Thank you and hello, everyone. On behalf of The Leukemia & Lymphoma Society, I’d like to welcome all of you. We have over 1000 people participating from across the United States, as well as from Australia and Canada on this program. Special thanks to Dr. Alison Loren for volunteering her time and expertise with us today.

Before we begin, I’d like to introduce Ms. Becky Dame, RN, BMT, CN, part of The Leukemia & Lymphoma Society’s Patient Access Team, who will share a few words. Becky, go ahead.

Becky Dame:
Thank you, Lizette. I would like to add my welcome to the patients, caregivers, and also healthcare providers attending today’s program.

The Leukemia & Lymphoma Society (LLS) exists to find cures and ensure access to treatment for blood cancer patients. Our vision is a world without blood cancer. For more than 60 years, LLS has helped pioneer innovation, such as targeted therapies and immunotherapies that have improved survival rates and quality of life for many blood cancer patients. To date we have invested over $1 billion in research to advance therapies and save lives. Until there is a cure, LLS will continue to fund promising research from bench to bedside.

As a chronic myeloid leukemia (CML) patient and transplant survivor, I have seen the progress of research through clinical trials firsthand. When I was diagnosed in the early 1990s, there were no oral medications available to treat CML. The first TKI, tyrosine kinase inhibitor, was not FDA approved until 2001. The standard polymerase chain reaction (PCR) testing to monitor CML disease levels was also not yet available. I am proud to be a part of an organization that contributes to finding cures for blood cancer patients like myself.

As you will hear from today’s presentation, being diagnosed or having a loved one diagnosed with CML can be difficult for any family. The Leukemia & Lymphoma Society’s Information Specialists are available to provide personalized support to individuals who have blood cancers by providing up-to-date disease and treatment information, including clinical trials, support resources, and helping families navigate the financial challenges associated with blood cancers.

LLS is the leading source of free blood cancer information, education, and support, and we touch patients through communities through our local chapters across the U.S. and Canada. LLS also acts as a voice for blood cancer patients. We advocate for patients, survivors, and their families, helping them navigate their cancer treatments, ensuring they have access to quality, affordable, and coordinated care.
We are fortunate today, as our presenter, to have Dr. Alison Loren, one of the leading nation’s experts in chronic myeloid leukemia. We appreciate her dedication to supporting our mission and her commitment to caring for patients with blood cancers. I’d like to thank her today for providing us with this important information on CML.

Thank you all. And now I’ll turn the program back to Lizette.

*Lizette Figueroa-Rivera:* Thank you and we would like to acknowledge and thank Bristol-Myers Squibb, Novartis, and Takeda for support of this program.

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**DISCLOSURES**

*Alison Wakoff Loren, MD, MSCE, has no affiliations to disclose.*

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**Slide 2: Disclosure**

I’m now pleased to introduce Dr. Alison W. Loren, is an Associate Professor of Medicine in the Division of Hematology/Oncology at the Perelman School of Medicine at the University of Pennsylvania in Philadelphia, Pennsylvania. Dr. Loren, I’m privileged to turn the program over to you.

*Dr. Alison Loren:* Thank you so much, Lizette, and thanks to the LLS for your amazing work, with our patients, with your advocacy, with your funding of innovative research. We’re very grateful to you for your help helping us. I want to welcome everybody to the program and thank you all for joining us.

I just want to first, let you know that I have no, affiliations to disclose.
Learning Objectives

- Treatment advances for chronic myeloid leukemia (CML)
- The concept of treatment-free remission
- Supportive care and side-effects management
- How communicating with your healthcare team can improve your quality-of-life

Slide 3: Learning Objectives

The objectives for today's talk will be to go over some new advances in the management of chronic myeloid leukemia or CML. We'll talk a little bit about the idea of a treatment-free remission, which is a relatively new concept in the management of this disease. We’ll talk some about supportive care and management of side effects and then also want to emphasize how important it is for the patients and caregivers, in the audience to encourage good communication with your healthcare team, to help improve your quality of life, and ultimately, I believe very strongly your overall prognosis with this disease.
A Few Basics: What is CML?

- Cancer of bone marrow stem cells
- Three phases: chronic, accelerated, blast
- Most patients are diagnosed in chronic phase
  - Often without symptoms
- Untreated, all patients progress to accelerated / blast phase within 3-5 years

Before we start in, I just want to go over a few basics. I know many of you are probably, either actual hematologists/oncologists or armchair hematologists/oncologists, but just to make sure we’re sort of all on the same page, CML or chronic myeloid leukemia is a form of blood cancer. It is a cancer of the stem cells in the bone marrow and these are the most fundamental early blood cells that ultimately give rise to all of the blood cells that we make in our bodies. And I’m sure many of you know that these include white blood cells, which help fight infections, red blood cells, which carry oxygen and nutrients to the tissues, and platelets, which help with clotting.

CML is described or characterized by one of 3 different phases: chronic phase, accelerated phase, and blast phase or blast crisis. Most patients are diagnosed in chronic phase, meaning that they have, sort of the more indolent or slow growing form of the disease. Many patients are diagnosed with CML without any symptoms and in fact with the wide availability of complete blood count testing, many patients are even diagnosed incidentally. They are going to get blood work for a procedure or just for routine management of their other health issues and they may be discovered to have CML based on an abnormal blood count.

The picture I know, as I said, many of you are armchair hematologists, but the picture on the left demonstrates CML in chronic phase. And here you can see that there’s lots of different kinds of white blood cells. Those are the big blue cells that are demonstrated here. The grayish cells in the background are actually red blood cells. And you can see there’s lots of different kinds, a lot of heterogeneity. Some, mature neutrophils. Those are the ones with sort of the wiggly nuclei and some less mature ones that look more kind of blotty. And then on the right-hand side, this is an image of a blast phase, which is the more accelerated form of the disease, and you can see that most of the cells here look all kind of the same and they’re all very immature white blood cells. These patients often are quite ill when they’re discovered to have this disease. They may have fevers and weight loss and be feeling poorly. That’s a more advanced version of CML.
A Few Basics: What is CML?

