What's on the Horizon for Chronic Lymphocytic Leukemia?

May 8, 2018  Speaker: Matthew S. Davids, MD, MMSc

Slide 1 – What's on the Horizon for Chronic Lymphocytic Leukemia?

Ms. Lizette Figueroa-Rivera:
Hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. We have over 800 people participating from across the United States and Canada. And special thanks to Dr. Matthew S. Davids, for sharing his time and expertise with us today. Before we begin, I would like to introduce Meredith Barnhart, The Leukemia & Lymphoma Society's Director of the Information Resource Center (IRC), who will share a few words. Meredith, please go ahead.

Ms. Meredith Barnhart:
Thank you, Lizette. And I would like to add my welcome to the patients, caregivers and healthcare professionals attending the program today. The Leukemia & Lymphoma Society exists to find cures and ensure access to treatment for blood cancer patients. Our vision is a world without blood cancer. For more than 60 years, LLS has helped pioneer innovations such as targeted therapies and immunotherapies that have improved survival rates and quality of life for many blood cancer patients. To date, we have invested over one billion dollars in research, to advance therapies and save lives. Until there is cure, LLS will continue to fund promising research from bench to bedside. As you will hear from today's presentation, being diagnosed or having a loved one diagnosed with chronic lymphocytic leukemia can be very difficult for any family.

The Leukemia & Lymphoma Society's Information Specialists are able to provide personalized support to individuals managing a blood cancer, by providing up-to-date disease information, including clinical trials, support resources, and helping families navigate the financial challenges associated with blood cancers. In addition, LLS is the leading source of free blood cancer information, education and support. And we touch patients and their communities. There are 56 chapters across the United States and Canada. LLS also acts as the voice for all blood cancer patients. We advocate for patients and survivors and their families, helping them navigate their cancer treatment and ensuring that they have access to quality, affordable, and coordinated
care. We are fortunate to have our presenter today, Dr. Matthew S. Davids, one of the nation's leading experts on chronic lymphocytic leukemia. We appreciate his dedication to supporting our mission and his commitment for caring for patients living with blood cancers. I would like to thank him for providing us today with the important information on CLL. Thank you all, and for now I will turn the program back to Lizette.

Slide 2 – Disclosures

Ms. Lizette Figueroa-Rivera:
Thank you, Meredith. And we would like to acknowledge and thank AbbVie, Genentech & Biogen, and Pharmacyclics & Janssen Biotech, for support of this program. If you are participating in this program on a computer, Dr. Davids' slides will display as you listen to the program. You can also view or print the slides from our website at www.lls.org/programs, or you can download and print the slides from the Events Resource tab on this program's web platform. Following the presentation, we will take questions from the audience. We are audiotaping and transcribing this program for future posting on our website.
Slide 3 – What’s on the Horizon for Chronic Lymphocytic Leukemia?

I am now pleased to introduce Matthew S. Davids, MD, MMSc, Associate Director for the Center of Chronic Lymphocytic Leukemia, and Assistant Professor of Medicine at Harvard Medical School, Dana-Farber Institute in Boston, Massachusetts. On behalf of The Leukemia & Lymphoma Society, thank you, Doctor, for volunteering your time and expertise. I am now privileged to turn the program over to you.

Dr. Matthew S. Davids:
Well, thank you so much, and I want to first start by thanking LLS for inviting me to do this. It is a great honor for me, and I have been supported by LLS ever since my days as a Fellow. So, they have provided a tremendous amount of grant support for my own research, and I am very grateful for that. So, I would like to say a nice hello to all of my patients who are out there, who I know are calling in, as well as too many patients who I do not know, and this is a great opportunity for me to share my perspectives on CLL for patients around the country. And we will focus today on what is on the horizon for CLL. But I know that there are some patients who may be newly diagnosed with CLL, so I am going to start with some basic facts about the disease, to get everyone up to speed, before we delve into some of the details on the latest and greatest treatments.
So, just to start, I do consultancy work for a number of different companies, advising them on how best to develop drugs for CLL patients, and we do get research funding for our work from a variety of companies, as listed here. Also, I will be talking about a couple of drugs, venetoclax and lenalidomide, and off-label uses during this presentation.
Slide 5 – The Big Picture

But just at the highest level, I want to talk about where CLL fits into the picture of other blood cancers. Non-Hodgkin lymphoma is one of the most common types of blood cancer, and about 66,000 new patients are diagnosed with this disease every year. The majority of patients with NHL have B-cell lymphomas, and these include both indolent and aggressive subtypes. About 30 to 40% of patients will have the more indolent forms of lymphoma, and of these SLL, small lymphocytic lymphoma, and CLL, chronic lymphocytic leukemia, comprise one of the largest groups, with about 19,000 new patients diagnosed per year. It is a little bit confusing that we call this disease a leukemia, but all this means is that there are cells circulating in the bloodstream that are leukemic cells, but most of the patients also have enlarged lymph nodes over time, and therefore the disease behaves more like an indolent lymphoma. So, you can really think of the disease as both.
Slide 6 – CLL | Fast Facts

Let's go over some fast facts about chronic lymphocytic leukemia. The median age at diagnosis is 72, although there is quite a range, and I have had patients in my clinic in their 30s, all the way up into their 90s at the time of diagnosis. Patients are often diagnosed on routine blood work, as increasingly primary care physicians are sending complete blood counts and may notice an incidental elevation in the lymphocyte count, which is later confirmed as CLL. There is a huge amount of variation in how this disease can behave, and therefore we send a variety of different powerful biologic predictors of response that can help inform when certain patients may need treatment, and what the best treatments are for those patients.

For patients with early-stage CLL who do not have symptoms, we can actually observe these patients for a period of time, and we will talk today about what the rationale is for that. But for patients who have advanced-stage CLL, and those who have significant symptoms from the disease, we have historically treated patients with chemoimmunotherapy, which has been helpful, and this has been a highly treatable disease, but historically most of our therapies have not been curative. Although we will begin to challenge that today with some new data that I will show you.

Bone marrow transplantation with cells from a donor, also known as allogeneic transplantation, may lead to long-term survival and even cure in this disease. Although we are not using this therapy as much these days, because we have a variety of novel oral agents that have recently been approved by the FDA, and have already started to revolutionize this field.
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Slide 7 – CLL | Diagnosis

How we make a diagnosis of CLL: The key is to send the peripheral blood flow cytometry test. This is just a simple blood test, usually one tube of blood, that can be run through a machine called a flow cytometer, which you can see in this picture. And this looks at the different proteins sticking off the surface of a CLL cell. And we know when we see a certain pattern of proteins, as listed here, with proteins such as CD5 and CD20 being on the same cell, that this is consistent with a CLL cell. However, the number of the cells is what is making the diagnosis here. ABC here stands for the absolute B-cell count. If that is greater than 5,000 and circulating in the blood, that makes the diagnosis of CLL. However, if there are fewer than 5,000 of these B cells, but they are present, this could be a condition known as monoclonal B-cell lymphocytosis, or MBL. MBL can be thought of as a precursor condition to CLL, kind of in the way a colon polyp may someday develop into a colon cancer. We need to monitor patients with MBL, but most patients can be safely observed for many years and will never go on to develop CLL.

One point of confusion is the difference between CLL and SLL, small lymphocytic lymphoma. Sometimes a lymph node biopsy, either through a surgical excisional biopsy, or a core biopsy done by a radiologist, is necessary to make a diagnosis of SLL. SLL is defined by the situation where a patient may have enlarged lymph nodes, but an absolute B-cell count of less than 5,000. Because they have the enlarged lymph nodes, this confirms the diagnosis of SLL, rather than MBL. Bone marrow biopsy is rarely needed at the time of diagnosis, because we can usually see the cells circulating in the bloodstream. Although occasionally if patients have low blood counts, like anemia or thrombocytopenia, which is low platelets, then a bone marrow biopsy may be helpful.

