to avail as many patients as we can to it.



## Treatment Free Remission, Here and Across the Pond

NCCN National Comprehensive Cancer Network®

**NCCN Guidelines Version 3.2021**
**Chronic Myeloid Leukemia**

**'Treatment Free Remission'**

**DISCONTINUATION OF TKI THERAPY**

**General Considerations**
- **Discontinuation of TKI therapy appears to be safe in select CML patients.**
- **Consultation with a CML specialist to review the appropriateness for TKI discontinuation and potential risks and benefits of treatment discontinuation, including TKI withdrawal syndrome.**
- **Clinical studies that have evaluated the safety and efficacy of TKI discontinuation have employed strict eligibility criteria and have mandated more frequent molecular monitoring than typically recommended for patients on TKI therapy.**
- **Some patients have experienced significant adverse events that are believed to be due to TKI discontinuation.**
- **Discontinuation of TKI therapy should only be performed in consenting patients after a thorough discussion of the potential risks and benefits.**
- **Consultation with an NCCN Panel member or center of expertise is recommended in the following circumstances:**
  - **Any significant adverse event believed to be related to treatment discontinuation.**
  - **Progression to accelerated or blast phase CML at any time.**
  - **Failure to regain MMR after 3 months following treatment reinitiation.**
- **Outside of a clinical trial, TKI discontinuation should be considered only if ALL of the criteria included in the list below are met.**

**Criteria for TKI Discontinuation**
- **Age ≥18 years.**
- **Chronic phase CML. No prior history of accelerated or blast phase CML.**
- **On approved TKI therapy for at least 3 years.[1,2]**
- **Prior evidence of quantifiable *BCR-ABL1* transcript.**
- **Stable molecular response (MR4; *BCR-ABL1* ≤0.01% IS) for ≥2 years, as documented on at least 4 tests, performed at least 3 months apart.[2]**
- **Access to a reliable qPCR test with a sensitivity of detection of at least MR4.5 (*BCR-ABL1* ≤0.0032% IS) and that provides results within 2 weeks.**
- **Monthly molecular monitoring for the first 6 months following discontinuation, bimonthly during months 7–12, and quarterly thereafter (indefinitely) for patients who remain in MMR (MR3; *BCR-ABL1* ≤0.1% IS).**
- **Prompt resumption of TKI within 4 weeks of a loss of MMR with monthly molecular monitoring until MMR is re-established, then every 3 months thereafter is recommended indefinitely for patients who have reinitiated TKI therapy after a loss of MMR. For those who fail to achieve MMR after 3 months of TKI resumption, BCR-ABL1 kinase domain mutation testing should be performed, and monthly molecular monitoring should be continued for another 6 months.**

[1] The feasibility of treatment-free remission (TFR) following discontinuation of bosutinib or ponatinib has not yet been evaluated in clinical studies. It is reasonable to assume that the likelihood of TFR following discontinuation would be similar irrespective of TKI in patients who have achieved and maintained deep molecular response (MR4.0; ≤0.01% *BCR-ABL1* IS) for ≥2 years, based on the extrapolation of findings from the studies that have evaluated TFR following discontinuation of imatinib, dasatinib, or nilotinib.
[2] Data from the EURO-SKI study suggest that MR4.0 (*BCR-ABL1* ≤0.01% IS) for 3 years or more was the most significant predictor for successful discontinuation of imatinib. Total duration of imatinib therapy for at least 6 years was also predictive of successful discontinuation (Saussele S, Richter J, Guilhot J, et al. Lancet Oncol 2018;19:747-757).

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

ELN European LeukemiaNet

**Table 8** Requirements for tyrosine kinase inhibitor discontinuation.

Mandatory:
- CML in first CP only (data are lacking outside this setting)
- Motivated patient with structured communication
- Access to high quality quantitative PCR using the International Scale (IS) with rapid turn-around of PCR test results
- Patient's agreement to more frequent monitoring after stopping treatment. This means monthly for the first 6 months, every 2 months for months 6–12, and every 3 months thereafter.

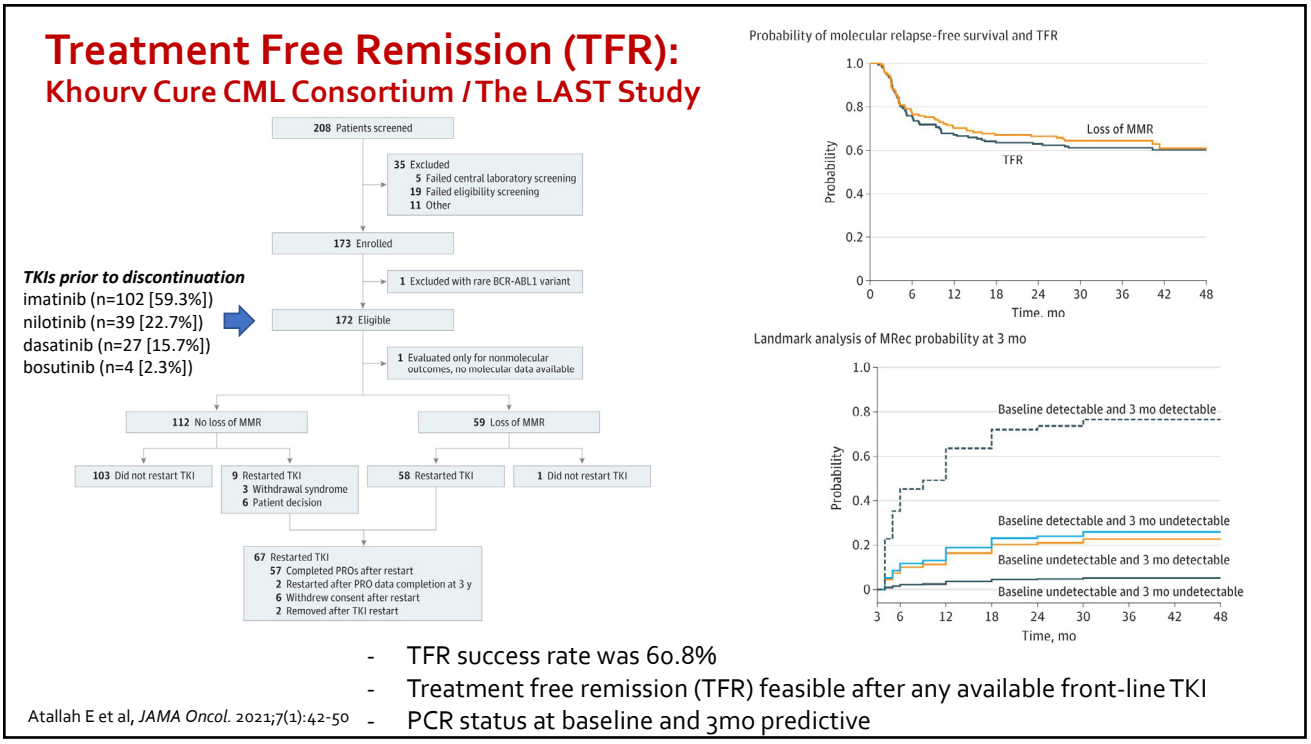
Minimal (stop allowed):
- First-line therapy or second-line if intolerance was the only reason for changing TKI
- Typical e13a2 or e14a2 BCR–ABL1 transcripts
- Duration of TKI therapy >5 years (>4 years for 2GTKI)
- Duration of DMR ($MR^4$ or better) >2 years
- No prior treatment failure

Optimal (stop recommended for consideration):
- Duration of TKI therapy >5 years
- Duration of DMR > 3 years if $MR^4$
- Duration of DMR > 2 years if $MR^{4.5}$

NCCN CML Guidelines, Version 3.2021, Accessed with permission, www.nccn.org 5/1/2021
Hochhaus A, et al, *Leukemia* 34(4):966-984, 2020

### Slide 47: TREATMENT FREE REMISSION, HERE AND ACROSS THE POND

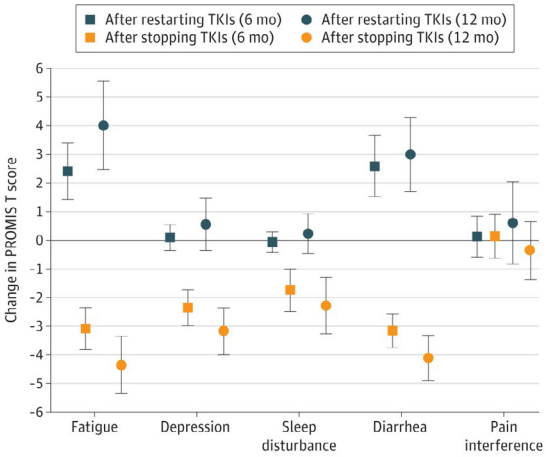
As I mentioned, guidelines have been set and have now been adjusted through the years, so the National Comprehensive Cancer Network (NCCN) in the United States and the European Leukemia Net both have guidelines for us to follow, and we encourage patients to look at these and of course providers to follow. These are the ground rules: who's eligible, how to do it, how to think about retreatment. If the molecular response may be lost or increases. So I think the devil's in the details but the ground rules are there, so we just have to follow them.

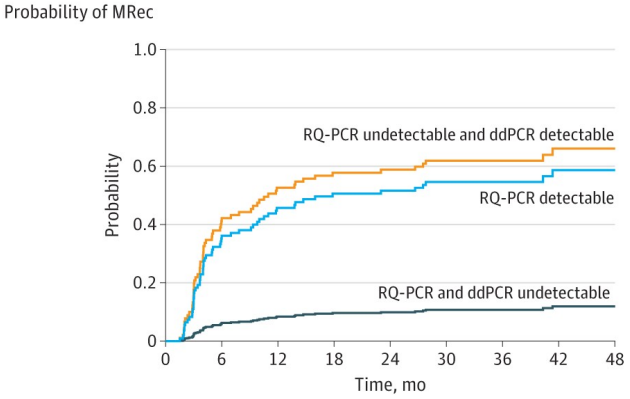



**Slide 48: TREATMENT FREE REMISSION (TFR): KHOURY CURE CML CONSORTIUM / THE LAST STUDY**

As I mentioned, there've been many different trials and our own Consortium did what I would say is the only independent, meaning non-pharma supported treatment-free remission study in the United States called the LAST Study, very aptly named, meaning that was the last pill patients hopefully had to take. And what we were able to show is that our success rates were very similar and matched the global experience, that the response parameters, the data we had on patients helped us actually predict how they might do, which is really helpful to advise patients on their expectations and maybe need to retreat.

## TFR: patient reported adverse events, and alternate PCR strategies in the LAST Study



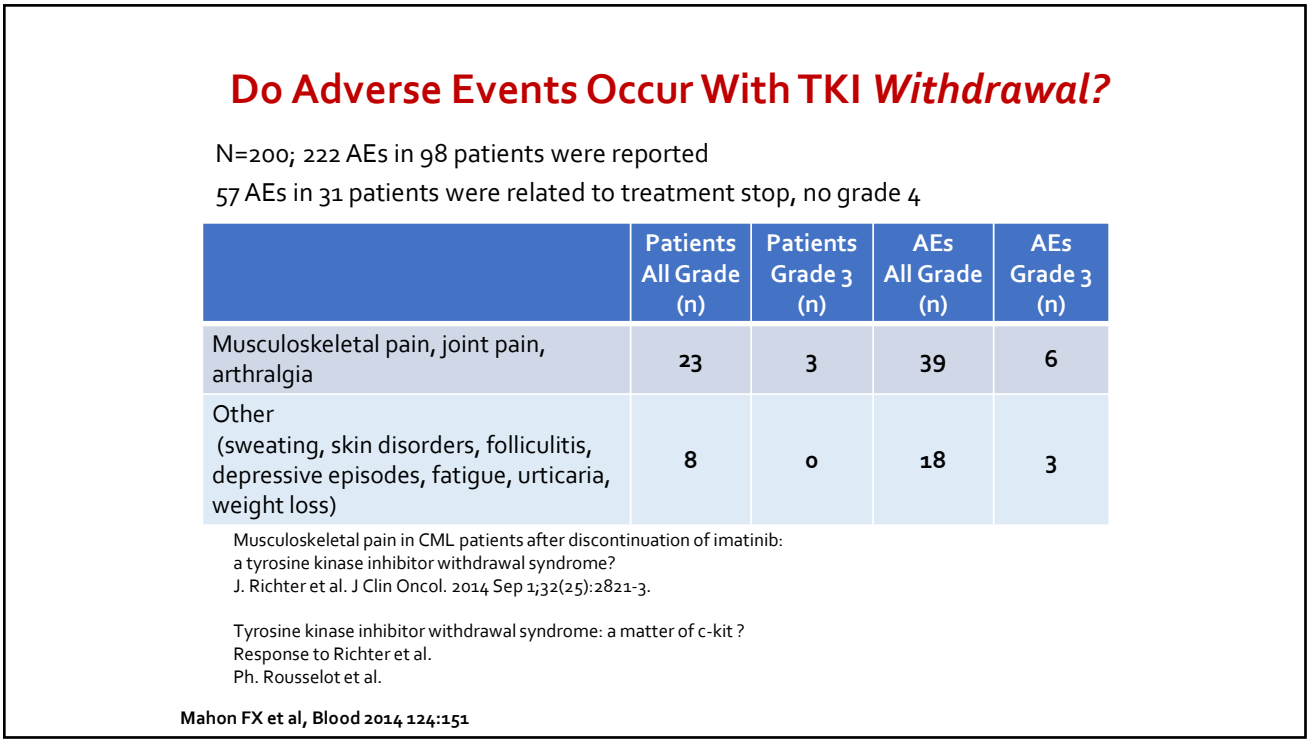

- AEs from TKIs clearly improve
- Digital Drop PCR (ddPCR) may add predictive value