- Characterized by a translocation between chromosomes 9 and 22, denoted as t(9;22) which results in an abnormal juxtaposition of two genes, bcr and abl

CML occurs when something called a translocation or switching of genetic material happens. There are packages of genetic material that are known as chromosomes in every single human cell and they come in pairs. You get 1 copy of each pair from each parent, so you can see that there’s like 2 copies of chromosome 1 and 2 copies of chromosome 2, and you get 1 copy from each parent.

CML occurs when there’s something called a translocation or switching of the genetic material between chromosomes 9 and 22. And so, you can see on the picture on the left that chromosome 9, one of the members of the pair, is a little bit long, the one with the arrow. And, one of the members of chromosome 22 is a little bit smaller. That’s also the one with the arrow. And, that little bitty chromosome 22 is what’s known as the Philadelphia chromosome. It was discovered in 1961, actually here at the University of Pennsylvania. And, ultimately it was discovered that when that translocation or switching of genetic material happens, these 2 genes, the gene called ABL, which normal lives on chromosome 9, and the gene called BCR, which normally lives on chromosome 22, are placed next to each other and that’s demonstrated in the picture on the right, where you can see that the ABL gene is red and the BCR gene is green, and usually if the translocation hadn’t happened, the green and the red would never be near each other. But, when the translocation occurs, the green and the red are right next to each other. And in the far-right picture, you can see that there’s a sort of green and red mixed signal that demonstrates the presence of the BCR/ABL fusion gene which leads directly to the development of CML.

And, that’s important because it helps us to understand how we monitor this disease. It’s very important when we are taking care of our patients to monitor whether our treatments are working.
How Do We Know If Treatment is Working?

- Hematologic response (CBC [complete blood count])
  - Normal blood counts
- Cytogenetic response (bone marrow cytogenetics [“karyotype”])
  - Major (MCyR): < 35% of cells have the Philadelphia chromosome
  - Complete (CCyR): 0% of cells have the Philadelphia chromosome
- Molecular response (Quantitative PCR, International Scale [qPCR, IS])
  - MR3 (0.1%) aka “major molecular response” or MMR
  - MR4.5 (0.01 – 0.001%)
  - Complete or deep molecular response (CMR or DMR): no detectable bcr/abl

Slide 6: How Do We Know If Treatment is Working?

And, so the first step is to achieve what’s known as a hematologic response, which means that the blood counts become normal. The second thing that happens is there’s a genetic response and by that we usually assess that in the bone marrow with a test called cytogenetics or a karyotype. And, that’s on the previous slide this picture on the left is a karyotype or a cytogenetic analysis. And, in that assessment we look for what’s called a major or a complete cytogenetic response. And, I’ve listed the abbreviations there. A major cytogenetic response is when there’s less than 35% of the bone marrow cells still having that Philadelphia chromosome that’s visible. And, a complete cytogenetic response is when the Philadelphia chromosome is no longer present.

The most sensitive way of testing to see if treatment is working is a molecular test that’s known as a quantitative PCR. And, the most up to date and most important thing to know about this test is that it needs to be run in a lab that performs the test based on a level of sensitivity that’s known as the International Scale. And again, just sort of to teach you the lingo, what we’re looking for is either a 3 or greater log reduction. And, I’ll show you on the next slide what that means. But, you’ll see people talking about an MR 3 and that’s when the amount of the BCR/ABL gene that’s detected on this PCR falls below 0.1%. And, that’s also known as a 3-log reduction. If it falls below 0.01%, that’s a 4-log reduction, and so forth, for those of you who love your high school math and like to think about logarithmic scales. And, then the other piece of terminology that you’ll hear when people talk about this test is something called a complete or a deep molecular response and that’s when the BCR/ABL transcript is no longer detectable at all. And again, it’s important that the testing is sensitive enough to reliably say that it’s not detectable.
Slide 7: How Do We Know if Treatment is Working?

So, on this slide it’s sort of a visible representation of what we just discussed, and so you can imagine that this is a patient and on the left-hand side you can see, the levels of response and on the horizontal axis it’s treatment, you know, response over time.

So, let’s say this person gets started on their TKI at a point where they have detectable BCR/ABL and they start on their medication and 3 months in they’ve had a 1-log reduction, which is a 10% level of BCR/ABL and that’s known as an early molecular response and that can be an important treatment milestone.

Eventually, usually at 12 months and sometimes it takes longer depending on the medication that you’re on, we would like patients to achieve a major molecular response, and you can see that’s a 0.1% level of BCR/ABL or on the far left what we call a 3-log reduction. Ultimately, we’re seeking a 4.5 or greater log reduction or a deep molecular response and that level is measured at 0.0032%. So, that’s sort of the gold standard now in terms of thinking about complete responses or deep responses and even considering things like treatment-free remissions, which we’ll get to in a moment.
Impact of TKIs

- Until imatinib approved (FDA 2001), most patients treated with supportive care, hydroxyurea, interferon, and allogeneic hematopoietic cell transplantation (“bone marrow transplant”)
- Tyrosine kinase inhibitors (“TKIs”) have revolutionized this disease

I want to highlight something that Becky said at the beginning of the call, which is that there has been an absolute revolution in terms of the way this disease is treated. And, as she told you, up until 2001 all patients were treated with either supportive care or hydroxyurea, which is an oral mild form of chemotherapy, immune therapies like interferon, and for patients who were eligible, an allogeneic bone marrow transplant, which is a very intensive form of treatment, and not offered many times to patients who are considered older and that is a little bit in the eye of the beholder, but typically, over the age of 60 to 70 to 75. And, the predominant patients are people who get this disease, as many of you know, are older patients. And so, for many patients with this diagnosis there was no cure and there was no hope for long-term survival. On average, people would live something between 3 and 5 years without treatment and maybe a few years longer with treatment. But, the overall prognosis was fairly grim.

And, with the approval of imatinib in 2001, everything in this disease has changed. And, with the approval of this pill, the long-term survival of patients with CML has almost approached that of the normal population. And so, you’ll hear me say the term TKI, that refers to tyrosine kinase inhibitors. That’s the family of medications that include imatinib and dasatinib and others. And so, if I use that terminology, that’s what that means.