One key point I like to emphasize is that both SLL and CLL are really part of the same disease continuum, and can be thought of in the same way, both in terms of the prognosis, as well as the treatments that we have available for patients. So, the distinction is really just a matter of the diagnostic criteria that I listed here.
This is a shot from a blood smear from a patient, looking at CLL cells. You can see that the red cells here are a patient's red blood cells, and normally in a field like this, we might expect to see a handful of these darker cells, which are lymphocytes. Lymphocytes are normal white blood cells that are there to help patients fight off infection. But in CLL, these cells accumulate gradually over time, and they start to arise in large numbers in the blood. And, as you see in this micrograph here, there is a great number of lymphocyte cells compared to what we might normally expect from other patients.
So how do we stage CLL? Some of you may be familiar with the Rai staging system which we use most commonly in the United States. I will mention that there is also a system known as the Binet staging system that is used more widely in Europe. But today, we will focus on the Rai system, which breaks patients down into five stages. This is a rare cancer that has a stage 0 as part of the staging system, and this indicates patients who only have an elevated lymphocyte count, but no other manifestations of the disease. And most of these patients can be observed for a long period of time. Other early stages of CLL include stage I, where lymph nodes can be felt on a physical exam, as well as stage II, where a spleen or liver can also be felt on a physical exam.

The more advanced stages of CLL are stages III and IV, which is when patients have infiltration of CLL cells into the bone marrow, which is like a factory for making blood cells. And when the factory is clogged up with CLL cells, patients cannot make the normal number of red blood cells or platelets, leading to anemia or thrombocytopenia. It is notable that this staging system does not require bone marrow biopsy or CT scan, but rather can be done purely based on physical examination and laboratory values from the blood.
Slide 10 – Key Prognostic Factors

As I mentioned, there is a great deal of variation in the behavior of this disease, and some patients may require treatment within a few months of diagnosis, whereas others may never need treatment. These are some of the key prognostic factors that we can send that can help to predict when patients may need therapy: Beta-2 microglobulin is a protein that can circulate in the blood, and when it is elevated tends to correlate with a more aggressive course for CLL. Cytogenetic abnormalities, such as the FISH test, immunoglobulin G mutations such as IgVH, or IGHV, as well as somatic mutations, as listed here, have become some of the key prognostic markers that we utilize for CLL patients. ZAP-70 and CD38 are older markers which do not have as much independent value prognostically, and therefore we do not use them as much these days.
Let's talk a little bit more about FISH testing. FISH is a form of looking at cytogenetics which looks at the different chromosomes inside CLL cells. In the top left, you see a routine karyotype, which is an older way to look at these cells, which is very challenging to look to see if there are little bits and pieces of chromosomes that are either missing or in excess in these patients. So, the FISH test was developed, in the lower left corner, which is a much more accurate way to assess for these abnormalities. This is an example of a patient who has trisomy 12, which means three copies of chromosome 12, and as you can see, it is easy to see that there are three red probes there, when there should normally be two. On the right, you see the percentage of patients at diagnosis with the different FISH abnormalities. About half of patients will have the deletion 13q, and then a smaller number of patients will have the other abnormalities as listed here.
Slide 12 – CLL | Prognostic Factors: IGHV

In terms of IGHV mutation status, this is another critical factor for CLL prognosis. On the left side, you see a more unfavorable scenario of what we call unmutated IGHV. These are CLL cells that were recently born, and then developed into the malignant cells, without the chance to mutate their DNA. Because they are young cells, they tend to be very activated, and as you see in the bottom left, they can undergo survival and proliferation, meaning growth, as well as apoptosis, which is the process of cell death. So, it is a much more active type of cell, and that is why historically it has been much more challenging to treat with our older chemotherapy regimens.

On the right side, you can see a mutated IGHV CLL cell which is arising from an older lymphocyte cell, which does not tend to be activated, or grow as quickly, and therefore these cells tend to be easier to kill with our traditional treatments. As I will show you in a little bit, some of our newer drugs, such as the drugs targeting the B-cell receptor pathway, seem to work equally well in patients with mutated or unmutated IGHV, which has been one of the major advances in the field.
Slide 13 – CLL | Prognostic Factors: Somatic Mutations

I will not go into too much detail on this complicated graph here, but I really just want to highlight that there is a number of different cellular pathways that can be affected by mutations in CLL. The most critical one is in the top left, the DNA damage pathway. One way that chemotherapy works is by damaging DNA, which then causes cells to die. And as you can see, there is a key gene in the second row there called TP53 that is necessary to kill the cells. When TP53 is either missing or mutated, it does not allow chemotherapy to kill CLL cells, and that is why patients with the deletion 17p have had typically a shorter response to chemotherapy-based regimens. Again, this is getting better with some of our newer therapies that can bypass this pathway. Notch1 signaling is also thought to be important, as well as some of the other pathways, as we see here.
So, let's talk about treatment. Why can't we just cut it out? So, that is a question that I do get sometimes from CLL patients, particularly those who may have only a small number of lymph nodes and would be hoping that if this was cut out, like with other cancers, that it may not come back. Unfortunately, CLL is a systemic disease and a blood cancer, so even if it only appears to be in a small number of lymph node groups, it is likely that it is circulating throughout the body, and that if those nodes were just cut out, it would come back somewhere else fairly quickly. And therefore, we have always approached this disease by using systemic therapies that can go throughout the body and treat CLL wherever it is trying to hide.
So, let's talk about the indications for treatment of CLL. When do we treat this disease? First, when we see low blood counts due to that issue I mentioned before, where the bone marrow factory gets clogged up with too many CLL cells, and that leads to anemia or low platelets. Some patients can develop bulky lymph nodes, or rapidly enlarging lymph nodes or spleen, that can be causing symptoms including pain or swelling, and other symptoms including fevers, night sweats, unintentional weight loss, fatigue, pain, can be reasons to treat, although these usually need to be in the presence of progressing disease elsewhere, both in the blood and the lymph nodes. A challenging situation is that many patients with CLL who are on observation have fatigue, and I always try to look hard for other causes of fatigue, since this is such a common condition. I have diagnosed a number of patients with low thyroid, sleep apnea, and other issues that can contribute to sleep deprivation, and that is a more common cause of fatigue than the CLL.

Autoimmune conditions refer to, in particular, things that can happen in the blood that are affected by the CLL cells. This includes low platelets, or low red blood cell count, due to the CLL misdirecting the immune system to kill off healthy cells in the blood. This can usually be treated with steroids or rituximab, which is an antibody-based therapy, but in some cases, if they are refractory to these early interventions, then we may need to do more definitive CLL treatment to control the autoimmune conditions.

One of the things here that you will see is the LDT, which is the lymphocyte doubling time. In other words, how long does it take for the lymphocyte cells to double in a patient? If this is less than six months, that does tend to suggest that the CLL is becoming more active. However, I will caution you that the white blood cell count alone is rarely a reason to treat this disease. For example, if a patient has a white blood cell count double from 30,000 to 60,000 over the course of three months, but is otherwise doing well and not having symptoms, and the other blood counts look okay, this is not an absolute indication for treatment, but does suggest that the patient should be observed more closely, because it is likely that these other manifestations of the disease may develop soon, leading to the need for treatment.
If none of the above are present, we do recommend observation. This is counterintuitive for many patients, who have been taught since an early age that if a patient has cancer, it is best to be aggressive and intervene early to try to obtain the best outcomes. This was not known in CLL, whether early intervention would make a difference, and therefore people got together and studied this in large numbers.

