Neil P. Shah, MD, PhD
May 21, 2015

Slide 1 - Welcome and Introductions
Operator
Greetings and welcome to **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
Thank you and hello everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. A special thanks for Dr. Neil P. Shah for sharing his time and expertise with us today. Before we begin, I'd like to introduce The Leukemia & Lymphoma Society's Senior Vice-President of Research, Dr. Rick Winneker, who will share a few words. Dr. Winneker, please go ahead.

Dr. Rick Winneker
Thank you, 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 ensure access to treatment for blood cancer patients. Our vision is a world without blood cancer.

For more than 60 years LLS has helped pioneer innovation such as targeted therapies, and immune therapies that have improved survival rates and quality of life for many blood cancer patients. And you will hear today about several of those targeted therapies that have had such a tremendous impact on the lives of patients with Chronic Myeloid Leukemia.

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 free blood cancer information, education, and support. And we touch patients in their communities through our 58 chapters across the United States and Canada. LLS also acts as the voice for all blood cancer patients. We advocate for patients and survivors and their families, helping them navigate their cancer treatments and ensuring that they have access to quality, affordable and coordinated care.

We are fortunate to have as our presenter today Dr. Neil Shah, one of the nation's leading experts in Chronic Myeloid Leukemia. We appreciate his dedication to supporting our mission and his commitment to caring for patients living with blood cancers. I'd like to thank him for providing us today with important information on CML, thank you all. And now I'll turn the program back to Lizette.

Ms. Lizette Figueroa-Rivera
Thank you, Rick. And we would like to acknowledge and thank Novartis Oncology for support of this program.

Slide 2 - Living with Chronic Myeloid Leukemia (CML)
Ms. Lizette Figueroa-Rivera
I am now pleased to introduce Dr. Neil P. Shah, the Edward S. Ageno distinguished professor in hematology oncology, leader of the Hematopoietic Malignancies Program and Helen Diller Family Comprehensive Cancer Center at the University of California in San Francisco, California. I am privileged to turn the program over to you, Doctor.

Dr. Neil P. Shah
Thank you very much. And thanks to everybody for joining. And I especially want to thank The Leukemia & Lymphoma Society for asking me to provide this presentation. And everybody who is listening, I hope, will understand the tremendous impact that The Leukemia & Lymphoma Society has made on the outcomes of this disease and is striving to make towards the outcomes of other diseases. And I certainly do what I can to try to support them in any way possible. And I strongly encourage you all to do the same.

Slide 3 – CML Background
So, what I would like to do next is go through some background about CML, touch upon some of where things stand today in terms of frontline treatments, as well as treatments for people who don't respond adequately to frontline treatment options and how we define who's not responding adequately. And also talk about some of the ongoing treatment investigations, including treatment discontinuation trials in people who are responding extremely deeply, as well as touch upon one agent in clinical trials that, at least to my eye, looks like it may be the next new therapy to hopefully be approved. It's still very early in its development, but the good news is there are multiple options for people living with this disease. And I, above all else, want to try to save time towards the end for questions that are coming through online or that people may have via telephone.

Slide 4 – CML - Clinical Features
So, to begin with background here. Chronic Myeloid Leukemia, clinically, in the United States, there are about 6,000 new cases every year. The typical age is somewhere in the 50 to 60 range. Of course there are people much younger than this. I have some people in my practice who were diagnosed at age 13, and I've heard of cases even below, before the age of 10. And then, of course there are people who are not diagnosed until their 70s or in some cases even their 80s. But, the typical is somewhere between 50 and 60.

Neil P. Shah, MD, PhD
May 21, 2015

Dr. Neil P. Shah
The number of new cases in the U.S. is only going up very gradually as the population size increases. So, we're not seeing anything that's hinting at an increased number of new cases relative to the population size. And we don't, therefore, have any sense that there are any convincing risk factors that we can put our fingers on. Now, of course, it's very natural when diagnosed with a blood related cancer to look back and try to figure out, was there something I could have avoided that caused this? That's a completely natural sentiment. Unfortunately the only really convincing risk factor that we know of is exposure to a high amount of radiation. This became clear following World War II in Japan. The atomic bomb survivors had a higher risk of developing a number of types of blood related cancers, including Chronic Myeloid Leukemia.

Of course, most people today do not, thankfully, have that risk factor. As far as whether lower levels of radiation--you know, people who maybe have numerous CT scans or x-rays and so on. Truthfully, it's hard to know for sure. We don't think that there is a level of radiation that's completely safe. And so, it's possible that people who are exposed to higher levels of radiation in our present day world may be at higher risk. But this has been very difficult to really pin down.

As far as the disease itself, it's useful to think of the disease in two broad phases. The first is the chronic phase. And we're gonna spend most of our time talking about the chronic phase. And the second is the advanced phase. And the advanced phase can come in a couple different varieties. One is what's called the accelerated phase, which is really an intermediate phase between the chronic phase and the blast crisis phase. And the blast crisis phase itself can come in two different subtypes. One is called myeloid blast phase and one is called lymphoid blast phase.

