***Jorge Cortes, MD***
***September 22, 2015***

**Slide 1: Managing Chronic Myeloid Leukemia**
**Operator:**
Greetings, and welcome to the **Managing Chronic Myeloid Leukemia** telephone and web education program. It is now my pleasure to introduce your moderator, Lizette Figueroa-Rivera.

**Slide 2: Welcome and Introductions**
**Ms. Lizette Figueroa-Rivera:**
Thank you, and hello everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. We are happy to spend time with you today on this year's World CML Day. We have over 450 people participating from across the United States and several countries around the world, including Argentina, Bolivia, Brazil, Canada, El Salvador, Georgia, Mexico, Spain, and the United Kingdom.

Special thanks to Dr. Jorge Cortes for sharing his time and expertise with us today. Before we begin, I'd like to introduce The Leukemia & Lymphoma Society's Executive Research Director, Dr. Yixian Zhang, who will share a few words. Dr. Zhang, please go ahead.

**Dr. Yixian Zhang:**
Thank you, Lizette. I'd like to add my welcome to the patients, caregivers, and healthcare professionals attending the program today. The Leukemia & the Lymphoma Society exists to find cures. It ensures access to treatment for blood cancer patients. Our vision is a world without blood cancer.

For more than 60 years, LLS has helped to pioneer innovation, such as targeted therapy and immunotherapy 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's a cure, LLS will continue to fund promising research from bench to bedside.

In addition, as this program demonstrates, we are the leading source of free blood cancer information, education, and support. And we touch patients in their communities through our 61 chapters across the US and Canada. LLS also acts as a voice for all blood cancer patients. We advocate for patients and survivors and their families, helping them navigate their cancer treatment and ensuring that they have access to quality, affordable, and coordinated care.

**Dr. Yixian Zhang:**
We're very fortunate to have as our presenter today, Dr. Jorge Cortes, one of the nation's leading experts in chronic myeloid leukemia. We appreciate his dedication to supporting our mission and his commitment to caring for patients living with blood cancers. I'd like to thank him for providing us today with important information on CML. Thank you all. And now, I will turn the program back to Lizette.

**Ms. Lizette Figueroa-Rivera:**
Thank you, Dr. Zhang. We would like to acknowledge and thank Novartis Oncology for support of this program.

I am now pleased to introduce Dr. Jorge Cortes, the Jane and John Justin Distinguished Chair in Leukemia Research; Section Chief of AML and CML; Deputy Chairman, Department of Leukemia, the University of Texas, MD Anderson Cancer Center in Houston, Texas. On behalf of The Leukemia & Lymphoma Society, thank you for volunteering your time and expertise. Dr. Cortes, I am now privileged to turn the program over to you.

**Slide 3: What is New in CML in 2015**
**Dr. Jorge Cortes:**
Thank you, Lizette, and thank you everybody for joining. Welcome to this presentation on CML. I think this is a good way we can remember this CML World Day and keep in mind all the work that has been done, and of course, the work that we still have to do. To my fellow Latin Americans, buenas tardes, bienvenidos.

I want to briefly go over what the status is now and our understanding on chronic myeloid leukemia. There's a lot of material that I want to cover, so I'm going to try to do it all within the time we have.

**Slide 4: Cumulative Relative Survival by Time Period and Age - SEER**
Very important, perhaps one of the most important pieces of information that I want to emphasize today, is that the outcome of patients that have chronic myeloid leukemia has improved very significantly over the years. In this slide, you see the expected survival of patients diagnosed with this disease over different time periods. And of course, to the very right, you see the time that represents introduction of the drugs that we generically call tyrosine-kinase inhibitors. These are drugs such as Gleevec®, Tasigna®, Sprycel®, Bosulif®, Iclusig®. All of these block the function of the Philadelphia chromosome. And they have translated into a survival benefit that is very clear.

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Very briefly, let me just explain--because I'm going to show several curves like this--how you read these curves, for those of you who are not that familiar. You start at the very top left with a hundred percent of the patients. And as events happen, the curve drops. In the case of survival, an event is the death of a patient. The higher the curve, the more patients that remain alive at the given times that are marked on the bottom. So, you can see for all the ages, when you compare to the left panels, the survival expected is improving very significantly.

**Slide 5: OS of Imatinib-Treated Patients - EUTOS**
Now, in this other curve, what I'm showing you are results from different settings. And the larger curve represents results from a multi-country analysis in Europe. In the smaller panel to the left you see results from a single institution, my institution, on patients that have been treated in clinical trials. And on the far right you see the results from a statistic from epidemiologic data in the United States.

It is clear that the outcome is improved for all patients in general, but it is also clear that the patients that are in the epidemiologic database are not doing as well as the other groups. There are many reasons why this could be. It could be that these patients may be sicker than some of the other patients. It may be that they are not being included as much in clinical trials. Many other reasons can be expected, but I show these to reflect that there is work to do so that every patient will benefit as much as we have seen with those patients that have been included in clinical trials in Europe or in the United States.

**Slide 6: The CML Journey**
For all of you who are patients or family members, I think it is very clear that what we're going through is a journey through CML. And in this journey there are many steps that we go through. Initially we go through diagnosis, knowing what the disease is, what is the stage of the disease, whether it's chronic, accelerated, or blast phase. And with all of that, we go through the treatment selection. What are we going to do to try to get rid of this disease?

