

Update on Chronic Myeloid Leukemia

February 3, 2015

Speaker: Harry P. Erba, MD, PhD

Slide 1. Welcome & Introductions

OPERATOR:

Greetings and welcome to the *Update on Chronic Myeloid Leukemia* telephone and web education program.

It is now my pleasure to introduce your moderator, Lizette Figueroa Rivera. Thank you Ms. Figueroa Rivera. You may begin.

LIZETTE FIGUEROA RIVERA:

Thank you. Hello, everyone. On behalf of The Leukemia & Lymphoma Society (LLS), a warm welcome to all of you.

Special thanks to Dr. Harry P. Erba for sharing his time and expertise with us today.

Before we begin, I'd like to introduce The Leukemia & Lymphoma Society's President and CEO, Dr. Louis DeGennaro, who will share a few words. Dr. Lou, please go ahead.

DR. LOUIS DEGENNARO:

Thank you very much, Lizette. I'd like to add my welcome to the patients, caregivers and healthcare professionals attending the program today.

The Leukemia & Lymphoma Society exists to find cures and to ensure access to treatment for blood cancer patients. Our vision is a world without blood cancers.

For more than 60 years LLS has helped pioneer innovation such as targeted therapies and immunotherapies that have improved survival rates and the quality of life of 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.

In addition, as today's program demonstrates, we are the leading source of free blood cancer information, education and support, and we touch patients personally in their communities through our 58 chapters across the U.S. and Canada.

LLS also acts as the voice for all cancer patients. We advocate for patients and survivors and their families, helping them navigate their cancer treatments, and ensure that they have access to quality, affordable and coordinated care.

Today we're incredibly fortunate to have as our presenter Dr. Harry Erba, one of the nation's leading experts in CML. 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 with this very important update on CML.

Good day to you all and I'll now turn the program back to Lizette.

LIZETTE FIGUEROA RIVERA:

Thank you, Dr. Lou.

We would like to acknowledge and thank Novartis Oncology for support of this program.

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Slide 2. Update on Chronic Myeloid Leukemia

LIZETTE FIGUEROA-RIVERA:

I am now pleased to introduce Dr. Harry P. Erba, Professor of Internal Medicine and Director of the Hematologic Malignancy Program at the University of Alabama at Birmingham in Birmingham, Alabama.

Dr. Erba, I am now privileged to turn the program over to you.

DR. HARRY ERBA:

Thank you very much and welcome to everybody. It's afternoon down here in Alabama.

I'm actually very honored to be asked to give this talk. And to be sharing this information with people from – sounds like all over the world. I hope you think I do a good job so you can ask LLS to invite me back because I'd be honored to speak to you on other topics that are important to people who are living with blood cancers.

But today I'm going to really focus on the diagnosis and treatment of chronic myeloid leukemia.

Slide 3. CML: Epidemiology and Etiology

In the United States there are about 5,000 people who are diagnosed annually with the disease, so it accounts for only about 5% of all leukemias. What's interesting, however, is that the prevalence – that's the incidence – the prevalence are the number of people living with this disease now, and that's continuously going up because the majority of people diagnosed with chronic myeloid leukemia are now living for many years with the disease, as we will see in some subsequent slides.

The other thing I want to point out and I'll make comments about as we go along, is if you look at registry data, so data regarding this diagnosis and some demographics about people, the average or median age is around the mid-60s to upper-60s. And yet some of the studies upon which we actually base our treatment decisions, have been done in people who have an average age of 15 to 20 years younger than this average age. And as we go along, I'm going to point out the reasons why this is important.

So it's always important for an oncologist when we see published data, to realize that the patient population treated in those studies may not completely reflect the patient population that we're seeing in our clinics.

About half the people who are diagnosed with CML are asymptomatic at the time. They have a blood count done for some other reason, maybe a preoperative visit or routine health maintenance, and the other half will have constitutional symptoms which are things like fevers and drenching night sweats, losing weight, they may have abdominal discomfort or trouble eating, called early satiety, getting filled quickly because of a big spleen, or easy bleeding or bruising due to either a very high white count or dysfunctional and low platelet count.

Most people who present with CML will present during what's called the chronic phase of the illness. And I'm going to come back to that because that's an important feature.

The natural history of this disease, meaning how it would progress if we didn't have an effective therapy, is that the majority of people would end up dying of this disease and that is typically due to the disease turning into a much more advanced form called accelerated phase or blast crisis. And we abbreviate that AP or BC. That's the cause of death in most people with CML.

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DR. HARRY ERBA:

And so I'm going to lay the foundation for what I'm going to be speaking on right here. The goal of my treatment for my patients with CML is to give them a therapy that can prevent the disease from progressing to accelerated phase and blast crisis. That is the most important reason for treating people with these oral medications, the ABL tyrosine kinase inhibitors that we're going to speak of.

In most people, we don't know why they develop this disease. There's clearly an association with radiation exposure. This comes from watching people who have survived or following people who survived the atomic bomb blasts over Hiroshima and Nagasaki. But for most people we don't know why it develops.

Slide 4. Diagnostic Considerations in CML

So when we see people with CML, there are a number of findings in their blood that we can see. One is that the white blood cell count is high. We call that leukocytosis. And what we see in the blood is shown there on the right hand side of the slide, is that there are increased numbers of immature white blood cells in the blood. We call that shift to immaturity or left shift. There are funny-looking cells called basophils, so that's very, very characteristic of CML. A person might be anemic. I'm sensing that this person was anemic because the space between those orange circles, which are red blood cells, is a little bit greater than it should be. So that tells me that they're anemic. And the platelet count can be normal, elevated or high. Platelets clot the blood. There's often a high number of eosinophils and, as I said, basophils.