Atallah E et al, *JAMA Oncol.* 2021;7(1):42-50

**Slide 49: TFR: PATIENT REPORTED ADVERSE EVENTS, AND ALTERNATE PCR STRATEGIES IN THE LAST STUDY**

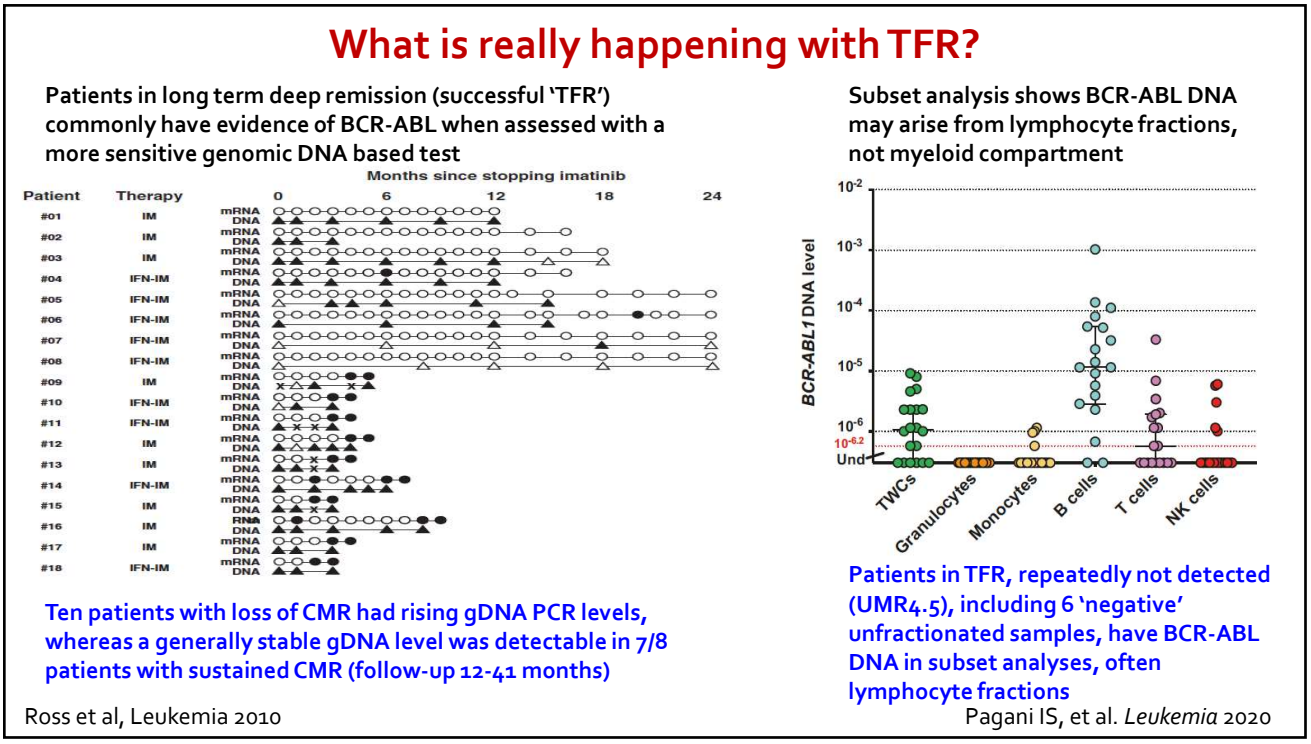
The other important element we learned in these trials was that side effects clearly reduce. And on the left you can see some of the side effects before and after on a scale and the stark reduction, yellow, sort of dropping to minus level below the norm, versus where the side effects were above the bar and positive, while patients restarting treatment did maybe bring on some return of side effects.

And then lastly, we'd like to get smarter about our PCR technology, which is the molecular testing for CML, to potentially predict even better who's going to do well and how well they're doing during this endeavor.



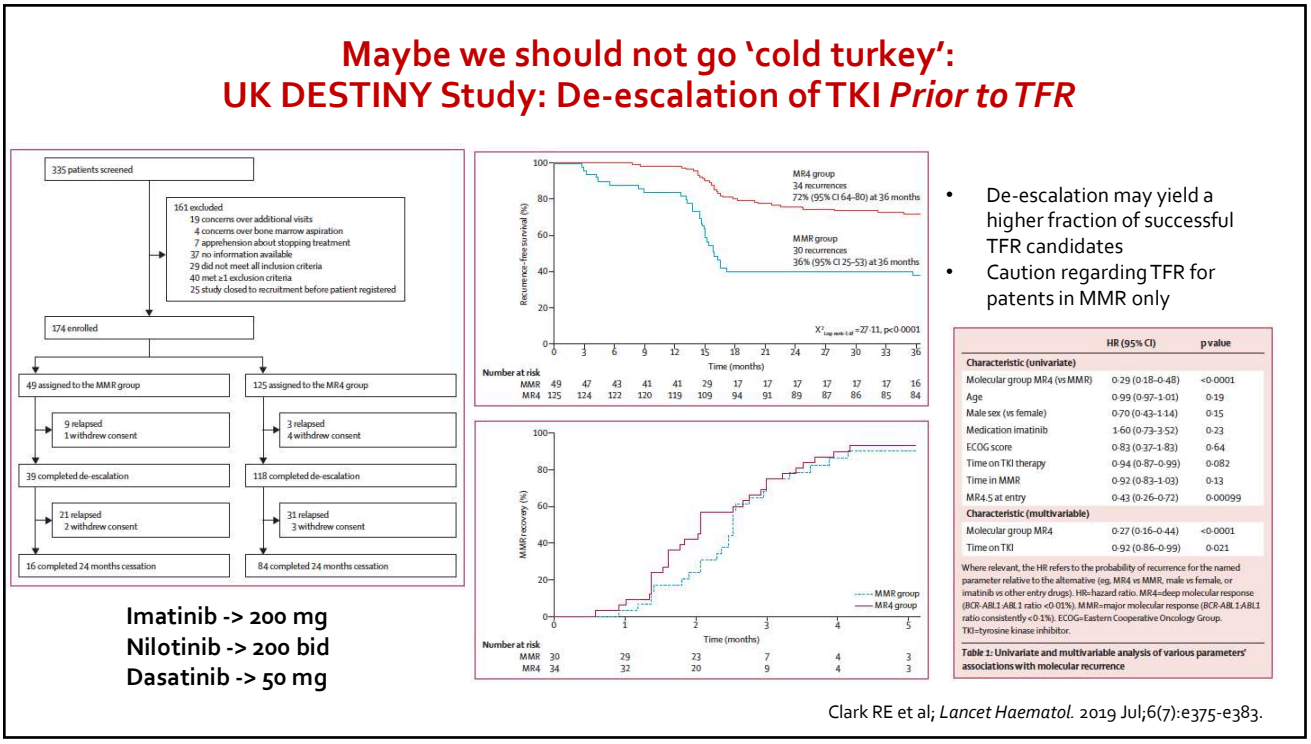

**Slide 50: DO ADVERSE EVENTS OCCUR WITH TKI *WITHDRAWAL*?**

Interestingly, it's not always about getting rid of all the side effects. There is this phenomenon called withdrawal syndrome, where when people move through, move into a treatment-free remission, they may have temporarily, in about a quarter of cases, increase in side effects which come from the absence of the drug. And it's not because it's the CML being active, it may be that there's another target or another mechanism at which the drug was affecting a pathway in the body that was now missing, and there's maybe some over-compensation or some reset that's happening. Thank goodness it's generally not a reason to have to go back on treatment, but it can be something to work through and something to know about.




**Slide 51: WHAT IS REALLY HAPPENING WITH TFR?**

The other interesting point to make about treatment-free remission is that I think in a simple world we'd love to say that the CML is gone, we can't see it, we stop treatment, we never see it come back again and people are cured. It's a little bit different than that. What we do with treatment is put people into stable deep remissions, where we can see very low levels of this BCR-ABL signal that don't change over time and it needs to be stable for a certain period of time before we think about stopping. If you go back to the very first 15 patients that stopped treatment back in 2007, go back in the freezer and dig out samples, you can actually with more sensitive PCR testing, you can still see the signal in these patients who were repeatedly negative, stopped treatment, remained repeatedly negative and never restarted their treatment. On the right is some interesting research that's probably telling us that there may be sort of a background signal that may be coming from cells that are not really part of the CML, might not cause the CML to come back of course, which would explain why the PCR may not always be negative, it may not be undetectable even after treatment are successful, after stopping, and again we just are getting smarter and smarter about how we use the technology and we shouldn't take this as a sign of failure or of inevitable relapse of the CML if PCR signaling or BCR-ABL positivity remains in some patients at certain levels.



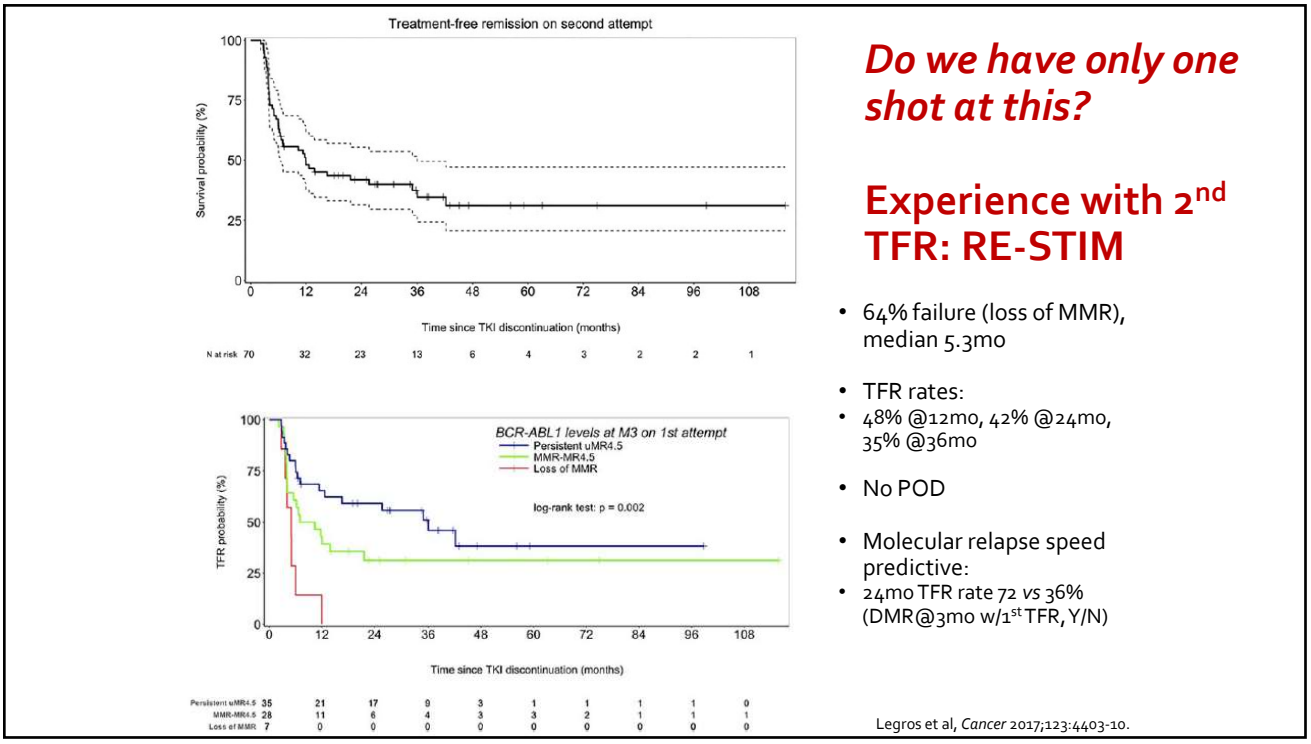

| | HR (95% CI) | p value |
|---|---|---|
| **Characteristic (univariate)** | | |
| Molecular group MR4 (vs MMR) | 0·29 (0·18–0·48) | <0·0001 |
| Age | 0·99 (0·97–1·01) | 0·19 |
| Male sex (vs female) | 0·70 (0·43–1·14) | 0·15 |
| Medication imatinib | 1·60 (0·73–3·52) | 0·23 |
| ECOG score | 0·83 (0·37–1·83) | 0·64 |
| Time on TKI therapy | 0·94 (0·87–0·99) | 0·082 |
| Time in MMR | 0·92 (0·83–1·03) | 0·13 |
| MR4·5 at entry | 0·43 (0·26–0·72) | 0·00099 |
| **Characteristic (multivariable)** | | |
| Molecular group MR4 | 0·27 (0·16–0·44) | <0·0001 |
| Time on TKI | 0·92 (0·86–0·99) | 0·021 |

Where relevant, the HR refers to the probability of recurrence for the named parameter relative to the alternative (eg, MR4 vs MMR, male vs female, or imatinib vs other entry drugs). HR=hazard ratio. MR4=deep molecular response (*BCR-ABL1:ABL1* ratio <0·01%). MMR=major molecular response (*BCR-ABL1:ABL1* ratio consistently <0·1%). ECOG=Eastern Cooperative Oncology Group. TKI=tyrosine kinase inhibitor.