Slide 5 – CML – Chronic Phase
But to start off, we're going to focus primarily on chronic phase CML. And in the United States about 80 to 90 percent of people with newly diagnosed CML are actually in the chronic phase. Many of these people have no symptoms whatsoever. If they do have symptoms, some of the more common ones are fatigue, night sweats, sometimes some weight loss. Sometimes people will notice some discomfort in the left side of their abdomen from an enlarged spleen.

And we know historically, before we had really effective medical treatment, so in the 20th Century, we could expect on average for the chronic phase to last somewhere around four to six years before it would transform to the more aggressive advanced phase accelerated and blast crisis phase. But, after 2000, with the advent of the therapies and we're going to be spending most of the time talking about this, it's really not clear how long the chronic phase will last. It's clearly greater than 10 years as far as average goes. And in most patients it's our prediction and certainly our hope that it will be long

Dr. Neil P. Shah
enough to allow most people to live an otherwise normal lifespan, provided that they're on treatment and or responding and responding well.

The most important thing I would say about the importance of chronic phase is that we've learned that whatever treatment we have for this disease, because this is an earlier phase of the disease, we have the likelihood of achieving more durable responses in chronic phase than we do in the more advanced phase, in general.

Slide 6 – CML – Blast Crisis Phase
Looking at the other end of the spectrum, the blast crisis phase, the problem here is that the cells have picked up additional mutations and now they don't actually mature fully. And so, we have all these immature blood cells that are preventing the formation of normal white cells, which should help fight infection, preventing the development of normal red cells, which carry oxygen, and the development of normal platelets, which help prevent bleeding. And so, people in the blast crisis phase typically suffer from consequences of this, such as bleeding, infections and profound fatigue due to anemia. And even in today's era, unfortunately, with medical therapy, the survival of blast crisis phase remains typically relatively short, as you see, six to nine months. It is possible to cure some of these people, but we first have to get them into remission and then get them to bone marrow transplantation. But, with medication alone our success rate with curing people in blast crisis is really very poor. We do need to rely on that cell transplantation.

Slide 7 - First Hint at the Cause of CML: The Philadelphia Chromosome
The first hint of the cause of CML, and, you know, it bears mentioning that we know more about this type of leukemia and this type of cancer at the molecular level than I think any other type of cancer. And the first hint of the cause was the identification of the Philadelphia chromosome. So, the Philadelphia chromosome is actually the result of a chromosome breakage within the leukemia cells that result in the inappropriate fusion of two separate chromosomes. Virtually all patients with Chronic Myeloid Leukemia will have a demonstrable Philadelphia chromosome within their leukemia cells.

Slide 8 - The Philadelphia (Ph) Chromosome Leads to CML
And so, this is generally very important in helping establish the diagnosis. At the molecular level what we've learned here, here I'm showing in red chromosome 22 and focusing on one particular region that is involved in the chromosomal breakage that occurs during the Philadelphia chromosome translocation event. And in blue-green you see the ABL gene on chromosome 9.

Neil P. Shah, MD, PhD
May 21, 2015

Dr. Neil P. Shah
So, what happens is these two genes, BCR on chromosome 22 and ABL on chromosome 9, end up being fused, you know, broken apart a little bit and fused together in a sort of a head to tail fashion as a result of the Philadelphia chromosome. And ABL belongs to a family of genes we call tyrosine kinases. These are very important for a number of processes and daily life. And for encouraging cells to grow when it's appropriate for them to grow. But, of course, as you can imagine, these types of genes and the proteins they encode are very tightly regulated because you don't want to have uncontrolled growth.

But, when you have this Philadelphia chromosome you have the tyrosine kinase activity of ABL activated as a consequence of its fusion to BCR. And it is not down regulated ever. And so, this leads the cells that have BCR-ABL to continue to grow, to continue to divide and this is what leads to the high white blood cell count and progression of the disease.

And, moreover, previous studies back in the 1990's demonstrated quite convincingly that it is specifically the tyrosine kinase enzymatic function of BCR-ABL that leads to the development of Chronic Myeloid Leukemia, at least in laboratory models of the disease.

Slide 9 - Chronic Phase CML - Goals of Therapy
So, moving on then, this led, of course, to efforts to target the tyrosine kinase activity and we're going to spend a fair amount of time talking about that in just a few moments. So, when we think about chronic phase CML, because chronic phase CML is not itself immediately life threatening, it's only the progression to blast phase that typically will end up causing significant life threatening consequences for people. If we could above all else, prevent that disease transformation, then people would be, in essence, functionally cured in the sense that they would not likely die due to their disease. And if all that we're doing is preventing this transformation and not really getting a deeper level of remission, and that would require lifelong therapy, and implicit in lifelong therapy, of course, are therapies that are well tolerated and that allow people to live an otherwise normal everyday life.

Of course, a higher goal is to actually truly cure the disease, which by definition means people are able to stop all treatment and not have the disease come back. We know that the best treatment modality that has been proven to achieve this is bone marrow transplantation, allogeneic stem cell transplantation, which has about a 70% cure rate in this disease in chronic phase CML. But, the part that's difficult for everybody to really be comfortable with is there's a 20% chance of short term death, not due to disease progression, but due to the toxicity of the transplant procedure itself. And of the 70% to 80% who survive the first couple of years, about 50% to 60% are at risk of developing chronic complications from something called graft-versus-host disease.