So when a hematologist sees a patient who has a high white count and the blood smear looks like you see on this slide, we are very suspicious it's CML. But you cannot make the diagnosis of CML without demonstrating the presence of a genetic change that has occurred in the bone marrow cells of that person. And we call it the Philadelphia chromosome or the BCR-ABL1 fusion.

Slide 5. (Bone Marrow)

So let's talk a little bit more about what this looks like. Let's look at the bone marrow and I'm going to show you on this slide what a bone marrow biopsy typically looks like.

So what you see on this slide is a low power, and then on the right a higher power magnification of a bone marrow. Some of you may have had bone marrow samples taken. The pink are bone spicules, parts of the bone. The purple are the cells that make blood. The white spaces are fat droplets of adipose or fat cells. And this is a normal bone marrow. Somewhere between 30 and 50% of it for an adult will have bone marrow-forming cells in it.

Slide 6. (Bone Marrow)

When a person develops CML, there is an increase in the number of bone marrow cells, blood-forming cells, in the bone marrow. So now you will see less fat, more purple. And so that would be very characteristic.

So as I said, that can help in making the diagnosis, but that is not sufficient for making the diagnosis. You need to find some evidence of a genetic event that has occurred in the bone marrow cells.

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DR. HARRY ERBA:

Now before we go further, I want to make sure it's very clear to everyone on the line that when we talk about these genetic changes, this is not a genetic change that a person was born with and then at the age of, you know, 50 or 60, caused the disease. Instead these are genetic changes that occurred only in the bone marrow and actually are sufficient for causing the disease. So these genetic changes you can't pass on to your children. You didn't get from your mom or dad. The genetic change of CML is not found in egg cells or sperm cells, so you can't pass them on, they're only in the bone marrow.

Slide 7. Diagnostic Considerations: Cytogenetic Analysis

In 1960 two doctors in Philadelphia discovered when they looked at the chromosomes in the white blood cells of people with CML, they saw the normal number, 46 chromosomes, but one of them was much shorter than the other – and the last row of those chromosomes, there's an arrow pointing to the Philadelphia chromosome. It was that very short chromosome that was seen. And it is found in most people with CML.

Slide 8. The Ph Chromosome and the bcr-abl Gene: The t(9;22) translocation

It wasn't until – that was 1960 – it wasn't until about 15 years later that Janet Rowley, a physician at the University of Chicago, demonstrated that that short chromosome was due to two normal chromosomes breaking at their tips and the tip rearranging partners. So the tip of chromosome 9, one of the longer ones, broke off and moved over to chromosome 22 and most of the – what's called the long arm of chromosome 22, broke and moved over to chromosome 9. So you end up getting a longer chromosome 9 that you see there on the right, and then on the very far right a shorter chromosome, the Philadelphia chromosome. And that's the chromosome that actually has the BCR-ABL gene fusion. The breakage of the chromosomes occurred right in the middle of the gene on chromosome 22 called BCR, and it broke in the beginning part of the ABL gene. And what it does is it creates a new gene that's always turned on in the bone marrow cells. And the ABL gene is turned on then by this event, and it shouldn't be. It should not be active. It should be quiet, it should be doing nothing. But when it becomes activated, it is actually what's responsible for causing the disease. If you take that genetic change and you put it into a mouse stem cell, a mouse bone marrow I should say, the mouse develops CML. So that's how we knew that the BCR-ABL gene and the product of it, the protein, the BCR-ABL protein was important for causing this disease.

Slide 9. Diagnostic Considerations: FISH

Now there's another way we can diagnose it, besides just looking at the chromosomes. We can actually screen hundreds of cells in the blood or the bone marrow for fusion of the BCR and the ABL genes. And the way this is done is through a test called FISH. You may hear your hematologist talk about it – fluorescence in situ hybridization – and basically without explaining the whole technique, we have a fluorescently-labeled probe that sticks to the BCR gene, it's green, and a fluorescently-labeled probe that sticks to the ABL gene called – that's red. This probe is going to stick to the gene no matter where it is in the nucleus of the cell, which is shown purple there. And so you'll see there's a normal ABL that's red, there's a normal BCR gene that's green, and then because you have the BCR-ABL fusion on two chromosomes, you see two fusion signals that turn out to look yellow. And so this would be considered a positive cell for the BCR-ABL fusion.

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This can look at hundreds of cells. So when we look at the chromosomes, it's about 20 that we look at and we could see if any of them have the Philadelphia chromosome. When we look at FISH we can look at several hundred. Some labs do 200 cells, some do up to 1,000. But you could screen a good number of cells that way and so be more sensitive at detecting the disease.

Slide 10. BCR-ABL Transcript Levels by PCR Correlate with CML Disease Burden

And then finally in this slide, I am trying to portray that by looking at the RNA – it's called the transcript, that is made from the gene – we can get an even more sensitive measure of how much disease is there.

At diagnosis most people have a 100% level of the RNA, called the transcript, made from the BCR-ABL gene. When they're in a complete cytogenetic remission, called CCYR, and those 20 metaphases, those 20 cells don't have the Philadelphia chromosome, the level is still about 1%. When there's 1,000-fold reduction in the amount of this BCR-ABL, that's .1%. A thousand-fold reduction from 100% to .1%. That's a major molecular remission.