And, you can see in the pictures here on this slide that looking at men and women, the blue dotted line is a life expectancy of the general population and the yellow line is the life expectancy of patients with CML. And, you can see that back in the ‘90s, patients who were 55 years old with CML might be expected to live a couple of years, maybe up to 5 years, whereas patients who were healthy with, who were 55, might be expected to live as long as 25 years. But now, with the approval of these medications, you can see that the survival of a 55-year-old with CML is just about the same as a survival of a 55-year-old without CML. And, that is just a remarkable achievement.

So, to get to sort of what we are talking about today, and I’m happy to address questions related to sort of standard treatments with CML at the end of the talk, we want to just cover sort of things that are new in CML. And so, one of the major things is development of additional tyrosine kinase inhibitors and other therapies.

You know, it’s interesting, one of my patients asked me, oh, you know, TKIs have been such a success, have people just decided that we’ve done good enough in CML and the research community might be moving on? And, I said absolutely not. You know, as wonderful as these drugs are, as many of you know, it’s not a total win and we need to keep working and keep getting better and better and better. And so, these newer drugs are part of that wave of trying to get things to be as perfect as they can be.
Treatment Advances for CML: TKIs

- **Bosutinib**
  - Overcomes most imatinib-resistant mutations
  - Approved for 1st line therapy in late 2017
  - BELA trial (2012), 502 patients: bosutinib 500 mg vs imatinib 400 mg, evaluated at 12 months
    - CCyR (primary endpoint) equivalent: 70% (B) vs 68% (I)
    - MMR better for bosutinib: 41% (B) vs 27% (I)
  - BEFORE trial (2017), 536 patients: bosutinib 400 mg vs imatinib 400 mg, evaluated at 12 months
    - MMR (primary endpoint) better for bosutinib: 47% (B) vs 37% (I)
    - CCyR also better for bosutinib: 77% (B) vs 66% (I)
    - Significantly more diarrhea (8% vs 1%) with bosutinib

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Slide 9: Treatment Advances for CML: TKIs

So, many of you may know about a drug named bosutinib. This is an FDA approved medication that was initially approved for second or later lines of therapy, but recently at the end of 2017 was approved as a fourth option for first-line therapy. Bosutinib is a very potent drug. It was initially trialed against imatinib and the results were reported back in 2012. This has a little bit to do with the way the study was designed. So, the authors wanted to look at the primary endpoint of a complete cytogenetic response and in that evaluation that means that at 12 months when a bone marrow test was done, how many patients had 0% Philadelphia chromosome cells in their bone marrow. And, on that study the numbers were about equivalent between the bosutinib and the imatinib groups. The depth of the response, meaning the molecular responses, were much more frequent in the bosutinib group, but because the study was not aimed at answering that specific question, the study did not enable bosutinib to generate a first-line approval. And so, a second trial, known as the BEFORE trial, was completed in 2017. Again, another 500 or so patients. Bosutinib at a slightly lower dose, related to side effects, which we’ll go over later were again reevaluated and this time the investigators changed the primary endpoint to be the major molecular response, which again was better in the bosutinib group. And, this study led to approval of this drug for a first-line indication.

You’ll note that there is substantially more diarrhea in patients receiving bosutinib and that is a very, very common side effect of bosutinib that can be limiting for some patients. Nevertheless, it’s great to have another option, either to start or as additional lines of therapy are needed.
Treatment Advances for CML: TKIs

- **Ponatinib**
  - The only commercially available TKI effective for patients with T315I mutations
  - Significant cardiovascular risks
- **Radotinib**
  - Structurally similar to imatinib and nilotinib
  - Approved in Korea for 1st line and later therapy
  - 2nd line: 77 patients (2014)
    - MCyR 65%, CCyR 47%, MMR 14% at 12 months
  - 1st line radotinib 300 mg vs imatinib 400 mg: 241 patients
    - MMR 52% (R) vs 32% (I), CCyR 91% (R) vs 77% (I)

*Radotinib is not FDA-approved

Slide 10: Treatment Advances for CML: TKIs

Another really exciting opportunity for treatment has come with the approval of ponatinib. Ponatinib is an incredibly effective drug that does have some serious side effects and risks that again we'll discuss a little bit later. But, some of you may know that the ABL kinase protein, the pocket that sort of activates the cell's growth, there are mutations that can occur that make it difficult for the other drugs to be effective. And, one such mutation, known as the T315I mutation, brings resistance to all drugs except for ponatinib. So, ponatinib has a very, very important indication, which is that for patients with the T315I mutation, ponatinib is the only drug that's going to be effective for those patients.

A new drug that's being developed and is not FDA approved yet is a drug known as radotinib. Radotinib's structure is very similar to imatinib and nilotinib. It is approved elsewhere for first-line and subsequent therapies, and the responses are excellent and really very similar to other TKIs. In the second-line setting, meaning that patients had tried another drug and either couldn't tolerate or didn't respond to it, when this other drug radotinib was started, a large percentage of patients achieved a major cytogenetic response. About half were able to get rid of the Philadelphia chromosome completely and about 14% of the patients achieved a major molecular response at 12 months.

A randomized study that looked at this drug first line, compared to imatinib, also compared favorably to imatinib in both the molecular and cytogenetic responses. So, this is something that's being tested now and considered as additional options.
Treatment Advances for CML

- **Asciminib (ABL001)**
  - Potent and selective inhibitor of BCR-ABL
  - Different site from other TKIs, allowing possible co-treatment
  - Promising early data
  - Resistance may occur
    - ABL mutations
    - Proteins that pump drug out of the cells
  - 4 open clinical trials, alone or in combination with existing TKIs

*Sasciminib is not FDA approved


Slide 11: Treatment Advances for CML
A very cool new drug that is also being tested, is known as asciminib or ABL001. And, what’s interesting about this drug is that unlike all the other TKIs, which work in the pocket of the kinase that’s on the right-hand side here, you can see that this drug works in a different part of the protein. And, essentially what it does is it sort of forces that pocket closed, so that the other drugs can’t get in there. And it’s very potent in combination with the other TKIs. And, it also is powerful by itself.

