

***Living With Chronic Myeloid Leukemia***

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***Michael Deininger, MD, PhD******November 2, 2016*****Slide 1 - Living with Chronic Myeloid Leukemia****Operator:**

Greetings and welcome to the Living with Chronic Myeloid Leukemia telephone and web education program. It is now my pleasure to introduce your moderator, Lizette Figueroa-Rivera.

**Ms. Lizette Figueroa-Rivera:**

Hello, everyone. On behalf of The Leukemia & Lymphoma Society (LLS), a warm welcome to all of you. Special thanks to Dr. Michael Deininger for sharing his time and expertise with us today. Before we begin, I'd like to introduce The Leukemia & Lymphoma Society's Director of our Information Resource Center, Ms. Beatrice Abetti, who will share a few words. Beatrice, please go ahead.

**Ms. Beatrice Abetti:**

Thank you, Lizette. I would 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 ensure access to treatment for blood cancer patients. Our vision is a world without blood cancer.

For more than 60 years, LLS has helped pioneer innovations such as targeted therapies and immunotherapies that have improved survival rates and quality of life for many blood cancer patients. To date, we have invested over \$1 billion in research to advance therapies and save lives. Until there is a cure, LLS will continue to fund promising research from bench to bedside.

In addition, as this program demonstrates, we are the leading source of blood cancer education and support. My team in the Information Resource Center provides information on the blood cancers, treatment options including clinical trials, and resources for better access to therapies. LLS also acts as the voice for all blood cancer patients. We advocate for patients, survivors, and their families, helping them navigate their cancer treatments and access quality, affordable, and coordinated care.

We're fortunate to have as our presenter today Dr. Michael Deininger, 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 giving us important information on CML today. Thank you all. And, now, I'll turn the program back to Lizette.

**Ms. Lizette Figueroa-Rivera:**

Thank you, Beatrice, and we would like to acknowledge and thank ARIAD Pharmaceuticals, Inc. and Novartis Pharmaceuticals Corporation for support for this program.

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### **Slide 2 - Disclosure**

#### **Ms. Lizette Figueroa-Rivera:**

I am now pleased to introduce Dr. Michael Deininger, Chief, Division of Hematology and Hematologic Malignancies; M.M. Wintrobe Professor of Medicine at the University of Utah; Senior Director for Transdisciplinary Research, Huntsman Cancer Institute in Salt Lake City, Utah. Dr. Deininger, I am now privileged to turn this program over to you.

### **Slide 3 - Living with Chronic Myeloid Leukemia**

#### **Dr. Michael Deininger:**

Thank you very much, Lizette. What I'd like to do in the next 20-30 minutes is to give you an overview of chronic myeloid leukemia and how to live with it. And this is supposed to be guidance for patients and caregivers, so I do sincerely hope that I'll not be talking over your heads. But, if so, feel free to shoot messages and we can clarify questions as they come up.

### **Slide 4 - CML Pioneers**

CML is a disease that we've known about for quite some time, and it was actually discovered or described first in the mid-19<sup>th</sup> century by three eminent people - Alfred Donné in Paris, and John Bennet in Edinburgh, and then, Rudolf Virchow in Berlin. And now, about 170 years later, I think we are in a position to say that most people diagnosed with CML will be able to have a normal life expectancy.

### **Slide 5 - Outline**

This is what I like to talk about - how CML is diagnosed, how it is treated/should be treated in 2016, how to deal with side effects, and lastly, upon your request, how we can address the question, whether therapy can actually be stopped in some patients.

### **Slide 6 - CML Basics**

So, the CML basics are that this is a pretty rare disease. It has a so-called incidence of about 1-1.5 cases per 100,000 population and year. The median age, at least in the developed world, is more than 60 years. But, in many developing countries, patients are diagnosed at an early age. It's more frequent in men, and importantly, it's not heritable and there are no real ethnic or racial differences. So, the incidence is about the same across the globe. The only risk factor that we know about is radiation or ionizing radiation, such as those patients who got exposed to radiation after the atomic bombings in Japan in the Second World War.

### **Slide 7 - Chronic Myeloid Leukemia – A Typical Case**

Now, a typical case of CML could present like this, and I guess many of you will have presented in a similar way. For somebody who has previously been really well, presents with night sweats, fatigue, weight loss, seeks medical attention. Physical exam shows an enlarged spleen, and then a complete blood count reveals slightly low hemoglobin--that is red blood cells--a lot of white blood cells with immature cells, and typically, also some increase in the platelet count.

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**Dr. Michael Deininger:**

And what you see in the middle of your slide here is the blood film of a patient just newly diagnosed with CML, and what you see is a whole variety of cells. So, some are these granulocytes here that are very differentiated, very mature, but there are also some more primitive cells like the one indicated with the arrow. So, this is a picture that allows the physician to suspect that this particular patient actually has chronic myeloid leukemia.

