Today’s program is called: Not Your Father's CLL and it’s going to be very provocative because CLL has been traditionally a field that in the recent past there was not much to do or talk about and it was something that was treated as much as what you didn't do as what you did do. Thankfully, that field has exploded with more options and better outcomes than historically we have ever seen. I would like to thank Dr. Pagel and his sponsors who are specifically Infinity pharmaceutical, Genentech and Biogen Idec.

Dr. Pagel:

This is a presentation where I'm trying to provide some education for patients. I am going to start showing some actual data that oncologists and hematologists use to make treatment decisions that I hope I can convey to you as important and might stimulate some questions and discussions as well. But the biggest thing I really want to say is that this is a fabulous title (Not your father’s CLL) because what we are learning here is that in CLL the idea of using chemotherapy is becoming almost in the past tense. We are not there yet because we still use it in some cases, but several people who are here or are watching this have past chemotherapy and may have a disease called chronic lymphocytic leukemia and will never see chemotherapy as an option, which is a fabulous thing. It is very positive because it eliminates side effects, it can prevent long-term issues caused by chemotherapy and really, what we are doing is helping people live longer. By using therapies like this, we are treating people who are in their 70's, 80's or even in their 90's in which with the past treatments we would have never treated. We are not only controlling their disease but we are controlling the quality of their life, so imagine how important this is.

We are going to cover different points, first, I'm going to mention that CLL or sometimes known as SLL (small lymphocytic lymphoma) is a disease from blood cells that are part of the bone marrow. The bone marrow makes different types of cells, mainly two kinds: the myeloid cells that include neutrophils, basophils and eosinophil, and there's the other group: the lymphoid cells, which are what we primarily call lymphocytes. Those cells have a job, in general, is to fight infections and to keep us healthy. These cells are born in the bone marrow as stem cells, they grow up and leave home to start circulating and arrive at the lymph nodes that converts into their new home where their job is going to fight infections. This is their normal maturation progress and in a stage, their function is to become antibodies or plasma cells and fight infections. In any of this stages something can go wrong, like an error in the replication and proliferation machinery where they might get stucked in that specific point of their maturation. So, CLL develops in what
we call a mature B cell, these are more matured and when they develop in more immature cells they are more aggressive and in more mature cells is more indolent. CLL is a disease of mature B cells that are circulating in the blood or in the lymph nodes.

Sometimes CLL and SLL can be confused because their essentially from the clinical point of view the same, but from the biological point they are different. If you look at the phenotype of the blood cells, CLL is blood based disease so there’s typically a high white count, maybe a little bit of adenopathy or lymph nodes, while SLL is the other aspect where you have a lot in the lymph nodes and very little in the blood. We treat them essentially the same way, so many times people will get confused about what they actually have or change between CLL and SLL, and that is fine.

CLL is the most common adult leukemia among older than median age, around 70 years. In fact, several patients are in their 50's or younger, for example, I have a 29 year old patient with CLL. We don’t know the reason of the age prevalence, it can be environmental exposure, but in general what we can tell patients about why they have CLL is bad luck, we can't really said what caused it or if there was some predisposition factors.

There are about in 10% of patients that have a familiar component to this, but if your disease is related to your family, it does not behave differently than if it wasn't part of a family. Therefore, we don’t screen all patients and their families, the changes of their relatives to have it too is extremely small and there is really nothing we can control.

So, how do people present with this? The vast majority of people feel perfectly fine with no complaints. Sometimes they present b-symptoms like night seats, fever and weight loss that lead to take a treatment or even sometimes the lymph nodes and spleen grow, and sometimes there could be involvement of the bone marrow that can lead to blood count disorders like anemia or low platelet count (thrombocytopenia). They are not common but it can lead to infections. Rarely have I seen CLL affecting the skin because generally its presentation is in the lymph nodes and in the blood. Just having a high white count it’s okay, that doesn’t cause symptoms and doesn’t need a treatment.