This test is incredibly sensitive. But like any test that a cancer doctor uses to detect cancer, it's imperfect. It cannot tell you when we got rid of every last cell. And so a point will come when even this test will be negative – we call that a complete molecular remission – but this inverted triangle is supposed to show you that in the very light blue at the bottom of the triangle, towards the vertex or point of it, there could still be a million, 10 million leukemia cells, and the PCR test, as sensitive as it is, won't detect it. And I'll come back to that at the end.

Slide 11. Definition of Response in CML

So using these tests we now will use these to define remissions. So when the blood counts normalize, which happens very quickly with the ABL tyrosine kinase inhibitors like imatinib, nilotinib, dasatinib, could happen with hydroxyurea, that's a complete hematologic remission. Cytogenetic remission is when out of 20 cells, none of them have the Philadelphia chromosome, that's a complete cytogenetic remission. And as I said for molecular response, the more sensitive a test of how much disease is there, a major molecular response is when that BCR-ABL ratio, a measure of the transcript level, falls to .1%, meaning there's been 1,000-fold reduction in the amount of disease. I'm going to come back to why these responses are important.

Slide 12. Overall Survival of Patients with Early Chronic Phase CML Has Improved

So let's look at the outcome, the survival, of people with CML over the decades and how it's improved.

In the 1960s and 1970s, predominant therapy for this disease were oral chemotherapy drugs like hydroxyurea and busulfan, and you could see in those purple curves – I'm sorry, the two lowest curves – that the average survival – so when you look over on the left and look for .5 and move over, you'll see that you hit the curve somewhere between three and five years, those two curves. That means the average survival of people back then was three to five years. And if you look at the bottom where it says ten years, you could see 10% or less of people were alive. Because the disease turned into blast crisis, okay?

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Now the next two lines are better, they're higher, meaning more people are living longer. Still at ten years it was only about 40% of people alive on one of those curves, and 60% on another. That was an era of time when we used interferon, an injectable drug, to improve survival. And it did it by improving the number of people who had cytogenetic or molecular responses.

Finally, the blue line at the top show you the survival of people treated at MD Anderson Cancer Center, given the ABL tyrosine inhibitors since the year 2001, basically reading for that, since imatinib became more widely available as the first ABL tyrosine kinase inhibitor, and you can see people are living longer now because of these. And they're living longer because fewer people are advancing to the advanced phases, accelerated phase and blast crisis of the disease.

Slide 13. Allogeneic Hematopoietic Stem Cell Transplant is Curative For (Some) CML Patients

Now before the ABL tyrosine kinase inhibitors were developed, the only potentially curative option was allogeneic stem cell transplantation. I don't want to belabor that point. It remains an option for some people with the disease, but in chronic phase we always start with ABL tyrosine kinase inhibitors first. You could see that some people can be cured, but even in data from some of the best institutions, only about 50% of people who undergo stem cell transplant are cured of the disease out at ten years. We know that with the drugs we're using now, imatinib, dasatinib and nilotinib at the time of diagnosis, that we expect way more than 50% of people to be alive ten years later. And so that's why transplant has fallen out of favor as initial therapy.

Slide 14. International Randomized Study of Interferon + Ara-C versus STI571 (IRIS)

So how do we get to where we are now? Well, we do that through clinical trials. We would not have advanced this far if people with this disease did not volunteer to be part of studies of new therapies. And a study that started in 2000 and finished very quickly in six months was the IRIS trial, that compared using imatinib to the standard of care at the time, interferon, and Ara-C. If a person was having side effects to one, they could switch over to the other if they weren't responding, they could switch over.

Slide 15. IRIS Trial: Progression-free Survival (Intention to Treat)

The FDA approved imatinib for the treatment of people with CML because by 18 months, more people treated with imatinib were alive and responding to the treatment, and had not progressed into the accelerated phase or blast crisis, compared to the interferon. So at 18 months, 92% of people given imatinib, Gleevec® as we call it, the trade name, were still alive and not progressing into advanced phase disease, compared to 73.6%. So a clear benefit.

Slide 16. Progression of CML-CP to AP/BC by CyR after 12 Months of Imatinib (IRIS)

We also learned that we can predict who is more likely to enjoy a longer survival. Now I have to say anyone starting on imatinib, they're going to do much better than we used to do with interferon in terms of side effects and also how long people are living. But we learned, if you look at those top two curves, the yellow and the bluish-green line, that if a person had a cytogenetic response, complete or partial, by 12 months of therapy, that they were living without progression much better than if they didn't achieve a complete or partial remission. Why is that? Well, it's shown on the next slide.

Slide 17. Decreasing Event Rate Over Time in the IRIS Trial: Imatinib Arm

DR. HARRY ERBA:

Even when we start imatinib, there are some people who have progression into the next phase of the disease, the accelerated phase, and blast crisis. And that's what we want to prevent. Remember I said that in the first slide, we want to prevent the disease from changing into accelerated phase and blast crisis. If you look at the burnt orange columns there, at one, two and three years, if you add up those numbers, you could see that about 6% of people had progression into accelerated phase and blast crisis in the first three years, started on imatinib. And then it went very low after that.

And so it's become important, in my mind, and this is my opinion now, that in order to improve how many people will be cured of the disease, or I should say live longer with the disease, it's important to try to decrease the number of people who have progression of the disease once you start the ABL tyrosine kinase inhibitor.

Slide 18. Survival Decreases After CML Progression to Accelerated Phase or Blast Crisis (IRIS)

Why is that important? Well, I'm showing this on the next slide. If you look at those people that are represented by those burnt orange bars, the people who progressed into accelerated phase and blast crisis, you will see that their average survival is only about ten months. And those little white dots on the orange curve that are out there around 48 and 62 and 72 months, those are people who underwent stem cell transplant. So what I'm saying with this slide is that if the disease progresses into accelerated phase or blast crisis, the life expectancy of that person is shorter, and really the only chance for more prolonged survival is if they undergo a stem cell transplant.