Once we select the treatment, we need to follow the treatment very closely and make sure that the treatment is being carried out as we know is optimal, that we don't miss any doses, etc. Throughout all of this it's very critical, and we're going to be talking about the importance of monitoring, making sure that the disease is responding the way we want it to respond, so that we optimize the outcome.

We also need to remember that some patients might be eligible for treatment discontinuation. And as you can see, the monitoring continues throughout the treatment discontinuation when that is an option. I think it is very important that events like these

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and many others that help the patients understand the disease, understand the goals, understand what the treatments can do, etc. are provided, so that that we all are understanding what we're doing, what we need to do, and how to improve the outcome.

Together with this, we need to look at what other diseases the patient may have that may be a factor on how we treat the disease, what other medications that patient is receiving or should be receiving to manage some side effects, or perhaps other things that are happening that are not related to the leukemia or the treatment for the leukemia. We need to make sure that we're taking the drug exactly as prescribed so that we optimize the possibilities of a good outcome. And this adherence to the prescribed treatment continues even after treatment discontinuation, in this case, adhering to the schedule of monitoring so that we make sure that the disease is not coming back or that we do something if it is. And, of course, a lot of this has to do with recognizing and managing adverse events when they happen. This means that we need to provide a lot of support to our patients so that we can always be there to help them with any issues that they may be facing.

**Slide 7: Predictors of Outcome in CML**
So, when we're talking about the outcome on a patient that has CML, how are they going to be doing long term? I want to emphasize that our goal in CML is not in the short term. We know we can do well many years from now, and we always need to keep sight of the future many years from now. So, to make sure that we have the best chances, we need to consider three important elements: the patients, the characteristics of the patient, their age, their other diseases, etc.; the characteristics of the disease, of the leukemia itself. Is it in the chronic, the accelerated phase? There are different elements that may determine the prognosis or response to treatment. And the management, what treatment are we using? How are we monitoring the patients? How are we managing the adverse events, etc?

And these three elements determine our response to treatment. They determine how likely is it that the patient's going to be alive and well in the long term. And it will determine whether we may have an option to even consider discontinuation at some point or whether we need to do that safely at some point.

**Slide 8: Evolution of Frontline Therapy**
So, the treatment has evolved significantly over many decades from the 1990's when we started using interferon. And it is very important that we remember this because this was the first drug that really started getting us towards the current status of the treatment that we know now. In the year 2000 we introduced imatinib as initial therapy for CML, and that has really changed things. Then we started exploring higher doses of

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imatinib, but then came newer drugs, such as nilotinib and dasatinib that eventually became standard of care also for initial therapy. And at some point we even tried ponatinib as initial therapy. And although it's a very effective drug for subsequent therapy, because of some concerns about arterial thrombotic events, we are not using that as initial therapy. We are using it as salvage therapy.

**Slide 9: Evaluating Response in CML**
Before I give you some idea of the results with these drugs, I want to remind you about the monitoring, because this is very critical that we understand what exactly we're doing and how we're measuring this. When you start treatments for CML, and the white blood cell count's high, the spleen may be enlarged, there's many symptoms, etc. When you start treatment and you control the white cell count and maybe the platelet count and the spleen and all these things, you get what we call a hematological response.

That is important, but it is not the goal of therapy. We know that we need to get much better at that because when we only get a hematologic response, there's a lot of leukemia still left in the body. Fortunately, we've gotten better with treatment and we can get cytogenetic responses. Interferon was the first that introduced a cytogenetic response, meaning we do a bone marrow, we count the chromosomes in cells in the bone marrow. Sometimes we can do that in the blood with FISH. And if we don't see the Philadelphia chromosome, then we call that a cytogenetic response. That's a deeper response.

But, even when you get there, you see where the orange area ends, there still a lot of disease left behind. Fortunately, we have even better treatments now and better tools to monitor the response, where we can go to what we call molecular responses using a test that's called a PCR. And that allows us to look even deeper to see if there is any more disease detectible once we don't find the Philadelphia chromosome. And we go to what we call three logarithms. That's something that we call a major molecular response, and MR4, which is four logarithms, and MR4.5.

And then we get to undetectable. Now, we need to recognize that there is a limit of detection of these tests. Even when we call it undetectable, there could be some disease that's just too little to detect with our current tests. But, at least for the moment, this is as far as we can go. This is the most powerful test that we have for the moment.

**Slide 10: What Do We Get?**
Now, what does it give us to get one of these responses? A hematologic response is usually associated with improved symptoms, but that's the main thing that we can expect. The complete cytogenetic response is very important because that is the one

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response that is associated with an improved survival, an improved probability of being alive in many years from now.

Major molecular response, the next level of a deeper response, it decreases the chances of the disease coming back. It doesn't improve any more the survival, the probability of being alive, but it improves the probability of the disease not coming back. And then what people call complete molecular response or PCR undetectable that makes us consider the possibility of treatment discontinuations, something that we need to do very carefully. And in clinical trials at the moment, it's not standard. But, it starts opening that conversation.

**Slide 11: TKI Frontline Therapy in CML: CCyR AT Time Periods (ITT)**
This is a summary of the results that we get with the different modalities that have been explored through the years. Each bar represents the percentage of patients who achieve a given response. In this slide I'm showing you complete cytogenetic response. As you can see with the blue bar, that's the treatment with the imatinib. And you see how fewer patients achieve a complete cytogenetic response at a given time, although eventually over time it catches up with the other modalities.