Here are some studies from the 1970s and 1980s comparing an early intervention strategy with a chemotherapy drug called chlorambucil, compared to a deferred treatment strategy where patients were only treated once they met the criteria I just discussed. This graph on the right shows that there was no difference between early intervention or later intervention, but patients who were treated earlier with chemotherapy had a poorer quality of life due to side effects from treatment. And therefore, study after study concluded that it is better to wait until patients actually need therapy before starting treatment.
Those older data have been challenged more recently by people who said that maybe if we use our more modern chemotherapy-based regimens, we may be able to make more of a difference compared to the older chlorambucil drugs. This was explored earlier in the decade with a trial called CLL7, conducted primarily in Germany, where they took patients who were recently diagnosed and randomized them, to half the group getting a regimen called FCR, which I will talk about shortly, and which is an aggressive chemotherapy regimen, versus the other half of the group watching and waiting with the traditional observation strategy, and then getting FCR treatment. What they found was that patients actually developed some serious side effects, including some serious infections in the arm that got treated early with FCR. And so far, now with several years of followup, there is no difference in survival in the patients who got treated earlier or later. And therefore, even in the modern era, with chemoimmunotherapy-based regimens, like FCR, there is no advantage to starting early with treatment.
Slide 18 – CLL12 is the First Study of Ibrutinib for High Risk Watch/Wait Patients

This has been challenged further with the development of new drugs that are better tolerated than chemotherapy, and also highly effective, and it is now being explored in another large study in Germany called CLL12, which is randomizing patients with higher-risk forms of CLL, to an early intervention strategy with ibrutinib versus placebo, and then monitoring over time to see when patients may need their next therapy, when they may have progression of CLL, and how long they live. This is an ongoing study, and we do not have any data back from it yet. So, given the lack of data, we do not support the routine use of ibrutinib as a high-risk strategy for patients who would not otherwise require treatment.
Slide 19 – “What Can I do to Slow this Down?”

So, a common question that I often get in my clinic, is what can I do, then, to slow down the pace of this disease?

This is one study that actually has provided some data that is useful in this regard, the so-called Polyphenon E, or green tea study, conducted at the Mayo Clinic. This study took patients with early-stage CLL and gave them a high dose of a green tea extract called Polyphenon E. Note, this is the active ingredient in green tea, so drinking green tea alone would not provide nearly sufficient enough quantities to replicate what was done in this study. What I am showing here on the top is a graph that shows the decrease in the absolute lymphocyte count for the patients on the study. You can see that most of the patients had at least some reduction in their lymphocyte count, although in most cases this was modest, in the zero to 30% range, although there were few patients who had a much more significant reduction, closer to 70%. On the bottom, you can see the change in the lymph node size, where some patients actually had very significant reductions in their lymph node size, although many of these patients were those who had small lymph nodes to begin with. Most other patients either had no change in their lymph nodes, or a more modest decrease. So, there does seem to be some biological activity of Polyphenon E when given at high doses, as in this study. However, there are some gastrointestinal side effects, and there is no evidence that this actually delays the time until the first treatment is needed, and certainly no evidence that this makes CLL patients live longer. So, as I say to my patients, if they feel compelled to do something to try to slow the disease down, I think this is a reasonable option to try, based on the data we have. There are many other types of interventions, both vitamins, supplements, and nutritional interventions, that have not been studied in CLL, and so those are not things that I could advocate, based on any data.
So, let's talk about more definitive treatments for CLL. And this is a timeline going back all the way to the 1960s, to show you the evolution of how treatment has improved over the last few years. In the 1960s we had the older oral drug, chlorambucil, which was chemotherapy, and rarely achieved a complete remission; only about 5% of patients would get there. By the 1980s, fludarabine had been developed, which is known as a purine nucleoside chemotherapy, and this was a much more potent drug that could induce a complete remission in upwards of 20% of patients. In the 1990s, fludarabine was combined with alkylating agents, such as Cytoxan, to achieve even higher complete remission rates, close to 30%. By the 2000s, we had some new tools in the armamentarium, including a new antibody called alemtuzumab, which was very potent, but had significant risks of infection, as well as a new chemotherapy drug called bendamustine, which even on its own could achieve complete remission in about 30% of patients. But the biggest innovation in the 2000s was the combination of the chemotherapy drugs with what we call immunotherapy, such as the antibody rituximab, and we call this chemoimmunotherapy. In some of the earliest studies, close to 70% of patients achieved complete remission using approaches like FCR. In later studies, these came down to closer to 40 to 45%, but nonetheless, many patients are achieving complete remission using these approaches. However, inevitably the disease would relapse for most patients, and therefore one of the big aims of our research in the 2010s has been to develop new drugs that are more targeted and can kill CLL cells even that are resistant to chemotherapy.

You can see a list of some of the new drugs that have been approved here, and I will talk about each one. But, briefly, obinutuzumab, ibrutinib, idelalisib, and venetoclax have really already begun to transform how we manage this disease. And there are several next-generation molecules in development which may be even better tolerated and highly effective for patients with CLL. Interestingly, as we will discuss, the complete remission rates are variable, and some of these molecules do not even cause many patients to go into a complete remission. Nonetheless, patients can do well in a partial remission for many years, without a lot of the side effects of chemotherapy.
Let's talk briefly about FCR: Fludarabine, cyclophosphamide, and rituximab. This is a regimen developed in Texas and studied further in Germany in a large, randomized trial that showed that this is really the standard of care for young, fit patients with CLL. In CLL, we think of younger patients as being under the age of 65, and these patients need to get growth factor support with drugs like Neulasta, to try to reduce the risks of infection. FCR is typically given in cycles, three days out of each month, for a total of six months.
Slide 22 – FCR has Curative Potential in Mutated IGHV CLL

One of the exciting developments in the field over the last couple of years is that we have learned that for a subgroup of patients with CLL, FCR actually has curative potential. These are the patients with mutated IgHV. On the left side, you can see the long-term followup from the original MD Anderson study of 300 patients treated with FCR. The black bar at the top is patients with the mutated IgHV. And you can see that about 60% of these patients are still without progression of their CLL, now 12 to 15 years after their initial six months of treatment. Presumably, many of these patients are, in fact, cured from their disease. On the right side, you see the data from the German CLL8 study, which looks very similar, again with about 50 to 60% of IgHV mutated patients still in complete remission, with a bit shorter followup on their study, but still several patients out now five to eight years.
Unfortunately, older patients, over the age of 65, do not tend to tolerate FCR as well. So, for patients in that age group, which is the majority of CLL patients, we have another chemotherapy regimen called bendamustine and rituximab, or BR, which is highly effective and better tolerated. This regimen was developed in East Germany, and was later brought to the West, and eventually to the USA in the late 2000s, and this has become one of our mainstays of therapy for patients with CLL. We do typically still give Neulasta on the third day, to boost up the infection-fighting white blood cells, and this regimen is given two days in a row, in monthly cycles, for up to six months.
Slide 24 – CLL10 Study: FCR vs. BR in Frontline

There has recently been a study called CLL10, which randomized patients to FCR versus BR for the frontline, or initial therapy, of CLL. On the left side, you can see in the blue the patients who got FCR had a significantly longer time until the disease came back, about 55 months, compared to 41 months in the patients who got BR. So far, there has been no benefit in terms of what we call overall survival, meaning that patients who got FCR or BR both did well and lived for a similar amount of time, but the followup on this study is short. So, over time it is possible that we may start to see that patients who received FCR first have an advantage in terms of living longer. Again, though, we need to restrict the use of FCR to patients who are younger than age 65, generally.
Slide 25 – CLL10 Study: FCR vs. BR Frontline Side Effects

Why is that? Well, here you can see the comparison of the side effects for each regimen. On the left, you can see that neutropenia, which is the main infection-fighting cells, was at a much higher rate with FCR compared to BR. So, this suggested that these patients would be at a higher risk of infection and, as you see, close to 40% of the patients did have a significant infection on FCR, versus 27% with BR. But which group were these infections in? Well, on the next lines, you can see that the major infections were primarily in patients who were over age 65, where there was a much higher rate of infections in the FCR-treated patients. But if you look at the patients under age 65, the rates of infection were actually the same between patients who got FCR or BR. It is important to note that there are patients who can develop other types of cancer after receiving chemoimmunotherapy. That is what referred to here as a secondary neoplasm, and we do worry a bit about the risks of other types of leukemias, such as AML or MDS. However, these rates are low, and the rates are higher with CLL patients compared to the general population to begin with, so it remains unclear how much influence the chemo treatment has versus the disease.
Slide 26 – Can we do Better than Rituximab in CLL?