So that's the benefit of imatinib.

Any drug that any doctor gives you for anything, as you know by listening to television commercials, is going to have side effects, and some of them, hopefully rarely, can be incredibly serious. It's very important that although all of these drugs have side effects, that you work with your physicians to manage the side effects as best as possible. Because I'm going to show you that staying on your drug is critically important.

Slide 19. Side Effects of Imatinib

This is a complicated slide. It just reminds me to tell you that imatinib, we know it causes diarrhea, nausea, vomiting. That's why we tell people to take it with plenty of food and a big glass of water. We know it can cause puffiness around the eyes and in the legs. We know it can cause muscle spasms and muscle aches and rashes, so it has a number of side effects. Most of them are, by an oncologist's standard, mild, because we're used to giving very intensive chemo. But for a person who has to take this pill every day, this gets old after a while, taking these drugs that cause blood counts and these other side effects. And so it's important that you speak with your oncologist about the side effects you're having and how to put up with it. Please don't sit in the chair in his office or her office and say everything is fine, Doc, I'm doing okay, and then go home and not take your Gleevec because you're going to go on a trip for a – or a hike for a day and you don't want to have diarrhea, so you hold it. It's important that you discuss these things openly with your physician, so that your physician can help manage those side effects. And usually we can manage it with other drugs or lifestyle changes. Sometimes we have to switch to a different drug.

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Slide 20. IRIS 8-Year Update

DR. HARRY ERBA:

Well, let's look at how people were doing if they were just given imatinib. This looks at that study I told you about, the IRIS trial, at eight years, and it asks the question, well, how many people at eight years were still taking imatinib? And basically – I like to round numbers – about half of the people, 45% of the people had come off the drug. And the reason for that, if you look all the way over on the right, 37% had an unacceptable outcome, meaning that they didn't have a response, they lost a response, or they were having side effects. So Gleevec is an incredibly important addition to our treatment, but the question is can we do better? Things are better than interferon, but can we do better than Gleevec?

Slide 21. ENESTnd Study Design and Endpoints

And so other drugs have been compared to Gleevec, again in clinical trials. The only way I can show you this information is because people volunteered to be part of a study. And what you can see here is one of those studies, sponsored by the Novartis pharmaceutical company, where they compared two different doses of nilotinib, now known as Tasigna®, to imatinib. They compared these. So in a randomized trial, people and their doctors knew what drug they were assigned to get, they were given those drugs, they were followed and they were followed to see how well they responded and what the side effects were. So there was no placebo, no sugar pill, it wasn't blinded, in other words the doctor and the patients knew exactly what they were getting. And the reason why the FDA approved nilotinib or Tasigna for the treatment of CML in chronic phase at diagnosis, is because in this study more people achieved a major molecular response at one year with one of those doses of nilotinib, than with imatinib. It was twice as many, twice as many people achieved that.

Slide 22. ENESTnd 5 Years: Cumulative Incidence of MMR

So again, if you look at the way we read this, is if you look down at the bottom, it's called the X axis where it says one year, and you look up, you could see only 27% of people had that major molecular response with imatinib, the yellow line, and it was double that, up to around 50% or higher with nilotinib. And what's important is over time, nilotinib continued to do better than the imatinib.

Slide 23. ENESTnd 5 Years: Progression to AP/BC on Study

Well, that's good, everyone likes to hear from their doctor, by the way, your drug is working, I know you're having side effects but it's working. But what's critically important to me, remember, I said it on the first slide is, yes, but does that drug prevent the disease from progressing. And this slide will show you that compared to imatinib in yellow, the two blue bars, the light blue and the dark blue are the two different doses of Tasigna or nilotinib – and fewer people had progression to accelerated phase and blast crisis if they started on nilotinib. So to me that's even more important than the response. I love telling my patients that they're responding and they've had a major molecular response, but the real benefit is fewer people progressed.

Slide 24. ENESTnd 5 Years: PFS and OS on Study

And in fact, something that is not discussed very much at this point, but I think may be coming out over time, in this complicated table taken from a presentation of the five year results from that trial, people

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who took nilotinib had a higher chance of being alive than people who took imatinib. This hasn't been shown in any other study. So this is something that's very important to follow up on.

Slide 25. ENESTnd: Newly Occurring or Worsening Grade $\geq 3/4$ Hematologic and Selected Biochemical Abnormalities

Now every drug has its downside and nilotinib is no exception. However, what I will show you on this slide, and I won't bore you with how to interpret a bar graph, I'll just say what it's telling you. This slide tells me that people who took nilotinib were less likely to have a low white blood cell count than people taking imatinib. They had the same chance of having a low hemoglobin, anemia, or a low platelet count. They had a higher chance of having some abnormalities in blood tests like lipase, which is a pancreas enzyme, or some liver tests. And very importantly to me, people who take nilotinib had a higher chance of having sugar problems. And so my diabetic patients, I always work with them and their internist, to make sure that they're having appropriate treatment of their diabetes.

Slide 26. ENESTnd: Selected Cardiovascular Events by 5 Years

So in terms of longer term followup, again, this is a complicated table, so I will just summarize what it's saying, with nilotinib there is a higher incidence of having events like heart attacks and strokes and blockage of arteries in the legs with nilotinib, compared to imatinib. Fortunately the numbers are very small, but I think it points out the importance of staying in touch with your internist. If you have CML and you're on these drugs, you want to make sure that high blood pressure and diabetes and high lipids are controlled. You want to stop smoking. Because we are getting very good at controlling the CML. We have to make sure that you live a long life by controlling other, more common diseases, that can lead to strokes and heart attacks and things like that. So very important to work with your internist and not forget about them.

