Thomas J. Kipps, MD, PhD
June 18, 2014

Slide 1 - Welcome and Introductions

Operator
Good afternoon and welcome to CLL: Current and Emerging Therapies, a free telephone Web education program. It is my pleasure to introduce your moderator, Ms. Lauren Berger.

Ms. Lauren Berger
Thank you and hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. Special thanks to Dr. Thomas Kipps for sharing his time and expertise with us today.

We would like to acknowledge and thank Genentech and Biogen Idec, and Pharmacyclics, Inc. and Janssen Biotech, Inc. for their support of this patient program.

You should have received or downloaded program materials, including a biography for Dr. Kipps and slides for his presentation. If you have not already accessed the slides, you can view or print them from our website at www.lls.org/programs. Following the presentation, we will take questions from the audience.

Before we begin, I would like to introduce The Leukemia & Lymphoma Society's interim President and CEO and Chief Mission Officer, Dr. Louis DeGennaro, who will share a few words. Dr. Lou?

Dr. Louis DeGennaro
Thank you very much, Lauren. I'd also like to add my welcome to the patients, caregivers, and healthcare professionals attending today's program.

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 immunotherapies that have improved survival rates and the quality of life for many blood cancer patients. To date, we have invested over one billion dollars 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, LLS is the leading source of free blood cancer information, education, and support. And we touch patients in their communities through our 61 chapters across the U.S. and Canada.

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 ensuring that they have access to quality, affordable and coordinated care.

Dr. Louis DeGennaro
We're very, very fortunate to have as our presenter today Dr. Thomas Kipps, one of the world's leading experts in chronic lymphocytic leukemia. We appreciate his dedication to supporting our mission and his commitment to caring for patients living with blood cancers. I'd like to personally thank him for providing us today with important information on CLL. I'm sure we'll all learn a great deal from his presentation. And now, I'll turn the program back to Lauren.

Slide 2 - Thomas J. Kipps, MD, PhD

Ms. Lauren Berger
Thank you. I am now pleased to introduce Dr. Thomas Kipps, Professor of Medicine, Division of Hematology Oncology, Deputy Director for Research at the University of California San Diego Moores Cancer Center in La Jolla, California.

Slide 3 – Disclosures

On behalf of the Leukemia & Lymphoma Society, thank you for volunteering your time and expertise. Dr. Kipps, I am now privileged to turn the program over to you.

Slide 4 – Chronic Lymphocytic Leukemia

Dr. Thomas Kipps
Well, thank you very much. I'd like to say hello to everyone and also start out by thanking The Leukemia & Lymphoma Society for their generous and tireless efforts to try and find cures for patients who have leukemia.

And I really am very much appreciative of all their efforts, but I want to say my gratitude has to go most importantly to the patients that have participated on clinical trials that have made possible the ability to evaluate the merits of new therapies, and have allowed us to progress and provide new and better treatments for patients today. So, that is really where we owe the most gratitude as we begin this discussion.

Slide 5 - Chronic Lymphocytic Leukemia (CLL)

I must say that the discussion on chronic lymphocytic leukemia is getting to be a very exciting time, because we have a lot more to offer patients. So, we have new weapons that we can use in the fight against leukemia.

Although we may not be there yet in terms of being able to define a cure for every patient, we have many more choices that make the ability to treat patients less of a problem than we had before, when we had a very limited number of tools to treat this disease.

Dr. Thomas Kipps
I'd like to say that one of the things about chronic lymphocytic leukemia that is sometimes very confusing and challenging is that it's still a disease that has a great variability. And some patients that I have had that have been recommended, for example, for transplantation straight away by being able to identify that they have features of indolent disease and following them and finding out they have indolent disease, have been able to go without therapy for many years. And so, I think it's very important to recognize that the course is highly variable and that many patients at diagnosis may be asymptomatic at diagnosis.

Even with the advances in therapy, the treatment is still not considered curative. So, the thought is that we should not treat right away because we do not know for sure whether patients may enjoy a fairly long period of time before they require therapy.

And I am of the opinion that there is no treatment that does not have some risk to it, even with these newer treatments. So, we have to be mindful of the risks of treatment and not to get into therapies that can cause greater harm than what the patient is currently facing.

The recommendations still stand to hold therapy until patients develop symptoms of the disease or complications, such as impaired marrow function with anemia or thrombocytopenia, or if they develop, for example, symptoms of an enlarged spleen or enlarged lymph nodes.

Obviously, if we can improve the quality of life with therapy, that should be a goal.

Slide 6 – CLL Prognostic Markers: Mutated vs. Unmutated IGHV Genes

Now, one of the features that has helped define differences is the genetic analysis of leukemia cells and many advances have been made in the last several years.

But, one defining feature has been to examine the biologic features of leukemia. And through the understanding of the biology, we have new tools now to offer for patient therapy.

One of the things is the nature of the antibodies that are expressed by the leukemia. The leukemia is a B-cell. And the primary job of a B-cell is to make antibodies to fight infections, and these leukemia cells are no exception. They make antibodies, and by analyzing the genetics of the antibody, you can find out whether there are mutations in the antibody or not.

And although it sounds counterintuitive, if you have mutations in the antibody gene, that's oftentimes associated with a more indolent clinical course. And those patients

Dr. Thomas Kipps
may enjoy not having to have therapy for years after diagnosis, whereas patients who have leukemia cells that express unmutated genes may more frequently require therapy earlier.

I think that this is an important message, because it helps to stratify patients and then maybe offer therapy that might be considered appropriate for those subgroups.

Slide 7 – Approved Drugs for Treatment of Patients with Chronic Lymphocytic Leukemia

Now, what are the therapies that are out there? On the left-hand side are therapies that have been available for some time now. Many fall into the classification of classic chemotherapy.

There are new therapies that have recently been improved, in particular, the kinase inhibitors, which I hope to touch upon, and also monoclonal antibodies. I've listed now four monoclonal antibodies that are approved for treatment of patients who have leukemia, and these have been a game changer. The antibodies have, for the first time, allowed us to say that there's a true survival benefit with therapy that we hadn't seen with the standard chemotherapy.

Slide 8 – Clinical Differences Between Patients with Common FISH Detected Cytogenetic Abnormalities

Now, in going over the description, I think it's important for any patient at diagnosis and prior to therapy to get what's called a standard genetic analysis.

This is something that could be done at any clinical laboratory that is offering a study called FISH, which stands for “fluorescence in situ hybridization.” And they can do a FISH panel for CLL cells and to find whether there are genetic changes in the leukemic cells. In particular, I would say that this is recommended for any patient that is going through therapy.

We are trying to understand some of the new genetic changes that might be associated with outcome. But, this standard FISH analysis is something that could be done.

And it's important information because I would say that, if you have a patient who has leukemia cells that have the deletion of chromosome 17p listed on the top, I would recommend that they think twice before entering a regimen that requires standard chemotherapy, because many times the standard chemotherapy will be less effective and only be effective against the bone marrow, and that's not a good situation to have.

Dr. Thomas Kipps
So, there are other genetic deletions that are listed here, which you can refer back to. In interest of time, I'm just going to move on.

But, I would like to highlight that the 17p deletion is one which represents a significant challenge to standard chemotherapy in that patients typically are not as sensitive to the drugs.

And the other deletions, such as the 11q, which is the deletion on the long arm of chromosome 11, oftentimes are associated with a more rapid return of leukemia after successful therapy.

Now, it's important to note that chemotherapy is now being considered maybe passé. We have advocated for many years that we should try to strive to get free of chemotherapy. And we think we can with advances. Now, even so, I think it's important to look at the data and to let the data be our guide.

Slide 9 – FCR100 First-line Treatment

And one interesting study that's undergoing discussion in the circles of the investigators in leukemia is the long-term analysis of some of the patients treated at MD Anderson with the drugs fludarabine, cyclophosphamide, and rituximab. This is a very commonly used chemoimmunotherapy regimen that was pioneered at MD Anderson and shown to be effective by the German CLL study group.

The drug combination does produce a high rate of clinical complete responses. And many of the patients may actually have responses where there's no evidence of detectible leukemia, even in the bone marrow. Those patients are said to be negative for minimal residual disease. And that may be an important feature because, if patients are not having any evidence for leukemia in their bone marrow, then chances are they'll enjoy a long-time remission without requiring additional treatment.

What was surprising about these data, as you can see, they were completed over 10 years ago. It's the long-term follow-up data.

Slide 10 – FCR300: Response by Characteristic

And in particular, these groups of patients were particularly younger, fit patients that were presented at the time, and they had a fairly high rate of clinical responses.

Dr. Thomas Kipps
And as I mentioned, the two groups of patients with leukemia cells that have unmutated antibody genes versus mutated antibody genes, their responses were very similar in that they both achieved complete remissions and partial remissions with this combination of drugs.

Slide 11 – FCR Time to Progression by IGHV Mutation Status

But, I think the long-term follow-up data has been rather striking. And in the green line, you can see patients who have leukemia cells that express unmutated antibody genes. And it seems that there's a relentless tendency for the patients to have disease relapse that requires additional therapy.

But, in the yellow line are patients with leukemia cells that have the mutated antibody genes. And you can see there is what we call a plateau, such that there are some patients who have not required therapy for 10 years or so. Are these patients cured? Well, some of these patients may do quite well.

I think it's important that we understand what types of patients might most benefit from this type of therapy and to be able to use it wisely, so that we can potentially achieve very long lasting remissions in patients that do not require additional therapy. This is something that is undergoing some consideration now in the circles of leukemia experts around the world.