**Slide 8 - Initial Testing if CML is Suspected**

But, in order to really ascertain the diagnosis, one needs to do a little more than just a blood film and a physical exam. The very minimum needed is to do a physical exam, of course, and to record the spleen size. That is done in a simple way by just measuring, by palpation, the tip of the spleen between the left costal margin. Then you need a complete blood count and a basic metabolic profile. It is also necessary to do a bone marrow aspirate and a bone marrow biopsy, because only these bone marrow tests will allow you to definitively say whether a patient is in the chronic phase of CML or maybe already in the accelerated phase or the blastic phase. And lastly, one needs to do chromosome analysis of bone marrow cells to ascertain that the disease is, in fact, CML.

What establishes the diagnosis of CML is the appearance of the blood smear and the typical bone marrow appearance. Then, the chromosome analysis will show something called the Philadelphia chromosome. Sometimes, additional tests, so-called molecular tests, are necessary to establish a diagnosis. And that is typically the case if a patient presents with what looks very much like CML, but on chromosome analysis, there is no Philadelphia chromosome visible. And then, the physician will order a test called FISH, or fluorescence in situ hybridization, or PCR for polymerase chain reaction.

**Slide 9 - Philadelphia Chromosome: The Cause of CML**

Just to give you a little bit of a flavor of what is causing CML. What you see on this slide are two chromosomes, chromosome 9 and chromosome 22. On the chromosome 9, you see, in red, a gene called ABL or ABL1, and on chromosome 22, you see a gene called BCR. What happens in CML is that the two chromosomes, 9 and 22, come very close to each other, and then there is a break. And, as a result of this break, there is a neat change of chromosomal material in these two chromosomes. And what you end up with is a so-called Philadelphia chromosome that now combines parts of chromosome 22 with the BCR gene and parts of chromosome 9 with the ABL1 gene.

That is, of course, nothing that should happen ever in a normal cell in the body, and so it's really a hallmark of CML. And from a lot of studies over the years, we know that the Philadelphia chromosome is the driver of CML, and there is no CML without the Philadelphia chromosome or without the two genes that are juxtaposed here - BCR gene and the ABL1 gene.

***Living With Chronic Myeloid Leukemia******Michael Deininger, MD, PhD******November 2, 2016*****Slide 10 - CML Phases (Stages)****Dr. Michael Deininger:**

So, as I already mentioned, CML is a disease that progresses in stages. Most patients, especially in the developed world, are diagnosed in the chronic phase. And, if you look at this left blood smear here, you see a very, very colorful picture, so all kinds of cells at different differentiation stages. In chronic phase, the big problem is that there are too many cells. But, all these cells will eventually complete their maturation, and if you look at them more closely, they actually function pretty normally.

Hardly any patient will die from chronic phase CML. The problem is that, if you don't treat it well, the instability of the chronic phase leads to a transformation to what we call blastic phase. That is shown in the right part of that slide. And now, compared to the left part, if you look at these cells, they all look alike, and we call these cells blast cells because they are very primitive, and actually, they don't function very well, so they don't fulfill the functions of normal white blood cells, such as fighting infections. In fact, if you found this picture in a patient you don't know, whose history you don't know, you would just say, well, this looks like acute leukemia.

And, so this is essentially what blastic transformation of chronic phase CML means. It is the transformation of the chronic phase to an acute leukemia. Blastic phase is much more difficult to treat and much more dangerous than chronic phase. And, in fact, it will be rapidly fatal in many patients. Over the years, the community of CML physicians has defined the avoidance of progression from the chronic phase to the blastic phase as the most important therapy goal in CML.

**Slide 11 - CML Therapy**

Now, if you look at what we have available to treat CML, this is what I think the situation looks like in 2016. There is a drug that many of you might have used, or at least have heard of, called hydroxyurea. That's been around for a very long time. It's a very good agent to lower the white blood cell count, especially as long as you don't know whether you're dealing with CML or not. But hydroxyurea doesn't make very deep cuts into the disease process. So, it controls the white blood cell count, but it really doesn't restore any semblance of normality in the bone marrow.

In the second line, you see tyrosine kinase inhibitors or TKIs. These are drugs like imatinib (Gleevec®), like nilotinib (Tasigna®), like ponatinib (Iclusig®). These are the drugs that are now being used for long-term therapy of CML. In those patients who have a failure of TKI therapy, there is still the option of stem cell transplant, which in many cases, or in many people's minds, is still the only treatment that can cause a true cure of CML.

**Slide 12 - Imatinib Greatly Improved Survival in Chronic Phase CML**

If you look at the next slide, you see a graph, and these are so-called survival curves. So, 100%, that's at the very top of this, means 100% of patients surviving. And what you look at is different curves that relate to the decade at which patients have been referred to the M.D.