Slide 27. Dasatinib vs Imatinib in Treatment-Naïve CML (DASISION)

Now the same has been seen with the other drug, dasatinib or Sprycel®. I will just show you that study that was done by a different drug company, Bristol-Myers Squibb, and they showed – what they did was they compared Sprycel or dasatinib to imatinib in that study.

Slide 28. DASISION 3-Yr Update

And this next slide shows you that again with dasatinib there was a higher response rate with dasatinib. More molecular responses, that's seen in the top table there. And in terms of the bottom table, there was similar survival, chance of being alive, very high in both groups. So very important to show you that both Sprycel-dasatinib and Tasigna-nilotinib lead to higher chances of achieving a response at these early time points, one, two and three years, without, however, much – with dasatinib – much difference in survival.

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Slide 29. DASISION 3-Yr Update

DR. HARRY ERBA:

Dasatinib has side effects just like nilotinib and imatinib do. They tend to be different and your hematologist – will consider these side effects and your own personal medical history when making a decision about what's the best therapy for you. So again, they're listed here. Some of the most important that I'll mention to you now is that you can have trouble with bleeding, and so it's important not to take aspirin or Motrin – I'm sorry, ibuprofen – blood thinners, while you're taking dasatinib. You can get fluid accumulation around the heart and lungs, those are called pleural and pericardial effusions, or high blood pressure in the lungs, and those things can cause shortness of breath. So if it happens you need to see your hematologist, if you get short of breath or chest discomfort. Don't forget to let them know.

Slide 30. The Goal of Therapy in Ph+ CML is Prevention of Progression to Advanced Phases

So how do we manage this disease now? Well, remember, again, I'm going to say it again, the goal of the treatment that I'm going to choose for my patient is to prevent the disease from progressing into accelerated phase and blast crisis. And what we have learned is that if at three months that BCR-ABL, measured by PCR, if it's less than 10%, that's good. And if they're in a complete cytogenetic remission by 12 or 18 months, that's good. Those are the goals of our treatment with the ABL tyrosine kinase inhibitors.

Slide 31. Depth of Early Molecular Response at 3 Months Correlates with PFS and OS

Let me show you why. Again, this data comes from people who have been in clinical trials and what you're going to look at here is a data from a university hospital, the Hammersmith College in London, where 280 people were given Gleevec. And they asked the question, how did people do if the BCR-ABL ratio was less than about 10% or over 10% at three months? And what you can see here is that the chance of survival and survival without progressing was much better, about 93%, if that landmark – if that milestone, I should say, was achieved, compared to about 57%. In fact, this has now been incorporated into NCCN (National Comprehensive Cancer Network) guidelines for how we monitor our patients with the disease. We want to check at three months the BCR-ABL. At 12 months we want to make sure that they're in a complete cytogenetic remission.

Slide 32. NCCN Practice Guidelines Recommendations based on 3 Month Milestone Molecular Result

If we look at three months as an example of one of those milestones that we want our patients to achieve, and let's say they're not achieving it, so they haven't achieved that milestone, what do we do? Well, look at that big rectangular box that's in kind of white color there. The most important thing we do is make sure you're taking the drug. And I'll show you why that's the case in a few slides. We make sure you're taking the drug. We make sure that someone hasn't started another drug that can actually cause side effects to occur when you're taking Gleevec or Tassigna or Sprycel. Or it could make the drug become less effective. We make sure that you are taking it appropriately, with or without food. We make sure you're not taking it with acid blockers because that can decrease absorption.

So those are important things that we do when we see people in clinic and we assess how they're responding. It's not just whether you're responding or not, but if you are not responding, why.

Slide 33. Compliance to Imatinib (Adagio)

DR. HARRY ERBA:

So compliance is important. I'm just going to flash these slides here very quickly. These slides basically say that if you have – if you're taking the drug as prescribed – well, this starts by saying how many people take the drug as prescribed. And this was imatinib, this was one study. You can see it was only 14% took it as prescribed. Most people, almost three-quarters, 71% were taking less than what is prescribed. Well, there are a lot of reasons for that and I'm going to show you the importance.

Slide 34. Reasons for Lack of Compliance

In terms of what are the reasons that people don't take it as prescribed, well, it could be that it's intentional that you don't want to take it. For example, you're having side effects from the medication, and they're not being managed appropriately, so that's why you need to talk to your doctor. You might be traveling, you don't want to have the side effects, you think you might have become pregnant so you don't want to take it while you're pregnant, you don't really think that you need it. And then there might be unintentional reasons like you forgot to take it or your doctor prescribed the wrong dose. Hopefully that doesn't happen too often.

A very common cause are the last two over there on the right, no imatinib or nilotinib or dasatinib available at the pharmacy, or delays in drug delivery from specialty pharmacies. I've seen this happen in my own patients. So it's important to try to minimize those from occurring.

Slide 35. Strategies to Improve Adherence

So the ways to do that are shown here. And probably the most important is to talk with your physician, okay? So to talk with them about compliance. That's what I do, why it's important. I'm going to show you data about why it's important. Educate people on the impact of not being adherent to it. Talk to them about their adverse side effects and try to manage those. And the reason why I continue to see people in clinic, no matter if they're doing well or not, every three months, at least every three months, is to make sure I'm recognizing if they're developing an intolerance or can't get the drug or have some other reason for poor compliance.