When we are assessing patients, it is very important to know what their stage is with a specific stage system. In the United States for CLL, we use the Rai staging system, people who present in the low or intermediate stage is really in the stage 0 or 1 meaning that they might have an elevation on their white count and they might have lymph nodes. It is very unusual to present with an enlarged spleen, anemia or thrombocytopenia but that can happen in a smaller subset of patients. SLL stages are in a different way, it's staged by a lymphoma staged system we call Ann Arbor's system. One lymph group above the diaphragm or one lymph node below the diaphragm as it shown above is stage I. One unit but essentially on the same side of the diaphragm is stage II, if you have disease on both sides of the diaphragm is stage III and if it's outside the lymph node is stage IV where the bone marrow can be involved. Most of the time we are going to be staging with the Rai system and assessing it as if it’s CLL.

After we staged patients, we like to give some prognostication on the person and one of the mayor tests we use is FISH. This is a very important test for patients to know about, FISH stand for Fluorescent In Situ Hybridization where we can take cells, maybe from the blood, bone marrow or lymph node and use a fluorescent marker or a probe to look for certain things in the DNA. What we look for are different chromosomes and the patters of those different chromosomes, so we can have a marker that might be green that looks for chromosome 17 and we might have a marker that is red that is looking for a different part of chromosome 17, same thing for 13 and the others. This is a major way we tell patients what their genetic profile of their tumor might look like and it is very important because if we have certain features we might treat the disease in different ways. We can be more aggressive with some areas than with others. One of the most important feature we want to know is a deletion of chromosome 17 that is called 17p deletion; but we also look for 11q deletions. It turns out that some of these are actually favorable to have, 13q deletion is the most favorable one to have and it is actually more favorable than having normal chromosomes.

We also look at a variety of other factors that might be related. We look for what we call “the mutation status” of the immunoglobulin heavy chain variable region (IGHV), so if your cells have become more mature they develop a specific antibody for that situation and it is a good thing to have in your CLL. If you don't have those mutations yet, there are
more immature cells with a higher prognostic disease. We look at other markers on the surface of the cell, CD38, Zap 70, β-2 microglobulin and all these factor play into an important decision making on the treatment and how patients are going to do with it. I won't say much about this part of the immunoglobulin heavy chain variable region (IGHV) mutation status, but if they are mutated or at least having 2% of mutations is considered favorable but if you are under that, is less favorable. It is important to know this new rearrangement of the immunoglobulins genes because it helps create new and more specific antibodies. If this part is affected then it will be called a somatic mutation so if your CLL has undergo this process is more favorable than in earlier stages.

This shows how people do with chromosomal changes based on very old data but as we are a rapid evolving field, we will understand how the surviving status is with these new treatments. However, we do pay attention to the cytogenetic and how chromosomes look like. Once the patient comes, we look at their stage, their prognostic information and what we sometimes do next is some imaging studies. We can make CT studies and PET scans if symptoms are present.

The next big decision is, how are we going to treat them? ---- It turns out that in 2016, with all these great drugs, we do not treat people unless there's a reason to treat them. So, if you are completely asymptomatic and feeling well, then you are going to live a long time no matter what we do. In such cases, we do not treat, we just watch, and that can happen not only in the time of diagnosis, but once people get in remission too.

So, what are the reasons to get treatment? ----- There is no advantage to treating CLL until symptoms develop regardless of genomic features. Treatment is advised once your lymph nodes are getting too big or are starting to cause some pain, making difficult to eat, have anemia or trombocytopenia. Those are reasons we can think of starting some treatment and that's where choosing the right treatment is extremely critical for understanding how people are going to do.

Now let's talk about a little about treatments and how we do them. They come in all shapes and flavors, of course, not long ago we used to have only chemotherapies. Drugs like fludarabine, bendamustin, chlorambucil will be used in some occasions in chemotherapies. Quite a while ago, we develop targeted antibodies like rituximab, that was developed 20 years ago leading to new antibodies that are now approved, some are in the list and many more are in development. They've been game changers on how we treat this disease, and I know many people that are in this room or are watching have received antibodies treatments like rituximab. We also have a variety of targeted treatments and that's where the excitement is now. We are going to talk about ibrutinib and idelalisib. There is also a new drug just recently approved two weeks ago; venetoclax or ABT199, and many more that are in development and will get to the clinical use.