Neil P. Shah, MD, PhD
May 21, 2015

Dr. Neil P. Shah
So, many people feel it's a kin to trading one disease, in many cases one that had relatively few symptoms, chronic phase CML, for another disease which can be more symptomatic in some cases. But, some people do very well with transplants and have a normal quality of life.

But, we have to look at the whole possibility of potential outcomes. Interferon alpha is an older drug that was used before the tyrosine kinase inhibitors were developed that we're gonna talk about. This has a low but real likelihood of potentially getting patients into very deep responses. In some cases patients took interferon more than 20 years ago for a relatively brief period of time. They've taken no treatment since and have not had disease relapse 20, 25 years later. So, a small proportion of people we think can be essentially cured with interferon. But it is a small proportion and this drug was associated with a large number of side effects that really rendered it, on the whole, relatively not useful for the vast majority of chronic phase CML patients.

Slide 10 - FDA Approval, May 2001
So, what changed everything was, of course, the tyrosine kinase inhibitor and the very first to be developed was imatinib, also known as Gleevec®. And when it was approved in 2001, it really represented a change in our paradigm of how we approached the treatment to cancer, because this was really the first treatment that where an identification of the specific genetic abnormality that was driving the cancer was successfully and highly successfully treated with a pill that was designed to counteract the effects of the activating mutation, the activating BCR-ABL mutation in the case of Chronic Myeloid Leukemia.

Slide 11 - Imatinib - Conclusions
To conclude with the first of the tyrosine kinase inhibitors, imatinib, this was approved in 2001 and very rapidly adopted by clinicians as standard frontline treatment. So, it's been approved now 14 years, almost exactly. And we had 8-year follow-up presented as the longest follow up from the initial study and the overall survival that was observed after 8 years in people who were randomized to start imatinib as their first therapy was 85%, which, if you recall, what we mentioned at the outset, we would have expected after 8 years far fewer than 50% of people to be alive. And so, this is obviously highly, highly encouraging. Approximately 7% of patients are estimated to have died due to their disease after eight years. And that's relatively low. We'd like to make further inroads into that, of course.

Dr. Neil P. Shah
In terms of the patients having deep levels of remission, we're talking a moment about the importance of achieving what's called a complete cytogenetic response. This is where there's no evidence of the Philadelphia chromosome in the bone marrow after typically 12 to 18 months. But, on this study with eight years of follow-up, over 80% of people had that level of response.

But, on the flip side, after 8 years, only 55% of the people who started the drug 8 years earlier were still on it and on the study. And so, there are a number of reasons for why that figure is relatively low, which largely includes, in addition to those 18% who did not initially achieve that level of remission, people who achieved it and then lost it. So, their disease became resistant, or people who had tolerability issues, and so on.

Loss of response is, thankfully, relatively uncommon, but it does occur. And usually if it does occur, it usually does so within the first 3 to 4 years, which speaks to the importance of careful follow up, especially during that time period.

We haven't learned of any new concerning side effects with longer term use of imatinib, so it's been used, as I mentioned, about 15 years. But many people do experience day-to-day bothersome side effects, and we'll talk a little bit in a few moments about things that we can do to try to minimize that and maximize quality of life.

Slide 12 – Imatinib Resistance
Let's take a moment now to now talk about the people who are not doing so well on imatinib and how do we define these or how do we identify these. And this has largely been done empirically through evaluations of patients and following them over time and asking can we devise tests that predict who is going to well versus who is not going to do well.

Slide 13 - BCR-ABL Level Following 3 Months of Imatinib Predicts Overall Survival (PCR)
One of the more recent ones to have been pretty widely adopted is shown here. So, this is using a test that can be done on the blood. This is called a PCR test (Polymerase chain reaction), that quantifies the amount of BCR-ABL in the blood, and here you're seeing patients divided into two groups based upon how deep their molecular response is after 3 months of imatinib therapy. So, if they've had a deeper response and their BCR-ABL level is less than 10% compared with what a standard patient would have pretreatment, you can see that their 8 year overall survival, close to 93%, is far superior to people who have a higher level of disease burden.

And so, this is actually very important, in my opinion, because we do have other treatment options for people who don't do so well on imatinib now, which we'll get to in a

Dr. Neil P. Shah
moment. And so identifying people early who start imatinib, who are not doing well, I think is very important to try to maximize treatment outcome.

Historically, we would wait a little bit longer to 12 months, to 18 months to try to determine how people were doing. This involved the repeat bone marrow biopsy. And we still do this on occasion, but, of course, I think, certainly, I don't have to speak for patients, but both patients and physicians would love to try to minimize bone marrow biopsies and maximize the use the blood draws if we can, instead.

Slide 14 - Chromosome Response After 12-18 Months of Imatinib Predicts Outcome
So, what this is showing is older data, looking at the likelihood of being free from progression to accelerated or blast phase. So, we'd like to stay close to 100% and not progress. And what you see here, first of all if you focus on the red curve you see those people who never achieved that complete cytogenetic response by 18 months. You can see that those people, 87% of them are free from progression, which is good. But, it's lower, significantly lower, than the green and the yellow curves. And those are patients that had a complete cytogenetic response. They're further subdivided into those that had a deeper response as assessed by PCR. And so, if you had a 3-log reduction, essentially in this analysis none of those patients actually progressed. A very small minority of those that had a complete cytogenetic response with less than a 3-log reduction did progress.