Slide 36. Imatinib Compliance (Pill Counts) Correlates With Achievement of CCyR in CML-CP

These next two slides I'm just going to flash quickly. This one and then skip the next one. But what these basically say is that if you do not take the drug, you are less likely to have a response. So for example, in that column, percent imatinib doses not taken, okay. In the people who had complete cytogenetic remissions, there were 98 of them, 9% of them, only 9% of them didn't take – I'm sorry, in that group, 9% of the imatinib doses weren't taken during that period. In the people who did not have a response, it was only 9 in this study, but those patients had a higher chance of or took less of their drug, 26% of their doses weren't taken.

Slide 37. Adherence is the Critical Factor for Achievement of MoIR in CML-CP Patients in CCyR on Imatinib

For your reference.

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Slide 38. Higher Copayments (Cost Sharing) Adversely Effects Adherence to ABL TKI Therapy in CML-CP Patients

DR. HARRY ERBA:

This very complicated slide just reminds me to tell you that if you have a higher copay, this was actually published, believe it or not, but this basically says if you have a higher copay, you're less likely to be compliant with therapy.

Slide 39. Second Generation ABL TKI in CML

So what happens if you are taking imatinib or nilotinib or dasatinib and your doctor tells you it's not working or you lose a response or if they tell you that the intolerance you're having cannot be overcome with medications for side effects, what can you do? Well, there are a number of drugs that have been approved and I want to be able to get to questions, so I'm going to talk about these very, very briefly in this slide.

The three drugs, the second generation drugs that have been approved, are nilotinib, dasatinib and bosutinib. And so if you're a patient who started on imatinib and you're intolerant of it or you're not responding any more, these are three choices and your doctor is going to take into account all of these characteristics shown on the left hand side of these three drugs, including what mutations that can occur that these work against, and how the drug is taken and other side effects to help in determining what is the best treatment for you.

Slide 40. Second Generation ABL TKI in CML CP Post-Imatinib Resistance

And again, they will be able to tell you what is the chance of that drug working, based on studies of people who were taking imatinib and the imatinib stopped working. And so they will be able to quote to you numbers of people who got switched to nilotinib or dasatinib or bosutinib and how many of them had hematologic responses, that's CHR, or complete cytogenetic remissions, that's CCYR, and how many were alive at two years. Just as some examples of what we look at in studies. And basically what you can see from this is in people who've been on imatinib and the disease, become resistant, number one, there's a high rate of response to these other drugs, and number two, there doesn't seem to be much difference between the three of them.

Slide 41. Second Generation ABL TKI in CML CP Post-Imatinib Failure

So again, your doctor is going to work with you in terms of what drug you might be able to tolerate the best and that is going to be based on some of the side effect profiles of these three drugs that are being shown here.

Slide 42. Response to Bosutinib as Third-Line Therapy

For your reference.

Slide 43. Ponatinib Phase 2 PACE Study Responses at Any Time

DR. HARRY ERBA:

There is one specific drug that I want to mention and that is ponatinib. Ponatinib is a drug that's been approved by the FDA because it is active when nilotinib, dasatinib and imatinib are no longer working, but specifically it's the only one that works in people who have a mutation in the BCR-ABL called the T315I mutation. And if you just look at that yellow line where it says total responses, this is in chronic – over on the left hand side of the table, and if you look at CCYR, about half of the patients had a complete cytogenetic remission with ponatinib, also known as Iclusig® after those other drugs failed to work, and 70% of the people who had the mutation T315I actually responded to ponatinib. The drug was temporarily taken off of the market by the FDA for about two to three months because it's clear that this drug is associated with higher chances of heart attacks and strokes and other cardiovascular complications, heart and brain and blood vessel complications. And so we recommend that people are on an aspirin if they can be. We use the lowest dose of ponatinib to control the disease. And finally, only use it in people who really need it, and in my practice it's people who have the T315I.

Slide 44. Ponatinib Phase 2 PACE Study Incidence of Vascular Occlusive events Over Time

For your reference.

Slide 45. Ponatinib Phase 2 PACE Study Multivariate Analysis of Arterial Thrombotic AEs

For your reference.

Slide 46. Omacetaxine for CML CP After Failure of \geq ABL TKI

For your reference.

Slide 47. STIM Trial Update

The last point I'm going to make is one – a question that comes up all the time and that is okay, Doc, when can I get off this drug? And right now the answer you need to remember is there is no good data to suggest that we should be stopping any of the ABL tyrosine kinase inhibitors. But there is some – one study called the STIM Trial, where people went on a study to see if they should stop. And basically it's a very wordy slide that you'll be able to see I guess on the web at some point. Out of 100 people who had a PCR test showing that they were in a complete molecular remission for at least two years, so this is after being on it for quite some time, 61 out of the 100 relapsed. Now almost all of them, in fact all of them, had a response again to imatinib when they had a relapse. Most of the relapses occurred pretty quickly within the first seven months. But there are some people who are doing better. Patients with lower risk disease who've been on imatinib for a longer period of time.

Slide 48. Kaplan-Meier estimates of CMR After imatinib discontinuation in STIM trial

So the jury is still out on the safety of doing this, of holding imatinib. I will say never stop imatinib without letting your physician know. In practice the best time, the best way to stop imatinib or those drugs, to see if you can be on a maintained remission, is part of a clinical trial. And those studies are ongoing. So if you're interested in that I would refer you to any of those clinical trials.