Slide 12 – First-line FCR: Conclusions & Comments

Now, as far as the conclusions I just made, the mutated antibody gene is one thing that may define that type of patient. There's another marker which is less specific, and that's called the beta-2 microglobulin level. That's an easy test that could be determined. And those patients that seem to have done the best are the ones that have leukemia cells that have mutated antibody genes and have a low level of this beta-2 microglobulin level.

I think we need to understand more the nature of this, but not to throw the baby out with the bath water in terms of staking out therapies that might be effective in the right type of patient.

Slide 13 – Monoclonal Antibodies

I'd like to move on to the monoclonal antibodies that have made such a big difference.

Dr. Thomas Kipps
Clearly, the addition of rituximab to the drugs fludarabine and cyclophosphamide was a game changer. This allowed for improvements in the overall responses and improvement in the progression-free responses. And I've boxed these in here. These are the antibodies that all bind to the same protein called CD20 on the leukemia cell surface.

This is the protein that's also found on other B-cells, including normal B-cells. So, when you use these antibodies, you will deplete normal B-cells as well as leukemia cells. But, they have been very effective in the treatment of patients with this leukemia.

They are called biologics. They are proteins that are made, genetically engineered, so that you can infuse them. The antibodies then target this protein on the leukemia cell and then set it up for destruction.

Slide 14 – Anti-CD20 Biologics: Dancing on the Head of a CD20 Pin

Now, the ones in red that are highlighted, rituximab being the first, are drugs that have actually been approved for treatment of patients with CLL.

Following rituximab, we have the drug ofatumumab, which was approved a few years ago based upon studies showing it had activity as a single agent in patients who had failed fludarabine and cyclophosphamide and rituximab.

And then, more recently, we have another player, which is called obinutuzumab. Ofatumumab is a drug which more recently has been called Gazyva®. And this drug is actually something that we find in studies here has been very effective.

As I mentioned to you, other antibodies are there. They're listed in black on this slide. They bind to the surface of this protein that's cartooned here that's on the leukemia cell surface, and they may bind to different sites on that protein. But, you can see it's a small territory. We have many proteins on the leukemia cell surface, and this is just one of many, and it's a small protein on the surface, too.

But, I think the reason we have all of these drugs is that, when you have a successful drug, then the pharmaceutical industry tends to want to concentrate on areas where there's been prior success, and that's been no different here.

Slide 15 – GA101: Obinutuzumab (Gazyva®)

Now, as far as obinutuzumab, this antibody has actually been genetically engineered to pack more of a punch.

Dr. Thomas Kipps
Namely, how the antibodies can work is that they coat the leukemia cell that's depicted on the left. And what they do is they target the leukemia cell for destruction by what's called effector cells, and these could be T-cells, or natural killer cells or NK cells.

And these cells will recognize cells that are coated with antibodies and try to destroy that cell. So, it's actually getting the immune system to work against the leukemia cell. And this is something that has been noted for some time. This antibody has been genetically engineered to be even more attractive to NK cells and T-cells so that they go about their job more effectively. And I think some of my patients have called this, "Rituximab with an attitude," because it seems to pack a stronger punch than the rituximab that we all know.

Slide 16 – Obinutuzumab plus Clorambucil in Patients with CLL and Coexisting Conditions

Now, as far as the approval of this drug, it came about from a groundbreaking study, which was a Phase 3 trial.

Phase 3 trials are where patients are not given the option to take one treatment or the other, but are what's called randomized, where patients are given either one type of treatment or given another type of treatment.

And in a study that was done by the German CLL Study Group involving many different countries, this was the drug trial that resulted in the approval of obinutuzumab for patients with leukemia. This compared obinutuzumab with the drug chlorambucil, which is a drug that is similar to the alkylating drugs that we know of, such as cyclophosphamide or bendamustine. And it's an oral drug that's used quite widely around the world. Obinutuzumab plus chlorambucil was compared in this study versus chlorambucil alone.

And this is the mechanics of the study: these patients were over age 65, and they were also patients who had medical conditions, preconditions, such as maybe some minor kidney problems or heart problems.

And as we know, as we get older, we may sometimes have other medical problems that make it sometimes more difficult to tolerate therapies, such as fludarabine, cyclophosphamide, and rituximab, or the FCR regimen.

Slide 17 – Clinical Trials Using GA101

Dr. Thomas Kipps
Patients who had these qualifications were randomized, if you will, to receive either of three therapies: either get chlorambucil by itself, as represented in the top box; or chlorambucil plus rituximab; or on the bottom box, chlorambucil plus the drug GA101, or obinutuzumab, GA101 being it's earlier name when it was a research drug. So, patients could be compared because the randomization was done not by the physician or the patient, but was done centrally.

Slide 18 – Response Rates

Now, the outcome of this study was quite striking. Everyone was expecting rituximab and chlorambucil to do better than chlorambucil alone. And that's shown here where the blue bar is compared with the green bar. And these are the patient's responses. So, clearly, the addition of rituximab to the drug chlorambucil has improved the response.

Now, in the purple bar is the response of patients treated with Gazyva, that's the "G", and chlorambucil, which is the "CLB." And that's compared with the green box, which is chlorambucil. And you could see that, in that case, there's also significant improvement in the response pattern.

I want to pay attention to the very lightly shaded box, and that's the patients who achieved a complete remission. And that is complete resolution in the lymph node enlargement and complete resolution in lymphocyte count.

And in that case, the patients treated with obinutuzumab, or Gazyva, had a higher rate of complete remission than patients treated with rituximab and chlorambucil. And it's shown here in these cartoons.

Slide 19 – End-of-Treatment Response Rates

This is a table, and I just want to focus attention onto part of that table that's in the red box.

And you could see, this is in the chlorambucil, which is CLB. That's the data for overall response rate, which is ORR. And you can see that in G plus chlorambucil, the overall response rate is much higher.

Then you have chlorambucil compared with rituximab and chlorambucil. We can see it's also higher. But, in the red box, those are the patients who actually achieved complete remission that were assayed for having residual leukemia cells.

Dr. Thomas Kipps
It's more important to look not just at the blood, but look in the bone marrow. And we and others have found that, after antibody therapy, you may get a false hope by looking only at the blood to look for leukemia cells, because you may get what's called a "false negative", in that some patients may still have leukemia cells in the bone marrow where they don't have any leukemic cells in the blood. So, you really have to focus on the cells in the bone marrow.

And what was striking here is, with this regimen, 17 percent of the patients had achieved what's called absence of minimal residual disease, or MRD negative.

Slide 20 – Investigator-assessed PFS (Months)

And that typically is associated with a prolonged remission and a prolonged progression-free survival. And that's dictated here, and these are the curves here.

So, in the gold line, that's the progression-free survival after therapy of patients treated with chlorambucil. And you can see it's the same in both diagrams on the left side and the right side.

And the difference is that, on the left side, you have the patients treated with chlorambucil and Gazyva, or obinutuzumab. And you can see it's much more prolonged over the yellow bar that's the time in which the patients enjoy not having a relapse in their disease.

And on the right side are patients who are treated with rituximab and chlorambucil. You can see that they also enjoyed an improvement in the time at which they did not have to require any additional therapy. But, it was actually not as good as with the Gazyva arm. So, it seems that we're getting deeper remissions with Gazyva, and we're getting more protracted progression-free survival.

And based upon these data, the FDA approved treatment of patients with this drug as initial therapy in combination with a drug such as chlorambucil. And so, that approval was made in November of last year.

So, this is increasing our number of new weapons that we have to use to treat patients, the drug obinutuzumab, which is now available, and that can be used as a drug similar to rituximab for patients.

Slide 21 – CLL Microenvironment

Dr. Thomas Kipps
Now, I think that we have been learning over the past several years the biology of leukemia cells. Cartooned here, you can see the leukemia cell is in the middle. And it's surrounded by a number of other cells. And some say that it takes a village. Well, in this case, it takes what's called a microenvironment.

The leukemia cell is sitting in lymph nodes in the spleen. And it's not sitting there in isolation, but actually can conscript other cells to join forces with it, and they serve a function. They have a dialog. They talk together. And they provide survival and co-stimulatory signals to each other. And so, basically, the leukemia cell is a social animal. It requires help from its friends in order to survive.

And so, part of the thinking now is to try and interfere with the ability of the leukemia cell to find its way home and deprive it of some of the signals that it receives from the microenvironment, and that lets the leukemia cell die by neglect. And that's something that's very much on the minds of researchers today.

Now, you could see that, of the signals, one of them is an antenna, and I've just circled it here. And that's the antibody itself. The antibody, which we make as proteins in the blood, is also a receptor of sorts. It's like an antenna that sits on the surface of the leukemia cell. And it actually provides a signal to the leukemia cell.

Slide 22 – B-cell Receptor Complex

And through the work of many investigators looking at how that signaling is done, you can see the wiring. The yellow is the antenna, and all the stuff underneath the surface, those bubbles there, that's the membrane. So, a lot exists underneath the hood.

Research has identified enzymes which can convey the signal that, when the antibody antenna engages with something, is tickled by what it's supposed to be binding to, like an antigen, and then the signaling complex conveys a signal to the nucleus of the cell that tells the antenna, "The fishing pole has caught something." And it has to convey that signal to the nucleus. And it does this through all these different enzymes that are patterned in the ovals.

Now, the thinking is that you can actually start to get inhibitors of these enzymes. And it's fairly easy to make inhibitors that block these enzymes. And that's opened up a whole new era of pharmacology in the treatment of this leukemia.