So, rituximab has been a very effective antibody for treating CLL cells, but some people asked a few years ago, can we do better than rituximab for CLL? And that led to the development of a molecule called GA101, which is now known as obinutuzumab. This graph here shows that obinutuzumab is an antibody, as seen in red, that can attach to the B-cell, which is the CLL cell, and kill the cell. Rituximab does not typically kill the cell directly, but requires these other effector cells to kill CLL cells, and GA101, obinutuzumab, does a more efficient job of harnessing those cells, as well. So, in more ways than one, this is a more efficient antibody for killing CLL cells.
Slide 27 – Obinutuzumab is Highly Active in CLL

So obinutuzumab was explored in a large randomized study called CLL11, which compared treatment of the GA101 with chlorambucil, that is obinutuzumab, versus rituximab and chlorambucil. In panel A, you see that the GA101 regimen led to a higher rate of response and more complete responses, close to 21% of patients. The obinutuzumab regimen also led to higher levels of what is called minimal residual disease undetectability, or MRD undetectability, which looks at a very sensitive way to see any microscopic evidence of disease left behind. And, again, the rates of this undetectability were higher using the more potent antibody. And in graph C, at the bottom, we see that this translated into a much more prominent benefit in terms of the time until the next treatment was needed. It took about 43 months from the time of obinutuzumab treatment initiation until the patients needed another therapy.

There are some toxicities to note with obinutuzumab. These side effects include infusion reactions, which can be like allergic reactions, as they are getting the antibody, as well as neutropenia, which is the low infection-fighting cells, and infections, although these are fairly rare.
So that was a summary of how we initially approached CLL therapy. What about when patients have already had therapy, and the disease comes back? We call this relapsed, or refractory. Typically, when we say refractory, we mean that patients have had less than two years of response to their initial chemoimmunotherapy. And when we say relapse, we mean that patients have had a response that has lasted for longer than two years, but then the disease has come back. When the disease comes back, we do recommend further evaluation. This includes rechecking the FISH test, to rule out a process called clonal evolution. What this means is that patients can have a very low-risk FISH profile when they are diagnosed; for example, the chromosome 13. But when they get the chemotherapy that can select out the more resistant cells, which we call clones, and so over time, when these clones come back, they can evolve to have more high-risk abnormalities, such as the deletion 17p. And because this can change so significantly, we do recommend rechecking the FISH test prior to initiating the next line of therapy. In contrast, the IgHV status, as we discussed, reflects the original type of CLL cell that arose. And this does not tend to change over time; it is what we call a stable marker, and therefore we do not recommend rechecking the IgHV status over time.
Slide 29 – Older Agents

So, historically, how did we approach relapsed/refractory CLL, particularly when it was refractory to chemotherapy? So, there is an antibody called ofatumumab, which is also FDA approved, for relapsed/refractory CLL. It is kind of somewhere in between rituximab and obinutuzumab, which we were just talking about. Ofatumumab binds to a slightly different part of the molecule CD20 compared to rituximab, so it does have some advantages in terms of how it can kill CLL cells. Alemtuzumab, also known as Campath, which you see in the bottom left corner, is a very potent type of antibody molecule that can effectively kill CLL cells, even those with the high-risk deletion 17p. However, it also kills T-lymphocyte cells, which are an important arm of the immune system, and this puts patients at risk for significant infections, which has limited its use more recently in CLL.

In the top right is a molecule called lenalidomide, which is FDA approved for diseases such as multiple myeloma and mantle-cell lymphoma, but not FDA approved for CLL. Nonetheless, the molecule has been explored in trials in CLL, and it does have some effects that are beneficial. But it can be challenging to administer this drug to CLL patients, due to issues with the disease flaring when they start the drug. Therefore, it is hard to recommend this on a routine basis for patients with CLL.

High-dose methylprednisolone is a form of steroid, different from what has been used by athletes, but very potent at killing CLL cells, particularly in patients who have large lymph nodes. And so, this high-dose methylprednisolone regimen is actually still utilized, particularly in combination with antibodies like rituximab or obinutuzumab in select situations.
Slide 30 – Hematopoietic Cell Transplantation

Another type of therapy that we have used historically to treat CLL patients is hematopoietic stem cell transplantation, also known as a donor bone marrow transplant, or an allogeneic transplant. In this process, a donor needs to be identified, and this can be a sibling, who typically would have a 25% chance of matching the patient, or someone from the National Donor Registry who would be unrelated but could be a perfect match for the patient. And the donor has stem cells collected, either directly from the bone marrow, or from blood. These cells are then processed and frozen down, and eventually ready for the transplant procedure. The patient then comes into the hospital and undergoes some chemotherapy to reduce any remaining burden of CLL in the bone marrow, and then gets an infusion, which is the transplant – it is not a surgery, it is more just an infusion, like a blood transfusion might be- of these thawed stem cells from the donor, and these go into the patient. These stem cells can then go and repopulate the bone marrow and create normal immune cells that can go around and kill off remaining CLL cells that may be in the body. Unfortunately, they can also kill off some of the normal cells in the body, a process called graft versus host disease, which can be very serious. So, this is a potentially risky type of endeavor.
So, given some of the risks with transplant, the guidelines are currently in flux, given that we have several novel agents, that we will talk about in a minute, which are very effective.

So how do we decide which patients we should recommend an allogeneic transplant for in CLL? On the right side, you see that patients who have lower-risk forms of CLL, based on the FISH cytogenetics and the IgHV, and those patients who are not refractory to chemoimmunotherapy, typically would not be recommended for a transplant, particularly if they are older, or have other medical conditions, and particularly if they do not have a good donor. On the left side, we see that if we have high-risk patients, those with the deletion 17p and mutation in the gene on chromosome 17, TP53, those patients in particular, if they are younger and have a well-matched donor and access to an experienced transplant center, should be considering still allotransplant, given the long-term benefits of this approach.
One of the exciting developments in CLL, and in other blood cancers, over the last few years, has been the technology known as CAR T-cells, which stands for chimeric antigen receptor T cells. In the top left, you see the process of how this is done. The main difference between this and what we just described, is that the cells are coming from the patient him or herself, rather than from a donor. So, with CAR T-cells, these T cells are collected from the patient, and outside the body undergo a process called transfection, which means that the cells are educated to recognize CLL cells more effectively. They are then grown up outside of the body to larger quantities, and patients are admitted to the hospital to then get some chemotherapy which, again, allows space for these cells to come in. The CAR T-cells are then infused into the patient, and patients are monitored for the effects. You can see on the right some detailed analyses that were recently published from the group in University of Washington on their results from their CAR T-cell study. I will not go into the details of all their graphs there, but just the highlights are in the lower left. They treated 24 patients with CAR T-cell-based technology, and about 70% of patients had a nice response to this approach. About 20% of patients had a complete remission, and 88% had complete clearance of disease from the bone marrow. However, there are some significant side effects and risks to CAR T-cell therapy. The majority of patients had something called CRS, which stands for cytokine release syndrome. This can be a serious condition, where patients can get very sick and have to go to the intensive care unit due to low blood pressure, and other phenomena that can make them susceptible to other complications. About a third of the patients also had what is known as neurotoxicity, where the CAR T-cells can affect the way the brain functions, and this is typically reversible, although in one case it was not. In general, the patients who responded well had a nice survival after this therapy, and I think this is impressive, because most of the patients who have gotten CAR T-cell therapy to date have already had most of the other therapies that I have described and will describe in CLL, and therefore they did not have other great options. So, I think these are very encouraging data, although there certainly is room for improvement with CAR T-cells, and I think over time this technology will become even more effective, and safer, and will become an important part of our treatment armamentarium for patients with CLL.
Slide 33 – “Hide and Seek”