It has been known to develop resistance, so patients can respond initially and then lose their responses either because there are mutations in the protein or that the cells develop other protein pumps that actually pump the drug out of the cell, so it really can’t do its job.

There are several trials that are open right now for this drug, either by itself or in combination with existing TKIs and this holds a lot of promise in my opinion for sort of a new mechanism, something different to either add or use instead of the standard TKI therapies.
Another area of active interest is the idea that there are what are called leukemic stem cells. So, I mentioned that CML is a cancer of blood stem cells and when those stem cells are cancerous or leukemic, they can be resistant for a whole range of reasons to the TKIs. And so, several investigators are looking at combinations of TKIs and other drugs to try to augment their effectiveness at killing leukemic stem cells. And, I've listed a few of these trials and options here. There's a lot of interest in continuing to develop these types of inhibitors or pathways because the prevailing thought is that eradication of the leukemic stem cell population is essential to long-term cures. And so, if there were a way to increase the number of patients who could enjoy a treatment-free remission, adding drugs like these to TKIs to kill the leukemic stem cells more effectively, might offer more patients the opportunity to come off of their drug.
Treatment-Free Remission

- Dec 2017: FDA approved a discontinuation indication for nilotinib
- History:
  - 2007: 12 patients on imatinib with undetectable bcr/abl > 2 years
    - 6 remained in remission
  - 2010: STIM trial: 100 patients (69 with 1-year follow up)
    - 39 patients (43%) remained in remission
    - Longer duration of imatinib predicted freedom from relapse
  - 2013: TWISTER, and others, confirmed that for about 40-50% of patients, long-term treatment-free remission is possible


So, let’s talk a little bit about the concept of a treatment-free remission. And, I just want to emphasize that this is not called cure and the reason that we don’t use that language is that no one currently has any idea whether patients who are able to enjoy a treatment-free remission will last forever, and whether you know what the long-term outcome will be for patients who are being discontinued off their medication.

So, this idea has been around for a long time, at least 10 years or so. You can see that the very first descriptive study of a small group of patients on imatinib who had long-term undetectable BCR/ABL levels were discontinued of their drug and about half of them remained in remission over the longer term. This led to something known as the STIM trial and I like the STIM trial because it enrolled 100 patients. So, that means that the percentages are always easy to figure out based on who responded. The STIM trial took 100 patients who had long-term deep remissions to imatinib. Only 69 of them at the time of publication actually had been followed for at least a year. And, about half of them or less than half of them were remaining in remission at the time of publication. And, one of the important observations from the investigators was that the longer that people had been on imatinib the more likely they were to remain free of relapse after discontinuation. And, this led to another study published in 2013 known as the TWISTER trial, and then several others that have now been published that demonstrate that for patients who meet specific study criteria and the criteria vary a little bit from study to study, somewhere between 40 and 50% of patients who stopped their TKI are able to remain off of it for the longer term. And, we don’t have very long-term follow up data for these patients, a couple of years is generally the longest, and so it’s a little bit hard to tell people what the 10 year expectation is and these drugs have only been around for 10 years in some cases, and so the long-term outlook is very hard to anticipate. But, based on this information, nilotinib received an unusual label from the FDA in December of 2017, the drug received a label saying you can stop the drug, which is sort of interesting, and not the usual way that FDA works.
Treatment-Free Remission: Who is eligible?

- Ability to monitor bcr/abl transcript on IS testing
  - b2a2 or b3a2 transcript
- No prior resistance to TKIs
  - Some recent studies suggest some 2nd line patients may be successfully discontinued
- No prior accelerated or blast phase
- Minimum of 3 – 5 years on TKI, but longer (8 years) is preferred
- Minimum of 12 months undetectable bcr/abl on IS testing, but longer (2 years) is preferred
- Willingness to comply with intensive follow up qPCR testing

There are some very specific criteria that make people eligible for considering a treatment-free remission and these include first and foremost, you have to be able to monitor the BCR/ABL levels effectively. It’s really important for people to appreciate that although BCR/ABL sounds like it’s just 1 mutation, there are actually a family of mutations that can occur, depending on the biology of that individual person’s disease. Most people have transcripts known as b2a2 or b3a2 and those 2 transcripts comprise the vast majority of people with chronic myeloid leukemia, and those are the transcripts that are detectable on most commercial international scale lab testing. If a person has a different transcript or a non-detectable mutation, that’s not typically detected on normal testing, that person is not eligible for a treatment-free remission trial because they can’t be monitored accurately.

Another group of patients who are generally thought to be not wonderful candidates for a treatment-free remission would be people who have had a history of resistance to a TKI in the past. So, people who have taken a medication and it didn’t work for them and then they had to switch to a second treatment, those patients generally are thought to be riskier in terms of their chances of relapsing. This is being questioned a little bit and there are some studies that are published demonstrating that even people who are on, quote, second-line TKIs, if they have an optimal response to that second TKI, a treatment-free remission trial could be considered, but that’s still hypothetical at this point, not proven to be safe.

Patients who have had a previous blast or accelerated phase are not eligible for a treatment-free remission, so chronic phase only. In general, because of the observation that longer duration of therapy is more favorable, we prefer that patients have had at least 3 to 5 years on a TKI, but longer, like 8 years, seems to be optimal. And similarly, a long duration of undetectable or deep molecular responses on the BCR/ABL testing is also preferred. A minimum of a year to even consider it, but 2 years again is preferred. And then lastly, patients who choose to pursue a treatment-free remission trial need to be intensively monitored. The recommendations currently are for monthly testing and that’s a lot to have to do every single month.
Slide 15: Graphic

So, this is a nice graphic that sort of tells us who is a good candidate or a worthwhile, you know, thing to think about, which is a treatment-free remission, that’s in green. So again, just reiterating the things we discussed, you know, patients who are not high risk, who have the mutations that are detectable on routine testing, who’ve only been in chronic phase, who have had the best possible response to first-line therapy with a lengthy duration of both TKI therapy and molecular response. The yellow group highlights patients who it could be considered preferably in the context of a clinical trial or in a situation where the patients are either really not tolerating their therapies well, lots of risks or toxicities or side effects, or it could be considered for a patient who’s contemplating a pregnancy. And, then the group of patients who we would not recommend TKI withdrawal are summarized in the red column there. And I for efficiency won’t summarize that.
Advances in Chronic Myeloid Leukemia
September 25, 2018      Speaker: Alison Wakoff Loren, MD, MSCE

Stage 16: Treatment Free Remission: How to monitor?