Clark RE et al; *Lancet Haematol.* 2019 Jul;6(7):e375-e383.

**Slide 52: MAYBE WE SHOULD NOT GO 'COLD TURKEY': UK DESTINY STUDY: DE-ESCALATION OF TKI *PRIOR TO TFR***

Many people ask, because if you think about treatment-free remission, many people know and say cold turkey stop if you will. Maybe we should ramp down, maybe we should de-escalate treatment. And there's a nice study from England called the DESTINY Study where that was done, and I think it's maybe leading the way to show us that that's another approach, maybe we could essentially narrow the population into the folks most likely to be successful by having a dry run with a dose reduction prior to stopping. Not standard, but certainly something that's being worked on.




**Slide 53: *DO WE HAVE ONLY ONE SHOT AT THIS*? EXPERIENCE WITH 2ND TFR: RE-STIM**

Lastly, for my part, if you try once it may be possible to try again. And there is some experience with trying a second time and this is some of the very preliminary data from a study from Europe called the RE-STIM trial, where it's not always a failure, it's more modest success. And clearly, I'm about to share with you some very exciting studies we're doing to potentially see if we can do better in this second attempt arena.

## Experience with Second TFR:RE-STIM

**TABLE 2.** Potential Predictive Factors of Treatment-Free Remission by Univariable Cox Regression Model Analysis

| Variable | No. of Patients | HR | 95% CI | P |
|---|---|---|---|---|
| Age at second discontinuation: < 60 vs > 60 y | 70 | 1.00 | 0.97-1.02 | .760 |
| Sokal risk score | 69 | | | |
| Low and intermediate | 60 | 1.00 | – | |
| High | 9 | 1.96 | 0.88-4.36 | .100 |
| Prior exposure to IFN | 70 | | | |
| No | 51 | 0.93 | 0.49-1.74 | .814 |
| Yes | 19 | | | |
| TKI duration at first discontinuation: < 59 vs > 59 mo | 70 | 1.00 | 0.99-1.01 | .692 |
| uMR4.5 duration at first discontinuation: < 32 vs > 32 mo | 70 | 1.00 | 0.98-1.02 | .905 |
| TKI type at first attempt | 70 | | | |
| Imatinib | 60 | 1.00 | – | |
| Dasatinib and nilotinib | 10 | 1.92 | 0.88-4.19 | .102 |
| First discontinuation molecular criteria | 70 | | | |
| 1 y ≤ uMR4.5 < 2 y | 20 | 1.00 | – | |
| uMR4.5 ≥ 2 y | 50 | 1.77 | 0.89-3.50 | .102 |
| Time to uMR4.5 loss from first TKI discontinuation | 70 | | | |
| <3 mo | 35 | 1.00 | – | |
| >3 mo | 35 | 2.02 | 1.10-3.70 | .024 |
| Time to uMR4.5 loss from first TKI discontinuation | 70 | | | |
| <6 mo | 59 | 1.00 | – | |
| >6 mo | 11 | 2.77 | 1.08-7.13 | .035 |
| Reason for first TKI re-challenge | 70 | | | |
| uMR4.5 loss | 28 | 1.00 | – | |
| MMR loss | 42 | 1.43 | 0.76-2.66 | .264 |
| First TKI-free duration: < 5 vs > 5 mo | 70 | 0.91 | 0.82-1.01 | .084 |
| Switch from imatinib to 2G TKI after first discontinuation | 60 | | | |
| No | 52 | 1.08 | 0.54-2.13 | .831 |
| Yes | 8 | | | |
| Second TKI duration at second discontinuation: < 32 vs > 30 mo | 70 | 1.00 | 0.98-1.02 | .670 |
| Total TKI duration at second discontinuation: < 103 vs < 103 mo | 70 | 1.00 | 0.99-1.01 | .420 |
| Second uMR4.5 duration at second discontinuation: < 25 vs > 25 mo | 70 | 1.00 | 0.98-1.03 | .903 |
| Total uMR4.5 duration at second discontinuation: < 68 vs > 68 mo | 70 | 1.00 | 0.98-1.01 | .577 |

40% w/o MMR loss

Abbreviations: 2G, second-generation; CI, confidence interval; HR, hazard ratio; IFN, interferon; MMR, major molecular response; TKI, tyrosine kinase inhibitor; uMR4.5, undetectable molecular disease.

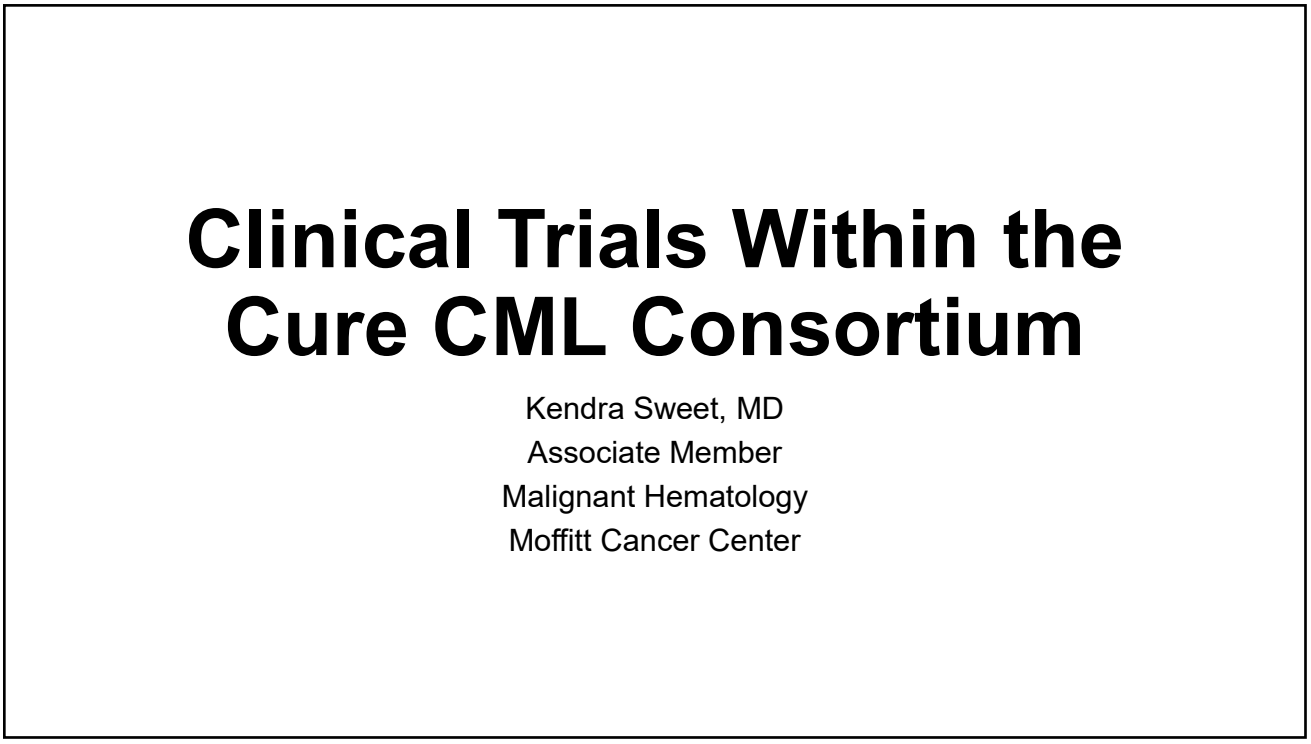
Legros et al, *Cancer* 2017;123:4403-10.

**Slide 54: EXPERIENCE WITH SECOND TFR:RE-STIM**

If you look at the details of these second attempts, what's also of interest is that the early trials, not all patients actually needed to be retreated. So, we have to look at the data carefully and understand and it's interesting that we can't sort of always push the panic button too fast. We have very clear parameters on what's a level of CML that needs retreatment and what's not, and we're becoming smarter about that, too. And we may be able to open this opportunity up to more patients as we learn more and more about this.


**Slide 55: THANK YOU FOR YOUR ATTENTION!**

So, I think this brings us to the end of my section.

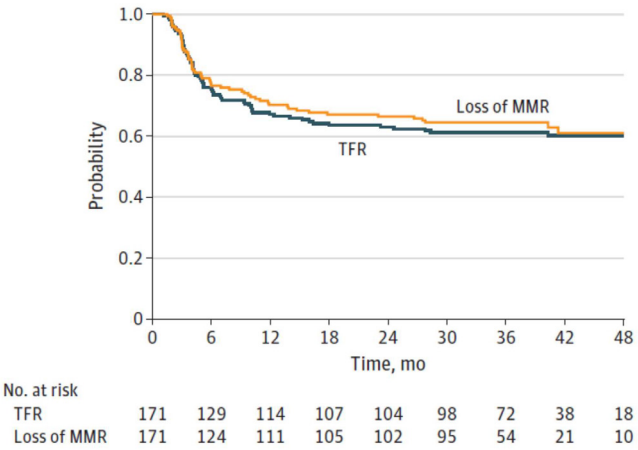



**Slide 56: CLINICAL TRIALS WITHIN THE CURE CML CONSORTIUM**

I just want to say that our colleague, Kendra Sweet, Dr. Sweet, who I'm going to introduce anyway, I think she's unfortunately now under more duress in Florida, is a brilliant physician, is a leader at Moffitt Cancer Center, is a leader and officer in the CML Consortium, is leading clinical trials with us in the CML Consortium, and I'm sorry that she can't actually present her slides herself. So I have the honor and the pleasure of just walking through her slides as well. And what Dr. Sweet had wanted to talk to us about in the last section was our trials in the Consortium that are related to curing CML.

# Life After Stopping TKI (LAST) Study

- Enrolled 172 patients from 14 US sites
- Primary endpoint: molecular recurrence defined as loss of MMR and patient reported outcomes
- Minimum f/u 3 years
- 65.5% remained in MMR
- 60.8% achieved TFR




| No. at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TFR | 171 | 129 | 114 | 107 | 104 | 98 | 72 | 38 | 18 |
| Loss of MMR | 171 | 124 | 111 | 105 | 102 | 95 | 54 | 21 | 10 |

Atallah, E. JAMA Oncology. 2020

**Slide 57: LIFE AFTER STOPPING TKI (LAST) STUDY**

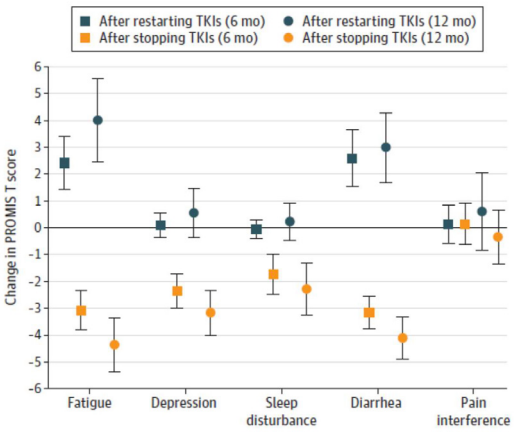
The LAST Study, which I alluded to earlier, this is recapitulation of that same figure, where we, again in the United States, outside of pharma, looked at 172 patients from broadly collected through the U.S., trying to understand the success rates in patients coming off-treatment, irrespective of what medication they were on, it was a much more real world and practical experience, and the results were very good that more than half the patients remained in MMR, which is the threshold at which we would think about restarting treatment, and we were able again to show that we could do it just as well as others had in other earlier experiences and that it could be done in a practical way in the United States in the CML Consortium.