**Slide 12: TKI Frontline Therapy in CML: MR4.5 AT Time Periods (ITT)**
Of course, when you use dasatinib or nilotinib, the responses happen a lot faster, and they remain very high throughout the treatment. And if we look at the deeper responses, what I call the MR4.5, that means 4.5 logarithms' reduction in the amount of disease, you see how that blue, the imatinib, the standard dose, you still get some patients with this response, although you'll get more with dasatinib and nilotinib.

**Slide 13: TKI Frontline Therapy in CML: Long-Term Outcome by Response Time**
Now, what does this mean in terms of event-free survival? That means being alive and free of losing response. You see that when you use dasatinib and nilotinib, which are the gold and the green curves, or even when you use imatinib at the higher dose, you get a better chance of being alive and well many years out compared to the imatinib at the standard dose. You also have a lower probability of progressing to the accelerated or the blast phase, as you see on the right side of this graphic.

**Slide 14: TKI Frontline Therapy in CML: Long-Term Outcome by Response Time**
But, as you see on the right side of this graphic, it really doesn't improve the survival that much. And that is because the survival with imatinib is already fortunately very good. Again, you can improve the chances of the disease coming back or going to the blast phase, but already patients treated with imatinib live very well, which is very good

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because we know many patients are being treated, will continue to be treated, and they can be treated very well with imatinib if we do it the right way.

**Slide 15: DASISION – The Final Report**
There have been studies that actually compare head-to-head these different treatment options. For example, these studies compared patients that were treated with dasatinib versus imatinib. They were at random assigned to receive one or the other. This started many years ago. And what we found is that with dasatinib you get more patients to respond, the responses are deeper, the responses are faster, and fewer patients transform to the accelerated or the blast phase. So, all of this is very good. Again, there was no difference in survival or at least there hasn't been any difference in survival after the five years that we've followed these patients.

**Slide 16: ENESTnd – The 6-Year Report**
The same thing can be said with nilotinib. More patients treated with nilotinib responded. Their responses were deeper, they were faster, fewer patients progressed to the accelerated and blast phase. But, again, there's no significant difference in survival. Here I show you that there are two different doses of nilotinib that we've tested. And the 600 milligrams, which is given in a split dose--300 twice a day--is a standard dose for the initial therapy of CML.

**Slide 17: Molecular Response at 3 Months by Therapy**
One of the important things we've known for many years, but little by little has been catching more attention, is the importance of an early response. This is taking data from the studies that I showed you, and it's probably easier to just look at the summary on the top. We know that the patients that are treated with imatinib, about a third of them will not have the best response that we want, which is having less than 10% on the PCR on the international scale.

When we use the newer drugs, dasatinib and nilotinib, there's also studies with bosutinib, but bosutinib is not approved at the moment for initial therapy. But they all showed that between 10 and 15% of patients do not get that great response. So, the number of patients that don't get the early response that we want decreases about by half or a little bit more when you use these newer drugs.

**Slide 18: OS and EFS by 3-Month Response in DASISION and ENESTnd**
This is a complicated slide, but in on the left I'm showing you what difference does it make to be lower or higher in this PCR at three months. So, the hatched areas, the bars, are the patients that have more than 10% at three months. And as you can see, their survival is around 80% in the long term. Whereas, for the other patients it's about

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95% for the patients who get lower levels of the PCR. The event-free survival, that's the survival without the recurrence of the disease, is about 75 versus about 92 to 93%. So, better outcome for the patient that tends to get a better response.

**Slide 19: What Do I Do With the Slow Responder?**
Now, what does this all mean? So, if I summarize all of these and talking only about what we call event-free survival, survival without the disease coming back, these are the green areas, the good. One important thing to remember is that even for the patients that have more than 10%, the majority are going to do well. So, this is very, very important to remember. Still 75% of patients are going to do well.

When we talk about these and we discuss with our patients about what do we do, we always have to ask ourselves, do we need to change therapy to all of these patients, because most of them, three-fourths of them are still going to do well.

**Slide 20: What Do I Do With the Slow Responder? (cont)**
Or should we do something to try to identify those 25% in red, which are really the ones that need help; and to that matter, also, the 7% of the patients who respond early.

One of our challenges now is to try to determine what else is needed. Certainly a slow response is one factor, but there's something else that we're still trying to understand that identifies those 25% of patients who are not going to do as well as we would like them to do in the long term.

**Slide 21: What Is the Dog Doing?**
And part of the reason why this is difficult is because when we look at just one time point, which is the three month mark, it's like looking at this picture. And some of you may recognize this, a painting by Goya, the Spanish painter. And if I ask you what is the dog doing, some of you may say, "Well, the dog is coming out from behind the hill." Others may see this as a dog that's sinking under sand or something. And others may think that the dog is just there standing, just looking at us. And the reason why we don't know is because it's just one time point. We don't have any follow-up. We don't know the sequence of events in this case.

**Slide 22: Early Response to TKI: 3 Months or 6 Months?**
One of the things that we can do to try to better understand what's happening with the patient is to check again three months later. So, not only at three months, but then we check again in six months. And when we do that, we see that some of the patients are going to catch up. By six months they've gotten to that low level that we wanted. And those patients actually do as well as the patients who did well at three months.