Dr. Thomas Kipps
So, we have inhibitors of the protein, which is diagrammed here, called Syk. We have proteins that can inhibit another enzyme called BTK. We have inhibitors that can inhibit a protein called PI3 kinase, or also the RAS MAP kinase.

Slide 23 – BCR-Directed Agents in Development for CLL

And these are various inhibitors. And there are more and more coming out each day. I've tried listing them here.

These are called B-cell receptor directed agents. These are the small drugs that can inhibit the enzymes that convey the signal from the antibody to the cell that tells it's caught something. And by blocking that signal, you can have the leukemia die of neglect, of not having sufficient signals to go into it.

Now, I don't have time to go over all of these different drugs. But, suffice it to say there are different categories depending on what enzymes they inhibit. And I must say that each of these drugs may have what's called off-target effects. Namely, when one drug is intended to inhibit one enzyme, it may also inhibit some other enzymes, too. And that might account for some of the other effects that we see with these drugs. And it's an area of hot research that needs to be taking place to find out how these drugs actually work and how these drugs might also cause complications.

Slide 24 – PCI-32765: First-In-Class Inhibitor of BTK

I want to highlight the first drug, which is ibrutinib. This drug was approved for treatment of patients with chronic lymphocytic leukemia in March of this year.

And it's basically a drug that's a small molecule you can take by mouth. And it does inhibit the enzyme called BTK. And BTK is one of the enzymes that I said is involved in the receptor signaling of the antibody, but it also is involved in other signaling commands that the B-cell uses, just like the B-cell that's like what we have. We have a nose and we have eyes. There are different receptors on the surface of the leukemia cell. And they allow the leukemic cell to home to these lymphoid organs, or to the microenvironment. So, basically, leukemia cells may direct a migration towards sites where they want to be. And this enzyme can inhibit some of that signaling as well. So, it confuses the leukemia cell, and it causes it to become unable to get some of the survival signals that it requires for it to survive.

Slide 25 – Pattern of Response to Ibrutinib: Blood Lymphocytes vs Lymph Nodes

Dr. Thomas Kipps
Now, in the study, what happens is that, when patients start this drug, on the blue line, you can see that there is characteristically a very high rate of increase in the white cell count. And that's because the leukemia cells that are in the lymph nodes and the spleen may oftentimes empty into the blood and cause the white blood cell count to go higher.

At the same time, in the green line, you could see that this is the line showing the lymph node reduction. You could see that that goes down fairly quickly. And the lymph node reduction is going on at the same time that the white count is going up. And that's because the leukemia cells are becoming confused. They can't sit in the lymph tissue anymore. And they actually empty into the blood.

And you can see, as the blue line indicates, over time, that number starts to come down. So, these leukemia cells start dying over time, mainly by a process that I call neglect. Now, obviously, this is the change that you can see in the lymph nodes. And it can be quite dramatic and occur within even a fortnight, within a couple of weeks.

Slide 26 – Maximum Change in Tumor Burden

And so, you can see that the dose, either at 420 milligrams a day or 840, the dose 420 milligrams is used going forward. That's indicated in the blue lines here. You can see you get fairly prominent reductions in the lymph nodes early on.

Slide 27 – Ibrutinib versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia

Now, one study that was just recently reported, the so-called RESONATE study, compared this treatment of ibrutinib versus the drug ofatumumab, which is one of the monoclonal antibodies that I mentioned earlier. It's an anti-CD20 antibody that can be active in patients with chronic lymphocytic leukemia.

Slide 28 – RESONATE™ Phase 3 Study Design

And ibrutinib here was studied--it was basically a protocol that I mentioned. The design is Phase 3, where patients were again randomized to receive either oral ibrutinib by itself or to receive the ofatumumab.

Dr. Thomas Kipps
Now, it must be said that in the ibrutinib arm, the therapy was to give this drug orally and to continue the therapy indefinitely, whereas ofatumumab is only given over a course of 24 weeks. So, the therapy duration is similar to what we have experienced in treating patients before, namely a defined treatment period.

With these new kinase inhibitors, that is not the case. And so, patients are recommended to stay on the drug indefinitely. And the reasons for that are many, and I can get into that.

But, one reason that we have is the lack of ability to achieve complete responses. So, even though there's dramatic improvement in the patient's wellbeing and reduction in lymph nodes, we're not seeing the complete remissions, namely eradication of leukemic cells from the bone marrow and the blood and the lymph nodes entirely.

And the reasons for that are many. And that's an area of hot research. How can we close the deal to make patients who are taking this drug actually start to eradicate all the leukemic cells? And we're trying to figure out why that doesn't occur here.

Slide 29 – Ibrutinib versus Ofatumumab

But, because patients achieve a partial response, patients are actually able to stay on the medicine. And as long as they stay on the medicine, then that partial response may be maintained. And that's something that is being observed right now.

You can see the partial response rate, some of it, like in the yellow box, partial remission plus lymphocytosis. So, in a way, these patients still have a white count, maybe in some cases, higher than they had before they started therapy. And yet, they are considered partial remission because their lymph nodes are much smaller.

And in the case of ofatumumab, you see that the partial remission was much lower, being only four percent of patients, and most of the patients have just stabilization of the disease.

So clearly, the use of ibrutinib in these patients had a higher response rate, if not just partial responses.

Slide 30 – Ibrutinib versus Ofatumumab

Now, here's the outcome of ibrutinib versus ofatumumab, and you can see what's called the progression-free survival. How long do patients go without requiring other therapies?

Dr. Thomas Kipps
Well, in one case (ibrutinib), they receive continuous therapy. And in this case, you can see that the number of patients that have come off therapy is relatively small compared to the ofatumumab patients, who are treated for the course of 24 weeks.

So, they came off therapy, and shortly after coming off therapy, you saw them having relapsed disease that required other forms of treatment. And I think that it's clear that the treatment-free or the progression-free survival is improved with ibrutinib.

Slide 31 - Ibrutinib versus Ofatumumab

What's surprising also is there seems to be a survival benefit, at least in this patient group. Patients receiving ofatumumab had events maybe due to disease progression or delay in getting started with other therapies, whereas, the ibrutinib-treated patients were actually having an improved overall survival benefit.

Slide 32 – Progression-Free Survival by Baseline Characteristics and Molecular Features

Now, one of the issues that I mentioned before, namely the FISH abnormalities, in particular the 17p minus, you could see all the different adverse features that we have listed on the left-hand side. And this is the graph where you can compare how patients are doing and what factors into a poor response with one arm versus the other arm. And you can see listed on the left-hand side are all these circles with the bars. They clearly favor the patients who are on ibrutinib.

So, no matter whether they had genetic deletions that would make them poor candidates for chemotherapy, or other factors, they seem to be doing better than patients treated with ofatumumab. And so, that's clearly something that is weighing out there.

Slide 33 – Safety: Adverse Events (≥15%) Regardless of Attribution

Now, as far as the side effects, you can compare them. And I have these here listed for your further review later on.

But, I want to point out that primarily in patients with ibrutinib and other kinase inhibitors, they have a higher incidence of diarrhea that many times can be managed through the use of Imodium® or other therapies. So, there's a higher rate of diarrhea.

There's also a higher rate of quirky arthralgias, aches and pains, in patients with ibrutinib that's poorly understood. And some of these can be controlled with non-steroidal anti-inflammatory drugs.

Dr. Thomas Kipps
But, I think that, of course, with the ofatumumab, there may be higher incidence of what's called infusion reactions. Because ibrutinib is an oral drug, you don't have those, of course.

Slide 34 – Safety Overview

So, as far as the safety overview, if you'll look at those serious adverse events, the ones that really are raising attention, you see that there's very little difference between the two arms of any grade, and that's important to take into account. So, the drug, it appears to be relatively well tolerated and stacks up pretty well against the single-agent monoclonal antibody ofatumumab.

Slide 35 – Patient Disposition

As far as what happened to patients coming forward, the patients clearly have progressive disease over time, and that was higher in patients treated with ofatumumab. But, we do see progression in patients treated with ibrutinib, even if they continue taking the drug. And that's something that is on the minds of researchers to try and figure out, why do some patients become resistant to ibrutinib over time? It oftentimes takes one to two years, and it's something that you can see over time.

Slide 36 – Disease Progression on Ibrutinib Therapy Is Associated with the Acquisition of Resistance Mutations: A Single Center Experience of 267 Patients

Now, one group that's had perhaps the largest experience with ibrutinib, the group at Ohio State, directed under John Byrd, has actually been trying to investigate what's the incidence of this resistance. And their work on 267 patients, they presented some of this data at the EHA and at the former ASH Meeting.

Slide 37 – Time to Progession

And you can see that, over time, in the orange bar, that patients are starting to develop a resistance to the ibrutinib. And that's something that is currently being investigated. There have been a number of studies now just recently published by the German CLL Study Group, as well as groups here in the United States. This is the group at Cornell, led by Rick Furman, where the patients who developed resistance with ibrutinib actually were found to have de novo mutations in the leukemia, and that's shown here.

Slide 38 – Mechanisms of Ibrutinib Resistance

Dr. Thomas Kipps
Here's that slide that I showed before where you have the yellow antenna of the antibody and these enzymes, and you can find mutations indicated by these yellow thunderbolts that are in the very proteins that we're targeting to be inhibited.