So, at the present time, what we think of as being one of the most meaningful treatment goals for people with chronic based CML is achievement of a complete cytogenetic response, ideally no later than 12 to 18 months after starting tyrosine kinase inhibitor or what we call TKI therapy.

Slide 15 - CML – Monitoring Recommendations
What is recommended for diagnostic and monitoring purposes of CML is bone marrow assessment at diagnosis in all patients. This should include chromosome analysis, as well a technique called FISH to look for BCR-ABL and a third technique called the BCR-ABL PCR, which we've talked about. The PCR testing is one of the most critical things we have to follow responsiveness on the disease, on treatment. And this should be done every three months following the initiation of treatment. And as I eluded to, the first treatment milestone, if you will, is a level of less than 10% on the international scale after 3 months or maybe as long as 6 months of treatment.

The reason I've underlined on the international scale is that unfortunately there are still labs that do not conform to this scale. And they use different units. And in some cases

Dr. Neil P. Shah
even at diagnosis, based upon the unit that they use, people can be confused and think that someone has very little disease to begin with, which is not the case.

Our second treatment milestone is a PCR of either 0.1% by 12 to 18 months or a bone marrow biopsy looking for the cytogenetic response and showing no sign of the Philadelphia chromosome. We do look for drug resistant mutations in people who lose response to treatment, assuming that they are reliability taking their medication. And also in some people who have not responded adequately initially to treatment.

Slide 16 – Current Treatment Options
So, moving forward to our current treatment options for imatinib resistant disease.

Slide 17 - Treatment of Imatinib Resistance or Intolerance
Imatinib resistance and intolerance are two issues that many patients have faced. And there were two drugs that were initially developed to deal with these issues. These are dasatinib and nilotinib. Now both of these drugs have activity against the vast majority of drug resistant mutations. Both were approved almost 9 or 10 years ago now. More recently, a drug called bosutinib was also approved, and appears very similar in terms of activity to dasatinib and nilotinib.

Now, all of these drugs had one weakness and that was that they failed to reliably treat people whose disease had evolved one particular resistant mutation called T315I. So, that mutation was resistant to all of these drugs and we had nothing that would work for that particular mutation until ponatinib was approved in 2012.

It's a very active inhibitor. It seems to be active against all potential drug resistant mutations that are found following imatinib or one of the other drugs. But, unfortunately, it is associated with a concerning rate of some side effects. And so we don't rush to use this. We use it essentially if we've exhausted the other approved tyrosine kinase inhibitor options.

Slide 18 - Non-TKI Treatment of Imatinib Resistance or Intolerance
There are also, I should point out, non-tyrosine kinase inhibitor therapies that are available. So, we talked, of course, about stem cell transplantation. So, we would normally only do this in today's era in people who either have had prior advanced phase CML, so those 15% of people perhaps who initially are diagnosed in accelerated or blast phase. If we can get them back into a chronic phase we want to them take them to transplant as quickly as possible.

Dr. Neil P. Shah
Certainly anybody who has resistance or intolerance to all of the approved inhibitors, collectively, should be considered for transplant if they're otherwise eligible. And anybody with a T315I mutation should similarly be considered for transplant. Omacetaxine is a protein synthesis inhibitor that was approved in 2012. It's active in a relative minority of cases, so the response rate that was observed was not on the same

order of what we've seen with tyrosine kinase inhibitors. But it does have some activity in some patients. It can cause low blood counts. It can cause hyperglycemia. And to date the responses don't seem to be as durable as what we've seen with tyrosine kinase inhibitors. So, although this is an approved treatment option, I think there are relatively few people who are taking it.

Interferon, coming back to this one, this is a drug that, as we mentioned at the outset, can be curative in some patients, but it's a very small minority. And side effects are problematic. But it is something that's out there and can be an option for people who've exhausted multiple other options. It is also believed to be safe for use during pregnancy, which is something that we do encounter, women who have CML and wish to become pregnant or are pregnant. We do encounter this, of course, from time to time.

Slide 19 - CML – Frontline Treatment for Chronic Phase CML Patients
In terms of the frontline treatment for chronic based CML in 2010 the FDA added nilotinib and dasatinib as options for newly diagnosed patients in addition to imatinib. Based upon large studies that showed that both these drugs, when compared with imatinib, got a higher proportion of patients to a deep cytogenetic response or a deep molecular response. So, based upon that, these drugs were approved. Many of us in the CML specialty world sort of prefer to use one of these drugs in newly diagnosed patients, but there's absolutely nothing wrong in today's day and age with starting somebody on imatinib.

Many patients do tolerate these newer drugs better than imatinib but not all. Some people tolerate imatinib better than anything else. The recommended starting doses are shown there. It is possible to dose reduce these medications. In general we like to do this only when people are showing signs of response, initially, before we go about doing something like this. But this can improve the side effect profile for many people and can improve quality of life.