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The patients that still at six months don't catch up, those patients are going to have a little bit worse outcome. So, you look again, for example, at the event-free survival, which is what I've been emphasizing, and you see that two-thirds of these patients are going to be alive and well. So, now it goes down to 66%. Now you could still say the majority of patients are going to do well. But, now we have a few more that are not doing well. So, at least having two time points probably helps us differentiate that better.

**Slide 23: Effect of Reduced Dosing on 3 Month PCR by Total Dose and Number of Missed Days**
Another important thing is what has happened before the three months. We know very well patients who have not taken 100% of the dose because they've had dose reductions or something, or the patients that have missed some doses, are much less likely, then, to have a good response at three months. So, it is very important to minimize interruptions, missing doses, dose reductions, whenever possible so that we try to get the best response possible as early as three months.

**Slide 24: TIDEL II – Outcome by EMR**
We've tried to change therapies, increase the doses or change to another drug for the patients who are lagging behind in this study, for example, that were more than 10%. And about 60% of the patients will improve their levels if we do some changes. But, other studies have also told us that if you just continue what you're doing, you may get the same 60% of patients who improve. So, it's not clear yet what we should do.

**Slide 25: TKI Frontline Therapy in CML: Treatment Discontinuation**
Now, on the other end another thing that we have is that in these studies where we've compared the new drugs to imatinib, we see that about 40% of patients have discontinued their therapy, even with the new drugs. They're more potent; they're supposed to be safer. And yet, 40% of patients have discontinued their therapy.

**Slide 26: Factors Influencing Early Discontinuation of 2nd Generation TKI**
And so, the question is, why are we discontinuing therapy? And I think sometimes we're discontinuing therapy perhaps a little too soon. And I think there are definitely some patients that have a lot of side effects and we need to seriously consider changes. Others who are not responding as well, but these are few. But some are having that.

But, I think that one of the problems that we are seeing is that sometimes because we have many treatment options, we tend to jump from one drug to another very quickly without giving it proper treatment, without properly managing side effects, without properly adjusting and managing what we need to do to give each drug the proper

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chance to work and each patient to have an opportunity to adjust to each one of these drugs. So, this is something that has to be carefully discussed between the patient and the doctor to make sure that each drug has the right chance to work.

**Slide 27: When Do I Change Therapy?**
I usually change therapy when patients meet definitions that we have established of what's called a true failure of the drug. Certainly if a patient loses the chromosome response, I change therapy. If the patient has true intolerance, not just some side effects, because many side effects can be managed, and also we need to be aware that all the drugs unfortunately may have side effects, so we need to manage them first. But, I don't change therapy when there's just a small increase in the PCR, when just because the PCR is still detectable, or in the first instance of most adverse events, because many of them can be managed properly.

**Slide 28: Molecular Response in CML: MR Rates at 36 Months (CCyR patients)**
Now, we talked about the possibility of treatment discontinuation, and we talk about that when the PCR becomes zero, becomes undetectable. This happens in about a third to 50% of the patients treated especially with dasatinib or nilotinib or with high doses of imatinib. It's about half of the patients that are treated with imatinib 400 as you see on the left, that pie that you see on the slide.

**Slide 29: Cumulative Rates of MR4.5 with Imatinib, Dasatinib and Nilotinib**
And in the two studies that I mentioned, randomized between dasatinib and imatinib or nilotinib and imatinib, you see how it reaches about 40 to 50% with dasatinib and nilotinib, respectively. So, that's about where we are getting, let's say, about half of the patients can become undetectable. So, importantly, not everybody becomes undetectable.

**Slide 30: Factors Associated with Sustained Undetectable PCR**
What are the factors that predict for this? Well, we've identified that older patients, interesting enough, tend to have a better chance of getting there. And we've seen that the younger patients, perhaps because they tend to miss more doses, etc., they don't have as much of a chance. Also, patients that take dasatinib, nilotinib, or at least high-dose imatinib have a better chance. And as mentioned, the patients with an early response tend to have a better chance of being undetectable. So, that's very important to keep in mind.

**Slide 31: Adherence to Imatinib**
We also know that patients that miss 10% of their doses or more, essentially none of them get to be completely undetectable. Now, if you think about it, 10% of the doses in

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a month is missing three doses. Three out of 30 days means 3 doses. So, it doesn't take too many doses missed to decrease the chances of getting to these deeper responses. So, it is very important to understand why this is happening. Is it because of some side effects that we should manage, etc?

**Slide 32: Relative Survival with TKI by Response to Therapy**
Now, why is it important to get to these deeper responses? One is our patients are living longer if they get to these deeper responses. This curve is showing what the life expectancy is of a patient with CML compared to what it would be for patients their own age, their own gender, if they did not have the leukemia. And as you can see, it's really almost 100% as soon as you get to the complete cytogenetic response. It's 97% if you just get a complete cytogenetic response. So, it's almost 100%, meaning we know that patients nowadays, especially if they get to complete cytogenetic response, are going to live essentially what everybody else their own age and their own gender would live. The deeper responses really don't affect that too much.

**Slide 33: Imatinib Treatment Discontinuation: STIM1 and STIM2**
Now, I mentioned earlier the main issue with these deeper responses being undetectable is the possibility of treatment discontinuation. There have been several studies. I'm showing you two of them here that suggest that patients that get to be very good responses and they kept it for some time, if you stop therapy, in about 40% of them the disease will not come back. It will not be detectable again, at least with the five years or so that we've followed the patients.