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Anderson Cancer Center. Now, if you look at the yellow curve in comparison to the lower curves, you see that there is a very big difference in patients treated with imatinib compared to the previous decades when imatinib was not yet available. So, in other words, imatinib made a huge difference in the survival of the patients with CML. It was not seen before with any other treatment, including stem cell transplant.

**Slide 13 - Disease Burden & Monitoring**

If you treat CML, it's very important to monitor their response to treatment. So, on this slide, I have written down what your hematologist may have told you as you went on treatment with a TKI. The first call of action is to get a complete hematologic response. Now, that means that the blood counts should be normalized and the spleen size should be normal, and any symptoms of CML should have gone.

However, that doesn't mean that the cells that you see under the microscope are now normal cells. In fact, in order to assess that, you need to do a cytogenetic or chromosomal analysis. Once you've determined that 20 out of 20 cells that you see in the bone marrow are, in fact, normal cells and not CML cells anymore, you call that a complete cytogenetic response. It's an important milestone because we know that most people who achieve a complete cytogenetic response will do well on TKI treatment.

If you go yet deeper, the next step of response is what we call a major molecular response. Now, that means that is a 1,000-or-more-fold reduction of CML cells compared to the baseline. And, if you go yet deeper, you come to a deep molecular response, which means more than a 10,000-fold reduction of CML cells compared to the baseline. That is a response that is also important, because it's only these patients who achieve that deep response who are good candidates for a trial of discontinuation of TKIs.

**Slide 14 - Recommended Monitoring**

Now, the European LeukemiaNet (ELN), and also, the National Comprehensive Cancer Network® (NCCN®) in the United States have developed recommendations for monitoring response in patients with CML. And what you see here is just a pre-summary of that. So, we do recommend that there is a bone marrow analysis and chromosome analysis at diagnosis, and then, on therapy at 3, 6 and 12-months.

Now, having said that, PCR technology, that is a blood test in contrast to the bone marrow test that you need for chromosome analysis--if PCR is available, then more and more centers will now recommend to monitor patients just with PCR. So, rather than doing a chromosome analysis on the bone marrow, they will recommend to do a PCR analysis on the peripheral blood. In those cases, if you achieve a good response, then you can relax the intensity of monitoring to some extent. And then, there's FISH, and also, a so-called BCR-ABL1 mutation screen that are indicated in certain circumstances, but not in the routine monitoring of patients.

**Slide 15 - Therapeutic Milestones****Dr. Michael Deininger:**

I don't really expect anyone to read that, but it's just to illustrate to you that we have to find milestones of treatment success. And I think one should look at these milestones, as a physician, at a time when we sit down with our patients. Go over the data, and then basically, make a determination whether we think that the patient's response is optimal. That is, that patient is doing just as expected, not any worse than the average CML patient would be doing. In that case, one would just recommend to continue the current treatment.

There is a middle category in yellow that we call a warning. These are patients who are responding but are responding not quite as well as we would like. In these patients, one will typically say, let's monitor them more closely, maybe bring them back after four weeks rather than up to three months, and see how things go and whether we need to make a change to the therapeutic strategy.

And then, on the right, these are patients who really have evidence of failure on the TKI. So, for example, at three months, if there is still not a complete hematologic response--so, still a high white cell count, for example. That would be an indication that one needs to think about a different treatment strategy.

**Slide 16 - CML Therapy – Available TKIs**

So, what are the available tyrosine kinase inhibitors? And I, quite frankly, admit that this is a reflection of what is available in the developed world, realizing that many countries in the not-so-fortunate parts of our world will not have access to the full spectrum of tyrosine kinase inhibitors. Imatinib, or Gleevec, is indicated for first-line therapy, and it's the drug that has been around longest. Dasatinib, nilotinib, and bosutinib are referred to as second-generation TKIs. Dasatinib and nilotinib, in the U.S. and Europe, are approved for first-line treatment, and also, for patients who develop imatinib resistance. Bosutinib is, I think, similar to both nilotinib and dasatinib and is currently indicated for imatinib-resistant patients. And then, lastly, there is a so-called third-generation inhibitor called ponatinib, or Iclusig. And this is indicated if other TKIs are not indicated or if patients have developed a certain mutation of their BCR-ABL.

**Slide 17 - I've been diagnosed with CML. Which TKI should my doctor pick?**

Now, of course, there's a considerable number of options here, and so the question is, what is the best tyrosine kinase inhibitor to start treatment, assuming that everybody has everything available. The key thing to consider is whether I'm in the chronic phase. If the chronic phase is diagnosed, then imatinib, that is Gleevec, nilotinib, Tasigna, or dasatinib, that is Sprycel, are all good options. If there's already evidence for progression to the accelerated phase or the blastic phase, then imatinib is not a good option anymore because it is the weakest of these inhibitors. And, typically, it's available when one would prefer a second-generation inhibitor.