Neil P. Shah, MD, PhD
May 21, 2015

Slide 20 - Nilotinib and Dasatinib: Some Distinguishing Features
Dr. Neil P. Shah
There are some distinguishing features that people need to know about these newer drugs. So, I have these listed here. So, nilotinib is taken twice daily on an empty stomach. It can cause hyperglycemia in people through a mechanism we don't completely understand. It can cause pancreatitis in a small proportion of people. There is a need to perform EKGs on people before treatment, after one week, and then monthly, because there is an FDA mandated warning related to what's called QT prolongation. It's a change in an EKG, which can predispose people to a potentially dangerous cardiac arrhythmia. And there have been some cases of unexpected sudden death. This is very uncommon, but, because of the nature of it, there is this warning.

And there's also been aftermarket evidence of something called peripheral arterial occlusive disease, this is basically like a thrombotic event, if you will, and ischemic heart disease seems to be higher for this drug than for imatinib.

Dasatinib is taken once daily with or without food. One of the unique toxicities of this is something called pleural effusion. This is collection of fluid around a lung, which can lead to shortness of breath. This tends to occur gradually, but it's something patients need to be aware of as a potential toxicity. There's a small chance of an elevated risk of bleeding. And then we've learned with experience that there are a small proportion of people who may develop something called pulmonary arterial hypertension, where the blood vessels that take the blood from the heart to the lungs become kind of constrictive and lead to this condition, which can also cause some shortness of breath.

So, these are things that people need to know about, of course, when taking these drugs and certainly physicians need to know about. On the whole we think of these drugs both as being really generally quite safe and well tolerated on a day-to-day basis. But, it is important to realize that there can be relatively unique side effects for particular drugs.

Slide 21 - Noteworthy Side Effects of the Approved TKIs for CML
Now, shown here in the middle of this kind of Venn diagram are common side effects of the five approved tyrosine kinase inhibitors, which include low blood counts, liver toxicity, fatigue, electrolyte abnormalities, and then are shown here some of the things that are more common with particular drugs. I want to caution one thing about bosutinib, although there are relatively few things listed there for bosutinib, it's the drug that we actually have the least amount of experience with. And so, I wouldn't walk away from this thinking that bosutinib is the best tolerated drug of all these. But rather, for instance, it does have a very high incidence of diarrhea, much higher than all the other drugs.

Neil P. Shah, MD, PhD
May 21, 2015

Slide 22 – Discussing Quality of Life Issues with Your Healthcare Team
Dr. Neil P. Shah
But, the good news of all of this is that, in most people we can find a therapy that's effective and the best tolerated for them. So, I want to take a moment now to talk about quality of life issues with your healthcare team. I'm sure I don't have to tell you the importance of quality of life. I think sometimes, to be entirely honest, physicians underestimate the impact some of these treatments have on quality of life of patients.

Slide 23 - Treatment-related Side Effects
I know I'm preaching to the converted here, but many people living with CML do suffer bothersome side effects of their TKI treatments. And given that at the present time, for most people, if not all at the present time, indefinite treatment is recommended. I think it's especially important to try to do what we can to maximize quality of life. It can be difficult in some cases to determine whether symptoms may be related to the treatment versus some completely unrelated cause. So, what I like to do is have patients take a brief break from their treatment. If they're in a nice deep response I see no danger in a 2-week break to determine whether their symptoms are potentially related to the treatment. If they are, sometimes there are supportive treatments that can be used. Sometimes we can try reducing the dose. Sometimes we can switch to an alternative therapy.

But, again, I think having multiple choices is really wonderful news for patients because it allows us to, in most cases, identify treatments that are both effective and minimally intrusive to everyday quality of life.

Slide 24 – Emerging Treatment Options
I wanted to take one moment to talk about something I alluded to, a new agent, which is looking relatively promising very early.

Slide 25 - ABL001
This is something called ABL001. This actually binds to BCR-ABL, so it is in some ways a tyrosine kinase inhibitor. But, it binds in a completely distinct region from where the region targeted by the other five drugs. And why this is important is that this may mean that it allows it to be active against the common drug resistant mutations for the standard tyrosine kinase inhibitors. But, it is itself vulnerable to its own drug resistant mutants. So, it'll likely need to be combined with another tyrosine kinase inhibitor. The hope is, by doing so, you'll be able to suppress almost all potential drug resistant mutations. This was also the hope, of course, of ponatinib. But, as we mentioned, due to its side effect profile, it hasn't ended up being up being clinically useful for that purpose.

Dr. Neil P. Shah
This agent is currently in early phase clinical trial evaluation. And some data were presented at the American Association of Cancer Research showing some signs of clinical activity. It's very early, but certainly, at the moment many people are very interested in seeing where this goes.

Slide 26 - Treatment Discontinuation?
So, treatment discontinuation, the last thing I want to mention is that many patients do have very deep remissions to the point where our most sensitive tests, which is the PCR test, can no longer detect their disease. There have been 100s of people who've had this level of sustained remission who have enrolled in trials to examine the impact of treatment discontinuation, and what has been learned, which has been rather eye opening, is that about 50% of such people seem to remain in a deep molecular response despite stopping their tyrosine kinase inhibitor for five years and counting now. There's only been about five or six years of follow-up. But, there's obviously some optimism that some of these people, if not most of these 50% who are remaining in this deep remission after five years will continue to do so. And that they may never need treatment again. But, of course, we don't know that.