So, in some ways, this is the old slogan that leukemia as well as cancer tends to be like Whac-A-Mole. We may put it down, but then somehow, it finds a way to become maybe resistant by having mutations that may be selected for, that now, the drug becomes less active in fighting off that leukemia cell that harbors that mutation.

So, this is clearly on the minds of many. So, the question is how we can close the deal on this. And one of the aspects is to try and see if maybe we can add monoclonal antibodies to ibrutinib.

Slide 39 – Ibrutinib + Rituximab: Ph 2 in Patients with Relapsed CLL

And one study that was done by the group at MD Anderson, where they combined it with rituximab in a group of 44 patients, you can see that this was very effective. The lady there had very large lymph nodes in her neck. And you can see that, with just two months of therapy, those lymph nodes went away. And cartooned in the graph, you could see that the elevation in the lymphocyte count was less dramatic. In other words, the patients didn't have as many increases in the white cell count as the patients who were just treated with ibrutinib by itself.

But, one of the problems here is, in the far right-hand corner, still, we're not getting a high rate of complete remissions, even with combinations of the ibrutinib and rituximab. We'd clearly like to have more complete remissions and possibly be able to stop therapy all together. That's something of a goal of ours. But, I think that that has to be with further research as to what combinations with ibrutinib might be able to allow for complete responses, allow patients to get off of therapy.

Slide 40 – PI3K Inhibitors

Now, one therapy category is what's called the PI3 kinase. These are other kinase inhibitors. This is cartooned here.

And I'm only going to have time to talk about one that's been more advanced that may come into registration for use in patients with chronic lymphocytic leukemia in the near future. This is the drug called idelalisib. And it clearly also has dramatic activity.

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Slide 41 – Idelalisib: Phase 1 Relapsed/Refractory CLL

Dr. Thomas Kipps
In an early study with idelalisib, you could see the lady on the left, and after treatment with idelalisib, you could see on the right, her lymph nodes were resolved.

And you had a very high overall response rate reflected here. Around 72 percent of patients who received this drug responded to the drug.

And now, what we have with this drug is it seems to give the same type of effects, namely, the white count can go very high, and it doesn't seem to come down as quickly as with ibrutinib, but it may come down over time.

Slide 42 – Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia

The idea of combining it with rituximab was seen early on as potentially an advantage. And so, one large study was completed last fall where patients who were treated with idelalisib and rituximab were compared with patients who received rituximab and a placebo.

Slide 43 – Idelalisib + Rituximab versus Rituximab

And that's cartooned here, where you see patients who have had prior therapy, and they may be randomized to receive rituximab with the idelalisib or rituximab and a placebo. And we really didn't know who had the placebo and who had the idelalisib.

Slide 44 - Idelalisib + Rituximab versus Rituximab: Progression-free Survival

And in that case, we could see that those patients who received idelalisib plus rituximab did better. They had higher rates of partial responses, and also, they had higher rates of progression-free survival, as shown here in the blue line, compared to patients who just were treated with rituximab by itself.

Now, it must be said, of course, that rituximab was, again, done for a defined period of time, and then patients stopped the therapy of rituximab and only received the placebo. In comparison, the patients who had rituximab with the idelalisib continued on idelalisib and maintain on therapy to this day.

Slide 45 - Idelalisib + Rituximab versus Rituximab: Overall Survival

But, again, as in the other trials, a survival benefit was seen with patients receiving idelalisib plus rituximab in this particular study. And that was the basis for stopping this

Dr. Thomas Kipps
study and then seeing if we can get the drug approved. I think that's being presented to the FDA for a possible registration study.

Slide 46 - Idelalisib + Rituximab versus Rituximab

Again, this is a graph I'm going to gloss over. But, suffice it to say, this indicates that all the different subgroups of patients that have genetic lesions, such as 17p, they appeared to have a favorable outcome when they were treated with these drugs compared to patients treated with rituximab by itself.

Slide 47 - Idelalisib + Rituximab versus Rituximab: Changes in the Measured Size of Lymph Nodes from Baseline

And this is the graph showing the dramatic difference. This is the lymph node changes. You can see that, in blue, is the decrease in lymph node size seen with idelalisib and rituximab compared to rituximab by itself, which does a fair job in reducing lymph node size, but not every patient enjoys the same degree of lymph node reduction.

Slide 48 - Idelalisib + Rituximab versus Rituximab

And you can also see that, as the therapy stopped with rituximab, over time, the red bar, that there's a gradual increase in the white count.

So, in a sense, rituximab, which is a finite course of therapy, versus idelalisib, which continues on, was able to maintain the white count lower.

Slide 49 - Idelalisib + Rituximab versus Rituximab

Now, some of the side effects are listed here. And I'm not going to have time to go into all of them. Suffice it to say that diarrhea still is a prominent thing that we see in patients treated with idelalisib versus patients treated with rituximab and placebo. And that was seen here.

Slide 50 - Idelalisib + Rituximab versus Rituximab

And this study's a fairly young study. In some of the earlier studies with idelalisib, diarrhea became more of a problem for patients months and months after therapy, something like seven to nine months after starting therapy.

So, I think we have to observe the side effects of any of these kinase inhibitors over time because we are just learning now about how these drugs are handled. And particularly, if we're advocating that patients take them for lifelong therapy, then the side

Dr. Thomas Kipps
effects that might crop up a year or two down the road are things that we're just only now beginning to be able to appreciate.

I think that it's clear to say that many of the other side effects, such as seen here in these slides, were not different, including laboratory abnormalities.

Slide 51 - Idelalisib + Rituximab versus Rituximab

And I wanted to say, parenthetically, that some patients can have elevations in liver enzymes with idelalisib that's not seen with rituximab, at least the higher incidence, and that seems to resolve over time if patients have the drug withheld and then have it started under the hands of an observant physician.

Slide 52 – Updated Results of a Phase 1 First-in-Human Study of the BCL-2 Inhibitor ABT-199 (GDC-0199) in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL)

Now, I want to get into another category of drug, and I see I'm running out of time. This is a very exciting category of drug called BCL-2 inhibitors. And BCL-2 is a protein that was identified many years in CLL. And it's expressed at very high levels, and it is one of the defining features of this leukemia.

Slide 53 – Background

In fact, research in the CLL Research Consortium with Carlo Croce identified some of the genetic lesions that account for CLL. And one of those genetic lesions accounts for a high level of BCL-2 expression in leukemia.

This protein protects the leukemia cell from dying. And if you get the ability to inhibit it, then the trigger is pulled on the leukemia, and it can undergo what's called cell death or apoptosis.

Now, recently there have been some small molecules that can interfere with BCL-2 function. And one that I'll just touch upon is ABT-199, also called GDC-199. And this is an orally active drug. This is the drug shown here cartooned. It's an inhibitor of BCL-2. And it is able to affect reduction in leukemic cell counts and quite powerfully.

Slide 54 – Dosing Schedule of ABT-199: Dose Escalation Schematic

This is the early dosing regimen we had, starting at a very low dose of drug and then escalating the dose as patients tolerated it.

Dr. Thomas Kipps
And you could see here in Cohort 1, patients started the drug and the first cohort had what was called tumor lysis. Namely, the leukemia cells started to melt away so quickly that it became a medical problem. And so, there was an attempt to go down to lower doses, as shown here.

Slide 55 – Best Percent Change from Baseline in Nodal Size by CT Scan
Well, at the lower doses, we could see it was really quite dramatically effective in lowering the node size. This was documented by CT scan.

Slide 56 - Best Percent Change from Baseline in Lymphocyte Count and Bone Marrow Infiltrate

You could see, similar to the kinase inhibitors, this nodal response. But, unlike the kinase inhibitors, there's actually reduction in the lymph nodes and lymphocyte count within a few weeks after starting therapy, as shown on the left.

And what's exciting is that there's also seemingly a reduction in the leukemia cells that are in the bone marrow. That's probably the most sensitive place to look for residual leukemic cells.

Slide 57 – Responses in ABT-199 Treated Patients

And so, this is something that is quite exciting. We have a drug that's orally active, and there's a high rate of overall response, 84 percent, as shown here, including those patients that have the deletion 17p, which are the patients who don't respond typically well to standard chemotherapy.

Slide 58 – Minimal Residual Disease: Preliminary Analysis

And the complete remissions actually involved several patients that we observed at our center. Now, others are being seen at other centers in that, when we do the marrow after several months of therapy, we see no evidence of leukemia in the marrow.

And I was very forceful in advocating that we maybe stop the drug and see how patients do off therapy. And I've been very pleased to see that patients, after having stopped therapy, continued to do well in having a complete remission that may be long lasting.

And so, in contrast to what we have with the kinase inhibitors, this drug may allow for patients to achieve a complete remission with eradication of minimal residual disease, and those patients may go on to potentially stop therapy all together. And this is something that we're looking into very aggressively.

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Slide 59 – Adverse Events (AEs) in ABT-199 Treated CLL Patients

Dr. Thomas Kipps
Now, obviously, there are adverse effects with any therapy. And of course, these are listed here, some diarrhea and also lowering of the neutrophil count that require attention. But, the most important side effect is the tumor lysis syndrome.

Slide 60 – Dose Limiting Toxicities (DLTs) and Serious Adverse Events (SAEs)

And unfortunately, when the dose escalated, not at our center, but at another center, where they received even a higher dose than seen in the last slide, there was tumor lysis syndrome that was severe. This patient had very large lymph nodes, some that were larger than a grapefruit size and some as small as a small basketball. The tumor melted so quickly that the contents of the tumor cell emptied into the blood stream. And that causes, among other things, the potassium level to go up. And that's not compatible with the heart beating.