- Most patients relapse within 6-9 months
- qPCR for bcr/abl in IS lab with prompt results:
  - Every 4 weeks during year 1
  - Every 6 weeks during year 2
  - Every 12 weeks during year 3 and thereafter
- Upon loss of response, re-initiate effective TKI therapy immediately and monitor bcr/abl every 2 weeks until MMR is regained / sustained
- Nilotinib (and imatinib) withdrawal syndromes have been described
- Not all patients wish to discontinue therapy

In terms of what happens to patients with who are trialing a treatment-free remission, the most important thing to know is that if a relapse is going to happen, it typically happens within the first 6 to 9 months. And, I recognize that first bullet is phrased in a little bit of a confusing way. It still seems that between 40 and 50% of patients will be able to remain off their drug and if a recurrence is going to happen, it usually happens relatively soon after the treatment is stopped.

As I mentioned, the monitoring for this situation is very intensive. BCR/ABL testing in an international scale lab that provides timely results needs to be done every 4 weeks in the first year after discontinuing therapy, every 6 weeks in the second year, and then every 3 months thereafter. And, as many of you know, as expensive as the drugs are, the IS testing is also quite expensive, and I know some patients have large copays to pay for the testing. And so, from a financial perspective, you know it may still be costly, even though there's a lot of cost savings that's anticipated with patients coming off their medications.

It's recommended that immediately upon losing a response, the prior TKI that was effective needs to be immediately resumed, and then very close monitoring of the BCR/ABL transcript until a major molecular response is regained.

There are increasing descriptions of patients who've developed withdrawal syndromes. So, patients -- for as sort of a terrible irony, as terrible as some people feel on these drugs, some people feel terrible when they come off of them. Where patients can have muscle aches and fatigue and other symptoms that are notable within the first few weeks to months after stopping the drugs.

And, another thing that I'll mention, and I see this a lot in my practice, is that many patients, especially those who are fortunate enough to be blessed with relatively few side effects and good insurance, such that the drug is not terribly costly, they don't really want to come off. I don't need to tell you that it can be very stressful and having a drug that works, that's tolerated, that's affordable, feels safer to them. And so, I've absolutely addressed this with many patients who have chosen not to participate in a trial of a treatment-free remission.
Supportive Care: Managing Side Effects

- Unfortunately, most patients with CML will not be eligible for a trial of treatment-free remission
- How to live well on these medications?
- Side effects are common (60-80% of patients)
- 3 areas of concern
  - Physical (side effects and health risks)
  - Psychological
  - Financial (“TKI handcuffs”)

Stage 17: Supportive Care: Managing Side Effects

So, moving towards thinking about side effects, if you think about it, most patients actually with CML will not be eligible for a trial of treatment-free remission. So, the group of patients who achieve this optimal level of response and maintain it for a long period of time is a relatively small percentage of all the people who have CML. And so, the vast majority of people with this illness will not be eligible to consider a trial of a treatment-free remission and so thinking about how to function and live while on these medications is a huge challenge.

The literature cites a 60 to 80% incidence or prevalence of side effects. I personally think the other 20 to 40% of patients are not being truthful, because in my experience just about everybody has some side effects attributable to these medications. And so, I’ve thought to break these side effects down into physical side effects, that include both symptoms and also risks to one’s health; psychological side effects and then financial. And, I often will call these the TKI handcuffs. People stuck to their financial or insurance situation because of the drug.
Supportive Care: Side Effects

- **Imatinib**
  - Once daily, with or without food
  - Muscle cramps, swelling, rash, nausea/diarrhea

- **Dasatinib**
  - Once daily, with or without food
  - Fluid around lungs (pleural effusion) in up to 30% of patients
  - Low blood counts, especially platelets

- **Nilotinib**
  - Twice daily, 1 hour before / 2 hours after eating

- **Ponatinib**
  - Once daily
  - Rash, constipation, nausea

- **Bosutinib**
  - Once daily
  - Diarrhea major side effect (85% although most cases mild/moderate)
  - Nausea
  - Low platelets

**ALL: FATIGUE!!!!**

**Slide 18: Supportive Care: Side Effects**

So, I’ve just discussed side effects for the 5 TKIs that are currently FDA approved. One major consideration is how the medications need to be taken. So, most of the drugs, as you can see, are needing to be taken just once per day. But, nilotinib is taken twice a day and needs to be taken on an empty stomach, which means 1 hour before or 2 hours after a meal or after eating. And, this really is true. It’s an honest to God empty stomach. And, for any of you who are on this drug or for anyone who’s ever tried to take an antibiotic on an empty stomach, it’s difficult. It is really a pain. I have patients setting their alarm, getting up at 3:00 in the morning so that they can take it on an empty stomach because there’s no other way that their lives work with this schedule.

Side effects with imatinib typically occur most prominently when the drug first starts, and they include muscle cramps, swelling, particularly around the eyes, rashes, and GI symptoms like nausea and diarrhea. Dasatinib is actually pretty well tolerated, some similar side effects to imatinib in the beginning. Dasatinib is very potent and often causes low blood counts. All of these drugs can cause lowering of the blood counts, but particularly potent with dasatinib. One very interesting and unusual side effect of dasatinib is the development of something called a pleural effusion, which is fluid around the lungs. And, that occurs with some frequency, up to about 30% of patients will experience a pleural effusion on dasatinib. And, what’s interesting about that is that it is not usually something that happens early. It can actually occur many months into their dasatinib treatment, even a year in where everything seems to be fine and then these pleural effusions can occur. It doesn’t always mean that the drug has to be stopped forever. Often dasatinib pleural effusions can be managed with lowering the dose of the drug and sometimes giving a short course of steroids. But, it is something that’s notable.