At the present time, this should really only be undertaken in the setting of a clinical trial where people can be effectively monitored. We have a couple such trials ongoing at my institution in San Francisco. But, I would certainly encourage you, if you think you might qualify for this and are potentially interested, to seek out a trial in your particular area, if available.

Slide 27 - Summary
So, to summarize, we have three approved TKIs, tyrosine kinase inhibitors, for newly diagnosed patients that are active. And in most cases I'd say reasonably well tolerated. We have two additional agents approved for patients who have resistance or intolerance to at least one of these. We have these other non-TKI treatments that have been around for a while, such as stem cell transplantation and interferon, as well as a newly approved one with omacetaxine. These are not as commonly used because most people seem to do very well on TKI treatment.

It's essential to have the disease carefully monitored to make sure that people are responding well and maintaining their response. Again, quality of life issues, I know I'm preaching to the converted, but I think discussing this with your healthcare team is a significant importance and we have a number of things we can do if people are having problems tolerating their drugs. And there are new treatments continuing to be developed, and as well as we're trying to understand more about who can safely potentially discontinue treatment.

Dr. Neil P. Shah
And so, I would highly encourage people with CML to try to seek out and continue to participate in clinical trials, because all these drugs that we've talked about, they've only been made possible in part due to the participation of people in clinical trials.

And so, that concludes my presentation. And I will now turn it back over to the moderator.

Slide 28 - Question & Answer Session
Ms. Lizette Figueroa-Rivera
Thank you, Dr. Shah, for your very clear and informative presentation. It is time for the question and answer portion of our program. For everybody's benefit, please keep your questions general in nature without many personal details so Dr. Shah can provide answers general in nature.

Ms. Lizette Figueroa-Rivera
We'll take the first question from our web audience. Dr. Ken states that he's alive thanks to Gleevec and participated in the Gleevec drug trials. He later had prostate cancer and successful treatment with radiation. And his question is, "Once you have CML, what is the likelihood of developing other cancers?"

Dr. Neil P. Shah
Yes, thank you very much for your question. Sorry you had to deal with two different types of cancer, but glad you're doing well. So, we don't really know the answer to this question. In the past we haven't had people with CML living long enough to really address the question. The only people who did survive long term underwent bone marrow transplant procedures. And we know bone marrow transplantation itself can lead to an increased risk of secondary cancers. But, now that we have the tyrosine kinase inhibitors and now that we have people living longer as a result, we're able to sort of begin to ask this question.

There was one abstract at the most recent American Society of Hematology (ASH) meeting that tried to look at this. What they did is they looked in Sweden at everybody or at a cohort of several 100 people who had CML and had been on imatinib for several years, and they looked at their incidence of secondary cancers. And they looked at a control population which they tried to gather people of similar age range and gender and so on, to determine what was the expected rate of some of these cancers in people who don't have CML.

And when they compared the two rates they found what appeared to be an increased risk of cancer in people with CML on Gleevec. Now, of course, there's no control of people with CML who were not on Gleevec. So, number one, we don't know whether or

Dr. Neil P. Shah
not this is conclusive. So, this needs to be confirmed. If it is, in fact, confirmed we don't know whether this is related to the Gleevec or whether just having a diagnosis of CML may mean that people are at potentially a little bit higher risk of developing cancer. Again, I caution people not to be very concerned about this. This is one small study from Sweden. It absolutely needs to be confirmed. But, that's the best answer I can give to this at the present time.

Ms. Lizette Figueroa-Rivera
Thank you, doctor. We'll take the next question from the telephone audience, please.

Operator
Our next question comes from Leonti calling from Florida. Please state your question.

Leonti
I've been Sprycel® for about four years. And I'm having a problem with fluid in the lungs. I was in the hospital three different times in March. Can you address that question?

Dr. Neil P. Shah
Yes, so dasatinib or Sprycel, as we alluded to, can be associated with collection of fluid around the lung. I presume that's what you were talking about, something called pleural effusion. It tends to occur more in people over the age of 60 and in people on higher doses. I would say in my clinical usage, I have not encountered it as much as the published frequency. And I think that's because I tend to more aggressively reduce the dose in people for side effects, for other side effect issues. So, that I don't have as many people, perhaps, on the full dose for a very long period of time, as perhaps, some other people do.

But, this is a toxicity that is known to be associated. It does improve generally with treatment interruption. We generally will try dose reduction. It can also improve with a brief course of steroid medications and diuretic medications. But, if it does recur despite continued dose reduction, then I think one needs to, perhaps, think about switching to another of the four approved tyrosine kinase inhibitors, if that's a potential option.

Ms. Lizette Figueroa-Rivera
Thank you, doctor. We'll take the next question from the web audience. We've been getting many questions in regards to pregnancy and CML. And Steven and Ericka ask if you could speak more about the options available for patients who are well controlled on a TKI who want to get pregnant.