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Now, I want to qualify that a little bit, because even in the chronic phase, you can distinguish between patients with high- and with low-risk. In the patients with low-risk, the outcome of all the three drugs that I already mentioned is very, very good. In patients with high-risk disease, high-risk chronic phase, there are some indications that they might benefit from the second-generation inhibitor. That is, of course, something that your physician needs to discuss with you, balancing the slightly lower efficacy of imatinib with some side effects that you might experience on the second-generation inhibitors dasatinib or nilotinib.

A third really important consideration is what other medical conditions a patient has. And, lastly, what is my lifestyle? Some of these agents such as dasatinib or imatinib are taken once a day and they can be taken with food, without food. It doesn't really matter whereas nilotinib is a twice-daily regimen, and it should be taken on an empty stomach. And, for some people, especially those, maybe, who travel a lot, have a very irregular life, this can be a real challenge.

**Slide 18 - High Risk CML**

So, I already mentioned high-risk CML in chronic phase. So, this would be a situation where everything is chronic, but there are some features that suggest that this disease might be behaving a little more aggressively than the average; for example, if there are immature cells present, if the platelet count is very high, or if the spleen is very large. And that portends a higher risk of progression from the chronic phase to the accelerated phase or blastic phase. And, as I've already mentioned, we think that these patients may be better candidates for treatment with a second-generation TKI.

If there is progression to accelerated phase or blastic phase, then we would typically also recommend to consider stem cell transplant. That, of course, can be a very difficult decision, and certainly, a decision that goes over the discussion we can have today that requires referral to a transplant center so that you can get expert advice on the risks, on benefits, of a stem cell transplant.

**Slide 19 - Past Medical History**

I already mentioned the past medical history, or concomitant conditions, as an important fact in picking the right TKI for a given patient. This is a table that is based partially on data, and also, partially on good judgment and experience. And what it shows is that the various tyrosine kinase inhibitors that we have available should be avoided in certain circumstances; for example, if somebody has a history of diabetes, or maybe even badly controlled diabetes, nilotinib (Tasigna) is not a good choice because it's going to make the glucose (blood sugar) levels even higher.

Conversely, somebody with a history of cardiovascular disease, thromboembolism, is not a good candidate for ponatinib, because there's a high risk of thromboembolic events like arterial occlusive events with ponatinib. So, we can use these preexisting conditions to help

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us pick the agent that is likely to have the fewest side effects; having said that, however, there is hardly any total contraindication. So, in other words, if the CML demands it, then you should use that as the overriding criteria to select the TKI. In many cases, however, you'll be able to take into account the preexisting medical conditions.

**Slide 20 - Side Effects of TKI Therapy**

Now, all the TKIs have side effects. But, I think we need to put that in some perspective, and I just made a couple of points here that I think are important to consider. The first one is that, prior to imatinib, the average survival on drug therapy, which was, really, not very well tolerated, was five years. Now, with imatinib, we think that most patients will have a normal lifespan.

Stem cell transplant was available as a curative treatment, but it can cause severe side effects, so even death. So, that would be death from the procedure itself and not from the disease. So, all TKIs do have side effects, but also, supportive care can frequently mitigate these side effects. It's really important to have a discussion about side effects with your physician and to devise a strategy how to minimize the side effects so that you can have good quality of life.

I think it's very important to make sure that, when you talk to your physician, to try as much as you can to distinguish between what is related to the TKI and what is related, maybe, to other things. So, for example, somebody has a little stress in his personal life. That could lead to depression, and that may have nothing to do with the tyrosine kinase inhibitor.

So, for the position, it's really important to know about that because only when we can ascribe the causality with some level of position, we'll be able to do the right thing. What we see more frequently is that patients very rapidly switch from one TKI to the next without making a concerted effort between them and their providers to manage the side effects. And so, in some instances, one comes full circle very rapidly, burning through all the available treatment options. And then, of course, at some point, you're back to step one again, and in these instances, it's really becoming quite challenging to find any TKI that eventually works.

**Slide 21 - Adverse Event Rates on Dasatinib vs. Imatinib**

On the next slide, I just give you a flavor of side effects in a comparison study that compared dasatinib versus imatinib. And what you see here is that, by and large, the side effects with dasatinib are less than the side effects with imatinib. So, there are some of these orange dots here that pull away towards favoring dasatinib over imatinib.

If you look at the overall tolerability, then the second-generation TKIs, dasatinib and nilotinib, and also bosutinib are better tolerated. The problem is that dasatinib, and nilotinib as well, have some side effects that didn't show up in the early studies. With dasatinib, for



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example, some patients have developed tight pressure in their lung arteries, which is a significant condition.