Ponatinib, in terms of side effects, is associated with GI symptoms and a rash. And, bosutinib in particular, is very commonly associated with diarrhea. About 85% of patients will develop diarrhea of some kind and this is a huge number obviously. But, most cases are mild-to-moderate and self-limited, but very, very significant, especially in the beginning.

And, every single one of these medications is associated with fatigue, it can be a very difficult symptom to live with.
Slide 19: Graph

Just a sort of pictorial representation of the side effects and how they are managed and I won't go into this in a lot of detail because I know you'll have access to the slides later on, but just to note that, you know, although all of the drugs can do anything, there are certain side effects that are more common with some drugs than others.
Supportive Care: Medical Risks

- All TKIs except imatinib increase risk of cardiac events:
  - Prolonged “QTc” interval
  - Congestive heart failure
- Dasatinib
  - Pleural effusions
  - Pulmonary hypertension

**Slide 20: Supportive Care: Medical Risks**

There are also medical risks associated with these medications. Again, important to realize that these medical risks, although they are real, generally are much lower risk than not taking the drug at all. Obviously CML is a very serious condition and can develop into a very significant or even life-threatening form of leukemia. So, even though these drugs have risks, I want to emphasize that staying on the drug is very important.

All of these medications can impact the heart, both its electrical conducting system, which we describe as a QTC interval, and occasionally are associated with heart failure.

I mentioned the pleural effusions with dasatinib and sometimes dasatinib can also cause elevated blood pressure in the lungs or pulmonary hypertension.

These are all serious concerns and one of the major reasons why all of your side effects and symptoms should be discussed with your healthcare team so they can help assess for these abnormalities.
Supportive Care: Medical Risks

- Nilotinib
  - Metabolic risks: elevated blood glucose, lipids
- Ponatinib
  - High blood pressure
  - Arterial clots (heart attack, stroke, clots in other blood vessels) in up to 33% of patients

- Patients should consider routine cardiology care and/or referral to an “onco-cardiologist”

Slide 21: Supportive Care: Medical Risks

Nilotinib is really known for causing metabolic issues, increased blood sugars, and increased cholesterol. And so, those things need to be monitored.

And, ponatinib, as I alluded to earlier, is also highly associated with cardiovascular risks and especially clots. And, some of you may know that ponatinib was actually temporarily taken off of the market and then reinstated because of its important role in managing patients with this T315I mutation. But, there is an increased risk of very serious clots in some patients and so these patients need to be monitored closely. And so, we usually recommend that particularly for patients who already have cardiac risk factors, that consideration should be given to co-management with cardiologists who are interested in the heart problems of cancer patients and this is sort of subfield of cardiology that’s becoming known as onco-cardiology. Sometimes they call themselves cardio-oncologists, but not everybody can be an oncologist, so I prefer that they continue to call themselves cardiologists.
Slide 22: Graph

This is a very useful summary of the monitoring recommendations from a review to discuss sort of what treatments or what testing should be done for patients on these various medications. And, you can see that for imatinib and bosutinib really just routine health screening things like blood pressures and EKGs are most indicated. Dasatinib has a slightly higher vascular risk because of the lung issues and so there’s a little bit more frequent monitoring associated with that. But really, the 2 medications that are most strongly associated with metabolic and cardiovascular risks are nilotinib and ponatinib. The Xs demonstrate the testing that’s recommended associated with these medications. And, you can see they include a lot more testing like fasting glucose levels or sugar, fasting cholesterol levels, pulse monitoring, and more intensive follow-up including even things like echocardiograms, which are ultrasound tests of the heart. And most oncologists, I would say prefer to collaborate with either a cardiologist or a general internist or family doctor to help coordinate that form of management.
Supportive Care: Psychological Challenges

- Living with chronic illness
- “The ‘good’ kind of leukemia”
- Fear of progression
- Pregnancy

I want to talk a little bit about psychological challenges. I think any time somebody has to live with a chronic illness, particularly when they’ve been healthy before, or even if they’ve never battled cancer before, it’s incredibly stressful to live with this disease and to have to take a medication every day and to remember that, that they have to deal with this on an ongoing basis, is incredibly challenging and really changes many people’s sense of themselves and who they are. It’s a real struggle to live with this dichotomy of knowing that you have leukemia, which is an incredibly serious blood cancer, and yet you look fine to everybody else. You aren’t bald, you haven’t, you know, needed chemotherapy. There’s a lot of guilt I’ve seen in my patients who feel like they’re terrified and they know that they’re sick and that this is serious, but other people don’t really appreciate that, and they feel guilty for being scared when they know that other people are really sick and it could be worse and there’s a lot of complex psychology that goes along with a diagnosis like this.

I hear a lot that people get frustrated by being told by others, oh, you have the good kind of leukemia, isn’t that great? You know, CML, although the advances in the disease have been incredible and more and more patients are able to live good long lives with this disease, there’s no such thing as good leukemia and it’s very difficult for patients to hear that and to talk about it and to rebut that to people who say things like that.

Obviously, everybody lives with fear that their disease will no longer be well controlled, and becoming pregnant on these medications is also contraindicated, so for young women that’s a very, very big challenge.
Supportive Care: Financial Toxicity

- 2001: Imatinib $26,000/year
- Price increased 10-20%/year until 2016: $146,000/year
- Costs of nilotinib and dasatinib are comparable (~$150,000/year)
- Generic imatinib has not brought prices down much
  - Generic price ~$96,000/year


Slide 24: Supportive Care: Financial Toxicity
I just want to address the finances of this. I know many of you are suffering or dealing with this. Imatinib, when it was first approved, cost $26,000 a year and that was thought to be incredibly expensive at the time. The price has gone up 10 to 20% per year until in 2016 it was priced at exactly the same as the newer drugs nilotinib and dasatinib. For people who are interested in this, there are a number of publications in the lay press about this, and ultimately imatinib was able to be brought to generic. Still very expensive, although cheaper than it was. And, I have several patients who feel that they want to change jobs, or they want to do something different with their lives, but they can’t because they’re stuck with their health insurance. And so, I call those the TKI handcuffs. They’re sort of obligated to stay with a job or they want to retire, and they can’t because of the costs associated with these medications that they need life-long.
Communication with your team

- Medication does not work if you don’t take it!
- Non-adherence is common (30-70% of patients)
- Adherence is a major predictor of response:
  - Patients who took > 90% of their doses had a 94.5% probability of achieving MMR, compared to patients who took < 90% of doses, who had a 28% incidence of MMR)
  - Treatment adherence is the only independent predictor of achieving CMR.
  - Patients with suboptimal responses missed 24% of doses, as opposed to those with optimal responses, who missed 7% of doses.