Let's just say a word about targeted treatment in regard of antibodies. Antibodies are a way to help our own immune system to recognize the cancer. We can make antibodies to fight infections; we can also make them in the laboratory based on a cancer cell. We can make targeted antibodies to something on the surface of the B lymphocyte of the CLL cell. That happens when the antibody is delivered to the patient in a specific parking spot. As an example, rituximab’s spot is called CD20, so if rituximab doesn't find CD20 he will move on to the next cell and find CD20 where it can fit. What rituximab does is to actually kill the cell directly, it can call effector cells to come into contact with the CLL cell and kill this cell. A variety of mechanisms in regard of the immune system are very valuable. So, we target CD20 and we can kill the cells directly and we can actually recruit the immune system to kill the CLL cell through the antibody. We learned that we can make antibodies more efficient by making them more humanized, and we make that through genetic engineering.

So, what do we do as a standard treatment? ---- Let’s say we have a young patient who is very fit and without risk features. In this case, we use what we have been using for years, chemo immunotherapy. The chemo part, of course, is drugs like fludarabine or bendamustine and the immune part is with antibodies like rituximab or obinutuzumab. This treatment and data has been incredible important to controlling the disease and taking care of patients. The Germans made a major study looking at upfront treatment of CLL. They recently compared the regimen of FCR to BR considering this will be used in a person that can tolerate and want to take chemotherapy. What was found from this trial was that the complete remissions rates were increasing. At least half of the patients would have complete remissions and the
overall response rate was 100%, but the toxicity can be significant. Part of that toxicity can be myelosuppression or lowering of the blood counts and the risk for infections, which are things we want to avoid.

What about people who are less fit or are older? ----- We will then use some mild treatments like lower doses of chemotherapy and a variety of antibodies. Well, this is just a partial list of what we could do. More recently, the German lymphoma CLL study group has pioneered in another approach for older patients that might not be particularly fit because it is a regimen of chlorambucil and obinutuzumab. This was a randomized trial comparing the standard chemotherapy of chlorambucil by itself to a regimen with chlorambucil and an antibody like obinutuzumab (the humanized antibody) or rituximab. Essentially, what was seen was that obinutuzumab was a game changer in older patients. So this is a standard approach, still using chemotherapy, but it is using chlorambucil which is an oral pill that is well tolerable. As for the antibodies, by the time when the disease would come back, it was greater if we use the newer and improved antibody obinutuzumab compared to rituximab.

Now let's talk about targeted treatments that are not antibodies, these are all these excitement new drugs. We know a little about idelalisib, ibrutinib and venetoclax. They target specific enzymes that are key to the production of life in the CLL cell. In general, CLL is a problem in two ways: they make too many abnormal cells and they are not dying. So, if we can put something that changes the normal cycle of proliferation and not dying, we can induce those cells to go to cell death and as a result we would control the disease.

The goals of these novel treatments are to improve therapies, target selective malignant cells and be less toxic to healthy cells, make the immune system stronger, and in the end lead to a cure. We have been able to cure CLL using and allogenic transplant, which makes an immune reset, but we are hoping to cure CLL without the use of a transplant.

With all these new treatments, should we stop using chemotherapy? ----- According to some new data it could be a reasonable option. For example, ibrutinib, a new oral pill, is an inhibitor of the enzyme BTK (Bruton's tyrosine kinase) that sends signals to the cell nucleus to proliferate, but if you inhibit BTK it will lead to the death of CLL cells. To prove this, we made a trial with randomized 65-year-old patients who we didn't wanted to give chemotherapy and compare the treatment with ibrutinib to chlorambucil. What we got was that 90% of patients responded to ibrutinib while only 30% of patients had a response with chemotherapy. It was overall a dramatic improvement where there was an 80% chance of progressing if you were using ibrutinib. After two years, 90% of the patients are still on the drug and had not relapse or had chemotherapy. In addition, ibrutinib is a common drug we used in the relapse setting instead of using antibodies.