**Slide 22 – Study Drug-Related Non-Laboratory Adverse Events ( $\geq 10\%$  in Any Group)**

On the next slide, you see a similar comparison now between imatinib and nilotinib, so between Gleevec and Tasigna. And again, if you look at the two yellow frames, if you compare nilotinib 300 milligrams twice daily to the standard dose with imatinib; you see that by and large, their numbers are lower, so nilotinib is better tolerated, but nilotinib has, also, an issue, because we've noticed that there is an increased risk of cardiovascular events, so strokes, heart attacks, or blood clots in the arteries in the limbs. So, if you pick a TKI together with your physician, it's really important to go over these issues, and then determine what the right choice is for you. Side effects are one consideration, convenience, as I mentioned, and of course, also whether your CML is low- or high-risk.

**Slide 23 - Survival on Imatinib and Nilotinib at 6 Years**

So, if we look at a question that is maybe critical, that is the question whether the second-generation TKIs have better survival compared to imatinib. It turns out that, at this point, it's very difficult to make that case. Here you see nilotinib 300 milligrams twice daily compared to imatinib. So, this is the left column versus the right column, and if you look at the green boxes here, you see the overall survival at six years. And, you see that, with nilotinib 300 milligrams versus imatinib 400 milligrams, there doesn't seem to be any significant difference. So, while the second-generation drugs are more powerful, and they also induce deeper responses, they have not yet delivered on the promise of better survival.

**Slide 24 - Survival on Imatinib vs. Dasatinib at 5 Years**

And the same, in fact, holds true with a comparison between imatinib and dasatinib where you see that the estimated five-year survival here, again, the green boxes, is literally identical between the two.

That is an important point to notice. Having said all that, when we come to the last part of the presentation--the question whether you can discontinue treatment. There is some suggestion that more patients with treatment of dasatinib or nilotinib will be able to achieve these deep responses that will eventually allow you to go off treatment. Whether or not that's indeed the case and whether this will hold, that we don't know for sure yet, and more data is required.

**Slide 25 - Adherence to Therapy is Crucial For Avoiding Failure**

Now, the next slide shows you something that I think is very important. And, if you just look at the right diagram, there are two curves. The upper curve is the progression-free survival of patients who are very adherent to their medication regimen, and the lower curve is the progression-free survival of those patients who skipped many doses of drug. So, in other words, what it shows is that whether or not you are able to take your medications on a really regular basis makes a very big difference in terms of your subsequent outcomes. That has

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been confirmed by a number of studies, so I think it really holds. Adherence to the medication regimen is very important. It also implies that, if you do have side effects that prevent you from having good quality of life, you do need to bring that up with your physician, and you need to try and develop a strategy that enables you to take your daily medication.

**Slide 26 - Well-managed CML Impacts Survival Less Than Comorbidities**

Now, that is a difficult curve on the next line, but I just wanted to make another case here. This is data from a big trial performed in Germany, and it looks at the survival in a large cohort, more than 1,000 patients with CML. If you look at the very upper curve there, this is what the entire cohort was doing. But, if you now look at this red curve, these are patients who have severe comorbidities, so who have, for example, cardiovascular disease or have diabetes, who have other health issues.

So, in other words, it is these comorbidities that impair their survival. It is not the CML. Or another way of phrasing it would be the treatment is so good that it has, essentially, canceled out the CML diagnosis as a major factor of survival. So, what that means in practical terms is that managing your comorbidities, managing hypertension, managing diabetes and so forth is very, very important and is as equally important as managing your CML.

**Slide 27 - Recognizing Therapy Failure**

So, the next slide shows what I call recognizing therapeutic failure. I wanted to draw your attention to the upper box here. A failure of TKI would be if you failed to reach milestones, if you lose your complete hematologic response, if you lose your complete chromosomal response. If that happens, one should not rush to conclusions, but always look at drug interactions, and of course, for us, if the physician considers that a patient may not be compliant. If the answer to these questions is no, then this is a significant event and a complete workup is required, that is: a physical exam and a bone marrow biopsy, chromosome analysis, and then, also, a BCR-ABL mutation screen.

**Slide 28 - Factors Influencing Selection of Salvage Therapy**

If that does happen, then again, we are faced with the need to select salvage therapy. And again, the disease phase, in this case, now, the mutation analysis, the previous treatment history and the past medical history are important to pick the right agent.

**Slide 29 – Resistance Due to BCR-ABL1 Point Mutations**

For the sake of time, because I'm a little bit over time, I'll skip this slide, and I'll just give you an overview, or a flavor, of what might be driving these decisions.

**Slide 30 - Second Line Therapy: Treatment History is Important**

Say a given patient is initially treated with Gleevec, but then, fails.

**Slide 31 - Treatment History and Salvage Therapy – Likelihood of a Complete Chromosomal Response**

**Dr. Michael Deininger:**

If you now consider a second-line treatment, then dasatinib, nilotinib, and bosutinib are all fairly good choices. They will give you a 40-50% rate of a complete cytogenetic response. Ponatinib is better, but since it has a lot of side effects, it's indicated only in patients who have the T315I mutant.

Now, say, the patient gets treated with nilotinib, but then, unfortunately, fails again.