# Patient Reported Outcomes with TFR

- 112 patients in TFR at 12 mos
- 80.4% with clinically meaningful improvement in fatigue
- 87.5% with clinically meaningful improvement in diarrhea
- 21.4% with clinically meaningful improvement in sleep disturbance
- 4.5% with clinically meaningful improvement in pain interference

Atallah, E. JAMA Oncology. 2020

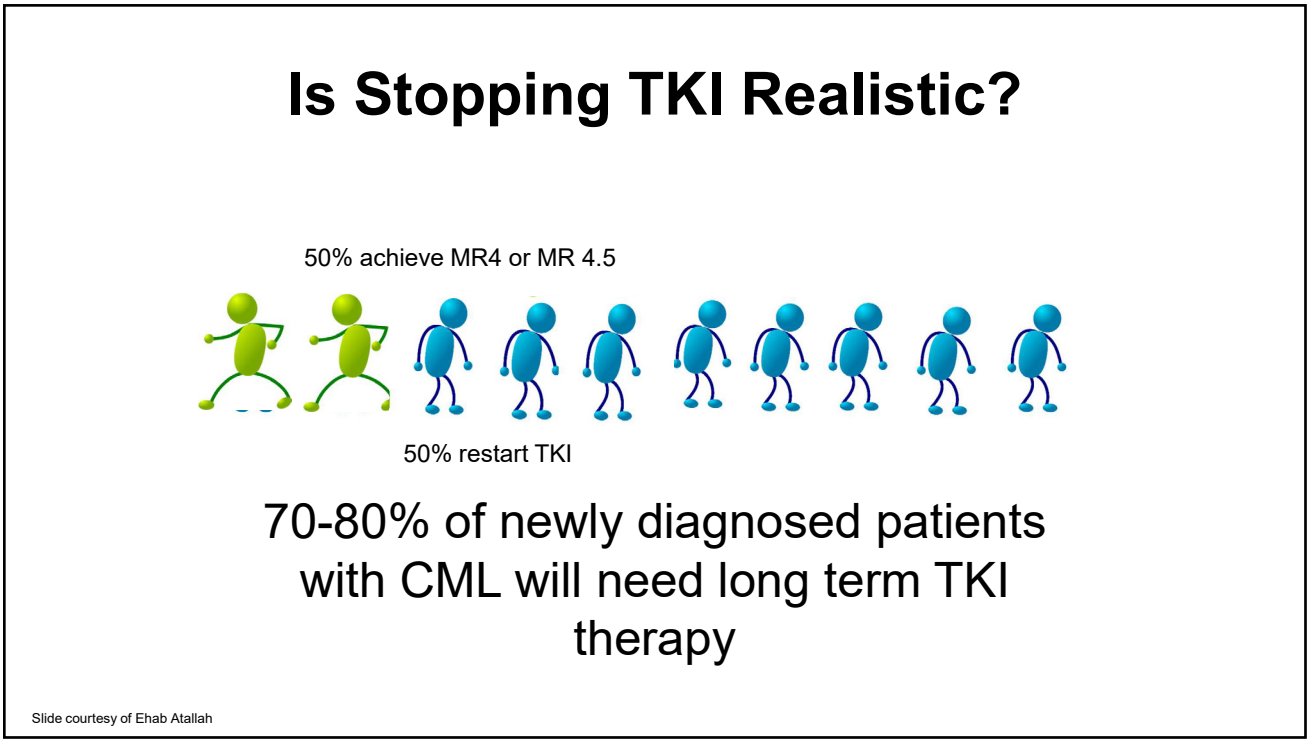
Figure 3. Mean Changes in Patient-Reported Outcomes After Tyrosine Kinase Inhibitor (TKI) Discontinuation and TKI Restart at 6 and 12 Months




Vertical lines indicate 95% CIs. PROMIS indicates Patient-Reported Outcomes Measurement Information System.

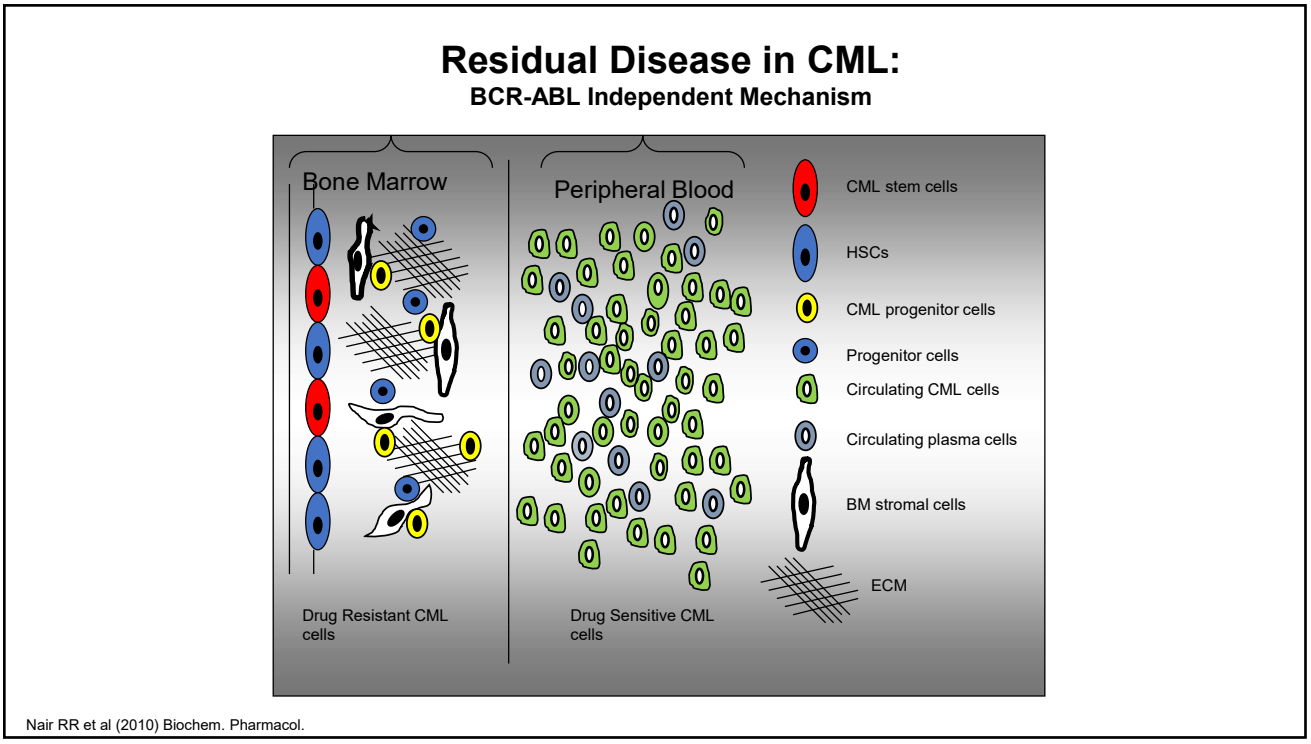
**Slide 58: PATIENT REPORTED OUTCOMES WITH TFR**

The patient-reported outcomes I had also alluded to, so I think Dr. Sweet wanted to underscore the fact that overall we generally see improvements in adverse events as we are able to take patients off-treatment. One of the strongest reasons why, of course we want to try once, but we also may want to try a second time.



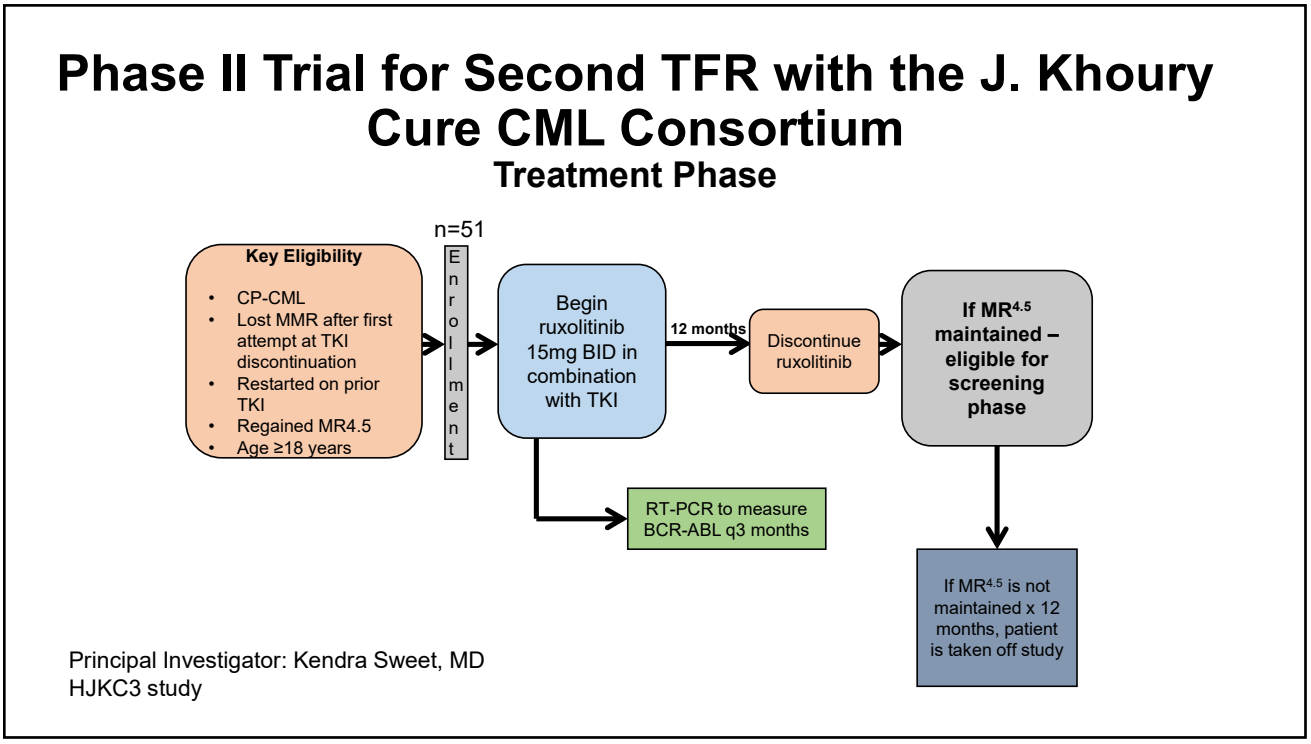

**Slide 59: IS STOPPING TKI REALISTIC?**

So if we think about it from the standpoint of numbers, how realistic is it and how do things look like, if you take a group of patients on treatment for CML and look at how many achieve a deep remission over time we may be able to squeeze out a bit more, but, so let's say roughly 50% of patients are able to easily achieve a deep molecular remission, the kind of remission from which a treatment cessation can be proposed. From those patients, unfortunately, maybe roughly half, sometimes a little bit more, need to restart. So our fraction of patients who were successful with this endeavor of treatment-free remission, if you look at some of these numbers, isn't what we want. Again to state it plainly, still the majority of patients need longer-term therapy and we'd really like to do better.




**Slide 60: RESIDUAL DISEASE IN CML: BCR-ABL INDEPENDENT MECHANISM**

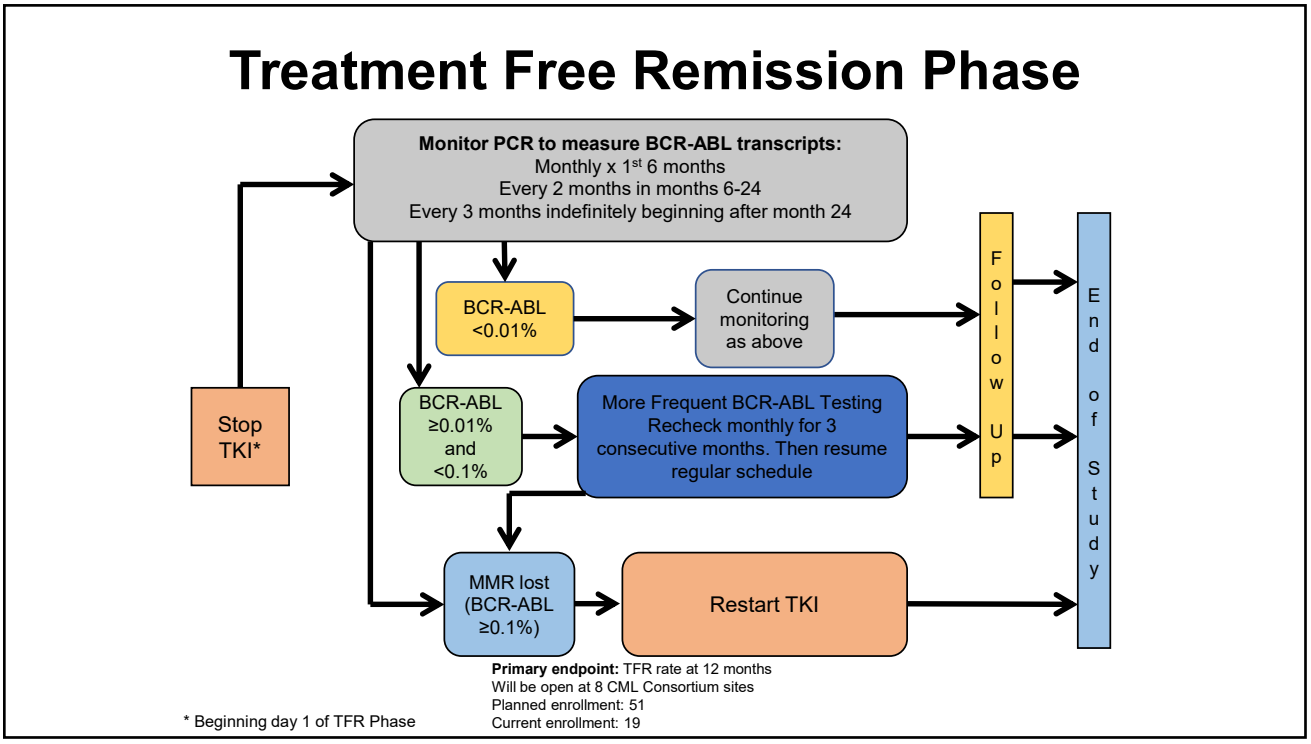
So, we continue to endeavor in our research beyond the LAST Study, and have looked at what could be the mechanisms by which CML persists, what are the reasons why perhaps stem cells, that may be somewhat dormant, somewhat specific in their function and activity, remain in the bone marrow, other contributing factors from the bone marrow, from the stroma, where the cells that support the blood and the bone marrow, are there different signals we could interrupt, and we have a couple of good ideas.