It is important to know how and why we use these agents. For example, many people who use ibrutinib or idelalisib have to know that their lymphocyte count will go up overtime and may stay there before it comes down. It is not an abnormal symptom, but it is because as the CLL cells are being killed, they start mobilizing out of the lymph nodes. As for the lymph nodes, they will shrink because CLL cells are dying. For example, I had a patient with an 11q deletion that started using ibrutinib and after 4 weeks, her lymph nodes from the neck had become much smaller. At the end, everybody, even high-risk patients, get benefit. To show it, we use something we call “forest plot” because imagining a tree, the trunk is something intermediate or normal and other results are the branches, so if the branches go to the left it means that ibrutinib was better. We are making major strikes on CLL because even if you were older, younger or had genetic mutations (especially 17p), the treatment with ibrutinib will work and you will get better results. As for side effects, they are very mild like muscle or joint aches, mild diarrhea or rash. Although they are very small, it is very important to always tell your doctor about them because every symptom is always related to the drug and can be a game changer in the treatment.

Idelalisib is another important drug. We made a trial with a combination of idelalisib and rituximab comparing to rituximab alone. We saw major improvement using the combination treatment in keeping the disease away. With idelalisib white count can go up, lymph nodes can go down and overall the respond is excellent in lymph nodes in just few weeks of treatment. In this drug, the side effects are unique and it’s important to be educated and know how to treat them.
There is also a new drug called venetoclax that most patients will interact with in the near future. This is a drug that targets a protein inside the cell, Bcl-2, that is an overexpressed protein in CLL that inhibit the cell's signal to die. If we can interact with Bcl-2 and inhibit it, we will lead that cell to death. There was great response of 8/10 patients in complete remissions that lead to the publication of several studies. The most recent was published in the New England Journal of Medicine for approval within the remissions stage.

Getting towards the end is important to know what to with chemotherapy. Should we stop using it? ------- That is a very controversial question, some experts are still using chemotherapy, and other would say that chemotherapy is already dead. In fact, the father of FCR, Michael Keating, is now even telling people that FCR will not be the best treatment in the near future. FCR still has a role though, in certain situations on the most favorable patients. Approximately, in 12 to 14 years young patients using chemotherapy will do well, so if you have none of the risk factors and have overall a good prognosis, chemotherapy will work for you.

Oncology and in particularly CLL is a fast moving shift. We are now not relying on chemotherapy anymore, but on the immune system itself because those kind of approaches are the ones that cure people. A new game changer has been developed, CAR- T cell therapy, is great for patients who maybe have given up on chances and have low long-term survival. This therapy works by taking the person’s own T cells and take them to the laboratory where we engineered them to have marker on their surface to target the CLL cell. The problem with this is that in patients who have CLL their immune system has ignored the fact that there are cancer cells so they scape surveillance of the immune system. What we have to do is to reeducate the immune system to recognize the cancer. With the marker we engineer, the T cell (and millions of copies) will be reeducated to fight CLL cells so it can absolutely work. In a recent patient that had been treated with chemotherapy and had no improvement, the T cell treatment was used and the patient was cured. Another patient who had had a prior transplantation and still had massive masses of lymph nodes on the abdomen, used CAR- T cell treatment and 27 days later the masses were gone. There are many new treatments that will improve the patient's life and right now we are just scratching on the surface of what will be a new age of treatments, so chemotherapy will be forgotten and it will not be your father's CLL.

Now to sum up, I invite people to participate in clinical trials because all the information and the exciting new improvement drugs we will have, has been and will be the result of clinical trials. Think about the new agents that are in clinical trials and how they can change CLL.