**Slide 34: Loss of MMR as Trigger to Restart TKI**
Now, on this graphic, one of the arguments right now is deciding what do we call a return of the disease? Whether a patient that was completely negative in the PCR and then it becomes positive, is that a relapse, a recurrence of the disease? Or should we wait until it goes above the level of the MMR, the major molecular response, to call it a relapse?

That's important, and it's most important for patients to understand and to ask the patients, because some patients would not feel comfortable when the PCR becomes positive again, even if they know that things are stable. But, they may not feel comfortable with just knowing that the PCR, of course, detects leukemia. So, there's a little bit of leukemia that we can detect. So, that's important to always discuss with your doctors.

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**Slide 35: Minimum Requirements for TKI Treatment Discontinuation**

Very important is that there are minimal requirements to consider treatment discontinuation. The patient has to have a very deep response, at least what we call an MR4.5. Stopping before that is not appropriate. It has to be sustained, detected for at least two years in a row, and ideally five years in a row, because that means a much lower risk of the disease coming back.

If a patient stops, they have to be monitored very closely every month for at least six months, then every two months for another six months, then every two months for a year, and then, maybe after that, every six months. And you always want to be continually monitored, even if you're not getting treatment, just to make sure that if the disease came back, you find it when it's just a little bit and not when it becomes a big problem. And then you resume therapy if it comes back. Again, we need to define what do we call a relapse? How comfortable do we feel with a little bit of disease detectible versus prefer not to have any disease detectible?

**Slide 36: EURO-SKI - Adverse Events after TKI *Withdrawal* (n=200)**

This is a complicated slide, but it's also important to remember that when patients stop treatment they may have some symptoms. Some patients have complained of kind of like flu-like symptoms, some achiness and joint pain, some bone pains and things like that. Even other things like fatigue and weight loss, etc. And another thing to keep in mind is that some of the symptoms that the patient may have been experiencing while on treatment may not go away. Fatigue is a common one. We need to remember that we get fatigue from just activities of daily life: work, family, stress, traffic, etc. So, not all goes away when you stop treatment because it may not be related to the treatment. So, we need to make sure that we continue paying attention to all the medical problems after treatment discontinuation.

**Slide 37: 2nd Generation TKI in CML CP Post-Imatinib Resistance**

Very briefly, I want to remind you that there's very good treatment for patients who have gone through imatinib and need additional therapy. There are three drugs that we call second generation: dasatinib, nilotinib, and bosutinib. At least half of the patients will respond to these drugs.

**Slide 38: 2nd Generation TKI in CML CP Post-Imatinib Failure**

They all have different side effects, so it's very important to try to match what we think would be more problematic for a given patient, depending on their age and their other medical history, etc., and try to match that best with what we can expect from the different drugs, and see not only what side effects are more common but also what side effects are more serious.

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**Slide 39: Response to Bosutinib 3rd Line Therapy**

Third line, so patients who have gone through two drugs, there're studies looking at bosutinib or Bosulif. About 40% of patients will respond if they've gone through imatinib and either dasatinib or nilotinib.

**Slide 40: Ponatinib Phase 2 Study: Responses to Therapy**

And also ponatinib, which is a very effective drug, very potent and it has a very high response rate. Sixty percent of patients who have received two or three or more prior drugs will respond do ponatinib. And these responses are very durable.

**Slide 41: Arterial Thrombotic Events with TKI**

Now, with ponatinib, we've started becoming more aware of the fact that some patients may have some arterial thrombotic events. These are events such as heart attacks, angina, strokes, occlusion of the arteries in the legs. And it happens to some extent with all of them. Of course, these things happen even in patients that do not have CML. So, we consider that perhaps what we see with imatinib is about what you would expect in the general population. But, some of these drugs may have a slightly higher risk. We've seen it with ponatinib, we've seen it with nilotinib. We've seen it to some extent with dasatinib.

One of the important things is that patients that have risk factors, diabetes, hypertension, high cholesterol, those are the patients with the highest risk. And it is very important that those issues are managed properly, as we manage the leukemia, so that we keep these risks as low as possible.

**Slide 42: Renal Dysfunction with TKI**

We also need to keep an eye on other organs. For example, sometimes the function of the kidney, which is what this graphic shows. You see in red it goes down some, not too much. It's very rare that a patient goes into renal failure or kidney failure, but it can drop a little bit, particularly with imatinib. So, we need to keep an eye on all of these.

**Slide 43: Simultaneous Binding of Two Inhibitors to BCR-ABL**

There are new drugs that are emerging. This is a new drug called ABL001. It's a drug that binds in a completely different area of the protein that comes from the Philadelphia chromosome. So, in the laboratory, we've seen that the mutations that affect the other drugs are not affected by this drug. And that is very welcome. So, studies are already ongoing in our institution and many others.

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**Slide 44: What Am I Doing to Make Treatment Discontinuation More Palatable?**

And we're also looking at adding other drugs in some patients that are doing well but they're not quite completely undetectable, to see if we can push that little last piece of the disease out so that they could eventually perhaps consider discontinuation.