**Slide 61: PHASE II TRIAL FOR SECOND TFR WITH THE J. KHOURY CURE CML CONSORTIUM TREATMENT PHASE**

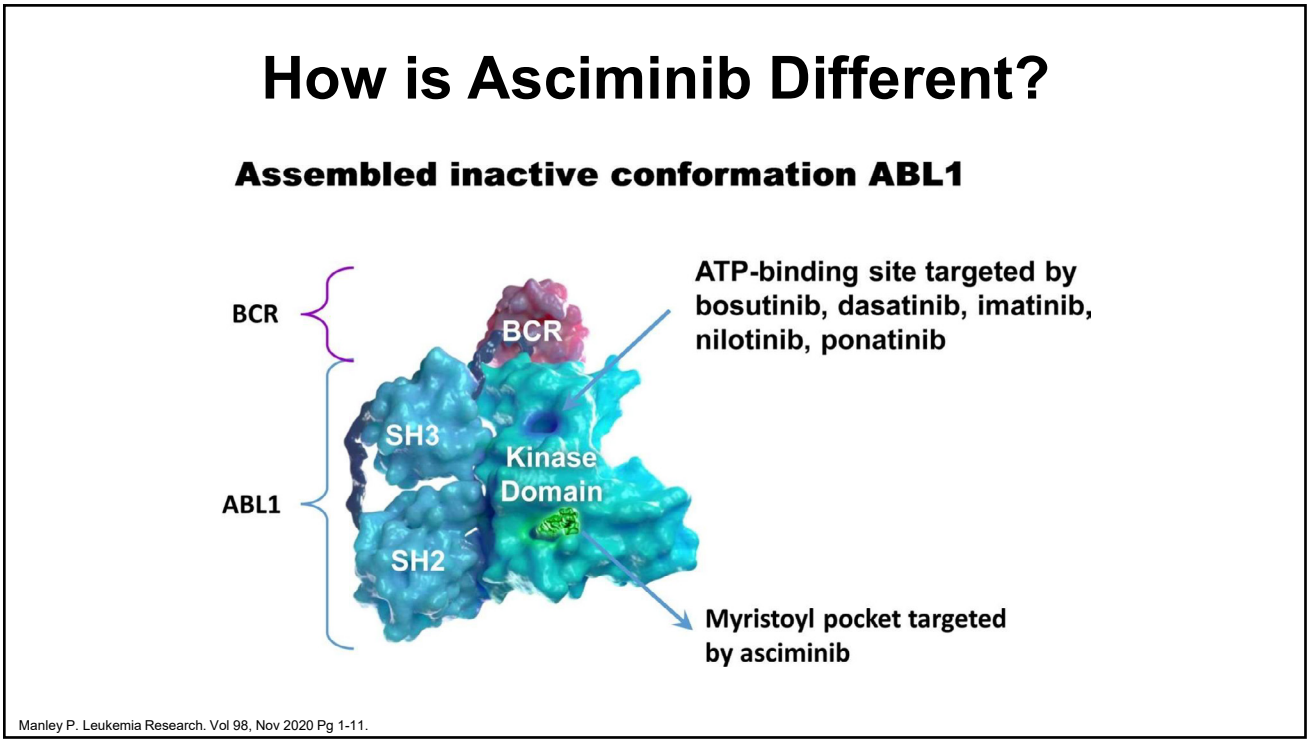
And this was a trial that was initiated by Dr. Sweet, the first of our second treatment-free remission trials in the Khoury CML Consortium, which essentially used the drug ruxolitinib (Jakafi®), which is a JAK/STAT pathway inhibitor, in combination with patients ongoing CML therapy, as a way to change the quality of remission to see if a second treatment-free remission would be successful. In essence, people who tried to stop, who were retreated, who were successfully back in remission, were then entered into a trial where they took a combination of their TKI, no matter what it was, which hopefully was going well and was at a previous tolerated dose, in combination with ruxolitinib, which had already been tested by Dr. Sweet and others at Moffitt Cancer Center, and we knew the combination was safe and well tolerated. They were followed for a year in a standard fashion and then both drugs were discontinued to see if a deep remission could be sustained with a second attempt.

A very smart trial design, which is an ongoing study in the United States. We've enrolled nearly half the patients, maybe a little bit less, and we're looking of course for patients interested, so please reach out to Dr. Sweet or the CML Consortium, Dr. Atallah, or myself.



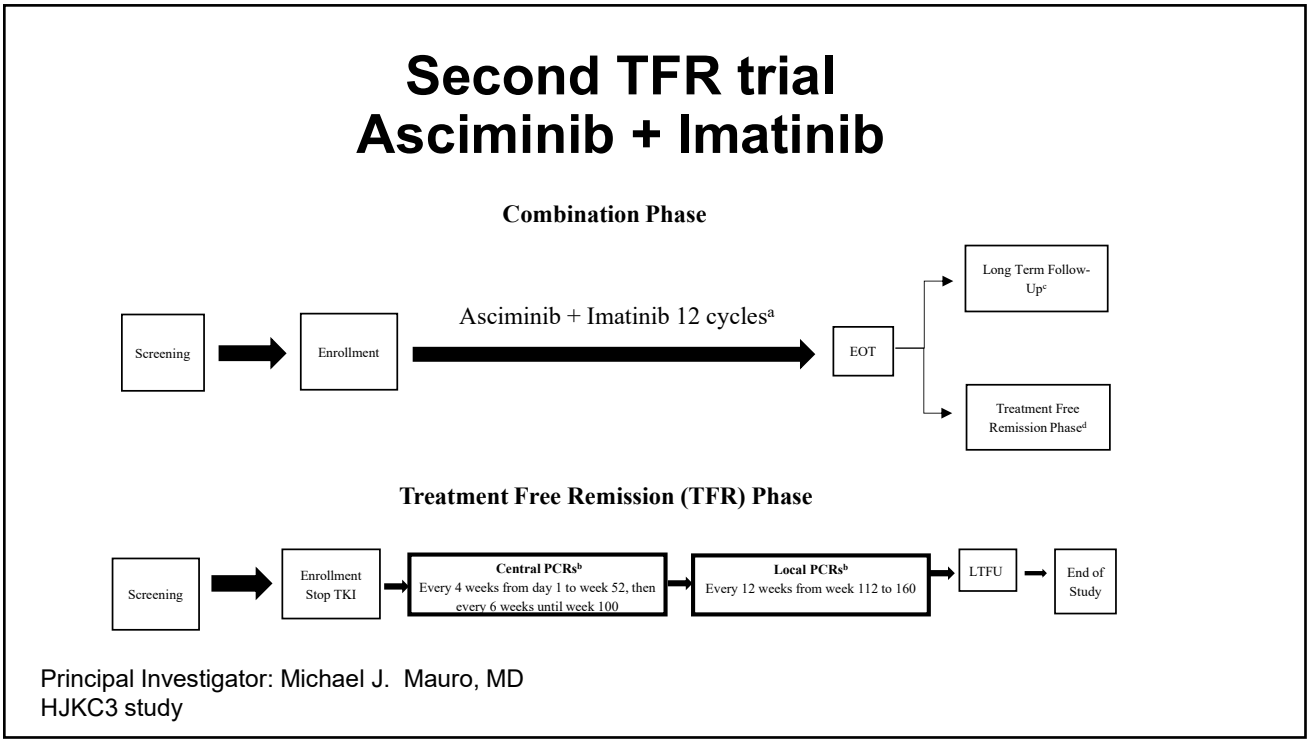

**Slide 62: TREATMENT FREE REMISSION PHASE**

This is how the treatment-free remission phase looks. This is exactly how it should be. Patients are monitored closely, monthly for the first 6 months and then every 2 months and then closely even thereafter, and under strict rules based on the PCR values, patients are able either to maintain off-treatment, either have their monitoring picked up if there's a sense that things may be changing, or they are restarted if unfortunately the PCR is fairly clearly rising.



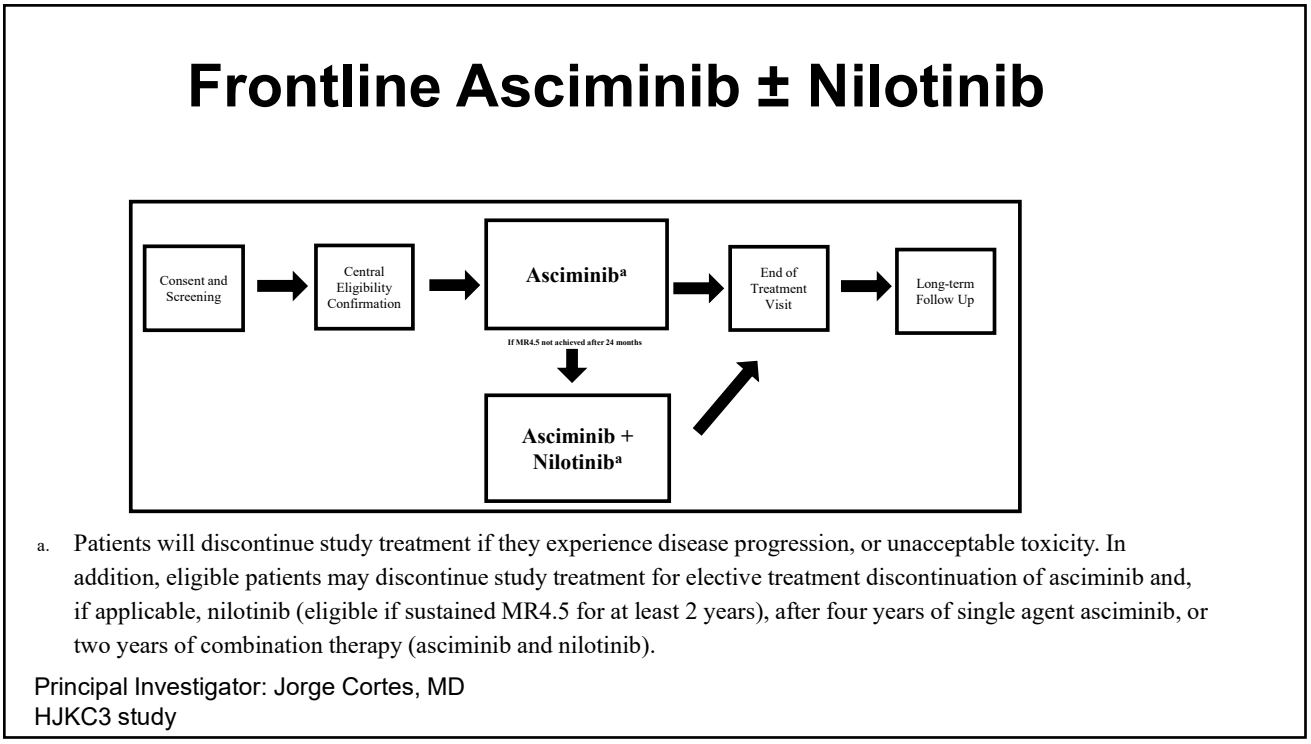

**Slide 63: HOW IS ASCIMINIB DIFFERENT?**

The compound asciminib, which I've had the pleasure of being involved in the development in its Phase I and its Phase III trials, I think it's a remarkably interesting drug. Very safe and very active in resistant CML, so it's quickly being moved back into earlier lines of treatment in other settings. So since asciminib is different and it targets what's called the myristoyl pocket, which is not the same area where all the other medications we have available, all 9, well, 8 of the other 9 drugs are targeting the ATP-binding pocket, so we essentially have a drug you can use together with one of the available TKIs, where they would both work.