Slide 49. Management of CML-CP with ABL TKI

DR. HARRY ERBA:

So what's important in the management is I encourage dialogue with my patients regarding the barriers to compliance. Right from the start I make it clear to my patient that it's important that I want to hear from them if they're having problems getting the drug, tolerating the drug, affording the drug, and things like that. It's important to monitor the disease. At three months we want to see a BCR-ABL ratio less than 10%, and by one year a complete cytogenetic remission. A major molecular response is not necessarily needed to guarantee, to ensure long-term survival. But a complete cytogenetic remission within a year or year and a half is important.

And that's the only thing that I would call failure, is if you don't – primary failure would be if you don't achieve a complete cytogenetic remission within the first year to 18 months. When failure does occur or if a person fails to respond, these mutations or genetic changes can be informative and help decide on which is the best drug to use after the first drug stops working.

I always at these visits review compliance and side effects of the drugs and go through the drug list to make sure they're not taking anything either prescribed or over-the-counter that can interact and make the CML therapy either less effective or more toxic.

What I really talk to my patients about is trying to avoid switching from one drug to another. None of us like to have side effects from our medication, but I want to remind everyone listening that this still remains a very serious disease. Once the disease progresses into accelerated phase and blast crisis, survival is very poor. And so the entire goal of our treatment is to find a drug that you can tolerate and that might mean giving you a drug and other medicines to help you tolerate those side effects. So manage adverse events effectively and keep all of your options in mind.

So I hope you've found this to – turned out to be an hour lecture on CML – helpful, and I'm glad to take any of your questions now. But again, thank you for tuning in and I appreciate the invitation from the LLS to give this talk. I should have warned them before I accepted that I tend to be wordy and talk way too much, but I've really enjoyed being with you for the last hour.

Slide 50. Question and Answer Session

LIZETTE FIGUEROA RIVERA:

And we've enjoyed your presentation. Thank you so much, Dr. Erba, for your very clear and informative presentation.

It's now time for the question and answer portion of our program. And we'll take the first question from our web audience. Dr. Erba, Donna asks if taking 600 milligrams of imatinib and in remission for five years, would it be acceptable to decrease dosage to 400 milligrams with monitoring?

DR. HARRY ERBA:

Good question. I guess it would depend on why the dose of 600 milligrams a day was chosen and what we mean by remission. So if a person is – and what kind of side effects you're having from 600. So if you're having side effects from it and they can't be managed, it would be with – if it's like edema and swelling and Lasix and avoiding salt don't help, or muscle spasms, which can be pretty devastating, keep people up at night, if you're having side effects at that dose, you could think about cutting down on the

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dose, assuming that you have achieved at least a major molecular remission. You may be in a complete molecular remission. And monitoring closely at the lower dose.

If the dose, however, was chosen not because you were in chronic phase, but because the physician thought you were in accelerated phase, I would try to maintain the full dose if possible.

So I would not reduce doses unless – if you're responding, I would not reduce the dose unless you're having side effects that cannot be managed appropriately and then in that case I think it would be reasonable to reduce the dose with very careful monitoring.

I'm assuming that when we talk about monitoring we're talking about peripheral blood, using a blood test to look for the BCR-ABL transcript.

LIZETTE FIGUEROA RIVERA:

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

OPERATOR:

Our first phone question comes from Audrey in Pennsylvania. Audrey, please state your question.

AUDREY:

Yes, I will be ten years this month actually, diagnosed with – response with Gleevec at 300 milligrams. What is the – is there people that go beyond the ten years? I mean I can't believe it, I'm ten years now.

DR. HARRY ERBA:

Well, you know, if this was 20 years ago, many of us couldn't believe that you'd be ten years. These drugs have completely changed the outlook of people living with CML.

Now that actually also leads to the next point and that is it's very hard for your physician or me to tell you what to expect ten years from now and the next ten years, because we only have – we have less than 20 years follow-up from the first person given Gleevec, which was in the late 1990s. So we can't tell you what 30 years and 40 years will bring, these medications, at this point. What we can say is we're impressed that most of the events of the disease turning into the blast crisis, which again is the most worrisome thing that we want to avoid, most of those occur early on, and if people remain compliant and in response, the chance of all of a sudden the disease turning into blast crisis is incredibly low. I mean we call them case reports, you know. We don't see it in usual clinical trials. It's pretty uncommon. So it's hard for me to say what's going to happen over the next ten to fifteen years, but I could say – or longer – but I could say that based on when we see most of the events of failure and resistance showing up, it's unlikely that things are going to change. What we can't answer for you is can you stop these medications. As I said, the people who have had – been able to stay in remission off of imatinib in that one study, are people who'd been on imatinib for a long time, more than five years, and had been in a complete molecular remission, using a very good PCR assay. They were more likely to stay in remission. The question we don't know the answer to is that risky. Even though you don't see it on the PCR, it might be risky to stop the drug because how about if the disease is there still at a low level and now you're not maintaining response with Gleevec or something like that? It's conceivable that the disease can all of a sudden turn into blast crisis.

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So I'm anxious about asking patients or agreeing with stopping the drug because of the unknown of being off of it. But in terms of should you be hopeful for the future, absolutely. You should live your life now like you have well controlled high blood pressure, and live it looking at all of your other health maintenance issues, to keep those under control. Especially any risk factors for cardiovascular disease like heart attacks and strokes, managing those may be actually very important in people who are taking drugs like Gleevec and others.

LIZETTE FIGUEROA RIVERA:

Thank you so much for that question. The next question, Doctor, is from the web, it's from Micky. He says, "My wife was diagnosed with CML on January 7 of this year and we have yet to receive her Gleevec that was prescribed for her. Has the risk of CML turning into AML or blast crisis CML drastically increased?"