**Slide 45: Eltrombopag for TKI-Associated Thrombocytopenia**

There are also drugs that we're investigating for managing side effects. For example, low platelets are a common problem for some patients. And we were adding this drug called eltrombopag, which is a drug that's approved for other reasons for low platelets. And it's been working well in that setting. We're exploring that in patients with CML that have low platelets because of a treatment with these tyrosine-kinase inhibitors.

**Slide 46: Monitoring Patterns in a Community Setting in the US**

The final thing that I want to mention is that, unfortunately, we have data like what I'm showing you on this slide of how often patients are being monitored in the United States. And you see at the very bottom here that at every time point when we recommend that patients are monitored, at least 60% of patients are not being monitored. And I think that that's one of the problems that we see.

**Slide 47: Overall Survival and Progression-Free Survival of CML Patients in Chronic Phase Treated with First-line TKI**

And you see in these graphics how the patients that are not being monitored as recommended, which are in the green curve, they have a worse outcome. Why? Because we don't recognize things early enough to be able to act on them. So, this emphasizes the importance of monitoring. Not monitoring would be something like driving your car without looking at the gas marker in your car, and you're just trying to guess when you're going to run out of gas. Maybe you know your car good enough, but it is likely that at some point you will probably run into trouble.

**Slide 48: Predictors of Outcome in CML**

So, to finalize, I was showing you how there is a connection between the patient characteristics, the disease characteristics, and the management; how they determine the responses, the survival endpoints, and the discontinuation. There's nothing we can do about the patient. You know, your age is your age, your gender is your gender, etc. There's nothing we can do about the disease. You know, how it comes is how it comes. But there is something we can do about the management, doing proper monitoring, taking the drug properly, optimizing the dose, etc. And with that, we know that we're going to improve the chances of good responses, good endpoints, and improve our chances of discontinuation.

***Jorge Cortes, MD***
***September 22, 2015***

**Dr. Jorge Cortes:**
**Slide 49: "If I seem unduly clear to you, you must have misunderstood what I said."**
So, I'm going to conclude with this, with a phrase from Alan Greenspan who was the Chair of the Federal Bank in the United States. So, "If I seem unduly clear to you, you must have misunderstood what I said."

**Slide 50: See you in NY – November 1st, 2015**
And I also want to say good-bye, telling you that I am going to be running in New York, on November first, in the New York Marathon to raise funds for The Leukemia & Lymphoma Society. So, if you're going to be there, just wave to me and try to encourage me to finish the race.

**Slide 51: Questions?**
So, I'm going to stop here. Thank you for your attention.

**Slide 52: Question & Answer Session**
**Ms. Lizette Figueroa-Rivera:**
Thank you so much, Dr. Cortes, for your very clear and informative presentation. And we look forward to cheering you on as well as all of our *Team in Training* participants at this year's New York City Marathon.

It is now time for our question and answer portion of our program. We'll take the first question from our web audience, please. Doctor, Elizabeth asks, "I was diagnosed with CML through PCR only. It has always weighed heavily on my mind that my provider did not feel a bone marrow biopsy was necessary. What benefits or risks would having or not having a bone marrow biopsy hold?"

**Dr. Jorge Cortes:**
The issue of doing a bone marrow is an important consideration. In my opinion, you can definitely make the diagnosis of CML only in the blood. You, however, cannot 100% stage the disease without doing a bone marrow aspiration. You can get a good idea, but the blast or the basophils could be a little higher in the bone marrow. Sometimes we find additional chromosomal changes that determine a different stage. And, of course, that is something that needs to be followed.

So, generally speaking, although, again, you can make the diagnosis for sure in the peripheral blood, at diagnosis I think a bone marrow aspiration does provide additional information that can be valuable for staging, for follow-up, etc. Even if your bone marrow is during the treatment to confirm a few other things, sometimes chromosomal

**Dr. Jorge Cortes:**
changes happen in other chromosomes. And that is important to know. It happens in about 10 to 15% of the patients. So, although we are doing a lot less bone marrows than we did in the past, a few of them are still useful.

**Ms. Lizette Figueroa-Rivera:**
Thank you, Doctor. And thank you, Elizabeth, for the question. We'll take the next question from the telephone audience, please.

**Operator:**
Our question comes from Michael calling from Illinois. Please state your question.

**Mr. Michael:**
Doctor, I'm a caregiver. My husband was diagnosed 15 months ago with CML, and he is undetectable. However, he experiences significant fatigue as a side effect from the Gleevec. Is there anything that can be done for the fatigue?

**Dr. Jorge Cortes:**
Well, fatigue is a difficult symptom. And so, I thank you for that question because it is something that's very, very common. And there are different considerations about the fatigue. Number one, there's cancer-related fatigue. We know that. And there's been many studies trying to look at adding drugs that manage the fatigue. And there's been only one study in CML, and the results have not been very conclusive.

Number two, patients in this case, for example, you mentioned he has a good response. So, you wouldn't expect that this is cancer-related fatigue. The question is, is it the drug? And I think the drugs are associated with some fatigue. But also, as I mentioned, when you suspect that the drug is causing that, particularly in somebody who has a very good response, sometimes we consider things like adjusting the doses a little bit. I am a little bit less concerned about lowering the dose in a patient who already has a very good response. I think that gives you a little more freedom to maneuver with the doses.

Now as I mentioned earlier, when we've done treatment discontinuations studies where we find out if sometimes you stop the treatment all together and the fatigue doesn't go away or at least not altogether, what happens is that fatigue tends to be a multifactorial thing, meaning there are many things that contribute to the fatigue. The drug may be one of them.