Slide 25: Communication with your team

And, the last thing that I want to talk about is how important it is for you to talk to your team about your medicine. Many patients don’t take their medications, and some say that there’s as many as a third to two-thirds of patients who report that they don’t take their medications as they should. Medicine doesn’t work if it’s sitting in a bottle on your bedside and not going into your stomach. And so, whatever we can do to help you take your medicine is something we want to hear about. It is very clear that people who take their medicine do well and people who don’t take their medicine don’t do well. In one study patients who took more than 90% of their doses of medication had an almost 95% chance of getting into a major molecular response, whereas those who did not take 90% of their doses only had a 28% chance of obtaining that optimal response. Adherence to your treatment is the only thing that predicts achieving a complete or deep molecular response. And, in another study, patients who had suboptimal responses missed 24% of their doses and those who had optimal responses only missed 7%.
Slide 26: Graph

And so, I want to draw your attention, I know this is a little bit hard to see, but on this bottom left picture, this picture shows the survival of patients based on their response to treatment and how well they take their medicine. So, the bottom line is the group of patients who achieved a major molecular response. So, those patients are doing very well, they do not have much risk of progression. The line just above that are patients who did not achieve a major molecular response, but still took 85% of their medication. And the top line, the people who have lots of events, lots of bad things happening to them, those are the patients who did not have a major molecular response but didn’t take their medication. So, what this tells you is that even if you don’t have an optimal response, taking your medication will keep you alive, and that’s a really important message that I’d like everybody to take home today.

Communication with your team

- Insurance and marital status impact the survival of patients under age 65 with CML
  - Medicaid patients: 83% increased risk of death
  - Uninsured patients: 93% increased risk of death
  - Single (vs married): 65% increased risk of death

- Talking with your doctor about your concerns — physical, psychological, financial — can help us take better care of you!


Slide 27: Communication with your team

And so, the last thing that I want to emphasize, and I’m telling you this because I want you to talk to your Congress people and vote, is that people with insurance live longer with this disease. Patients who had Medicaid and those who are uninsured have substantially higher risk of dying from their CML, compared to people who have private insurance.

And also, having a partner who’s going to nudge you to take your medicine also helps save lives. So, if you’re single, make sure you take your medicine. Set an alarm, get yourself a pill box, get a dog, whatever it is you need to do to help yourself remember to take your medicine is key.

And last, I just want to emphasize how important it is for you to talk to us so that we can help you, make sure that you take all your medicine, so that you can live a long, healthy life.

And this concludes my presentation. I’d be happy to take questions.
Lizette Figueroa Rivera:
Thank you so much, Dr. Loren, for your very clear and very informative presentation. It’s now time for the question and answer portion of our program.

Lizette Figueroa Rivera:
We’ll take the first question from our web audience. Doctor, Brian states that his son was successfully treated for non-Hodgkin’s lymphoma about 18 months before being diagnosed with CML. Are there any correlations between the 2 cancers and/or treatments?

Dr. Loren:
So that is a great question and I think just to repeat the question is, if somebody is treated for, in this case non-Hodgkin’s lymphoma, and then subsequently develop CML? So, CML like other forms of blood cancer, particularly the myeloid forms of blood cancer, can be associated with exposure to certain toxins. Radiation, certain chemicals, and certainly radiation and chemotherapy are known risk factors for developing myeloid cancers. And so, it is possible that the treatment that you receive for a first cancer could actually trigger or contribute to the development of CML. So, that is possible, and I absolutely have patients just like that who have been treated for a range of things, Hodgkin’s, prostate cancer, so CML can be a secondary myeloid cancer triggered by exposure to something, say chemotherapy or radiation.

Operator:
Yes, our next question comes from Bob from Connecticut.

Dr. Loren:
Hi, Bob.

Bob:
Hello. Thank you for the excellent presentation. So, for someone who has been on, say, imatinib since it was available or shortly thereafter, and really has had minimal side effects and has had a major molecular response for a long time, but is hesitant to discontinue for all the reasons you mentioned, what are the downsides of continuing if it is not an economic issue as well?
Dr. Loren:
Thank you for that question, that's a great question. To be totally honest with you, and this is my opinion, imatinib has the longest safety record of all of the TKIs and it does seem to have the least risks in terms of long-term toxicity or side effects. And so, in my opinion the risks are minimal. Perhaps cardiovascular, perhaps metabolic, but many of those things can be mitigated by a healthy lifestyle. And, I don't think there's really any known downside at this juncture to continuing. It would be great to answer the question by doing a randomized trial of having some people stay on and other people come off and comparing the outcomes, but it's difficult to imagine that that's a trial that'll ever realistically be completed. And so, in my opinion, if you're having a great response and the medication is tolerable and affordable and it's working, at the risk of sounding very unsophisticated, if it ain't broke don't fix it. And, if you're comfortable, I think that's the right plan.

Lizette Figueroa Rivera:
Thank you. And, the next question comes from the web. Vera asks if young age has any effect on successful cessation.

Dr. Loren:
That's an interesting question and not to my knowledge. The outcomes are much more strongly influenced by the other things we talked about, duration of therapy, depth of response, things like that.

Lizette Figueroa Rivera:
Thank you. And, we'll take the next question from the telephone audience, please.

Operator:
Yes, our next question comes from Daniel from Maryland. Please state your question.

Daniel:
Yes, thanks. My wife was diagnosed fairly early with CML and has been on imatinib and Sprycel® for 6 months or so, just today was told that basically has to be on it for two and a half years. My question gets into the scientific aspect of this. If you get to that .000, that very, you know, positive point in one of your charts, and things are looking very good, are we talking about actually having effect of the DNA of the cells?