That's a very lethal thing and has to be treated as a medical emergency. And this unfortunate event is that one patient had the tumor melt so quickly that it became a life-declaring event.

And so, the study was put on hold for some time and was only restarted from interactions with the FDA that allowed for the study to continue and also to look at the combination of this drug with a drug such as rituximab.

Slide 61 – ABT-199 (GDC-0199) Combined with Rituximab in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia: Interim Results of a Phase 1b Study

And that's the result of this study that was reported at the recent EHA meeting in Europe and also the ASCO and the ASH meeting in December.

Slide 62 – Dosing Schedule of ABT-199 and Rituximab – Cohorts 3 – 6

And you can see the dose escalation scheme here was to use very small doses and only ramp up very gradually and then, later on, to use rituximab after you have found the patient to be on a stable dose, because this tumor lysis syndrome starts when patients start the drug. And so, these drugs are typically given to patients who are in the hospital, and we can very closely monitor their blood counts as well as the potassium levels and other counts.

And I think it's very incumbent on any use of this medicine to try and involve close monitoring of the blood count so that patients who are experiencing tumor lysis can be

Dr. Thomas Kipps
treated effectively, because the tumor lysis itself may be without symptoms, and it only can be recognized with a chemical test.

Slide 63 – Adverse Events (AEs)

Now, fortunately, with these safeguards, we've not seen evidence of clinical tumor lysis syndrome. The adverse events that have been seen more recently are similar to ones that have been seen in earlier trials with the absence of tumor lysis syndrome. So, the question is whether we can learn how to safely administer this drug, which appears to be very powerful in eradicating the leukemic cells.

Slide 64 - Responses of Patients Treated with ABT-199 and Rituximab

Now, I want to say parenthetically, that we do see a high rate of complete response. The overall response rate is shown here, 84 percent. And complete response with this drug, or in combination with rituximab of 36 percent, is higher than when it was used by itself, which is around 20 percent.

And the question is if you combine this drug with the new anti-CD20 antibody called obinutuzumab, whether that complete remission rate will go higher.

So, one of the research questions that we're trying to struggle with now is, why doesn't everyone get a complete response? And for the patients who achieve a partial response, can they stop therapy safely without having the disease come back?

Clearly, we are not able to cure everyone. And we don't know, for example, the duration of how long the remissions will last if we do stop therapy. So, there are still a lot of unanswered questions. But, this is another weapon that clearly has some activity.

Slide 65 - Minimal Residual Disease (MRD)

And this is, again, the rituximab and ABT-199 trial. You could see that, now, not only our center, but other centers are seeing negative bone marrows. And this is listed here. So, quite a few patients are achieving what's called MRD negative status. Now, I understand that we have a limited time on our teleconference. I was hoping to go onto other aspects.

Slide 66 - Complete Remission: Discontinuation of ABT-199

But, an exciting aspect about this drug is that patients who have achieved complete remission with absence of minimal residual disease now can stop therapy. And we're just observing some of those.

Dr. Thomas Kipps
And some of our patients we've been observing now for close to a year, this July. And we're going to be following up to see if they have recurrent disease. So far, we have not seen that clinically. But, this is something we have to monitor closely.

I know we have very limited time, but I just want to mention this drug, lenalidomide, because it works through a totally different mechanism.

Slide 67 – Lenalidomide

Lenalidomide was a drug that was derived from thalidomide, which was formerly banned from the planet because it resulted in terrible birth defects in Europe.

And the drug actually has many activities. It's called an immune-modulating drug. It also can destroy angiogenesis. That's part of the reason why it was so teratogenic in developing kids. And it should not be used by anybody who is contemplating having childbirth.

Clearly it can be active in patients with myeloma for which it's approved and in patients with leukemia. Now, what's interesting about lenalidomide is that it's a drug that has potent activity in patients with leukemia.

And I must say the dose is very important. So, the lenalidomide dose that you give to a patient with myeloma is not the same dose that you can give to patients with leukemia. And for reasons that we don't quite yet understand, patients with leukemia are much more sensitive to lenalidomide than patients with myeloma. And so, what you really need to do is scale down the dose to 5 milligrams a day, down from 25 milligrams. And sometimes, we actually start patients at 2.5 milligrams a day.

Slide 68 - Lenalidomide Toxicity Profile

We still have these toxicities, namely low white count and low platelet count, that we have to manage. But, I think that for some patients this drug is very well tolerated. For some patients they can't tolerate it as well. And so, part of our work now is to try and figure out ahead of time what patients can tolerate this drug and what patients can't. I would say that about a fifth of the patients may not have a good tolerance of this drug. And some patients may take this drug very easily, and it may be very active.

Slide 69 - Response of Patients Over 64 Years of Age to Initial Treatment with Lenalidomide

And this is just the treatment of patients, elderly patients over age 65 with lenalidomide. You could see the response, even complete responses we're seeing in patients typically

Dr. Thomas Kipps
after 21 cycles, which is 21 4-week cycles of therapy, and you can get some complete responses in patients with this drug.

Slide 70 - Lenalidomide in Elderly CLL: Overall and Progression-free Survival
And I must say that it does seem to improve survival, and it is active in patients who have 17p-minus deletion.

We have a paper that is currently being reviewed by *Blood*. We hope that it's published soon, where we've actually been able to find that this drug has direct activity against the leukemia cell. It seems to block the leukemic cell from proliferating. And so, this is a very important idea that we can maybe stop leukemia cell growth and then, maybe combined with these other agents, we might be able to also keep it or make it die more quickly.

And so, we have to understand how these drugs work to make them better and to be able then to combine them with other drugs effectively and with minimal toxicity.

Slide 71 - Percent Change in Ig Levels of Patients Treated with Lenalidomide

But, I must say another thing about these drugs that's somewhat attractive is that they seem to improve the immune system over time. And that's something we're not seeing with other forms of therapy.

You can see the immunoglobulin levels in treated patients may actually go up over time, both with IgG levels and IgM levels. And so, this may be a way of reconstituting the immune system as well.

Slide 72 - Lenalidomide + Rituximab in Relapsed CLL Overall and Progression-free Survival

And of course, when you combine it with rituximab, you can see some improvement in the overall response rate as well as the improvement in progression-free survival.

And I don't have time to go over all of these things. But, I think that it's important to just note that this is a drug that requires a physician that is well acquainted with the use, and the early toxicities that manifest within the first month have to be managed very carefully. And if patients are tolerating the drug after the first month or two of therapy, they typically may derive a benefit from the use of this drug. And it has activity that's different from the other drugs that I mentioned.

Slide 73 – Monoclonal Antibody

Dr. Thomas Kipps
I just want to carry on a few more minutes. These are all the antibodies that are undergoing experimental trials. You could see there's quite a few against many different antigens. And it's an exciting new area of pharmacology.

I just want to focus on one, which is the antibody that's directed against ROR1. Now, what's ROR1? It's actually a protein that we and others have discovered on the leukemia cell surface. And it seems to be a leukemia antigen, which is also an embryonic antigen.

Slide 74 – ROR1 is Expressed in CLL, but Not Normal B-cells or Normal Adult Tissue

And this protein is not found on normal B-cells and other cells in the body. So, it may be allowing us to be more selective in giving antibodies that don't also target normal B-cells that may reduce our immune response to antigens and reduce immunoglobulin levels.

Slide 75 – CLL Microenvironment

And so, this is another one of these receptors. And it's cartooned here. It's one of the survival signals that may be acquired from the microenvironment. And all these different signals here may be useful targets for developing therapy.

Slide 76 – UC-961 Dose Response Targeting CLL Cells in Primary CLL Xenograft Model

But, ROR1 has been able to generate antibodies that react against the leukemic cells, and in model systems, seems to be able to clear the leukemic cells.

Slide 77 – Phase 1 Clinical Trial Design

I just want to mention this is part of the activities of The Leukemia & Lymphoma Society, which is a trial that is funded in part by The Leukemia & Lymphoma Society and also by the California Institute for Regenerative Medicine, that hopefully will be initiated this summer, where this anti-stem-cell-type antibody may be used against this leukemia.

Slide 78 – Chimeric Antigen T-cell Receptors

Another area that's causing a lot of excitement is genetically engineering T-cells to go after either leukemia cells or tumor cells. And what we can do is take an antibody that

Dr. Thomas Kipps
is very specific for the tumor cell, and use part of that antibody to combine it to the antennae that are normally found on T-cells. And what that does is it gives the antibody-type antennae that ordinarily are found on B-cells and gives it to T-cells.

Slide 79 – Chimeric Antigen Receptors (CAR)

And these are cartooned here. And the T-cell is fooled into thinking that's one of the receptors that really gets it activated when, in part, it's activated by binding to the tumor cell because of the portion that is from the antibody. And that's why it's called a chimeric antigen receptor or CAR therapy.

Slide 80 – CD19 CAR Therapy at Penn

The group that's really been doing some work on this, too, is the group at the University of Pennsylvania. They published two prominent papers, in the *New England Journal* and also *Science Translational Medicine*.

Slide 81 – CD19 CAR Therapy at Penn

And I have just some of the data on that approach. This is the CD19 CAR therapy program at Penn. Patients can receive their own T-cells that have been genetically engineered to go against CD19, which is an antigen or protein found on all B-cells, including leukemia cells. And you could see here that patients were infused with these cells.