But there may be other things, if there are other diseases. I don't know, diabetes or heart conditions or something like that or even just the daily life activities, etc. So, some of the fatigue may be related. Some of the fatigue may not be related. So, it's important

**Dr. Jorge Cortes:**
to look at all these other factors. Look at the thyroid. Look at all these factors and manage them as well just to minimize the input.

**Ms. Lizette Figueroa-Rivera:**
Thank you so much for the question. We've had many questions surrounding fatigue and CML. The next question, Doctor, is from our web audience. Jack asks, "What happens if my PCR is not standardized, that the labs have not utilized the international scale?"

**Dr. Jorge Cortes:**
Well that's, unfortunately, still a common problem because the standardization is still an ongoing process. The way we do the standardization is perhaps not the optimal way. It's a great one because at least it's provided some reference, but it's not optimal. So, we still have a lot of labs that don't have standardization.

And we need to keep in mind that there are two important elements for a lab. One is that it's standardized, and the second one is that it has enough experience and quality controls that the results could be reproducible. So, if your lab is a reputable lab that does a lot of these tests and whatever, and it's always monitoring you in the same lab, then at least you have the reference of what's happening with that PCR from one measurement to the next one.

So, at least that gives you some reference. Of course, you cannot extrapolate that to, for example, when we talk about the 10%. That's with the international scale. So, you wouldn't be able to tell what the results in that lab would mean in terms of that 10%. But you would be able to tell how that is dropping, again if there is that quality control, etc. So, though it is ideal that the labs are standardized and that the results are reported international scale or at least translated into the international scale, we know that's not the reality for everybody.

Then what is important is that the lab is a good quality lab that has a lot of experience with the test, and two, that then you do your testing always in the same lab so that you can tell with the same methodology, with the same scale, how the disease is evolving.

**Ms. Lizette Figueroa-Rivera:**
Thank you, Jack, for the question. And the next question comes from the telephone audience, please.

**Operator:**
Our next question comes from Gary calling from Ohio. Please state your question.

**Gary:**
Thank you very much, Dr. Cortes. Awesome. I'm a five and a half year survivor of CML. I had a Gleevec failure six months into my treatment, switched to Tasigna at 800 milligrams five years ago; been on full dose since. Four of my last six PCRs have been non-detectable. Each time my doctor and I wanted to lower my dose to 600, I have a little blimp. So, we're at that crossroads whether or not to lower from 800 to 600. As I say, four of the last six PCRs were non-detectable. Any suggestions on lowering dose?

**Dr. Jorge Cortes:**
The communication here came with a little bit of an echo. But, if I understand correctly that the PCRs have been negative, and the question is whether there is an option to decrease the dose from 800 to 600. Is that correct?

**Gary:**
Yes, sir. Five years on Tasigna 800 milligrams, yes, sir.

**Dr. Jorge Cortes:**
So, I think that my approach to the treatment is I do not lower the dose for the sake of lowering the dose if there's no need for that. Just because if something is working well, I don't need to lower it. But, there are many times when you do have side effects or issues that make you consider the possibility of lowering the dose. And evidently, when there's a patient that has a very good response, I feel like there's a little bit more freedom to work with the dose, as I mentioned to one of the other questions earlier, where it's likely that you can maintain a good response with a lower dose.

Sometimes what can be considered is, if you're going to lower the dose and there are concerns whether that would be still a good dose, maybe do another PCR a little bit more frequent than you would otherwise if you stayed at the same dose, just to decrease the risk of missing something or at least to keep everybody with peace of mind that you're not going to lose any ground. So, that is something that can be done. Sometimes, you know, if I'm doing on a six-month routine, I may recommend to my patients to do it at the three months this time just to see that that didn't cause any bleeps on the PCR.

**Ms. Lizette Figueroa-Rivera:**
Thank you so much for the question. And we'll take the next question from the web audience. Pamela asks, "Dr. Cortes, did I understand you to say in your presentation that you recommend that a patient take a 600 milligram dose of imatinib in two 300 milligram doses daily rather than taking 600 milligrams together at one time daily? Thank you."

**Dr. Jorge Cortes:**
Well, I don't think I addressed that, but that's a good question. First of all, I want to clarify something. I made reference to high-dose imatinib many times during my presentation. But, I want to clarify that starting at a higher dose, 600 or 800, which is what we were using in these studies, is not standard therapy. It would still be considered investigational. The standard is 400 once a day.

Now when we were using higher doses, we were splitting the doses into two doses. Like, we were doing 800, we would do 400 twice a day; or 600, 300 twice a day. But, that came initially because we only had 100 milligram pills, and it was hard for patients to take eight pills at a time. I think that I still prefer to do it twice, split it in two because what my patients have told me is that it tends to be a little easier on their stomach to split it, and there's no negative effect of splitting it. But, for a patient who prefers to take it once, just once, take it all together at once, it can be done. So, there's no contraindication to do it one way or another.

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

**Operator:**
Thank you. Our next question comes from Kimberly calling from California. Please state your question.

**Kimberly:**
Yes, hi Kimberly. I went off my dasatinib in the middle of May just due to so many side effects. I've been on it seven years. My last PCR in July showed that it had accelerated one cell for every 100. For about a month, I felt really, you know, pretty good. I have an appointment with my oncologist on Wednesday to do another PCR. I still have the fatigue, the bloody arms, the muscle weakness, the headaches, the joint pain, without it, the same as when I was on dasatinib. Is that normal? And if my cells do double when I see him this time with the PCR, would you recommend I go back on dasatinib?