**Slide 32 - Treatment History and Salvage Therapy – Likelihood of a Complete Chromosomal Response**

Then, for the third-line therapy, dasatinib and bosutinib are not great choices because they will give you only about 20% complete cytogenetic response rate, whereas ponatinib will give you 50-70%. So, in other words, we need to know the history of a patient to make the right pick in terms of any kind of salvage treatment.

**Slide 33 - Treatment-Free Remission (TFR)**

Now, lastly, let me cover treatment-free remission. This is a study that was published a few years ago that looked at 100 patients who were treated with Gleevec, and then, became negative by PCR and remained negative for at least two years. And then, they stopped treatment altogether, and when you look at this left part of a curve, is the likelihood of maintaining in remission without continued treatment. And then, you see that this is about a 40-50% rate. So, in other words, somewhat less than half of the patients maintained their responses despite no continued treatment.

Now, that study has been updated now with a five-year follow-up, and what we see is that, once you have maintained a response for about two years, you're very, very likely to maintain that response with subsequent follow-up. So, in other words, patients who are prone to have a recurrence of their disease will declare themselves relatively early.

**Slide 34 - Maintenance of Deep Molecular Response After TKI Discontinuation in ~ 40% of Patients**

That has been confirmed by a number of other studies, predominantly outside of the United States. But, we are just about to complete a trial called *The Last Trial*, where we essentially look at the same connection, and I predict that the data will look quite similar to the ones I just showed you.

**Slide 35 - EuroSKI Study**

The biggest study that looked at this issue is the *EuroSKI* study, and just to remind you that the data in all of these studies are very, very similar.

**Slide 36 - Recurrence-Free Survival****Dr. Michael Deininger:**

The only difference that you see and that you might discuss with your peers is the definition of recurrence. If you are a little bit more lenient and you define recurrence as the loss of this major molecular response, so a loss of the 1,000-fold reduction of leukemia cells, then successful discontinuation rate goes up to about 58-60%.

**Slide 37 - Longer Duration of Imatinib Exposure and of Deep Molecular Response Predict TFR**

Now, we've tried very hard to figure out who are the best patients to recommend that, and the two parameters that came out repeatedly is the duration of TKI therapy. In the middle here, you see patients with more than eight years of treatment versus patients with less than eight years of treatment, and you see that those with longer treatment do better. The same holds true if you look at the time that patients maintained their molecular response, again those who maintained it for longer do better, have a better likelihood of maintaining their response, than the patient who maintained their molecular response for a shorter period of time.

**Slide 38- Factors Associated with TFR in Various Studies**

So, that can be used to really guide us a little bit in terms of who to recommend a trial of treatment-free remission.

**Slide 39 - Withdrawal Syndrome Accompanies TKI Discontinuation in Some Patients**

Is that without any side effects? It turns out it isn't. There are about 25% of patients who will have what we call a TKI withdrawal syndrome. This is a syndrome that is associated with bone pain, joint pain. Some patients experience flushing, and fortunately, it always goes away with time, except in some patients who may have some underlying condition that for some reckless reason, was controlled with a TKI and has, really, nothing to do with the CML. But, on the good side, about three quarters of patients will not experience significant side effects when they discontinue their TKIs.

**Slide 40 - Treatment-Free Remission – When is it Safe to Try?**

So, what we've done in the community is to really figure out what we can recommend to patients outside of a clinical trial, and this is what I think we would recommend at this point. You should consider patients only if they have at least three years of TKI therapy and have maintained deep molecular response for at least two years. It's also important that PCR monitoring was fairly dense so that you can be sure about the molecular response. And then, if you decide to do that, it's really important to have frequent lab monitoring, initially, every month, and then, subsequently, every two to three months. And, of course, if you do have a relapse, you have to go back on a TKI, because otherwise, the CML would come back with full force.

## ***Living With Chronic Myeloid Leukemia***

***Michael Deininger, MD, PhD***

***November 2, 2016***

### **Slide 41 – Summary**

#### **Dr. Michael Deininger:**

In summary, patients in 2016 who are well-managed, have chronic phase CML, can expect a normal lifespan. Dasatinib, nilotinib and imatinib are all acceptable options for front-line therapy of chronic phase. Dasatinib and nilotinib should be considered in patients with high-risk. In case of side effects, we should try to manage those first as supportive care and not switch rapidly. But, if we consider a patient intolerant, then a switch is mandated.

### **Slide 42 – Summary (continued)**

Failure of first-line TKI therapy is a significant event and, really, should trigger careful workup and a decisive management change. Progression to accelerated phase or blastic phase should trigger a referral to a center, and treatment-free remission is safe only if it is attempted in the right patients and with proper monitoring. And, again, we would recommend that a center be consulted in this case.

And with that, I conclude, and I look forward to your questions.

### **Slide 43 - Q&A Session**

#### **Ms. Lizette Figueroa-Rivera:**

It is now time for the question and answer portion of our program.