DR. HARRY ERBA:

During this one month? No, it hasn't. In fact, if you look at the length of time between diagnosis and starting an ABL tyrosine kinase inhibitor, the average time is somewhere between two and four weeks. So you're not really far out of the average time it takes. Partly for making the diagnosis, partly for prior authorizations, which quite frankly, drive us all crazy. That definitely slows down the whole process. Your physician can sometimes do things. All of the drug companies will have programs to get patients started on medication with a free month's supply, for example. So that may or may not be an option through your physician to get things going. But the risk of the disease progressing during that one month is very low.

To put it in perspective, data from a long time ago, when we didn't have these drugs, the ABL tyrosine kinase inhibitors, and we were using Hydrea®, during the first year of using a drug like Hydrea to control it, there was a 25% chance of the disease progressing in the first year. So if you look at just the first month, yeah, there's a chance it could progress, but it's very low.

But modern healthcare being what it is, I would be on the phone with my physician's office and insurance provider to see what the holdup is. But I wouldn't be overly concerned that the disease is all of a sudden going to progress into blast crisis.

I often give patients, by the way, I'm sorry, I often give patients a few weeks of hydroxyurea to get the counts down before I start Gleevec anyways, or drugs like it.

LIZETTE FIGUEROA RIVERA:

Sure, and Micky, you can always call our Information Resource Center for assistance and we could also advocate on your behalf. You can call them at 1-800-955-4572. Or you can email them at infocenter@LLS.org and they're available to speak with you from 9 AM to 9 PM Eastern Time. Again, we could definitely advocate for you and your wife, thank you.

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

OPERATOR:

Our next question comes from David in Georgia. David, please state your question.

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DAVID:

Yes, I was wondering, my son is 17 years old, was diagnosed in September. He's on dasatinib, 100 milligrams, one day 80 milligrams, another – they're alternating because of the quality of life on the 100 milligrams truly affected him. Is there a possibility after he's on this drug for some time that the dosage would be reduced at some point?

DR. HARRY ERBA:

I guess it would depend on how it's affecting his quality of life and what specifically the symptoms are. If he's that symptomatic from the disease, you might – and it can't be managed – I would rather in that situation, especially given his young age, switch to a different drug if he can't tolerate dasatinib at the full dose.

Having said that, one thing that I've been impressed by is that some of the side effects that occur as we start these drugs are worse and then they get better with time, even without dose changes. So like fatigue, bone pain, can be worse at the beginning and then get better as the disease comes under control. So I would definitely give it some time before making changes.

LIZETTE FIGUEROA RIVERA:

Thank you so much, Doctor. And our last question comes from Joan, although we've had many people asking this question, knowing that imatinib is going generic, the question asks, if generic drug versus branding drug, if there's any trial results or any efficacy studies between the generic and imatinib.

DR. HARRY ERBA:

None. There are no studies that have been conducted. And there are – there are companies that are going to be doing bio-similar studies, but it won't be – it's not the same as a generic. A generic is the exact same drug, just made by a different company usually, or sometimes the same company, but not under the brand name. Bio-similars are drugs that are similar in structure and may do the same thing and a company has to – a sponsor has to prove that it's just as effective as and not more toxic than the brand name drug. But nothing, no study like that has happened yet. So it does cause some concern about how are we going to know the generic drugs are just as effective. It also may affect the choice of initial therapy. Will insurance carriers refuse to pay for second generation drugs if your physician thinks that's the best option for you because we have the cheaper imatinib? That will be generic at the time. And all these questions really haven't been answered yet.

I can tell you if – I always consider when I'm seeing a person in my office, what would I say to my mother or my brother if they had this disease, and my feeling would be to continue to give the drug that I think has the best chance of preventing progression into accelerated phase and blast crisis that's tolerable. And so that affects my choice more than the cost of these drugs. But these decisions might be taken out of our hands by third party carriers and it's going to be interesting to see what happens over time. I'm not quite sure, none of us are sure of the answer. So I really can't give more information on that.

The last thing I'll say is that there have been reports, and these are just anecdotal reports of people getting non-brand name drugs, maybe in other countries, and, you know, losing response at that time. But is that because the drug was generic, not brand name, or is it because of something about the disease? And it's really hard to sort that out. So unfortunately, no answer to a very good and important question.

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LIZETTE FIGUEROA RIVERA:

Sure, thank you. And thank you for explaining the difference between generic drugs and bio-similar. I know that topic has come up a lot in our Information Resource Center.

DR. HARRY ERBA:

I'll give you my opinion, as long as I've got an international audience. We have so much to do in the treatment of cancer in this world. And little time to do it. People are being diagnosed with these diseases daily obviously, and we need to move ahead. And so as a clinical investigator, and that's my role, when I'm asked to take limited resources at my cancer center and devote them to one type of study or another, I'm more interested in devoting resources to trials that may actually improve upon what we have as opposed to get another drug approved that's really basically the same thing for the same disease. But it is important for people with cancer to continue to participate in well-designed clinical trials of novel therapies that might advance the treatment of CML and other blood cancers or cancers in general.

Slide 51. LLS Resources

LIZETTE FIGUEROA RIVERA:

Definitely, Dr. Erba. And we definitely agree with you, and our advocacy efforts at The Leukemia & Lymphoma Society, will stand up with you, as well as all doctors, in trying to make our patients get the best quality of care and the access that they need to get that care. So thank you so much for speaking to our patients and caregivers today.

And we hope this information will assist you and your families.

Dr. Erba, thank you so much 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.

[END]