Slide 82 - CD19 CAR Therapy at Penn

And I must say this infusion was well tolerated. But, afterwards, some of the T-cells would expand and cause what's called a cytokine release syndrome.

Namely, it's almost like having a bad flu. But, it can be quite serious. In some cases, you have to use some very specialized tools, such as received in two patients, where they had antibodies against IL-6 receptor, which is part of the process of inflammation that can be seen.

Slide 83 - CD19 CAR Therapy at Penn

But, some of the responses have been truly outstanding, in that the T-cells persist, and the patients may have absolutely no B-cells and no leukemic cells. And they may be cured of their leukemia. And these patients seem to have persistent T-cells in their body that keep the leukemic cells from coming back. Because they have no B-cells, they do require maintenance with IVIG to protect them from infection.

Dr. Thomas Kipps
And I must say that this is something that is of excitement. The questions that remain is, how can we make this therapy more effective for more patients, and therefore, also safer? Can we find ways to actually eradicate the disease?

And I share the view of The Leukemia & Lymphoma Society. I don't think we should rest until we can find improved treatments for every patient that are appropriate, that are not toxic, and that are well tolerated, and that might be able to cure this disease outright.

I find it embarrassing that we can't cure this leukemia because I think it's a low-lying fruit of cancer that we should be able to cure before we're able to tackle other cancers, such as pancreatic cancer or lung cancer.

But, I think this is just one battle that we need to wage. And I do believe it's a battle that we can win with the help of all the patients who actually participate in the clinical trials. These are the true heroes here. And I want to just congratulate them and thank them tremendously, because, through their participation in clinical trials, they've made possible the advances that we have today for everyone. And they deserve to be called our true heroes today.

So, my gratitude is to them and gratitude to The Leukemia & Lymphoma Society and other societies that have helped to support the research against this disease. So, thank you very much.

Slide 84 – Question & Answer Session

Ms. Lauren Berger
Thank you so much, Dr. Kipps, for all the information you presented, a lot of really good new information in such a clear way.

It is now time for the question-and-answer portion of our program. We'll take the first question from the Web audience. And Linda asks, "How frequently should a FISH test be done for an unmutated patient?"

Dr. Thomas Kipps
I recommend getting FISH at diagnosis so that you know what you're dealing with. And some patients at diagnosis will have the 17p deletion or 11q deletion. But, this is oftentimes increased in frequency, particularly after treatment with chemotherapy regimens.

Dr. Thomas Kipps
So, what I would recommend is that you have it at diagnosis. And I recommend that you get it again before therapy. And I think this is helpful because you want to look before you leap with therapy. And we advocate getting the FISH before every type of treatment so that we can understand whether we have changes that might affect outcome.

Ms. Lauren Berger
Thank you for your question, Linda. We'll take the next question from the telephone audience, please.

Operator
Our first caller is Trudy from Florida. Please proceed with your question.

Trudy
Yes, hello, Dr. Kipps. My question is, have you found many cases with CLL with having angioedema?

Dr. Thomas Kipps
Yes, we have seen cases with angioedema and CLL. And there must be a relationship there.

It's hard to define why that should be. But, I have had patients who have had angioedema as part of the clinical constellation with their CLL. And I've seen other cases with various types of autoimmune disorders. The most common autoimmune disorders that we see associated with CLL are antibodies against the red cells or against the platelets, which can cause, respectively, autoimmune hemolytic anemia or IT and ITP. And I think that angioedema must have something in relationship to the immune dysregulation that occurs.

The leukemia cell is part of the immune system. And when you have part of the immune system sick with a leukemia, it can actually gum up the works and cause deficiency so that there's a poor response to infection. That's why I always advocate being very careful about infections and start antibodies promptly.

But, also, there could be an increased incidence of some of these so-called autoimmune conditions that may require therapy on themselves.

Ms. Lauren Berger
Thank you for your question. We'll take the next question from the Web audience. And Ann asks, "How high can your white blood count get? Mine is currently 262,000. But, my hemoglobin and platelets are in normal range. I have never had treatment."

Dr. Thomas Kipps
It's a very good question. I once had a cowboy who came down from Montana to see me. And he was lassoing cattle. And when he came down to see me, his white count was approaching 1.5 million. And he was still standing and lassoing cattle.

But, I was nervous at that because I think that there comes a point where the leukemic cell count can be associated with increased problems, namely what's called thromboembolic problems, where there may be clotting. I have, however, been following patients that have had high white counts who have wanted to eschew therapy for some time.

I really want the patient to participate in their care and not to force therapy on anyone, provided I don't see either complications or disease-related symptoms that are really impairing their quality of life, when I try to advocate for the patient to maybe take some therapy.

But, as far as a white count of 200,000, I have seen patients do well over time. I do think that, when it gets to areas of 500,000 or so, and some have argued when it gets over a couple hundred thousand that there may be a higher incidence of these thromboembolic conditions.

And I think that it's hard to say because this has not been studied in a very rigorous fashion. And so, it's just from my anecdotal history that I have been able to call on patients who've had higher white counts who have not had these conditions.

But, I do think a white count of 200,000 is something that you want to monitor. You want to stay well hydrated. You also want to see your doctor if you have any new symptoms or problems of any nature, to stay on top of any medical conditions that might develop in that setting.

Ms. Lauren Berger
Thank you for that question. We'll take the next question from the telephone audience, please.

Operator
Our next question is from Crystal from Delaware. Please proceed with your question.

Crystal
Yes, I'd like to know, with all of the numbers being in the normal range, I also see that my numbers are around 67,000. But, I'm experiencing a lot of body pain. And I'm constantly told it's not related to the CLL. My primary doctor is now looking at some follow-up with me to check for fibromyalgia.

Crystal
Is there any connection between the two because I now have CLL. That because it's dealing with my immune system that I could also be experiencing some other issues, such as fibromyalgia?

Dr. Thomas Kipps
That's a very good question. And I must say that all the symptoms related to leukemia are somewhat general symptoms. And it's difficult because there's not one symptom that can't be related to something else.

And I've had patients, for example, with either fibromyalgia or just fatigue from other medical conditions that are also with leukemia. And I'm never saying never. I do not want to discount the potential for a relationship here. But, I do think we have to also bear in mind that we shouldn't jump the gun and conclude without any evidence that there is a relationship.

And what I do in my practice is, I try to take a careful history of patients and what sort of problems that they may be dealing with, either problems of aches and pains, such as you described, or fatigue. And I try to get a handle on the level of symptoms that they're having. And with follow-up, I try to also measure the leukemic cell count as well as the lymph node size to get a handle on where the disease is going.

Namely, can I assess over time, is the disease progressing? Is it getting worse and worse? And at what level, what tempo, is it getting worse and worse? And if the symptoms that I see in the patients are getting worse in the same tempo, then I would say that there may be a relationship. And that oftentimes can be relieved with successful therapy against the leukemia.

I will say this, though. I've had patients come to see me when they've been treated with their physician soon after being diagnosed because they complained of being tired. And they said they went through all this therapy, and they're still tired. And it turns out they have other medical conditions that caused the fatigue. So, I think it's very important that we try to identify whether the symptoms are truly related to the leukemia and not related to other medical conditions.

So, just to summarize, when you have these other symptoms, it's important to get evaluated for other medical conditions that can also cause such symptoms and then to get therapy for them.

I want to say that one symptom that's quite common, and more common than we know, is a problem of sleep apnea. And that sometimes could be exacerbated when the lymph nodes and the tonsillar area becomes engorged with leukemic cells. Where patients may be otherwise asymptomatic, they may have a problem with sleep apnea.

Dr. Thomas Kipps
And they don't get a restful sleep. They maybe have relatives that may complain of them snoring. And this could also produce night sweats. It can produce fatigue. And patients can feel very tired during the day and just feel drowsy all the time. I've had several patients undergo sleep studies and find that it's sleep apnea and not the CLL that's causing the night sweats and the fatigue.

So, important to view the entire patient, view the leukemia, how fast it's advancing, how fast are the symptoms advancing, and then to use therapy to try and improve the quality of life of the patient and not to incur greater risks of some therapy because the symptoms are related to other medical conditions.

Ms. Lauren Berger
Thank you for your question, Crystal.

We'll take the next question from the Web audience. And this one's from Janet. And she asks, "Is it common to have a local oncologist and in addition have a CLL expert oversee your healthcare and treatment? Also, would most insurance plans cover this arrangement?"

Dr. Thomas Kipps
Yes, that's a very good question. I think it's helpful to have a local oncologist who is someone that you can reference to and see and develop a relationship with. I do think that this is a very quickly moving field. And it's helpful to work together. We have many patients that we see but are also seen by a local oncologist. And I think that it helps because they can then get insight into what may be evolving in terms of treatment strategies or clinical trials that maybe opened up, but then to work closely with their local physicians. And I think that forms a very good team relationship.

I must say that I always welcome the involvement of other physicians in the care of patients. I think if they're doing this in a team way, and I always question any doctor that refuses or does not wish to invite other physicians to comment on the clinical care.

As far as insurance coverage, this varies depending on the insurance provider. I know that some of the HMOs, which is typified by programs such as the Kaiser Permanente system; they may allow for only one visit but not cover any laboratory charges or any follow-up visits.

So, I think it depends on the type of healthcare coverage that you have. It's important to enquire ahead of time whether the insurance carrier that you have allows for outside consultation.

Dr. Thomas Kipps
And then you can maybe take advantage of being able to consult with a leukemia specialist because of the special nature of some of the facets of this disease, but maintain a close relationship with your local hematologist oncologist. That makes the best of both worlds.