In the last part of the talk, I am going to focus in on the novel agents in CLL, and I liken this to a game of hide-and-seek, because for many years we did not understand where CLL cells were hiding. We knew that we could effectively kill them in the blood using our chemotherapy-based approaches, but inevitably the disease would come back. And really just recently, over the last decade or so, many scientists have been working on this problem, and discovered that CLL cells are often hiding out in lymph nodes and bone marrow, where they are protected by a variety of other cells.
Slide 34 – Novel Targeted Agents

That is illustrated in this cartoon here. The larger cell in the top part here is the CLL cell. But underneath it is something we called the stromal microenvironment. These are other cells in the lymph nodes or the bone marrow, such as T cells, NLCs, which we call nurse-like cells, since they nurse the CLL cells back to health, and BMSCs, which stands for bone marrow stromal cells. Without going into all the details, these cells submit a different array of signals into the CLL cell, where they can then interact with all the different proteins in the CLL cell, to cause the cells to survive, and in some cases to grow.

The key insights over the last decade have been to interrupt these survival signals using a number of targeted agents, the first of which to come along targeted something called the BCR, which you can see in the top left. This is the B-cell receptor pathway. This is really one of the key signaling pathways inside the CLL cell. And two of the key targets here include BTK, which stands for bruton tyrosine kinase, and PI3K, which stands for phosphoinositol 3 kinase. These are really the key signals in the CLL cell, and by shutting these down, it causes the cells to die. What is important is that these proteins are more important for the functioning of CLL cells compared to other cells in the body, which makes these very targeted therapies.

One other pathway critical to the survival of the CLL cell is the pathway of apoptosis, or cell death. We can see that toward the bottom of the CLL cell, where there is a mitochondria, and which is the power house of the cell. Targeting this pathway shuts off the lights in the CLL cell and causes it to die very quickly. And so, we now have approved agents that can target each of these different key targets in the CLL cell.
Slide 35 – The BTK Inhibitor Ibrutinib Leads to Comparable PFS/OS Regardless of IGHV Status (PCYC-1102 Study)

I am going to start by talking about ibrutinib, which is an inhibitor of bruton tyrosine kinase.

As I alluded to earlier in the presentation, ibrutinib leads to a comparable level of survival in patients irrespective of their IgHV status. And you can see that in the graphs here. On the left side is how long it takes patients from the time they start ibrutinib until the time their CLL progresses, and on the right side is how long they have survived since starting ibrutinib. You can see the greenish and red curves are superimposable, meaning that there is no difference in the survival of patients on ibrutinib, based on their IgHV status. And this is with now over five years of followup for these patients. I think this is a truly remarkable finding because every prior therapy we have ever had, such as chemotherapy, or antibody-based immunotherapies, has always had a shorter survival for patients with unmutated IgHV. It is a very exciting development for patients with unmutated IgHV, who are doing particularly well on these new drugs.
Slide 36 – Ibrutinib Leads to Durable Response in Most FISH Subgroups

These are the curves for the progression-free and overall survival for patients treated on ibrutinib in the relapse setting with CLL. As you see in the top, the patients with deletion 13q or trisomy 12 have done very well over five years of treatment with ibrutinib. But the patients with deletion 17p and, to a lesser extent, patients with 11q, have had a shorter amount of benefit from the ibrutinib, and therefore these are groups that we think we need to target with newer approaches that may be combining new agents together.
Slide 37 – Frontline Ibrutinib is Effective Even in Patients with TP53 Dysfunction

Ibrutinib has now also been explored as a first treatment for patients with CLL, and it has been found to be very effective. On the left side, you see a group of patients who do not have the deletion 17p so, in other words, the standard-risk group of CLL patients. Where ibrutinib was compared to the older drug, chlorambucil, it was clearly beneficial, and most patients were still in remission after a couple of years of therapy. On the right side, you see an even harder group of patients to treat, those with deletion 17p, the highest-risk form of CLL. And you can see whether they were relapsed or refractory to other therapies, or whether ibrutinib was used as the first therapy, these patients tended to do very well, with over 80% of patients still in remission by two years. Ibrutinib does have some potential risks and side effects, and these include: Diarrhea, which typically is early on in the course; bruising, which can occur throughout the course, as well as a higher risk for bleeding, and so patients need to know to stop ibrutinib if they need to have a surgical procedure. It can lead to hypertension, which is elevated blood pressure, as well as to abnormal heart rhythms, such as atrial fibrillation, in a small number of patients. Infections are common in CLL patients, and we have certainly seen infections on ibrutinib, as well as we have with other novel agents.
Why not use indefinite ibrutinib monotherapy?

- Achievement of CR is rare
- Duration of response in del(17p)/del(11q)/ complex karyotype is shorter
- Resistance mutations already described
- Long term adherence issues
- Co$t

C’Hirar et al., ASH Annual Meeting, 2016
Wayarch et al., NEJM 2014

Slide 38 – Why not use Indefinite Ibrutinib Monotherapy?

Since ibrutinib is such an effective drug, it is natural to ask, why not just use indefinite ibrutinib monotherapy? Meaning only use ibrutinib, because most patients will do well for a very long time. But I think that may be appropriate for some CLL patients, but there are some limitations to ibrutinib. First of all, the achievement of complete remission is rare and, as I just showed you, the duration of response in patients with higher-risk forms of CLL is shorter. Moreover, patients with resistance to ibrutinib have been shown to have mutations in the BTK gene. You can see that in the graph at the top. These are cells from a CLL patient who is resistant to ibrutinib, and you can see in the red line there that these cells were much less sensitive to ibrutinib outside of the body compared to patients with the nonmutation BTK form. And this has been validated now in other studies. Also, it can be challenging to stay on a long-term therapy, in terms of remembering to take the pills every day, and it can be expensive to take this drug for many years at a time. So, I think these are all reasons why we need to explore combinations of ibrutinib with other therapies, as well as combinations of other therapies with antibodies and novel agents, and we will get into that a little bit more toward the end of the talk.
Slide 39 – Novel Targeted Agents

Let’s go back to our graph here and talk about another important molecule, idelalisib. Idelalisib targets PI3 kinase which, like BTK, is a key mediator of the signals for survival inside the CLL cell.

Slide 40 – PI3K Inhibitor: Idelalisib (GS1101/CAL-101) -δ-specific

<table>
<thead>
<tr>
<th>Common side effects</th>
<th>Percentage</th>
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<tr>
<td>Diarrhea</td>
<td>30%</td>
</tr>
<tr>
<td>Elevated liver function tests</td>
<td>24%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>22%</td>
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Idelalisib was explored initially in an early phase study, the results of which are reported here. And I show this on the left side to show that there were dramatic reductions in the lymph node disease in most of the patients on the study, including those in the dark bars here, who had the most aggressive deletion 17p mutation. On the right side, you can see that the lymphocyte count, as with ibrutinib and idelalisib, can go up, in the blue line here initially, but the lymph node size, seen in the green, comes down rather quickly in the patients who respond. Idelalisib can also cause diarrhea early on in the course, and a more significant type of toxicity called colitis, which is a severe form of diarrhea, later in the course. So, patients even who have been doing well on idelalisib for six to 12 months, need to remain vigilant for this later toxicity. Liver tests need to be monitored, because the liver can become inflamed in patients on idelalisib, and patients, again, with CLL are at risk for pneumonia, and some patients with idelalisib have also had pneumonitis, which is inflammation of the lungs in the absence of infection, and so patients with shortness of breath on idelalisib also need to be evaluated promptly.