Dr. Loren:
Thank you for your question, Bob, that's sort of the million-dollar question I guess in 2018, maybe it's a billion-dollar question. There's no doubt that being on the medication when it's working does eradicate or get rid of that BCR/ABL transcript. So yes, on some level you are affecting the DNA of the cells. And, the question about sort of how long the person needs to be on treatment and so forth I think is still in evolution. As we talked about earlier, at this moment, at least 3 to 5 and probably 8 years is the safest. I know that's hard to consider when you're looking at it from the beginning. I don't think that anyone should be starting a TKI with a specific end date in mind. I think it's an open question as to how long and the field is moving so quickly, maybe we'll learn that there are other things we can add that will shorten those time frames, but I do think that, when I meet my patients, I usually counsel them the expectation is that they should be on it for the foreseeable future.

Lizette Figueroa Rivera:
Thank you. And, we'll take the next question from the web audience. Tom asks, have any differences been found between generic Gleevec® and brand name Gleevec, regarding log reductions and/or maintaining an undetectable BCR/ABL reading?

Dr. Loren:
That's a really important question. And, the answer is there is no answer yet. As of now, the drugs are thought to be equivalent, and there's not been any demonstrated differences. But the generic you may recall has really only been out for I think a little less than 2 years. And so, it's a little soon to know. And, I know that people are looking at this question and we are looking forward to publications on this in the future. But as of now, we don't believe that there's any difference.

Lizette Figueroa Rivera:
Thank you. And, we'll take the next question from the telephone audience, please.

Operator:
Our next question comes from Susan from Pennsylvania. Please state your question.
Susan: 
Yes. I have three. Number one, I’m taking Sprycel and my doctor told me with my disease I have to be on this medication for the rest of my life. There was no time period involved at all. And number two, I do have a lot of hair loss, which has really affected my entire life. I don’t feel good about myself any more. And, number three, I have high cholesterol and I took a cholesterol medication back in October of last year, which gave me very, very bad stomach pains. After I stopped taking the medication, I had horrible stomach pains, which I still have off and on, and it’s been a year, and nobody can help me. So, that’s my question. The hair loss. What do I do about my cholesterol? I still have these stomach pains, it’s been a year. And, I don’t know what to do.

Dr. Loren: 
Okay. These medications can be very frustrating and for all the people who seem to do just fine on it, there’s lots of people who have issues. Hair loss is something that’s not typically seen, it’s not common, but it certainly can happen. But there are lots of reasons why people may lose their hair, including other medical disorders, thyroid disease and so forth. And so, I think there should be an investigation to make sure that there’s nothing else going on before attributing it to this, to the Sprycel. Not that Sprycel can’t do that, but it’s just not usual and we don’t want to have you miss something else.

In terms of your cholesterol and other interacting medications, that can be a very big challenge. Sometimes switching to a different TKI might avert those interactions. Sometimes, we have to accept that perhaps the TKI won’t be as well absorbed or as effective, but as long as it’s effective enough, meaning that the BCR/ABL responses are what you want them to be, I think that’s okay. And so, that’s a conversation that really needs to take place between you and your internist and your oncologist to sort of help prioritize and figure out what the changes need to be to sort out the cholesterol issue. I share your concern, running a very high cholesterol is certainly worrisome and definitely can be a risk to your health.

In terms of the abdominal pain, again I think that probably is something that needs additional attention. Certainly, these medications can upset people’s stomachs, but it’s usually nausea and not so much pain. And, there’s lots of other things that can cause abdominal pain, so I would recommend again talking about this with your internist and also with your oncologist and making sure that there’s no other testing that needs to be done to sort that out.

Lizette Figueroa Rivera: 
Thank you, Doctor. And, the next question from the web, Greg is asking is the use of CAR-T cell therapy a possibility for CML?

Dr. Loren: 
We would love that. That’s a great question. The challenge is that in order for CAR-T cells to be safe and effective, they need to target a protein that’s unique to the cancer cells. And right now, the only apparent option is the BCR/ABL protein itself. There are some technical challenges with making that happen, but there’s a lot of attention to this and all I can say is stay tuned, there’s lots of interest in trying to develop CAR-T cells that target both CML and other myeloid cancers.

Lizette Figueroa Rivera: 
Thank you. And, our last question today, Demetria asks is it safe to get pregnant if you have CML and on Gleevec? What treatment should you take not to harm the baby, if safe to get pregnant?

Dr. Loren: 
I’m glad you asked that question. Unfortunately, it is not safe to be pregnant while taking Gleevec. Gleevec has definitely been described to harm developing fetuses and so it is contraindicated to stay on Gleevec while pregnant. And so, there are a few options for young women who have this illness, who are interested in becoming pregnant. One option is to consider discussing taking one of the very potent TKIs like dasatinib or nilotinib, to try to usher in a deep molecular response more quickly. Those drugs tend to work faster than imatinib and may be able to obtain a response sooner, such that you could then consider coming off of the drug to have a pregnancy, deliver the baby, and then go back on. There are other options that you can talk more about with your oncologist or with a gynecologist, including considering things like egg harvesting and having a gestational carrier. So, your eggs are okay, it’s just the idea that you can’t carry the pregnancy. So, I know that’s a lot to think about and it’s overwhelming, but that could be an option. But, my advice would be to think about trying to obtain as deep of a response as quickly as possible to enable you to consider coming off the drug for a period of time to carry a pregnancy.

Lizette Figueroa Rivera: 
Thank you, Dr. Loren, for your continued dedication to patients.
For those of you who participated in today’s program, we hope the information presented today will assist you and your family in your next steps.

If we weren’t able to get to your question today or want more information, you may speak to an LLS Information Specialist at 1-800-955-4572 from 9 AM to 9 PM Eastern Time or reach us by email at infocenter@LLS.org. Information Specialists are available to answer your questions about treatment, including clinical trials, and answer other questions you may have about support, including financial assistance for treatment.
Again, we’d like to acknowledge and thank Bristol-Myers Squibb, Novartis, and Takeda for support of this program.

Dr. Loren, thank you again for volunteering your time with us today. And, on behalf of The Leukemia & Lymphoma Society, thank you all for joining us.

Goodbye and we wish you well.