Ms. Lauren Berger
Thank you. And for additional help on questions about insurance and how to broach this topic, as well as help in formulating questions to ask your doctor or the consultant that you're going to, the expert, please reach out to the Information Resource Center at LLS. And the telephone number is 1 (800) 955-4572.

We'll take the next question from the Web audience. And this one asks, "What is the role of allogeneic transplant in CLL?"

Dr. Thomas Kipps
I think it's a very good question. And I must say that the target is moving. Obviously, in the past, when we had just chemotherapy, those patients who had the deletion on the chromosome 17, the 17-minus deletion, were often times factored into allogeneic transplantation, provided that they had a well-matched donor and they had absence of medical comorbidities that would not pose a problem for allogeneic transplantation.

I think that with the advent of newer treatments, that is now changing. And so, we have to ask the question of what patients should be going to allogeneic transplantation.

Now, we are seeing with some of the newer therapies, too, the issue of transformation, where patients may transform to develop a more aggressive disease, more aggressive lymphoma. And that's the so-called Richter's transformation.

And you can also see more aggressive leukemia. And if you're having issues with regard to Richter's transformation, those patients should be considered for allogeneic transplantation.

I will say this that the clinical studies on allogeneic transplantation have shown the following features affect the outcome of patients: namely, the size of the lymph nodes before allogeneic transplant is a big deal with regard to that.

So, patients with very bulky lymph nodes going into transplant typically do not fare that well. It is to say that it's important that the disease be under some control before they go to allogeneic transplantation. If the disease is out of control, then the allogeneic transplant typically is not successful.

Dr. Thomas Kipps
So, as far as what candidates for allogeneic transplantation, I think younger patients, patients who have potentially more aggressive disease who are not amenable even for these newer therapies, and patients who may have been identified as having Richter's transformation.

If you can't get the Richter's transformation under control with various treatments that are being developed, then they may not have a long-lasting disease-free survival. And they should be considered for transplant so that you can have that work its magic with regard to graft versus leukemia effects.

Ms. Lauren Berger
Thank you for the question. We'll take the next question from the telephone audience, please.

Operator
Our next question is from James in California. Please proceed with your question.

James
I have CLL. And I took the standard regimen of CFR. And the treatment was successful for about 16 months, and my symptoms came back. And then I just finished a round of six months of bendamustine with Rituxan.

I do have a deletion in the long arm of my 11 chromosome. Does this kind of suggest that I will be having more and more treatments, or is there a possibility that this last treatment will be long lasting?

Dr. Thomas Kipps
Well, I think the experience that you have is not too uncommon for patients who have the deletion on chromosome 11. And we're trying to understand why that should be.

But, with what's called chemoimmunotherapy, namely, as you call it, CFR or FCR, the responses tend to be good, but the duration tends to be shorter than you find for other patients.

Typically, on average, patients after FCR may enjoy three to five years. Sixteen months being a year and less than a year and a half is not getting much bang for the buck going through that regimen.

And I say that the definition for being refractory to a regimen is usually six months or less. So, some patients even don't enjoy 16 months.

Dr. Thomas Kipps
But, I think 16 months is short. And I would suspect that, with the bendamustine and rituximab regimen, if you've had a good response, then it may be a remission that may not be as long lasting as we would like and should be followed very closely for any signs of the disease coming back.

But, with the advent of some of these newer regimens that are coming out, it gives you more options so you don't have to do the chemoimmunotherapy route again. One thing that's also very important is to repeatedly check your FISH before going forward, particularly with any more of the chemoimmunotherapy.

Ms. Lauren Berger
Thank you for your question, James. We'll take the next question from the Web audience. And this one's from Robbie. "Please address how staging influences personal treatment planning. I was diagnosed with Stage 0 CLL eight years ago. My blood counts have remained stable. Should I be proactive and consider treatment at this time, or should I keep with the watchful waiting program?"

Dr. Thomas Kipps
Well, I think that's a very good question. There is an entity that's now been recognized called monoclonal B-cell lymphocytosis or MBL.

And those are for patients who typically don't have lymph node enlargement, but they may have an excessive clone of cell which can be identified as having features that are similar to CLL, but it's not really called CLL because it doesn't seem to have the same tendency for progression. About 1.5 percent of patients per year have what's called MBL and may progress into a leukemia that requires therapy.

So, if you do the math, 1.5 percent per year, if I told you that there's a 1.5 percent chance of it raining outside, you'd probably not bring your umbrella to work.

So, I think it's important for you to be observed, periodic blood tests, and a good lymph node exam, which could obviate having to do repeated CT scans. So, a good physical exam and a lymphocyte test, you want to look for any development of enlarged nodes or enlarged spleen, but more importantly to look for any fall in your hemoglobin or fall in your platelet count.

And also, we do monitor your immunoglobulin levels, which can fall in CLL, but less so in MBL. And if those start to change, then that may be evolving into CLL.

Dr. Thomas Kipps
Now, to answer your question, I think that, sometimes, we have conditions where it may be a problem if we engage in therapy. And it's similar to having a slow leak in your faucet at home and having only a sledgehammer to fix it.

Now, clearly, you might have to do work with the sledgehammer if the faucet is really losing a lot of water. But, in cases of this nature, we cannot say for sure that the problems with therapy may be less than the problems you'll have with this condition.

So, I'm of the opinion that, if you are not having any evidence of disease progression, you're not having any symptoms related to disease, you're not having any complications, then it's mainly a chemical test or blood test that said that this is the condition.

And I think careful follow-up is much recommended over being aggressive and trying to fix something. As they say, "If it ain't broke, don't fix it." And that would be my opinion today still.

Ms. Lauren Berger
Thank you for your question, Robbie. We'll take the next question from the telephone audience, please.

Operator
Our next question is from Marilyn in Arizona. Please proceed with your question.

Marilyn
Yes, I was wondering how trisomy 12 and deletion 6q affect treatment and prognosis?

Dr. Thomas Kipps
Well, the trisomy 12 is commonly seen, and the deletion at 6 is also seen.

I think the most important facet about trisomy 12 is that it does seem to be associated with the tendency for the disease to maybe progress a little bit more quickly than patients who do not have trisomy 12. And in particular, there may be other facets that might be associated with trisomy 12, such as some of the new genetic changes that we're trying to identify now.

And I must say, parenthetically, about these new genetic changes, with the advent of deep genomic sequencing, that there's been a whole series of new mutations that have now been found that might be associated with the leukemia that may be only seen in a percentage of patients.

Dr. Thomas Kipps
And we're still trying to understand why they should be associated with it and, more importantly, what the clinical outcome is of those mutations. And I think that we need to learn more before we use them as any means for making recommendations.

With trisomy 12, you find that, oftentimes, the level of the protein CD20 is a higher level on the leukemia cell surface.

And so, typically, patients may do fairly well with antibody regimens that incorporate the rituximab or ofatumumab or now, the new kid on the block, obinutuzumab or Gazyva.

Ms. Lauren Berger
Thank you for your question, Marilyn.

We'll take the next question from the Web audience. And Margaret asks, "Because of a lack of long-term studies on ibrutinib and idelalisib, do you recommend these drugs for patients in their 50s or early 60s who have not responded to FCR?"

Dr. Thomas Kipps
This is a very good question. And I think the major point there is not have responded to FCR.

If you have had a poor response to FCR, then I guess the other options are to go into a clinical trial, and I think that there are several that could be testing newer agents. There's also the potential option of considering treatment with a drug such as lenalidomide, which should be done under a physician who is well acquainted with the use of that drug.

But, I think, also, the use of ibrutinib or idelalisib certainly can be effective in that type of patient. And we should not divorce ourselves from using these new weapons. I will say that it's clear that these are new drugs, and that the experience of these drugs has not been very extensive, and there may be issues that crop up over time.

That's why I think we need to continue our efforts to find better treatment so that patients who eventually may fail ibrutinib, for example, those patients will have other treatments that we can use.

And I think that we have to continue finding new treatments. I don't think we should just stop where we are and say, "We're done." I think we're far from being done.

But, I'm very pleased to see that we have new weapons that we can use in settings such as that for patients who have had unfavorable responses to FCR.

Ms. Lauren Berger
Thank you, Margaret. We'll take the next question from the telephone audience, please.

Operator
Our next question comes from Arlene in New Hampshire. Please proceed with your question.

Arlene
Are any of the drugs you've mentioned another name for Imbruvica®? And what do you think of Imbruvica?

Dr. Thomas Kipps
Yeah, Imbruvica is ibrutinib. They're the same thing. Imbruvica is the company name. Ibrutinib is the generic name. That's the name that's been given to them to register the drug. So, when I say ibrutinib, I mean Imbruvica.

Ms. Lauren Berger
Thank you for your question, Arlene. We'll take the next question from the Web audience. "My mother was diagnosed on June 13th with CLL B-cell type Stage 0. She is 80 years old. Will her age impact her doctor's decision regarding which course of treatment to pursue?"

Dr. Thomas Kipps
I think it has to. You know, as we get older, everything starts to wear out a bit. You know, our knees may start to wear out, but you know, maybe our kidneys are not working as well as they used to.

And so, our metabolism and our ability to handle drugs may actually change over time. And that's one of the key features that has been noted in that some of the regimens, such as the FCR regimen, which has been very successful for younger patients, the right type of patient, may be poorly tolerated by somebody in their 80s.