**The PI3K-δ inhibitor idelalisib is active in R/R CLL, including those with TP53 dysfunction**

These were some of the data from the Phase 3 trial of idelalisib, which compared it in combination with rituximab, in the blue line at the top, to rituximab alone, in the bottom line. And clearly there were benefits to the idelalisib combination. On the right side, I think, is another remarkable graph, which shows that patients who have the high-risk deletion 17p had the same benefits as patients without that abnormality when they were treated with idelalisib and rituximab, again suggesting that these newer drugs may help to overcome some of the poor prognosis that we used to observe with chemotherapy for these patients.
Slide 42 – Novel Targeted Agents

Finally, the last pathway that I am going to talk about is the apoptotic pathway with venetoclax. Venetoclax targets a protein called Bcl-2, which is the key protein in the mitochondria of the CLL cells that help to keep the cell alive.
These are venetoclax pills, which look innocent enough, but when given to the first few patients, we saw dramatic effects. These are the first three patients treated in Australia with venetoclax, and you can see in the red that the lymphocyte count decreased dramatically, even just within the first eight hours. And these patients also did have decrease in their lymph nodes, as noted by the clinicians who were taking care of them. However, at the same time, the LDH test, in blue, went quite high for all these patients. LDH, or lactate dehydrogenase, is just an enzyme that is present inside the CLL cells. So, when it goes up at rapid rates like this, it suggests that CLL cells are bursting open very quickly.
So, when it goes up at rapid rates like this, it suggests that CLL cells are bursting open very quickly. Essentially, this drug was like a supernova for CLL cells. It caused them to die so quickly that it was actually dangerous, because it was releasing the toxins from the cells into the body. So, in collaboration with Abbott and AbbVie and Genentech and all the academic investigators, we all were able to help devise a new scheme to escalate venetoclax dosing, starting at a very low dose of 20 milligrams, which is about one tenth of the dose that I just showed you used in those first patients, and then patients need to be slowly ramped up week by week to an eventual dose of 400 milligrams. By doing this, venetoclax was still able to result in great responses, but with a much safer approach, and no further evidence of this condition called tumor lysis syndrome causing problems in patients.
Venetoclax causes profound disease reduction even in pts with TP53 dysfunction, with some risk of TLS

Here, from the Phase 1 study, you can see that the absolute lymphocyte count, the lymph node size, and the bone marrow disease all decreased dramatically in patients treated with venetoclax. On the right side, this was then confirmed in a Phase 2 study that focused on patients who have the high-risk deletion 17p. Again, on the top you see the lymphocyte count decrease, and on the bottom right you see the lymph node size decrease, and most patients had dramatic decreases in both. About 80% of patients responded very nicely to venetoclax as a single agent. And this led to the FDA approval of the drug, specifically for patients with relapsed CLL with the deletion 17p.
Venetoclax dosing: follow the directions!

Slide 46 – Venetoclax Dosing: Follow the Directions!

Venetoclax dosing is a little tricky, and so it is important to follow the directions. This is the packet that has been developed by AbbVie that makes it very clear that each week has a different dose, and that patients need to stay well hydrated as they escalate the dose, with careful laboratory monitoring from their oncologist or hematologist.
One of the advantages of venetoclax-based therapy is that a significant proportion of patients with CLL can achieve MRD undetectability, which I mentioned before is minimal residual disease. I think this is an important concept to think about, because it can actually help us to figure out a strategy to try to achieve cure for more patients with CLL. So, I will take you slowly through this chart, which was developed by my colleague, Peter Hillmen in the United Kingdom. If you start on the top left, you can see that the tumor load for all these patients starts out the same. In the category on the right, which you see is clinically measurable disease, meaning we can feel lymph nodes, we can see cells circulating in the blood, and we can see bone marrow disease from CLL. So, once patients are treated, all these lines come down, if they are getting an effective therapy. Some therapies will be able to get the disease into this kind of gray area, where we cannot see the disease anymore clinically, meaning we cannot feel any enlarged lymph nodes or see them on CAT scans, we do not see any cells in the blood, and we do not see any cells in the bone marrow when we look with a microscope. This is what we would call MRD positive, or MRD detectable, disease. These patients can be in a complete remission, but because it is not that deep a remission, over time you can see, to the right, these lines start to trend up again, and these patients will eventually relapse after a few years.

So, in contrast, if you look at the bottom two lines, the lighter blue line first, we see that this comes down into this darker blue area, which is MRD-undetectable disease. So, some patients can get to an undetectable MRD state, but then eventually still relapse, although they tend to relapse later than the patients who are MRD detectable. So, the group that we want all patients eventually to be in is this green line, where we can get a therapy that can achieve such a deep remission that the MRD becomes undetectable, and eventually these cells...
What's on the Horizon for Chronic Lymphocytic Leukemia?

What's on the Horizon for Chronic Lymphocytic Leukemia?

May 8, 2018
Speaker: Matthew S. Davids, MD, MMSc

completely disappear. And as you see this green line coming across the bottom as a horizontal, these patients over time we can call cured, and we can try to ascertain what level of MRD undetectability will get to that level, and you can see some hypotheses listed here, as a 0.0001%. So, a very, very tiny number of CLL cells. So, this is the type of approach that we are working on as we develop combination therapies for CLL.

Diverse mechanisms allow for many possible combinations

Slide 48 – Diverse Mechanisms Allow for Many Possible Combinations

So, the title of this presentation is What is on the Horizon, and I think the horizon for CLL is going to be all about combination-based approaches. We are very fortunate in this disease that, as you can see in the chart on the left, we have a diverse array of mechanisms to allow for many different combinations of therapy. I would like to think of these in terms of three broad categories: A novel agent, NA, plus chemoimmunotherapy; a novel agent plus the CD20 antibodies, like rituximab or obinutuzumab; and then novel agent/novel agent combinations without the need for chemotherapy or antibodies. I will give you an example of each of these.
Slide 49 – Ibrutinib + FCR (iFCR) is a Promising New Frontline Approach for Young, Fit CLL Patients

This is our own study combining ibrutinib with FCR for our younger and fitter CLL patients. We treated patients for up to six months of the combination, what we called IFCR, followed by up to two years of maintenance therapy with ibrutinib alone, followed by close monitoring. We were able to get to rates of MRD undetectability in the bone marrow of 83%, which is higher than we have seen for any prior chemotherapy or novel-agent-based regimen for the initial therapy of CLL. Importantly, as you see on the graph on the right, these responses tended to deepen over time, in both the IgHV mutated and unmutated patients who were on ibrutinib maintenance. So, we are now exploring whether we can stop ibrutinib after these two years of maintenance, and hopefully these patients will remain in an MRD-undetectable state, and hopefully many of these patients will be cured. And there are a number of other studies looking at this type of approach, including one at the MD Anderson Cancer Institute, combining ibrutinib with FC and GA101, or obinutuzumab, and that is also a promising study that is still underway.

What about getting rid of chemotherapy completely? That would certainly be great, if we could do that, and there are other studies exploring this. Here is some data on venetoclax with rituximab. On the left side, you can see data from an older Phase 1b study, and an early phase study, where about half of patients achieved complete remission, and a little over half with MRD undetectability. What was interesting in this study is that patients were allowed to discontinue venetoclax once they reached this MRD-undetectable state. You can see in the graph on the left that patients in the green were on venetoclax, and then achieved remission, and then in the lighter purple bars, you see that is the time off venetoclax, and all the patients who were undetectable for MRD who stopped venetoclax remained undetectable for MRD, with a median of 9.7 months after discontinuation. So, this looks promising. We do not have
long-term follow-up on these patients, but it does seem that we will be able to get patients off of therapies, even if we can just get them to this MRD-undetectable state, and even if this is just briefly, it certainly is an advantage over continuous therapies for patients.