We'll take the first question from our web audience. Doctor, Christine and Beth are both asking if there have been any studies on the effects of the new generic imatinib compared to imatinib (Gleevec) in patients that have changed to the generic.

#### **Dr. Michael Deininger:**

There is data available from Canada from Jeff Lipton's group, and the way I interpret that is that there's really no difference, no visible difference, between the generic drugs sold in Canada, and presumably, that are sold in the United States and the brand Gleevec. I think in some developed countries such as India, there are generic drugs on the market that are not as active as imatinib, and there a great deal of caution is required.

#### **Ms. Lizette Figueroa-Rivera:**

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

#### **Operator:**

This question comes from Bob calling from Connecticut.

#### **Bob:**

Well, thank you. I actually just had the same question that was just referenced. Doctor, could you elaborate on the differential between the drugs you mentioned in the Canadian study and the ones in India? So, how would that compared to what's available in the United States today?

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**Dr. Michael Deininger:**

I think, in the United States, it can be really certain that these drugs are not worse than the brand name because it's highly regulated and there's a lot of scrutiny over these medications. In India, I think, there are more than 20 companies that make Gleevec, and I've heard about data that is somewhat sparse, that some of these preparations don't really contain active agent. So, in these countries, there is a rather big danger to undertreat with the generics. In the United States and any other developed country where drug supplies are highly regulated, I would not foresee any difference.

**Ms. Lizette Figueroa-Rivera:**

Thank you, Doctor, and the next question comes from our web audience. Edward asks, "Are there any signs that would tell me if my CML is advancing without my having to have new blood tests performed?"

**Dr. Michael Deininger:**

Well, I think if your CML was progressing to the accelerated phase or blastic phase, then you might get symptoms such as night sweats, or you might lose weight. But, these would be considered very alarming and very late symptoms of progression. There is no symptom that would allow you to detect an early relapse on a TKI, so the only way of catching that is the regular blood testing.

**Ms. Lizette Figueroa-Rivera:**

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

**Operator:**

The next question comes from Madeline calling from New Jersey.

**Madeline:**

Hi, Doctor. My question is what drug is it that causes the blood clot in the arteries?

**Dr. Michael Deininger:**

The risk is high for nilotinib. That is Tasigna, and it's really, really high for ponatinib. That is Iclusig. So, these two drugs have been associated with considerable risk of these blood clots.

**Ms. Lizette Figueroa-Rivera:**

Thank you, Doctor, for clarifying. And the next question from the web is from Jennia, and she asks if there's any research on pregnancy for women with CML.

**Dr. Michael Deininger:**

There is research in the sense of collecting data of patients who got pregnant while on Gleevec or other TKIs or who discontinued TKIs because they wanted to get pregnant. So, for the patients who got pregnant while they were taking Gleevec, there is an indication that



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there is a higher risk of fetal abnormalities. So, it's highly recommended to avoid that, especially in the first and second trimester. The third trimester is probably okay. That is true only for women, so there's no evidence that children fathered by men on Gleevec or other TKIs have an increased risk of fetal abnormalities.

Now, if a young woman who has been diagnosed with CML and is on a TKI considers pregnancy, then it's really important to have a very informed discussion with your oncologist how to manage that, and there are various strategies to do that. What we would recommend is to see whether you can achieve a deep response in the first place. Then, you'd discontinue treatment, you'd become pregnant, and one would monitor the CML very closely and hope that there's even no recurrence or a slow recurrence that allows you to carry the baby to term. And then, you could go back on a TKI.

Other people have recommended to treat patients during pregnancy with interferon, which is an old agent for CML that we hardly ever use today. But, it is somewhat efficacious, and that would then serve to keep the disease at bay. I would also recommend to involve a gynecologist because we would consider these pregnancies to be high-risk, and they just require a lot of attention to detail. But, it's an issue that comes up many times nowadays, and there are many patients who gave birth to children taking the appropriate measures to avoid exposure of the baby to imatinib or another TKI.

**Ms. Lizette Figueroa-Rivera:**

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

**Operator:**

Our next question comes from Ming-Hsuan calling from California. Please state your question.

**Ming-Hsuan:**

My question is, I was diagnosed in April this year, and I just got Sprycel until now. I thought it was 100, and from the PCR it's gone down to 20%. And then we keep checking it, and it decreased and I was so happy. And my body, in all of September, had a lot of cold sores. Then, the blood test went down, so I have to run to the hospital to get the blood transfusion. And, now, the PCR tests show the cancer cells were back to 53%, so I'm waiting for a second opinion, however, I'm so scared. So, my question is, what does that mean?