Neil P. Shah, MD, PhD
May 21, 2015

Dr. Neil P. Shah
Yeah, well, this is a nice problem to have in some ways because before the improvement in outcomes, if we go back 20 years, you know, younger people diagnosed with this disease wouldn't even contemplate having children because their future was so uncertain. But, of course, you know, it's nice to have this problem.

But, what we've learned is that we don't believe that the tyrosine kinase inhibitors can be safely given to women who wish to conceive. There appears to be, at least from imatinib, where we have the greatest amount of data, a small increase in the number of some birth defects. Many kids are born normally to women who were taking imatinib for at least part of their pregnancy. But, again, there does seem to be a little bit higher risk of some birth defects. So, to be conservative we recommend avoiding the tyrosine kinase inhibitors altogether for women.

For men, the available data suggests that it's not really much of a concern at all for men who want to have kids. They can continue their medication and don't need to do anything special. But, for women, you know, it raises the question, so what do you do then? My personal approach, what I like to see, of course, is a patient who has a very deep molecular response before stopping their kinase inhibitor therapy to try to become pregnant.

So, what I mean by that is I want their PCR level to ideally be no longer detectable and to have maintained that for, perhaps, as long as a year if possible. If not, then, of course, our expectation is the disease is likely, the PCR level is likely to rise. And so, it needs to be monitored.

As far as what we can do if it rises, you know, during pregnancy, it all depends on the amount of risk that the woman is willing to take. If she wants absolutely no risk whatsoever to the child, then the thing to do is just to watch the disease, maybe if the blood count goes too high to do a procedure called leukopheresis to temporarily reduce the white blood cell count. But, what makes us uncomfortable as physicians about that approach is that we worry that the disease may progress, and that it may lead potentially to accelerated or blast phase disease. And so, we would, of course, like to try to avoid that.

Another approach, which as I alluded to in the presentation that most of us believe to be safe during pregnancy is Interferon. Now, it's not as effective, but at least we feel like we're doing something potentially for the disease. And then other medications, hydroxyurea, are believed to be safe after the first trimester.

So, it is a tricky situation. We have to balance both the potential risk to the developing child, as well as to the mother, the risk of not having effective treatment to the mother

Dr. Neil P. Shah
versus the risk to the developing child of being potentially exposed to something that could carry a higher rate of potential birth defects. And, ultimately, it comes down to sort of a level of comfort that the mother needs to decide upon. But, it's a very tricky issue.

Ms. Lizette Figueroa-Rivera
Thank you, doctor. And that has been a very concerning issue with many of our patients. We'll take the next question from the telephone audience, please.

Operator
Our next question comes from Kim calling from California. Please state your question.

Kim:
I was on Gleevec for 18 months and then went on to Sprycel. I've been on it for eight years. And I've just gone off of it. I am trying natural and holistic. I'm just asking the survival rate. Has anyone gone off Sprycel and stayed in remission. My labs actually from being on everything I've been on now, all got better and higher and really great since I got off the Sprycel. But, I'm just wondering is there any sort of life span off Sprycel, off treatment?

Dr. Neil P. Shah
Okay, yeah, thank you for your question. So, this comes back to sort of the treatment discontinuation. I don't know what level of remission your disease was in, but hopefully your PCR was undetectable. Again, we don't encourage people to do this outside of a clinical trial because we'd like to get an answer to your question. We'd like to know what happens over the longer haul. And the only way we're gonna get that information is through participation in clinical trials.

I can tell you that there have been people who've discontinued imatinib or dasatinib or nilotinib they've been very deep molecular remissions, and somewhere around 50% of them seem to maintain that deep molecular remission once they stop their treatment. Again, this has all been done on clinical trial protocols where they have been very carefully followed with monthly PCR testing during the first year on average. And so, that's the best answer, you know, I can give.

Dr. Neil P. Shah
We're still gathering data. One thing I will say is that these drugs have been transformative for this disease. This is a disease where, when we meet people today, you know, the typical conversation I have with them is that, you know, my expectation for the vast majority of them is that they will have an otherwise normal lifespan, but that is because of the medications. And so, the lifespan without treatment from the outset, which I know you took treatment for almost 10 years now, but the life span for treatments without effective therapy, if someone just stops, or if someone's not responding well and they just decide to go off their treatment, I would expect that their life expectancy would be back to about five to six years.

And so, I think it's especially important, in my view, to really make sure that you're being carefully followed by a hematologist and that you don't risk anything more serious. And if you were having side effect issues on dasatinib but you were responding really deeply, as I mentioned, you could try a lower dose to see if you tolerate that well, or we could try switching to an alternative agent. And hopefully then there are others that you've not tried that might also help you feel, perhaps better if you weren't feeling particularly well on the Dasatinib.

Ms. Lizette Figueroa-Rivera
Thank you, doctor. And we'll take the next question from the web audience. Wayne states that he understands the patent for imatinib or Gleevec expires this year, and that a generic form will be available next summer. Can you confirm this information and what would you expect the cost to be?

Dr. Neil P. Shah
Great question. So, yes, my understanding, which is largely based upon things that I've read is that imatinib will go off patent, I believe July 4th of this year, and that by February of next year we may have a generic form of imatinib available in the United States. There are generic versions of imatinib in other parts of the world, of course, and there have been for a number of years.