Slide 50 – Venetoclax + Rituximab is Highly Active in R/R CLL

So, this is now being explored in a much larger study called the Phase 3 Murano study, as you see in the top right. The complete remission rate here, with the venetoclax/rituximab combination was lower at 27%, but most of the patients still got to an MRD-undetectable state in the blood. This is what is known as a registrational study, because it compared venetoclax with rituximab to a standard chemotherapy regimen, bendamustine and rituximab, and as you can see on the right graph, this was a highly positive study in favor of venetoclax with rituximab. As such, we think it is likely that this will lead to a full approval of venetoclax with rituximab for patients with relapsed/refractory CLL in the near future.

Venetoclax is also being explored with the newer CD20 antibody, obinutuzumab. On the left, you can see some data presented at the ASH meeting, American Society of Hematology, this past December, showing that about half of patients can achieve complete remission, with about 63% getting to MRD undetectability, with no evidence of clinical tumor lysis syndrome; that is where the cells are bursting open too quickly. There were a fair number of patients who had allergic reactions to the obinutuzumab, but in general this was a well-tolerated regimen. And on the right side, you can see some very preliminary data on the first 12 patients treated in the CLL14 study, which is a much larger study of venetoclax in combination with obinutuzumab, compared to the older drug, chlorambucil with obinutuzumab, which is an ongoing study in Europe. And, again, these are studies for patients who have never CLL treatment, and if they are positive they could represent a new option for patients for the initial therapy of CLL.
Venetoclax + obinutuzumab is safe and active in frontline CLL

<table>
<thead>
<tr>
<th>GP28331</th>
<th>CLL14</th>
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<tr>
<td>All 32 patients responded</td>
<td>Overall response rate (%) (N=12)</td>
</tr>
<tr>
<td>CR/Cri: 56%</td>
<td>Complete response 58</td>
</tr>
<tr>
<td>BM MRD-neg: 62.5%</td>
<td>Partial response 42</td>
</tr>
<tr>
<td>No clinical TLS observed</td>
<td>Minimal residual disease in peripheral blood (%) (N=11)</td>
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<tr>
<td>56% rate of infusion reactions</td>
<td>Negative (&lt;10^-4) 91</td>
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Flinn et al., ASH Annual Meeting, 2017  
Fischer et al., Blood, 2017

Slide 51 – Venetoclax + Obinutuzumab is Safe and Active in Frontline CLL

So, what about getting rid of the antibodies and the chemo, and just using pill-based regimens, oral therapies, so-call novel/novel combinations? There are many of these currently underway and in development, and I will show you an example of one of our studies that has actually been supported in part through The Leukemia & Lymphoma Society, and this is a Phase 1/1b study of umbralisib, formerly known as TGR-1202, plus ibrutinib in relapsed/refractory CLL. We are also looking at this in mantle-cell lymphoma.
A PI3K-δ/BTK doublet has shown promising efficacy and safety in R/R CLL

On the left side here is a signaling pathway similar to the one that I showed you from that CLL cell before, and this one just highlights that BTK and PI3K are parallel pathways inside the CLL cell. The idea of our study was, rather than blocking one arm or the other of this pathway, to try to block both at the same time. The patients are given both the umbralisib and the ibrutinib at the same time, and on the right side you can see some of our preliminary data that we have presented, suggesting that this gets patients into very deep responses. About 90% of patients have responded, and we are starting to see more complete remissions as time moves along. This has also been a very well-tolerated approach, without any significant side effects from this combination.
Slide 53 – Several Ongoing Studies of Ibrutinib + Venetoclax have Shown Early Promising Data

The other very promising approach currently underway is to look at the combination of ibrutinib with venetoclax, and the early data for this looks promising. Some of the data were presented at the ASH meeting this past year, and the CLARITY study, which is being run in the United Kingdom, where patients are given a combination of venetoclax and ibrutinib until they become MRD undetectable, and then the combination is stopped and patients are monitored. There were also important data presented at the ASH meeting from the MD Anderson Group, looking at their study of ibrutinib with venetoclax, where also this looks like a promising approach, both for patients who have relapsed with CLL, and also as an initial therapy for this disease.

So, we have just gone through quite a bit of data, and I am sure some of this is new to folks, but some patients on the line may be quite familiar with it.
So, I would like to transition now to a question, just to get a sense from the audience of what the opinions are, and here is the question: We are curious now, based on the data that I have just presented, what you think are the most new emerging therapies, which of these are the most exciting? Would you say A) CAR T-cell therapy? B) A novel targeted monotherapy? In other words, just using one drug at a time - the ibrutinib, the idelalisib, or the venetoclax? C) A combination of the existing drugs, like FCR, for example, with novel targeted therapies, or an antibody like rituximab with a novel therapy, and then D) is just combining the novel therapies with each other, for example, the ibrutinib/venetoclax combination. So, we are going to transition over now to the survey, and you will actually have a chance to vote.
So, I think this is interesting. So, we saw votes for all the different categories. It looks like we had over 200 people vote, so a good number of people have voted here. And it does seem like the winner is D right now, with about 63% of patients saying that the combinations of novel therapies with each other is kind of the most exciting thing, and certainly a large number also suggesting that novel agents with existing therapies is promising, as well as CAR T-cell therapy. Less popular was the idea of novel agent monotherapy, which I would tend to agree with for the majority of patients because, again, if we can put together combinations of these novel agents, it may allow us to have these time-limited approaches, and in some cases have the potential for cure, and that is certainly what we would all be striving for, for this disease.
Ongoing randomized trials may define a new standard of care for frontline CLL treatment

Slide 56 – Ongoing Randomized Trials May Define a New Standard of Care for Frontline CLL Treatment

Okay, so I am going to transition back to the presentation, and we will wrap up with a few more slides here. So, how are we going to sort all this out? As I alluded to at our ASH meeting this year, we had a number of exciting presentations from earlier phase, typically Phase 2 trials, that have looked at these exciting new combinations. But eventually we are going to need some Phase 3 data, where we compare these studies head to head, and these new regimens, to know what is the best therapy for CLL patients. And I just wanted to highlight a couple of the ongoing studies right now that I think are important.

The first, on the left side, is called the FLAIR trial, being run in the United Kingdom. And this is randomizing nearly 1600 CLL patients to either the traditional FCR chemotherapy, ibrutinib with rituximab, ibrutinib alone, or ibrutinib with venetoclax. On the right side, you can see some of the ongoing German studies. I mentioned, on the left, in red, the CLL12 study, which is that early intervention study with ibrutinib, and on the right the study of venetoclax with obinutuzumab, CLL14. But one of the ones that I am most excited to see the results from is the CLL13 study, which is the gray one in the middle because, again, that is comparing chemotherapy with either FCR or BR, with venetoclax in various combinations such as rituximab or obinutuzumab. Because these are initial therapy studies, frontline studies, they are going to probably take several years to read out, which is a good thing for CLL patients, because it means that the patients are doing very well on these therapies. But, eventually we will have some data to help us decide what is the optimal therapy for individual patients based on their different characteristics of their disease.
Slide 57 – Treatment Summary: TP53 Dysfunction

So, to summarize how I think about approaching patients with CLL in terms of the therapies, I think there are two broad categories. The first is what I call TP53 dysfunction. So, this refers to CLL patients who have deletion 17p, or they have a mutation in the gene TP53, which is on chromosome 17. So, on the top left you can see the current treatment options for these patients, which include ibrutinib, which should be considered the standard of care for any patient with those characteristics who can tolerate ibrutinib, although occasionally we do have patients who may not tolerate ibrutinib, and there we may think about older regimens, such as the high-dose methylprednisolone steroid, or alemtuzumab (Campath). When patients with TP53 dysfunction progress on ibrutinib, there are a number of options on the right side that are now available. These include venetoclax, idelalisib with rituximab, and then allogeneic transplantation, or donor stem-cell transplant, which is an important option for these patients with the highest-risk form of disease. If patients happen to get other therapies besides ibrutinib in the initial therapy setting, then they should get ibrutinib as their next therapy in most cases, although venetoclax also remains an option for those patients, as it is approved in that setting.