**Slide 64: SECOND TFR TRIAL ASCIMINIB + IMATINIB**

So I endeavored to extend the efforts in the CML Consortium and I had crafted the second of our second treatment-free remission trials where we're going to use a combination of asciminib with imatinib. This is exactly the same idea which was proposed and is ongoing in Dr. Sweet's trial, where patients who have stopped treatment and then they were on imatinib, unfortunately they needed to be retreated, they were then treated back into remission with imatinib and they're going to add asciminib to their imatinib and be followed for a year under standard conditions, and then undergo a treatment-free remission during which again they're followed per guidelines in meticulous fashion to either be able to maintain off-treatment, to be able to be followed more closely if there's a sense for relapse, or if relapse is apparent, they'll be quickly retreated and brought back into remission. So we're very hopeful that these trials will yield better success for second treatment-free remission, we're really encouraged to build this Consortium and continue the endeavors really inspired by Jean Khoury and all of us now together in his spirit that we believe we can cure more CML.




**Slide 65: FRONTLINE ASCIMINIB ± NILOTINIB**

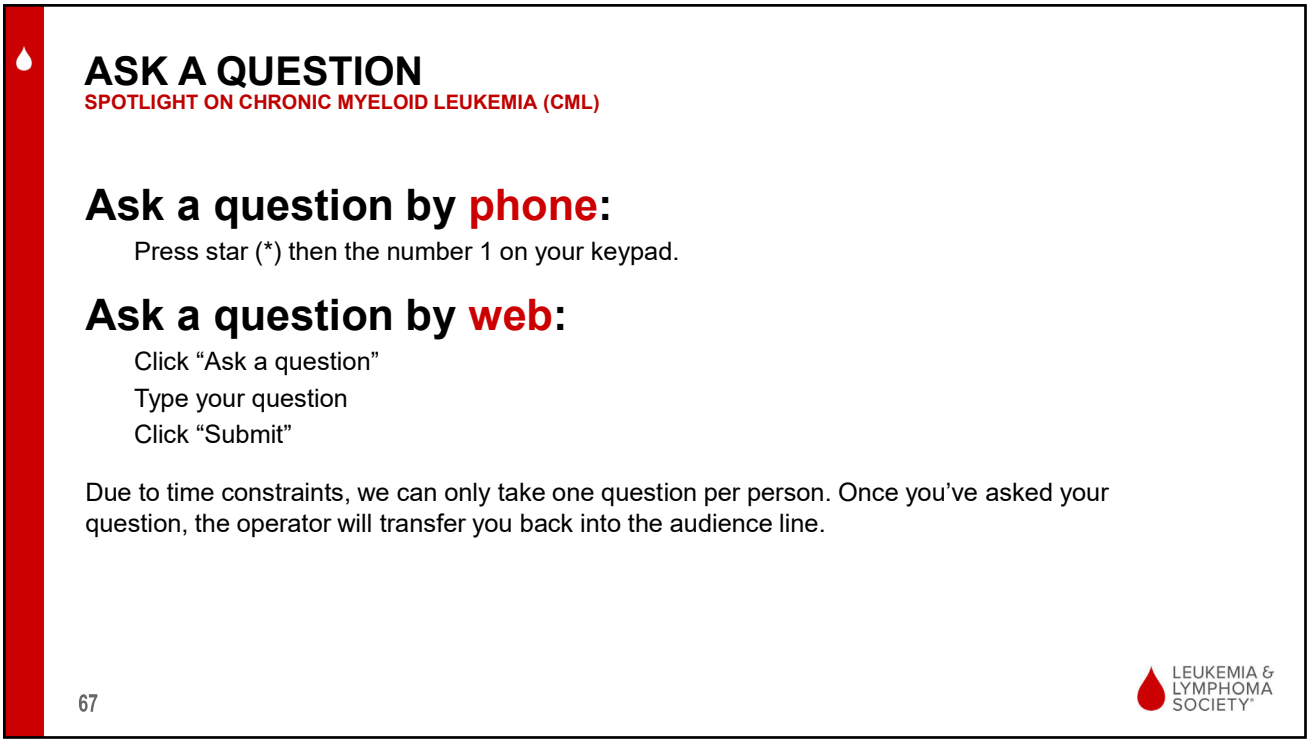
And lastly, just one slide on an additional trial in the Consortium where Jorge Cortes, another brilliant leader in our field, has written and we're going to pilot the use of asciminib as first therapy for CML, which shows you our enthusiasm for this drug. And one nuance in this trial is that if things don't go essentially ideally, patients will be able to take advantage of this combination strategy and can add nilotinib to asciminib to try to recover any shortcomings with initial treatment using this approach. So this trial has just opened as well and we encourage people, if this is the setting they're looking for first treatment to reach out.


**Slide 66: THANK YOU!**

So with that, I'll borrow Kendra's thank you slide. I don't think Tampa looks like this at the moment and I hope hearts go out and our thoughts go out to all those that might be affected and thank goodness we know our colleague is safe, but I think it was very difficult for her to join and we're sorry for that.

But I'll stop there and turn it back to our moderator and open things up for our Q&A.

00:47:17




**Slide 67: ASK A QUESTION**

**Ms. Figueroa-Rivera:**

Thank you so much, Dr. Mauro. Yes, Dr. Sweet did have to move location due to the hurricane, so we do wish everybody, as you mentioned, safety during this time.

Thank you so much for such great information and for all that you’re doing for our CML patients. It’s great to see that experts in the field have really come together for the greater cause of curing CML. And I know that with all of you working together a cure is surely on the horizon.

So, it is now time for our question and answer portion of our program. For everyone’s benefit please keep your questions general in nature without many personal details, so that the doctors can provide answers that are more general in nature.

We’ll take the first question from our web audience. Michael is asking, if I have other health conditions, such as high blood pressure and multiple spinal fusions, am I still a candidate for clinical trials as I’m not tolerating TKIs well? Dr. Mauro, did you want to take that?

**Dr. Mauro:**

Sure. The average patient with CML has what we call comorbidities, other health problems, probably more than half. And those are common things, diabetes, high blood pressure, heart problems. I know we emphasized that some of those side effects can come with treatment. If we know about conditions beforehand and we manage them carefully, we can still avail patients to most therapy options. And some clinical trials do have restrictions and have some eligibility criteria, but they’re not designed to exclude people who have common conditions, who are being treated well. They’re really geared potentially to maybe keep offering more safety and protecting some patients who don’t have clear safety known with a new drug, meaning where we’re worried new side effects or new problems may occur or specific health conditions could be a major concern. So I would always encourage someone to look into

clinical trials. And we go through a screening where we'll look at someone's health carefully, make sure we review to informed consent all the risks and benefits, and I think I would encourage someone to expect that they should be able to get the best of everything even if they have health conditions that are common, such as those.

**Ms. Figueroa-Rivera:**

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

**Operator:**

Our person on the phone is Thomas from Missouri. Go ahead.

**Thomas:**

Doctor, I have a question about, I've been on Sprycel® for 7 years for CML and one of the gray areas we have is, when is it safe for someone to go off this drug, to take a drug holiday, and not to advance into the more serious phases. Can you shed any light on that if there's any new data on that?

**Ms. Figueroa-Rivera:**

Dr. Atallah, did you want to take this one?

**Dr. Atallah:**

So, Thomas, yes, there are guidelines who can be considered for what's called treatment-free remission, which is stopping the drug. So, the people who would be eligible for that are patients who have been on drug for at least 3 years and they have the PCR level is less than 0.01% for at least 2 years. Chronic phase CML and so those are the patients that would be eligible for stopping.

If you do fit these criteria and you do consider stopping, when patients stop, your PCR needs to be checked monthly for the first 6 months, every 2 months for 12 to 18 months, and then every 3 months forever. The side effects that can happen with stopping include nervousness about coming in to check your PCR, annoyance that you have to come in and get your PCR checked, and also musculoskeletal pain, which is like a withdrawal syndrome, which usually patients mostly describe it as pain in the hands, joints, and that usually resolves, if it does occur, usually resolves by 6 months. So that's one way of just stopping.

The other way you could consider, or someone who's thinking of stopping, is to cut the dose in half if you do fit these criteria, which is deep remission for 2 years, on drug for at least 3 years, to cut the dose in half, stay on that half a dose for a year. If the PCR remains good, undetectable, then you can stop after that.

So these would be the 2 ways that you go around doing that. Of course, after talking with your physician and making sure that your physician is onboard and is going to check your PCR and such.

**Ms. Figueroa-Rivera:**

Thank you. This question could go to both doctors. Jerry is asking, have you determined if taking a TKI can help protect against COVID?

**Dr. Mauro:**

That's a very interesting question. Without getting in too far down in the rabbit hole, I'll tell you that there is a mechanism by which BCR-ABL inhibitors, by inhibiting ABL, there are viral versions of ABL might be some of the tools that viruses use, and the list of viruses goes beyond COVID. It actually extends to Ebola and SARS (SARS COVID-1, SARS COVID-2) that's one of them. And there was research during the Ebola crisis from any agent with that capacity and imatinib was a candidate. There was a lot of work of course during COVID, we wanted to use anything we possibly could, we thought might be effective and imatinib was part of clinical trials. Patients without CML were given imatinib potentially as a means to limit COVID illness. The results unfortunately never were able to yield because thank goodness vaccines were developed, so many clinical trials ended too quickly.

So, I wouldn't say that we know that imatinib is protective or can help against COVID.

On the other hand, the International CML Foundation, of which many of us are part of and have contributed, I know Dr. Atallah for sure and Dr. Sweet have registries where we've looked at the outcomes of patients with CML during COVID before vaccines were available and after. And thank goodness I think it's fairly neutral, and that the risk of COVID has been mainly age-based. There is maybe some negative impact for somebody who's really just getting into remission or still doesn't have stable CML, but for stable responsive CML, COVID illness has been fairly similar to what you'd expect with someone without CML not on treatment. And that's what I generally tell my patients.

**Ms. Figueroa-Rivera:**

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

**Operator:**

Certainly. Our next question comes from Susan from New Jersey. Go ahead, Susan.

**Susan:**

I did the original clinical trial in New York at Cornell back in 2000 and I've been undetected since 2001, but I didn't stop my Gleevec until February of 2018. I am now almost 5 years TFR and I was curious if this could continue a lot longer?

**Ms. Figueroa-Rivera:**

Dr. Mauro?

**Dr. Mauro:**

Oh, gosh, I was clapping for you, if you didn't see that. You are definitely a pioneer ma'am. You're just what this call is all about, you were a brave participant in clinical trials, you navigated treatment for decades, or a decade and a half there at least, and you sound like a successful treatment-free remission. And you're almost on the leading edge, but there are patients from the original trials started in 2007, so it's now 2022, so there are patients more than 15 years in treatment-free remission successfully like yourself. So, I think the future looks very bright.

We continue to ask questions, so I encourage you just to stay in close touch. And another effort we'd like to see some day would be what we call a survivorship approach to CML, where we follow your CML hopefully, or the lack thereof, and any other health issues you might have to learn about your success, so congratulations, and I expect your future is very bright.

**Ms. Figueroa-Rivera:**

Right. And it is great to hear about somebody doing so well, right?

Our next question comes from Amanda. Amanda is asking about weight gain with many of the TKIs. Can you address that, Dr. Atallah?

**Dr. Atallah:**

Yes, Amanda, weight gain has been reported with the TKIs. Initially we were not really sure because patients with CML before they had treatment, they were losing weight, not feeling well, and once they started the TKI they started feeling well and gained weight. We know there's also with some of the drugs, changes with cholesterol, so that's something reported. The second thing that can also cause weight gain is fluid retention, so not real weight just fluid buildup and you would notice that by having swelling of the legs, swelling of the eyes. So these are the 2 possible mechanisms for weight loss, sorry, for weight gain. If it is fluid, you would have symptoms; shortness of breath, swelling in the legs, and maybe your doctor could consider using a diuretic, which is a medication to make you lose water. If that's not the case and it is actual weight gain, there is no specific fix for that outside the regular exercise and diet that's suggested.

**Ms. Figueroa-Rivera:**

Thank you. Our next question Dr. Mauro, Leah is asking if an autoimmune disease can trigger CML or affect CML treatment?

**Dr. Mauro:**

That's a very good question, very interesting question I think. What causes CML is probably ironically still somewhat elusive. I think some of the interesting facts we know are that the Philadelphia chromosome event can be detected in certain studies that have been done far more often than you'd expect and doesn't always lead to CML, so it may be an error that happens because the way our blood divides, where the chromosomes are in cells, and because of unfortunately some susceptibilities. The only clear instances where CML incidence has been seen higher than what we'd expect, unfortunately are some pretty obvious situations such as nuclear weapons during World War II, which is a tragedy, to be honest. So now that we have such a high proportion of CML survivors, I think we're going to be able to ask those questions but I don't know if we have any answers yet. I don't know if we have a risk factor or disease state or another illness that we know leads to CML, so I wouldn't say it leads to it.

The second part was would it impact treatment and I think it definitely could. Some of the TKIs have some inflammatory and immune complications. I don't want to pick on it, but I would say dasatinib probably has more of that than any other. So I would definitely enter into treatment for CML with a little bit more attention to detail and caution in someone with autoimmune disease, making sure that that was well looked after, treated, well described, because we may see greater, sometimes we might see less symptoms. There've been reports, anecdotal reports in both directions. I don't think it's an obvious concern or a major concern but it's certainly a possibility.