The question regarding price is actually an excellent question and I don't have a whole lot of insight. I've talked to some people who say that they expect it to be 30 to 40% of what imatinib currently is, which would still, by my calculations, put it at somewhere around $30,000 a year. There are other people who think it's going to be just a few dollars or a few hundred dollars a month. I wish I had some insight into that. I don't know. But it is an excellent question.

You know, many of us are very concerned about price escalation that's gone on with therapies, especially, such as this class, where these are medications that are leading people to live longer, which is wonderful, but the current recommendation, as I said, is

Dr. Neil P. Shah
that people stay on medication. So, a lot of us are kind of concerned if the prices continue to escalate, how does our society and how does our healthcare system accommodate that? This is just one disease. The hope is there will be other types of cancer that this happens to. And we need to come up with ways of insuring, on the one hand, that there is a reason for pharmaceutical companies to exist and to make reasonable profit, but also to keep in mind the greater cost to society and making sure that this is sustainable.

Ms. Lizette Figueroa-Rivera
Thank you, doctor. And the next question from the web comes from Bo. Bo asks, "Do you recommend that your primary care physician take a complete blood count to include a white blood cell count during your annual physical. I ask this in light that you said earlier that 85% of people are diagnosed with CML in the chronic phase. This would identify CML earlier, perhaps, in a chronic phase, correct?"

Dr. Neil P. Shah
Yeah, that's a great question. So, at the present time, the incidence of CML it is one per 100,000 to 200,000 people per year will be diagnosed with CML. So, I agree that if everybody had to have an annual complete blood count we would certainly identify people earlier with CML. And the hope is that, you know, you'd identify more people, relatively speaking, in chronic phase. I'm not the sort of person that thinks a whole lot about cost type issues, but if you think about a cost of a CBC recommended for everybody and when relatively a small number are destined to get CML or any other particular blood related cancer, I think people would probably question the cost effectiveness of that.

But, on a theoretical basis, I agree with you, that if people were being routinely tested, then one would expect to identify people a little bit earlier. But, I don't see that likely to change.

Ms. Lizette Figueroa-Rivera
Thank you, doctor. And our last question comes from Molly. She's asking if other people are having trouble getting dasatinib. Her pharmacy supplier has stopped carrying it and it sounds like other suppliers may also be phasing it out. And she also asks if there's any way that she can get in touch with other parents of pediatric CML patients. Her son hasn't grown in a year and a half and he's 12 years old.

Dr. Neil P. Shah
Okay. So first of all I'll talk about the growth issue. First of all, I'm very sorry to hear that you have a pediatric age family member with this disease, you know, my best thoughts go out to you.

Dr. Neil P. Shah
Growth retardation, you know, has certainly been observed with certainly imatinib. I'm not sure about the other kinase inhibitors. They haven't been used as much. But, it wouldn't surprise me if this was also an issue for the other kinase inhibitors. But, truthfully, I don't know about that, but definitely for imatinib this has been something that's clearly occurring.

And so, but to answer your question about dasatinib availability, I'm actually kind of surprised to hear that because dasatinib, to my understanding, within the U.S. and much of the world, after imatinib, is the most commonly prescribed tyrosine kinase inhibitor. I think there are, in some cases, health insurance plans, I don't, myself, agree with this, but health insurance plans are actually, in some cases, you know, requiring physicians to prescribe one drug in preference to another drug that's not based on anything scientific or with the patient in mind. It's just based in maybe cost or deals that a particular pharmaceutical company may have brokered with the insurance company.

Dr. Neil P. Shah
And, again, I don't myself, think that's a very good idea. I think access to multiple options is in the best interest of patients. And so, I am surprised to hear that.

I imagine there are probably people at The Leukemia & Lymphoma Society that you can contact to help guide you towards people who can help make sure that you're not having undue difficulty gaining access to your medication.

And similarly, back to the other issue, I think The Leukemia & Lymphoma Society is probably an excellent resource for people who have children with Chronic Myeloid Leukemia. They are out there. But, of course, for the reasons we mentioned earlier, thankfully is a disease that doesn't tend to hit people that early. But, it does happen, as you know too well.

Ms. Lizette Figueroa-Rivera
Thank you, doctor. The LLS advocacy team also works to ensure that patients are able to access the treatment that they do need. And, Molly, we invite you to contact our Information Resource Center as they will be able to provide you with resources, such as our online chats or Patti Robinson Kaufmann First Connection program, which can provide you with the opportunity to share experiences with other caregivers.

Slide 29 - Resources to Make Informed Treatment Decisions
Thank you so much, Dr. Shah, for your continued dedication to CML patients. You and your colleagues' research successes have really made a positive impact on people's lives. And for everyone on the call today, we do hope this information will assist you and your family in your next steps.

Ms. Lizette Figueroa-Rivera
And we invite all of you to contact our Information Resource Center. Our Information Specialists are available from 9:00 a.m. to 9:00 p.m. Eastern time at 1-800-955-4572 or you can reach them by email at infocenter@LLS.org. And Information Specialists are available to answer your questions about treatment, including clinical trials or answer other questions you may have about support, including financial assistance for your treatment.

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