And it's also true of the bone marrow. Typically, we tell our medical students that the cellularity, if you will, the amount of cells that occupy the bone marrow, is 100 minus your age. Now, that does not mean that, when we get to be 100, we run out of bone marrow. But, my point is that, over time, our ability to tolerate treatments may go down.

So, I think it's important that we look at some of these other types of treatments that I've just discussed today that could be useful for patients who have these medical comorbidities.

Dr. Thomas Kipps
I do know that there are some issues with these newer drugs, too. For example, there may be a higher incidence of atrial fibrillation with ibrutinib that's not seen in the other arms of therapy. So, we have to always pay attention to complications that can arise from even these newer drugs.

And I must say that clinical studies involving patients who are 80 years old are less frequent because, many times, those patients do not go to medical centers for obvious reasons, and get enrolled into clinical trials.

I will say that the trial that led to the approval of obinutuzumab or Gazyva, that new anti-CD20 that I mentioned to you, was specifically for patients who were over age 65. So, no patient under age 65 got into the study. And I believe that the median age of patients was well in their 70s.

And many times, the patients also had to have medical comorbidities. You know, they had either renal insufficiencies or heart problems that they associate with getting older. And that was the purpose of this study, to use this drug obinutuzumab in combination with the drug chlorambucil, which other studies have shown is an orally active drug that, like bendamustine or cyclophosphamide can be well tolerated if used in low amounts under the hands of a caring physician.

So, I think that study, where you used obinutuzumab with chlorambucil, showed that, even with this so-called mild regimen, we've had lower amounts of chlorambucil used, there was a fairly high response rate, including about 17 percent of patients that achieved a complete response, which allowed them to stop therapy and be free of their disease. And that's something that I think deserves some notice, particularly for elderly patients.

I will say this, that with these antibody treatments, and obinutuzumab is no exception, there is a problem of infusion reactions. These are reactions that you may have when you first get the antibody. And it does need to be done in a center that has experience in giving these antibodies.

And one thing is that, when a patient gets started on these treatments, typically, after the first one or two infusions, the patient can accept these very easily without these infusion reactions. And they can be well tolerated, even by patients in their 80s.

I know I've treated patients who have been in their 90s. But, I do think we do worry about added complications when patients get older. And I think it needs to be done again under closer supervision, and hopefully your mother will become okay.

Ms. Lauren Berger
Thank you for the question. We'll take the next question from the Web audience. And Stephen asks, "How can I find out about clinical trials or even discuss clinical trials with my doctor, who seems to have just enough time to discuss my current treatment with me?"

Dr. Thomas Kipps
Well, I think that's a very important question. There is clinicaltrials.gov. I think the trials may be listed on the website. That's a government service.

Also, one can look on the websites of organizations. I believe The Leukemia & Lymphoma Society has some trials that I mentioned.

I think that perhaps looking at websites of known centers where you have CLL having a special emphasis would be useful and getting information from those sources.

I do think it's important to be aware of the clinical trials that are being done, because those are potentially the treatments of the future that might be useful today and give us a way of thinking outside the box and getting into what we hope might be a way to actually cure this disease outright. And I know that's a very big goal of both clinical investigators as well as The Leukemia & Lymphoma Society.

Ms. Lauren Berger
Thank you. And for The Leukemia & Lymphoma Society, the Web address is www.lls.org/clinicaltrials. So, you can get information there or call an Information Specialist at (800) 955-4572, and they will help you individually with information about clinical trials.

We'll take the next question from the telephone audience, please.

Operator
Our next question is Herbert from Virginia. Please proceed with your question.

Herbert
Yes, I am 75, diagnosed in '94, have had three treatments, a fludarabine arm clinical trial, Campath®, and then I had AIHA with a splenectomy. Since the day after the splenectomy, all my blood counts shot up into the normal range, and they've been there for over seven years.

The question is, if I start developing symptoms and I'm falling out of remission, do I need a new FISH test? And what therapy might be best for me?

Dr. Thomas Kipps
Well, I think that your clinical course of, first, the splenectomy, I must say that we do recommend splenectomy for patients who have very severe autoimmune hemolytic anemia or ITP, because that's a condition where the body starts reacting against the red cells, and the red cell count can go down very low, and actually life-threatening levels of anemia can be there. And there have been very few studies that look at the outcome analysis of patients who have their spleens removed. But I think it favors those patients who have their spleens removed under those circumstances.

And as you mentioned, the spleen can sometimes even keep the counts from getting up to the levels that you would enjoy seeing. And I typically can spot that in patients where you do the bone marrow biopsy, and you can see that they're making quite a few red cells and platelets and that bone marrow looks fine, and yet we don't see them in the circulation. And oftentimes, that may be due to the fact that the spleen is being overly aggressive in taking out the cells. And if you remove the spleen, then you can enjoy the benefit of the bone marrow putting out those cells.

And also, patients, if they do have recurrent autoimmune hemolytic anemia, it doesn't go down as low as when their spleen was there.

As far as the treatments, you know, I think getting follow-up care, it's great that you've been out for seven years. I hope it's for seven more years. I think it's important to get followed up and to look for any sign of the leukemia coming back or having symptoms that are concordant with the leukemia coming back.

And you know, it's a moving field right now. We have had two new drugs approved within the last several months. I look forward to having more drugs approved for this disease. And I think that when time comes for therapy, you might even have a better playing field than we have currently.

So, I think, before therapy, as you mentioned, whether you should have FISH again, yes, I do believe you should have FISH again. It should be easy to do that test, and it could provide information for you, particularly for patients that are being considered for any form of chemoimmunotherapy. We are just now beginning to understand what genetic changes might lead to maybe a poor outcome with some of these newer agents. I think that work is being done as we speak.

So, we might have some other tests in addition to FISH that can get a genetic profile of mutations or changes that could be associated with poor outcome with one type of therapy versus another. And that's work that we need to complete.

Dr. Thomas Kipps
So, I think, because it's a moving playing field, I would not recommend any one way of action, but it really depends on a number of factors that have to be made at the time when you might be requiring new therapy.

Ms. Lauren Berger
Thank you for your question. We'll take one more question from the Web. David asks, "Are you aware of any further research into the efficacy of EGCG as found in green tea for treatment of CLL or any other holistic?"

Dr. Thomas Kipps
Well, we are very attracted to these epigallocatechin. It is the EGCG that may be found in green tea and also to some extent in black tea.

The green tea has these and other chemicals. And research that was done several years ago found that it was actually, in some ways, a mild BCL-2 antagonist.

And I mentioned that category of drugs, the BCL-2 antagonists. I only mentioned one of these drugs, which is ABT-199.

And I remember a discussion I had with a professor at the University of Beijing, where they had all sorts of herbal remedies. And I got very excited. I said, "Well, that's great. We can try to understand what are the active ingredients and maybe try to improve upon them?"

And as I was saying that, he looked like I was punching him in the stomach. So, his opinion was that the herbal remedy was already perfection and that any attempts on Western medicine to find the active ingredients was ill advised.

I do subscribe to the notion that it's important to know what is in things that work the way it does because I know that there can be batch-to-batch variations in any herb, depending on drought conditions or weather conditions.

And so, it's hard to recommend if the drug has potency, the drug has potential side effects as well. So, any drug that's potent has also potential danger. And so, knowing what the active ingredients are and being able to tweak them I think is very helpful.

Now, in the case of epigallocatechin, there have been a few clinical studies done. But, I unfortunately think that it might be difficult to drink enough green tea in order to have the clinical benefit. Some patients take the epigallocatechin pills, which look like large horse tablets.

Dr. Thomas Kipps
But, I think that, with the advent of some of these newer anti-BCL-2 agents, they have been the work of sort of molecular engineering to try and figure out exactly how the BCL-2 protein works and to try to find small molecules that can inhibit this.

And they seem to be even more selective and more effective. So, I think that, getting back to the green tea, I think it's great. I drink it myself. I recommend everyone subscribe to a healthy diet.

And the only test I would say is that, if the herbal remedies that you have are putting you out of house and home and costing a tremendous amount, then I would probably try to ask for the data that might exist to substantiate the claim that they are effective.

And unfortunately, sometimes that data are not very forthcoming. And I think that's the reason we need to do clinical trials because all these agents that I described today are only found to have value by doing a critical clinical trial and finding out whether they truly pass muster. Are they providing the benefit that allows us to assume the risk of taking these drugs?

And I do believe that every treatment decision has to be a risk-benefit ratio. And that goes as well to herbal medicine, too. What's the risk of taking an herb that we don't know about versus the potential benefit? And that ratio's difficult to calculate.

Ms. Lauren Berger
Thank you for your question, David. And thank you, all, for your questions. We hope that this information will assist you and your family in your next steps. And thank you to Dr. Kipps. We really appreciate the time and expertise that you shared with us today.

Slide 85 – The Leukemia & Lymphoma Society Contact Information

Ms. Lauren Berger
The Leukemia & Lymphoma Society also offers online chats that provide forums for patients and caregivers to share experiences and to support each other. These chats are moderated by oncology social workers. And for more information on how to participate, please review the flyer in your packet, or you can go online at www.lls.org/chat.

If we were not able to get to your question today please call The Leukemia & Lymphoma Society's Information Resource Center and speak to an Information Specialist at (800) 955-4572, or reach us at infocenter@lls.org. Information specialists are available to provide information and answer your questions about treatment options, including clinical trials, support services, and financial assistance.

Ms. Lauren Berger
Thank you to Dr. Kipps and to all of you for spending your time with us today. We really appreciate it.

Goodbye and we wish you well.