**Ms. Figueroa-Rivera:**

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

**Operator:**

Certainly. Our next question comes from Patty from Washington. Go ahead, Patty.

**Patty:**

Hi, thank you for taking my question. I had started with Dr. Mauro I believe in 2001, diagnosed in 2000, and I've been in remission for years on Tasigna®. And I want to know, if you relapse, do you get major symptoms right away or do they come on slow? I recently got a whole bunch of symptoms like when I first got leukemia, night sweats, fevers, itchy throat, I mean a lot of things. And thank God, I had a PCR done and it's not that, but how do you know?

**Dr. Mauro:**

Did you want me to take that one? I'd be happy to.

**Ms. Figueroa-Rivera:**

Yes

**Dr. Mauro:**

Patty, it's nice to hear from you, I'm delighted to hear from you. I think you asked a great question and there's a pretty strong message we'd like to put out there, is that patients need to be monitored regularly and carefully, and if things are done right, no CML relapse or change in CML response status should be something that is unlikely to be triggering symptoms. I wouldn't say it's impossible, it shouldn't be likely, because we should be managing small changes, missed milestones, sort of changes at a level where the leukemia may go from its 10,000 times below the untreated level to now it's 1,000 times or 100 times below, and we have to do something about it before it's back to square one, where symptoms are usually present. So sometimes we don't have that kind of control, sometimes leukemia decides to be more aggressive and it can present with symptoms, but it should be rare. And if we keep our eye on the ball, hopefully we cannot see CML relapse or CML changes manifesting as symptoms, but it's really that we have news of it before by careful testing and particularly molecular testing that should be done regularly. And I say that because some studies we've done in the U.S. and actually overseas as well, is that that's not always the case. So I always encourage people to make sure you're being monitored properly and if you're not, just keep pushing the button, and if you're not getting an answer, ring up one of the other specialists in your area or through the country or otherwise to get the right answers.

**Ms. Figueroa-Rivera:**

Thank you.

Dr. Atallah, Rhonda is asking, is there a list of subsequent medical issues after taking interferon and TKIs for many years, such as hypothyroidism, metabolic issues?

**Dr. Atallah:**

Rhonda, I don't have a lot of experience with interferon long-term, so I don't know how long you were on interferon. The TKIs, there are some reports of thyroid effects, but it's really a rare thing, but it is reported. And it becomes a little hard to know because, uh, thankfully, patients live for a long time, so you can develop other medical problems, but whether truly related to the TKI or not, it's hard to tell, but there are definitely reports of hypothyroidism happening for patients with CML on a TKI. We'll be looking into that. We are hopefully going to get funding for a large registry for patients, 700 to 900 patients, where we'll be able to follow patients for 8 years and then be able to tell some of these things.

**Ms. Figueroa-Rivera:**

Thank you. And just continuing, Dr. Atallah, Marie is asking about the treatment for fluid in the lungs and around the heart with TKIs, is that something that is common?

**Dr. Atallah:**

Marie, the fluid around the lungs and the heart is, I don't know if you would call it common, it happens in about 20% of patients who are on dasatinib. It's also reported with bosutinib, mainly in the second-line as opposed to the first-line. So both of those drugs have that association with fluid buildup. It's usually treated by holding the drug, tapping out the fluid, and sometimes considering starting at a lower dose if you are responding well. If you're not responding well already at this dose, cutting down the dose is not the best idea. I would consider switching to a different drug. So that's how I'd make a decision of whether to switch or reduce a dose, depending on how well you're responding. Or the other thing, if it keeps happening, keeps repeating, you drain the fluid out, you go back on the drug at a lower dose, and then you get the fluid buildup again, then I would consider switching. So again, it happens in about 20% of patients on dasatinib, and a little less than 10% for patients on bosutinib.

**Ms. Figueroa-Rivera:**

Thank you.

**Dr. Atallah:**

One more thing, imatinib is more likely to cause fluid buildup in the lung, not outside the lung.

**Ms. Figueroa-Rivera:**

Okay. Our next question is interesting. It's from Jeff. Jeff is saying, is it true that 10 to 20% of the healthy population is Ph positive, so Philadelphia chromosome positive, why do only a very few of these contract CML? And this could be for either Dr. Atallah or Dr. Mauro.

**Dr. Mauro:**

I think I might have opened up that can of worms, so I think I'll try to close it up a little bit here. So what's been done is studies using very sensitive molecular techniques has looked at people who don't have CML, just sort of healthy, normal people, and said can you detect a Philadelphia chromosome event. And it's not just one study, but there're a few studies where yes, it's been shown. But that doesn't mean that someone's walking around with the Philadelphia chromosome, it means that at that moment, using very sensitive techniques, you might catch a genetic error that's happened in a blood cell or evidence of a genetic error. To be honest with you, genetic errors are happening all the time. When you go out in the sun, you're not just worried about getting a sunburn or a skin cancer, your skin's getting damaged by the sun and it's undergoing DNA damage from the sun in real time. So please wear sunscreen. But, the body repairs DNA damage or it deletes things that are abnormal, so that's what's happening. So it's not that people are walking around with the Philadelphia chromosome and they don't have CML and some unlucky people are also walking around with the Philadelphia chromosome and they get CML, it's that genetic errors happen. This genetic error is a strong one and in certain individuals, probably for reasons that we'd love to know more about, it actually manifests and takes hold and grows and causes a disease, where in other patients it's deleted or it's corrected or it just doesn't have the wherewithal to create a disease.

I hope that explains that phenomenon. And I don't want people to worry that it's contagious, it's in the family, it's in the water, it's in the bloodline. There may be other instances where there are common genetic errors that we see and [there are] the more we dig deeper into the genetic landscape and the molecular landscape, the more we learn. And

there are a lot of conditions people have and they may develop a blood disease or blood cancer because of a finding we see, or a potential error that maybe manifests in the blood. Our blood just ages, to be honest with you, and that's a new field of clonal damage or clonal hematopoiesis in the blood, just for the record.

**Ms. Figueroa-Rivera:**

Thank you so much for that explanation.

**Dr. Atallah:**

Lizette, can I follow up?

**Ms. Figueroa-Rivera:**

Sure, Dr. Atallah.

**Dr. Atallah:**

One thing Mike, so that's also a really good question for patients who go off-drug for the treatment-free remission, because some of those patients, some patients can have a detectable BCR-ABL and despite that just stay in remission without clinical disease for a really long time. And we don't have an explanation for that. Like why would someone have CML, go off drug, stay with a detectable Philadelphia chromosome, but never actually develop disease. Mike, do you want to add anything to that?

**Dr. Mauro:**

I was trying to explain that and in my slides I was showing some of the investigations that may be postulated maybe that CML causes a disease in what's called a myeloid cells, and then some cells in the lymphoid compartment or other cells in the blood also carry the mark of the CML, but they can't cause the CML to come back and they're not cells that divide any more, they're done. But they may not, they may not be extinguished, so they may lead to that background noise or that background signal. But Dr. Atallah's point is really worth emphasizing because it's confusing and it's sometimes frightening to people who think about treatment cessation or how good their remission is, when they say how come it's not gone, how come it's not zero, how come it doesn't stay zero, how can it be okay for me to be off treatment if it's not zero? It is. And it's a little bit of trust there and a lot of explanation that's needed to work through that. But that's why we use the terms functional cure and treatment-free remission, because we're learning as we go and we've learned a whole lot over almost 2 decades now in this area.

**Ms. Figueroa-Rivera:**

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

**Operator:**

Thank you. The next question is from Roz from Georgia. Go ahead.

**Roz:**

Yes, I had leukemia starting in 2003 and I've been on Gleevec and Sprycel. Now I'm on Tasigna. Did those other 2 stop working, is that why I'm on Tasigna? And what is it doing that's different?

**Ms. Figueroa-Rivera:**

Dr. Atallah, Dr. Mauro? Dr. Atallah, do you want to start?

**Dr. Atallah:**

I can. So, for patients who switch in general, switching from one drug to another happens because of 1 of 2 main reasons really. Either it's not working or that the patient is not handling it well, which is intolerance. Like these are really the 2 main reasons for someone to switch from one drug to another. So without seeing your records or knowing, it's hard to tell which one it was. But I think that's something you definitely should be discussing with your physician. And like Dr. Mauro mentioned earlier, if you're not getting answers then you should have a goal to go, uh, get an opinion from a CML specialist.

The other question of what difference is the Tasigna doing? So, all these drugs have the same mode of action, but they bind in slightly different spots. Remember we talked earlier, I don't know if you were there earlier when we talked, that these drugs bind to a certain part of the protein, the abnormal protein, which is telling the cell to divide, that that protein is the messenger, the messed up messenger. So these drugs bind to that protein. And each drug binds in a slightly different way to that protein, so that's why for one patient, one drug may work and the other one might not because of the way it binds.

**Dr. Mauro:**

I don't have much to add to that. I think those are great answers. And I always encourage people to get more specific questions answered by their physician. Keep asking.

**Ms. Figueroa-Rivera:**

Our next question is from Stephanie. She's asking about allowing patients the choice to pursue different fertility options. She's saying that NCCN (National Comprehensive Cancer Network) has tight parameters on discontinuing a TKI, but there should be some wiggle room for those of reproductive age. I know, Dr. Mauro, that you have had patients that have had successful births and successful pregnancies. Would you like to speak to that?

**Dr. Mauro:**

Sure. I think we're all interested in this area. Anyone who's thinking about treatment-free remission in the back of their minds has people of childbearing age, particularly women of course, childbearing age in mind, because that goes hand in hand. So it's true that formal guidelines and formal expansion of what to do to allow for women to have safe pregnancies and to conceive around a CML diagnosis aren't available yet. There's a lot of guidance out there, a lot of knowledge. And I would say simply that if we can just marry the 2 agendas, and if someone is eligible and/or potentially in the mode of a treatment cessation, pregnancy certainly should be something that can be discussed.

A little bit more on the other side of the fence would be that taking TKI therapy during pregnancy really is not something that we would say is acceptable. There are some instances where it has been accomplished without bad outcomes, but there's a lot of uncertainty there and it varies by the medication. And honestly, the FDA puts labels on medications for reasons because it may not be that it's terrible, it's just that we don't understand and we always want a healthy patient first and then of course healthy children if they can successfully achieve pregnancy and deliver. So it can be done. And I would encourage women to also, much like anyone on the call of course, this type of question really requires a lot of push, because you may have to find specific people who have handled this question, collaboration between higher risk obstetrician and a CML expert is probably necessary, and I'd like to keep building a wall of fame of photos I have of children that have come from moms who had CML and whom both mom and baby are happy and healthy.

**Ms. Figueroa-Rivera:**

Definitely. We would definitely continue to want to see healthy pregnancies and all of our families growing.

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

**Operator:**

Next question comes from Steven from California. Go ahead, Steven.

**Steven:**

Yes. Is there variability in terms of what lab measures the level, therefore you should always have it drawn in the same place, or are they all fairly comparable, and if you get it drawn somewhere else one time it's not a big deal?

**Ms. Figueroa-Rivera:**

Sure. Dr. Atallah, Dr. Mauro? Dr. Atallah, did you want to start?

**Dr. Atallah:**

Sure. Yes, there is variability from lab to lab for sure, Steven. However, the international scale (IS) ratio is supposed to equalize all the measurements across different labs, so we can all speak the same language. Having said that, what the IS ratio really is, it normalizes if your lab measures 10 and my lab measures 1, then we take your value and divide it by 10 and that's the standardized ratio. However, if your lab is measuring 10 that's wrong or different, then there's no really enough correction to fix that, if that makes sense. So yes, there is variability from lab to lab. Most large labs do okay when you compare them to each other, I always prefer to stick to the same lab. Getting an occasional lab check outside to see how you're doing, for example, if you're traveling or something like that, is perfectly fine, as long as overall the numbers remain okay. You always need to look at the lab and say okay, this one is a little different than my home lab, acknowledge that, but as long as you stay in the good, like in the good response, the criteria that I showed, it's okay.

**Dr. Mauro:**

Yeah, I would second that. I think ideally PCR, especially when you get down to low levels, is probably best checked in the same lab. But the international scale, our international standard, helps us to make sure the values are close and a big jump or a big change obviously is a flag, but otherwise it may be reasonable to compare values between the labs.

**Ms. Figueroa-Rivera:**

Thank you so much. And our next question, Dr. Mauro, Sandy is asking, after stem cell transplant, I tested negative for 14 years and then the BCR-ABL came back positive. What might have happened, is this common, is it unusual? And I just did want to note for our participants that some patients with CML have gotten transplants as a treatment.