If you have any questions contact Dr. Pagel at http://cancergrace.org/forum/q-and-a-ask-us/new-questions

Questions about the conference:

1. **One of the issues in dealing with CLL is judgement on different medical problems at the same time and how it can possibly cause greater toxicities. How can you decide if the most aggressive treatment that may affect other medical diseases and cause short and long-term effects is the best option for the patient?**

   It is an incredible important question and something to talk about here. A bit part on the decision making process revolves around the relationship between the doctor and the patient, understanding what the patient’s goals are and also having some experience in those kind of settings. The most important way to achieve that kind of relationship is for the patient to be his or her own advocate. To accomplish this is important that you as a patient knows that the doctor is listening. As a doctor, we have to inform you with all the treatment options, from very conservative to a most aggressive approach, some of them will not be appropriate for you because it depends on what patient you are and the risk you are willing to make. Perhaps an older patient is willing to take less risk to avoid side effects like infections with the idea that they may not have a remission. Otherwise, someone who takes a more risky approach with higher chance to get an infection will probably get into remission faster and hitting a home run. It is all part that the doctor understands the patient, being on the same page and that they talk about their options. Medicine used to be more paternalistic about what you should do as a patient and now you have to talk about all the options the patients has.
2. **How much of a concern it is to interrupt treatment? Is it an immediate problem?**
For most treatments based on the data, that we have is to use them indefinitely, meaning the treatment will stop until the disease is growing again or if there was another side effect more powerful. We do not have enough information, but several clinical trials are in progress to make people go into remission and stop the disease. In general, that is a safe strategy but it should be done in conjunction with your doctor. We are still learning when to stop treating patients. For example in another scenario in chronic myeloid leukemia CML where we have may agents that are oral pills for 20 years that are game changers for CML The first one that was ever approved was a drug called gleevec which had to be taken every single day and had to continue for the rest of their lives. Now, we have people that stopped taking the pill for 15 or 20 years and have not get the disease back, so we learn that the pill did not had to be taken for the rest of their lives. We are way too soon in CLL to know when to stop treatment but we are making progress in that area.

3. **Why is the participation in clinical trials so low? Are they not available to all patients?**
It's a combination of factors actually. In the oncology clinic you get the standard of care and that works, but in clinical trials we have the option to give them a better option and we sometime not use in all trials placebo. It's an issue of education and to know how clinical trials are made because all treatments that are used now were in certain time on clinical trials. To get more information you should ask your doctor where you can get information and where these clinical trials are been done.

4. **Why most of the clinical trials are for patients that have already used some kind of treatment and not for patients who have not received anything?**
It is because we do not want to harm people so we tend to reserve these new treatments for people who have fewer options and are willing to take the risk. It's a flaw on how we do this but we don't treat patients unless there is a reason to treat them. In CLL is problematic because if you are 70 years you are going to live the same time no matter what treatment you take so the decision to choose treatment has to be the one that involves less risk.

5. **About the patterns of resistance, how often does a patient whose cancer progresses in first and second line therapy ever benefit from third line therapy? Is there any cross line resistance?**
It is very different because each treatment has their own mechanism to kill the CLL cells; it is not like chemotherapy where every drug used will make you resistant to a different kind of drug that is part of chemotherapy. With these new treatments in CLL, every drug has a different target and that is why if the first line does not works, the second one will usually work.

6. **Is there any way to screen or identify early to have a prevention for CLL?**
So far, the answer is no, and it is because we have never looked. Right now, there is a trial where we are taking patients to figure out at the genetic level and determine why they are developing cancer. There is another one where we take remission CLL patients and sequence their DNA and looking at their genes and proteins to determine if and when are they are going to relapse. With that data we would be preventing the disease as opposed of just treat it. Unfortunately, there are several years to accomplish this but it's definitely on the horizon.

7. **How often and how do skin symptoms manifest?**
It is very unusual but it can definitely happen. It can look like a nodular rash that does not go away. It may be a little tender because cancer is making it stretch. In general the chance of getting skin involvement in your CLL is less than 1%.

8. **How much of incremental is critical to have a very focus immunological specialist?**
I would say that the best advocate is yourself, so some will feel comfortable by being treated with their general oncologist and some will feel better with the specialist. Also, second opinion is always a very valuable decision and that will make the patient more calm. At the end, experts will always have better information that may lead to a better treatment but not everyone needs a specialist, so, again it all depends on the person.