**Dr. Michael Deininger:**

So, it probably means that your CML is not responding quite as well as it should to the TKIs, because I think, by now, you should certainly be lower than 50%. And it seems that you cannot really tolerate the Sprycel, so the dose, the intensity of the treatment, is not good enough to really induce a good response. So, you may have to switch to another TKI. One should certainly do a thorough analysis to figure out whether one can see a reason why you

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are not responding like most people respond, and then, base decisions on this data. Depending on how old you are, we would probably look at all that, and then, also, refer you to a transplant center to basically evaluate you and get all the data in place. But I think it's good, too, that you get a second opinion, and I see you need to change your strategy.

**Ms. Lizette Figueroa-Rivera:**

Thank you, Doctor, and the next question comes from our web audience. Michael asks, "I take Imodium® (loperamide) one to two times a day. Are there any other suggestions for controlling diarrhea?"

**Dr. Michael Deininger:**

I'm afraid not really. So, I think you have to titrate the Imodium so that you don't get too much of it. There are other antidiarrheals, like Lomotil® (diphenoxylate hydrochloride and atropine sulfate), that you could try if Imodium doesn't really do it for you. I'm afraid there is little else in terms of controlling that. Depending on what you take, you could try and split the dose in two to try and control it a little bit more, but the gastrointestinal side effects are quite significant in some patients.

So, what I would do, I would take up to two pills of Imodium, and that's four milligrams. Then, if you start to get cramping, I would try Lomotil and see whether that works better for you. If that didn't work, then I would try to split the dose.

**Ms. Lizette Figueroa-Rivera:**

Thank you, Doctor. A lot of patients are writing in about severe side effects, and Tony also asks about fatigue. "Is there anything that could be done for fatigue?"

**Dr. Michael Deininger:**

I think fatigue is a side effect that we have underestimated for a long time. I would approach it like this. First of all, try to understand whether there are other factors could contribute or account for the fatigue, so maybe, that would be a situation where I would recommend just go off drug for a week or so and see what kind of difference it makes. If you notice a significant difference, then I think the next question would be, is your hemoglobin value low. Some patients develop anemia that can contribute to the fatigue.

And then, with that information, I think you should have a discussion with your physician whether switching to another TKI is indicated. I would put the threshold relatively high because all the TKIs do that to some extent. I think Gleevec is probably the worst offender, but all of the TKIs can do it. So, if you did switch, I think it should be based on as complete a data set as it can get. Beyond that, I think the recommendations would be of a very general nature. That is, we've seen success with people getting on a regular exercise program, so physical exercise like going to the gym, doing everything that helps you furnish

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**Dr. Michael Deininger:**

your body. But, against the fatigue itself, I'm afraid there is no agent that really controls that very well.

**Ms. Lizette Figueroa-Rivera:**

Thank you, Doctor, and we'll take another question from the telephone audience, please.

**Operator:**

Our next question comes from Shirley calling from Tennessee.

**Shirley:**

Hello, Doctor, and thank you for your help. I was diagnosed in '93, so I am a long-time survivor. And I was on Hydrea® (hydroxyurea), and then we tried 9 million units daily of interferon. And I did that for three or four months and couldn't tolerate it. Anyway, I've been on Gleevec since Christmas of '99, and in the last couple of years, maybe three, I've developed peripheral neuropathy, and I can deal with the cramps and all of that. Does that peripheral neuropathy cause muscle weakness, because that's a problem that I'm just losing my legs and my hands, the use of them, and I was wondering if that was a side effect of the peripheral neuropathy, which I know is caused from the Gleevec.

**Dr. Michael Deininger:**

So, in order to sort that out, you should see a neurologist. There are two types of nerves: the ones that, basically carry sensation, and the nerves that deliver an impulse to your muscles to make them work. With Gleevec, it's typical sensory nerves, or the ones that carry sensitivity to touch and so forth, that are affected. I think muscle weakness would suggest that you have an issue with the nerves that stimulate your muscles, and I don't think this would easily be ascribed to the Gleevec. So, what I'm saying in way too many words is I think you should see a neurologist and have a thorough evaluation. Also, to see whether there's any other cause that might explain that; if you have ruled out any other cause as much as you can, then I would think, if one says this is possibly Gleevec related, you should switch to another agent. Switch to a second-generation TKI.

### **Slide 44 – Support Resources**

**Ms. Lizette Figueroa-Rivera:**

Thank you so much for your question, Shirley, and thank you all for your questions today. Shirley, it's always nice to hear from a long-time survivor. And special thanks to Dr. Deininger for your continued dedication to CML patients. You and your colleagues' research successes have really made a positive impact on so many people's lives.

LLS has a specific financial assistance program for CML patients to pay for your PCR testing costs. Please contact us for more information toll-free at 877-614-9242 or [www.LLS.org/pcr](http://www.LLS.org/pcr).

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**Ms. Lizette Figueroa-Rivera:**

Again, we would like to acknowledge and thank ARIAD Pharmaceuticals, Inc. and Novartis Pharmaceuticals Corporation for support of this program.

Dr. Deininger, 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, and we hope that you will join us in the future as we strive to keep you up to date on the latest advancements for CML, as well as all of the blood cancers.