**Dr. Mauro:**

Absolutely. Well, that's a very interesting question. There's always details in context, so I probably can't comment specifically on this scenario, but what I would say is that there're different patterns of PCR results after someone's had a bone marrow transplant, it doesn't always disappear immediately, it sometimes can fade with time. There are some different risks associated with people who have PCR that is detectable after transplant after a few years. We expect people to be cured with transplant, that's the ideal. Dr. Atallah and I both have been speaking about this phenomenon

where PCR can be seen, but it doesn't always mean that CML is back. You don't want to make that assumption, and in a transplant setting, of course, much attention should be paid to a change in status.

And then lastly, I think it has been reported where sometimes CML can occur again or CML might actually be present in the donor bone marrow, which sounds very unfortunate, but hopefully would be very treatable. I think there's a couple of different situations to consider there and I would definitely encourage someone to make sure they're getting close follow-up and get those questions answered on the ground. But the good news is hopefully that may not always mean that the transplant is no longer effective or that all is lost. There may be a number of different options to consider.

**Ms. Figueroa-Rivera:**

Sure. And Doctor, are transplants being utilized still for CML with the availability of TKIs?

**Dr. Mauro:**

They certainly are. The number of transplants is much lower just because the number of patients who need allogeneic stem cell transplant is much lower. But it's definitely still a consideration. Before we had TKIs, CML was one of the most treatable and curable blood cancers by means of an allogeneic transplant. That's sort of a great problem. And then we came up with TKI treatment approaches and now we don't necessarily need to use it very often. So the most important nuance there would be not to wait until it's too late, or not to think about or pursue it when now transplant success isn't what I just mentioned, so it should be always on the table, particularly for when things are not going well with TKI treatment and particularly before the CML moves out of a chronic phase.

**Ms. Figueroa-Rivera:**

Sure. And Dr. Atallah, Walter's asking, what is the history or prognosis of those young patients, so those patients under 25, with reducing their medication by half or more?

**Dr. Atallah:**

So Walter, overall the prognosis for those patients remains good, understanding that we don't have 50 years of follow-up, right? I mean, but as of right now, the prognosis remains good for those patients. Reducing the dose is definitely an option if someone is responding well and that's something that really needs a discussion with the physician for monitoring and looking at the response, where the patient is at right now, how things have changed. So reducing the dose really takes some expertise and discussion of risks and benefits and close monitoring.

The biggest challenge I have seen in my clinic really for younger patients is staying on the drug. Younger patients have a very difficult time of staying on the drug, they're very busy, go to school, go to work, don't want to feel bad. And that's really been a big challenge for me is to convince my younger patients you really, really need to stay on drug, you really, really need to stay adherent to the regimen, hoping that one day you would get to a deeper remission that you would actually be able to stop. So that's really been the challenge, the biggest challenge is adherence.

**Ms. Figueroa-Rivera:**

Thank you. This question, is our final question is from Elizabeth, she's curious for both doctors, what is the longest period of time one of your patients has been able to remain off of a TKI once achieving treatment-free remission?

**Dr. Mauro:**

I can say since neither of us are French, although some of us may speak French, but the original studies originated in Europe and then they came over across the Atlantic. But I have some patients who have been off treatment for roughly 10 years that I'm able to follow. Also depends on where you're practicing. I used to practice in Portland, Oregon, Oregon Health and Science University and some of the patients actually were on the call today, which is great, but I had to pass those patients over to someone else, so I think I have some patients that may be now successful off-treatment longer that I took care of once. Dr. Atallah?

**Dr. Atallah:**

My longest is between 7 and 8 years.

**Ms. Figueroa-Rivera:**

Wow, that's great to hear. I just wanted to ask you, since it's the end of this call, we typically didn't utilize the term cure for CML, being more of a chronic disease. So I just wanted to ask both of you and Dr. Atallah, you can go first, why the Consortium and why physicians are now striving to utilize the word cure for CML?

**Dr. Atallah:**

So why are we striving? I think if you look at the history of CML, we had nothing, and then you need a transplant, you could be cured with a transplant, that's great. And then we switched to taking a pill and then we're like wow, this is great, take a pill every day. But then we, as CML specialists, we're seeing patients like yourselves every day and we just know that that's not good enough. There are symptoms, there are things that linger, question of like 50 years on this drug, what's going to happen to me. So sort of our mindset has changed gradually with a goal that we really need to get people, more people off-drug, more people cured, do more research for CML, just because patients take a pill every day and they're doing okay doesn't mean that that's good enough. The goal of the Consortium is CML is by definition a rare disease, however, the number of patients is high because patients live for a long time, but CML is a rare disease and that's why we have this collaboration. We each bring something different to the table from experience, whether clinical experience, lab experience, population science experience, and that's the goal of the Consortium, to put all our experiences together, to move the field forward.

**Dr. Mauro:**

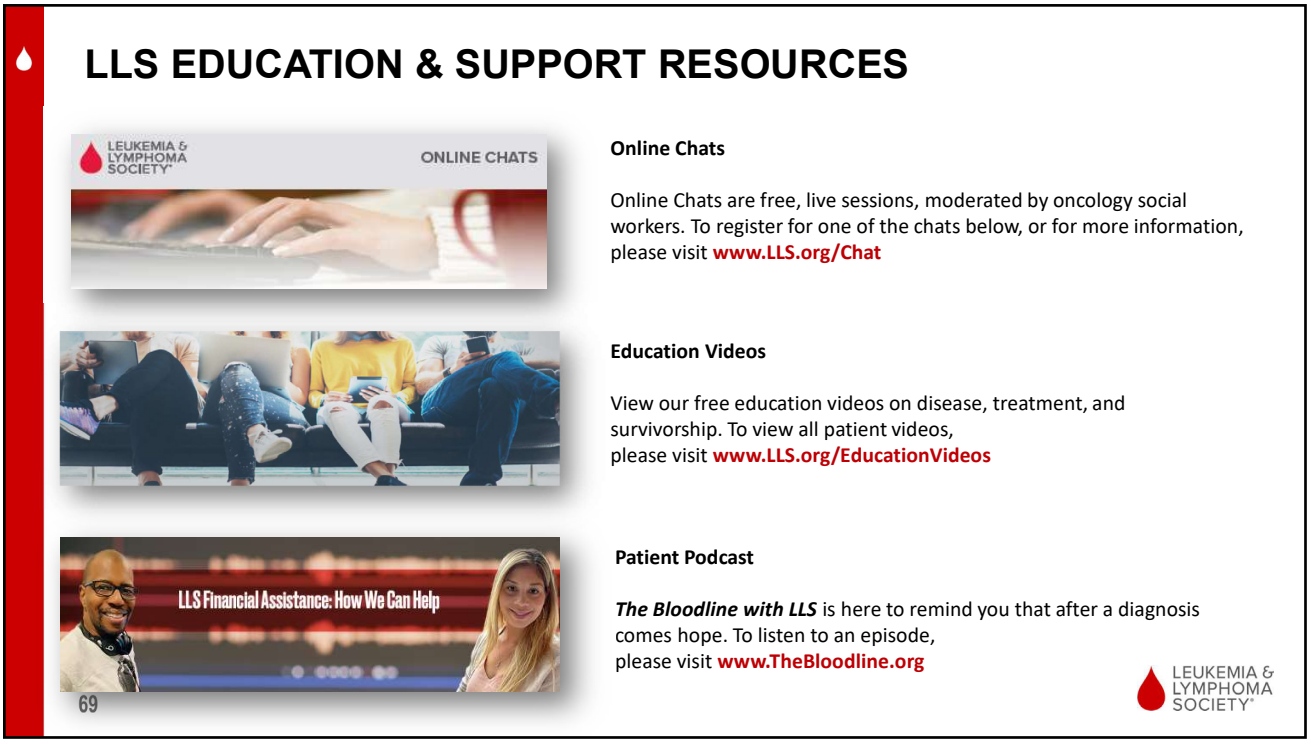
I don't have a lot to add to that except to say that our perspective kept changing in CML. We didn't think targeted therapy was going to be as successful as it would be and it was. And we didn't understand how deep remissions could be and we dug deeper. And we created a new paradigm where people were on therapy indefinitely and that wasn't typical in cancer. People historically with conventional chemotherapy took it 4 cycles, a few cycles, 3 cycles, 6 cycles, until the disease was gone, and then we watched and waited and we hoped the cancer didn't come back. Targeted therapy opened a new era where now people were on therapy for infinity, sort of open-ended. So naturally when things got better, things got deeper, as Dr. Atallah mentioned, we clearly wanted to take it all into perspective, we don't want side effects, we don't want to have any collateral damage. Look at how successful these treatments have been. We immediately endeavored to think about how could we cure this. Our definition's a little bit unique and the approach is always very specific, but I think it's coming, its time has come and we're all enthusiastic and we're here to serve you better in North America and we're glad to partner with LLS and everyone else to make that a reality.

**Ms. Figueroa-Rivera:**

Well, thank you so much, Doctors, for being on this call today. All of you, Dr. Atallah, Dr. Mauro, Dr. Sweet, thank you all for volunteering your time with us today. We are excited about seeing the new advancements with CML treatment.

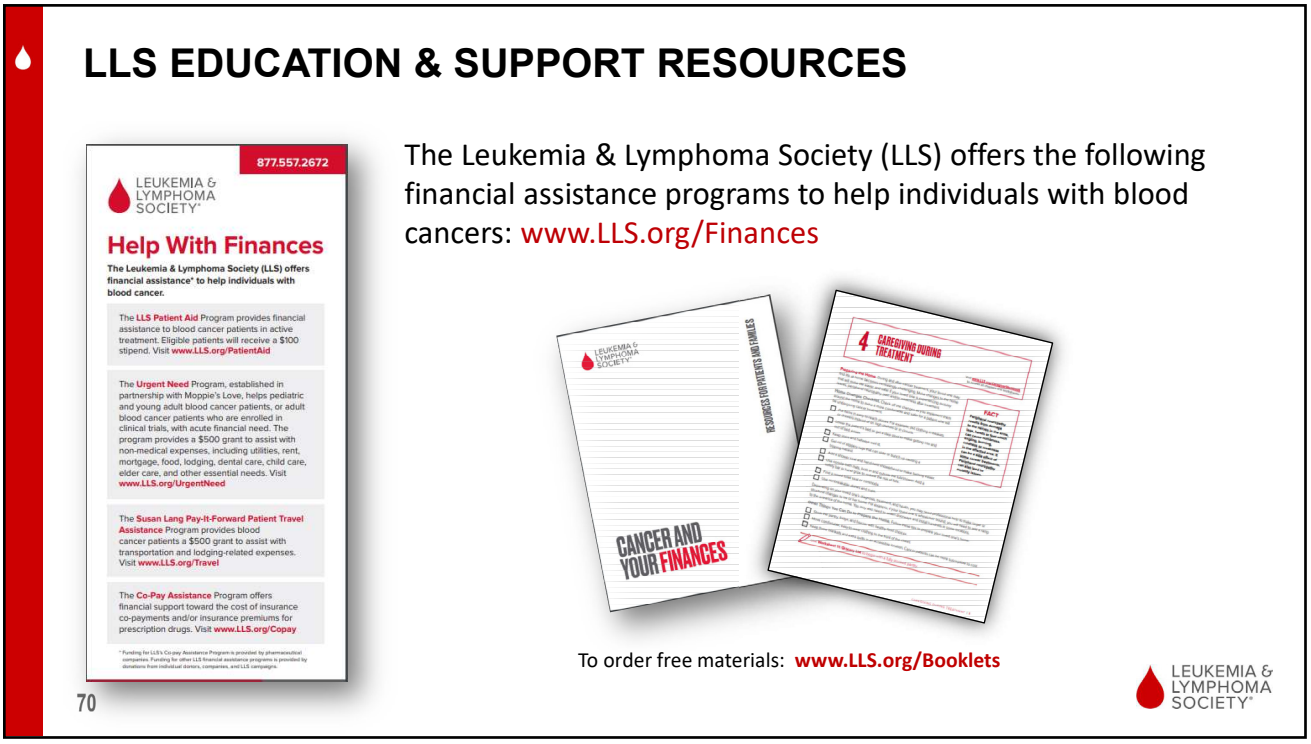

**Slide 68: LLS EDUCATION & SUPPORT RESOURCES**

For more information, you may speak to an LLS Information Specialist at 1-800-955-4572 from 9 AM to 9 PM Eastern Time or you may reach us by e-mail at LLS.org/ContactUs.




**Slide 69: LLS EDUCATION & SUPPORT RESOURCES**

We'd like to acknowledge and thank Bristol Myers Squibb, Novartis, and Takeda Oncology again for their support of this program.




**Slide 70: LLS EDUCATION & SUPPORT RESOURCES**

And as a reminder, you can download and print the slides as well as listen and view the audio and video for today's program at LLS.org/Programs.


**Slide 71: THANK YOU**

Again, Doctors, thank you for volunteering your time and thank you so much for really getting together and collaborating and making it a reality that the research for CML is really following through and providing patients not just with new treatments but with hope for a cure, as well as a better quality of life.

Thank you so much.

**END**