**Dr. Jorge Cortes:**
Okay. So, there are two elements of this question. Number one, the symptoms, and the question was, "Are these normal?" And they are. They're common. And I was referring to that some during my presentation. It is very common that we see that as patients come off the therapy, some or sometimes all of the symptoms remain.

***Jorge Cortes, MD***
***September 22, 2015***

**Dr. Jorge Cortes:**
And we need to keep in mind that whenever we get symptoms of some type as we're taking a medication, it doesn't necessarily mean that they are caused by the medication. So, the fatigue and aches and pains and things like that, they could be related to something else. And of course, when we have a serious disease like a leukemia and we're taking a serious drug like any of these that's, you know, they're not chemotherapy, but we obviously understand them as being very important drugs, we become more aware of our symptoms, which is a good thing.

We want to be mindful of what's happening to our bodies, but they may not be related to the drugs. So, I think it is important to find out if there are other reasons that could be causing some of these symptoms. And they probably were not related to the dasatinib or at least the dasatinib was just part of the contributing factors to the disease.

The second part of the question is what to do if the PCR is going up. And now this is, from the way you describe it, it's one of those examples where it's not in an international scale, so it's a little bit difficult to relate to what's being presented in the studies, where part of the controversy is do you restart treatment when it becomes positive again or when it gets to losing a major molecular response?

And I think that this is something that has to be a conversation between our comfort level and of the patient, meaning do I feel comfortable now that I find that the leukemia is there, very little, but it is there. Do I feel comfortable with that, or do I prefer to start treatment and get it back to where I don't see the disease anymore?

So, that is something that the patient has to think about and then discuss with their doctor to see when they do feel more comfortable. This whole issue of treatment discontinuation is a very personal decision. Not everybody wants to discontinue therapy. Many of my patients who meet the criteria don't want to discontinue therapy, and I think that's perfectly okay.

The patients who want to discontinue therapy, that's perfectly okay, as long as we do it the right way. Same thing, when to restart the patients who want to start as soon as it becomes positive. That's fine. The patients who want to ride it a little more and see what happens with when it's just a very little disease. That is also fine. As long as you do it properly and monitor it very closely. My job is to guide them with one or the other.

**Ms. Lizette Figueroa-Rivera:**
Thank you, Doctor. And we'll take our last question from the web audience. Janice asks, "What information is available regarding children and teens with CML, long-term prognosis on the oral meds, and potential resistance to the oral medications after being on them for so many years?"

**Dr. Jorge Cortes:**
The main things that we know about children and adolescents and even young adults are one, for children, children that are very young and still growing, we know that they end up not growing perhaps to their full height. So, they end up being a little shorter than you would have expected. So, it affects their growth. Not the development, you know, their maturation is normal. Their brain is normal. Their intellect is normal. Everything, all their abilities and their capacities and their muscle development, everything's normal. It's just the height, as far as we know, that is affected some. It's not major, but it is some. So, that is number one.

In terms of long term effects, to date we have not identified any other problems with this. Now of course, keep in mind the first patient with imatinib, which was the first one of these drugs, was treated in 1998. So, we're not quite there at 20 years. And for a 15-year old, 20 years, they're only 35. That's nothing. You want them to be 85 or 95, not just 35.

So, we obviously need to continue following the patients that we started treating 20 years ago and continue doing studies so that we understand these questions with even longer follow-up, but so far, nothing that we can identify that's bad. We did identify that the adolescents and young adults have a somewhat worse prognosis. They don't get as good a response, and they do have a little bit more risk of transformation.

But, it appears to be an issue of adherence to the treatment. They tend to miss more doses and not take the drugs as well and all that. I think that for the younger patients it's a little bit more difficult sometimes to remember to take the drugs. I think as we get older, we get a little bit more conscious about our health and the need of watching our cholesterol and watching our weight and watching all these things, that when we're young we probably don't see that as an immediate threat, especially when they're feeling okay.

So, that is something that we just need to keep working on with the younger patients. But no real negative impact on the drugs themselves that we can tell with the follow-up that we have.

**Ms. Lizette Figueroa-Rivera:**
Well, thank you so much, Dr. Cortes, for your continued dedication to CML patients. You and your colleagues' research successes have really made a positive impact on people's lives. And we hope this information will assist you and your family in your next steps.

**Slide 53: Resources to Make Informed Treatment Decisions**
If we were not able to get to your question today, please call The Leukemia & Lymphoma Society's Information Specialists at 1-800-955-4572 from 9:00 AM to 9:00 PM Eastern Time, or reach them by email at infocenter@LLS.org. Information Specialists are available to answer your questions about treatment, including clinical trials, or answer other questions that you may have about support including financial assistance for treatment.

LLS can now assist CML patients in paying for their PCR tests. No cost is too small. Patients who are insured or uninsured may apply. Please visit www.LLS.org/PCR or call toll-free 877-614-9242 for more information.

Dr. Cortes, thank you again for volunteering your time with us today. On behalf of The Leukemia & Lymphoma Society, thank you all for joining us for this program. Goodbye and we wish you well.