In terms of the future of the approach for patients with this type of CLL, you can see on the bottom left that in the frontline setting, we may be combining ibrutinib or venetoclax with the CD20 antibodies, or perhaps we can combine ibrutinib with venetoclax, with or without a CD20 antibody. And then we have second-generation novel agents coming along, which I alluded to at the beginning may be better tolerated, and may be more suitable to combination-based therapies. On the bottom right, we see patients with TP53 dysfunction in the future, who may have relapsed and, again, will have access to all these different combination regimens. Plus, I think this is the setting where CAR T-cell therapy may be useful, as well as allogeneic transplant.
Slide 58 – Treatment Summary: TP53 Intact

For patients who have what I call TP53 intact, meaning the majority of CLL patients who do not have this deletion 17p, it gets a little bit more complicated in terms of how we approach the disease. I will not go through all the options in detail here, because you will have access to these slides after the presentation. But I do want to highlight that we use the IgHV mutation status to help guide us toward chemotherapy versus novel-agent-based approaches. On the top left, currently for the young, fit patients, particularly those with mutated IgHV, FCR does remain the standard of care. There is still no data available for young, fit patients being treated with ibrutinib, although patients who have unmutated IgHV tend to have shorter responses to chemoimmunotherapy, and so this could still be a discussion. For the older, frailer patients who have mutated IgHV, they are candidates for chemotherapy-based regimens, or ibrutinib, and patients who have unmutated IgHV also are candidates for the chlorambucil, obinutuzumab or ofatumumab regimens, or ibrutinib. Once patients are relapsed or refractory, in the top right corner, you can see here that we typically would not offer chemotherapy-based approaches alone anymore. And this is because we have so many good novel agent therapies that can be effective for patients with less risks than chemotherapy. I do put up here ibrutinib or idelalisib with bendamustine and rituximab, because there are now Phase 3 data suggesting that these novel drugs, when given in combination with bendamustine and rituximab, are more effective than bendamustine and rituximab alone. However, I will caution that there is no data suggesting that the combination of the new drugs with bendamustine and rituximab is better than the new drug alone on its own. Therefore, for most patients with relapsed/refractory CLL, I would recommend a novel-agent-only-based approach, without the need for chemotherapy.

On the bottom, you can see the potential future treatment options for young, fit and older, frail patients. And these reflect the various combination-based approaches with novel agent plus chemotherapy, novel agent plus CD20 antibody, or novel/novel combinations, which I just discussed. And, again, on the bottom right, we can see similar combinations, newer-generation novel agent molecules, and CAR T-cell-based approaches.
Conclusions

- We have reached the end of the beginning of the NA era
- We now have a powerful toolkit of NAs, with more coming
- Sequencing should be guided by patient characteristics, prognostic markers, and response to prior therapy
- NA monotherapy may be appropriate for frail patients
- Fit patients (especially those with high risk markers) should consider combination therapy
- Active participation in clinical trials is critical

Slide 59 – Conclusions

So, a lot of data but, to conclude, I would say that we have reached the end of the beginning of the novel agent era, which I would define as the time when showed that each of these drugs on its own was an effective new strategy for CLL patients, leading to the FDA approval of these drugs. We now have this powerful toolkit of novel agents, with more coming along, including second-generation molecules. So, how we sequence the new therapies in CLL patients should be guided by a variety of factors, and these include patient characteristics, prognostic markers, and the response to the prior therapies. There may still be a group where novel agent monotherapy is appropriate. I typically think of older patients who may be frail due to other medical conditions, and in those patients it may be appropriate to put them on a novel agent alone for a period of several years, and if they do have progression of the CLL, to switch them to a different novel agent at that time. However, for younger patients who are fit, and especially those who have higher-risk markers, particularly deletion 17p, we should be considering combination-based therapies, combining novel agents with either other novel agents or older therapies. And this is what is now being explored in clinical trials. Therefore, active participation in clinical trials remains critical, so that we can continue to develop these new therapies for CLL. So, if you have access to an academic medical center, it is great to be seen there and followed there, in case a new clinical trial is available, so that your local hematologist and you can decide whether that is a good option for you. And LLS can have great resources available to help track down where the nearest site is that may have clinical trials for your disease.
Finally, I will just say that we have a real opportunity now in CLL, as did our predecessors in the earlier era when chemotherapy was being developed. On the left side here, you can see some of the pioneers in the development of the original chemotherapy regimens back at the National Cancer Institute in the 1960s and 1970s. These giants of the field inherited a variety of new chemotherapy drugs that had been developed as single agents by an earlier generation of oncologists, and they began to put them together creatively in new combinations over time. And this is what has led to the development of curative chemotherapy regimens, such as R-CHOP for aggressive lymphomas, and ABVD for Hodgkin lymphoma. There is no reason why we cannot do the same in CLL. And we now have this new armamentarium of therapies to do this. It is a veritable alphabet soup of therapies in CLL, including chemoimmunotherapy, ibrutinib, obinutuzumab, idelalisib, venetoclax, ofatumumab, and allotransplant. And the challenge over the next few years is to put these together in creative ways that will be safe and effective for therapies, and ultimately lead to a cure for more patients with CLL.
Slide 61 – Questions?

With that, I would like to take questions, and I will turn it back over the LLS, who will help to moderate that portion of the program. Thank you.
Ms. Lizette Figueroa-Rivera:
Thank you so much, Dr. Davids, for your very informational presentation. It is now time for our question and answer portion of our program.

Ms. Lizette Figueroa-Rivera:
And our first question comes from the web. Doctor, Mary asks, "Does CLL ever change to an acute disease, and why would this occur?"

Dr. Matthew S. Davids:
Well thank you for that question. That is one area that I did not cover due to the time limitations in the lecture, but I think it is important to bring this up. So, the first thing is that CLL does not convert on its own to an acute leukemia. This is a common point of confusion, because once the word "leukemia" is used, people sometimes think of acute leukemia, which is a completely different disease. However, CLL can transform into a more aggressive form of lymphoma, typically a diffuse large B-cell lymphoma, and this is a phenomenon known as Richter syndrome. And typically, when this happens, patients are having very significant symptoms, such as drenching night sweats, a rapidly enlarging lymph node out of proportion to other lymph nodes, and other features like that. So, it is important in that situation to have a biopsy of the lymph node because the treatment for Richter syndrome is very different compared to the treatment with CLL. But that is the main scenario where we might see CLL becoming much more aggressive.

Ms. Lizette Figueroa-Rivera:
Thank you, Doctor. And we will take the next question from the telephone audience, please?

Operator:
This question comes from Trudy, calling from Florida. Please state your question.
Trudy:
Yes, I heard you say something, but I missed the beginning, about patients with CLL and some of the programs that you have for the CLL. If you have ulcerative colitis and angioedema, what would be the best course of action?

Dr. Matthew S. Davids:
So, patients who have other inflammatory conditions typically can be successfully treated with chemoimmunotherapy-based regimens and, in fact, those types of regimens can suppress the immune system and actually lead to improvement in some of those other features. So, typically we would recommend starting with a chemoimmunotherapy-based approach. I would say in the relapse setting, one area just to be careful with is that some of the novel agents can cause inflammatory side effects, and in particular this is the class called the PI3 kinase inhibitors, such as idelalisib, so I may proceed with caution using those agents in that scenario, but otherwise the other therapies I discussed should be safe.

Ms. Lizette Figueroa-Rivera:
Thank you. And the next question comes from our web audience. June asks, "Who can I speak to about my side effects, as I don't have much time with my hematologist? I don't know if my extreme fatigue is normal, and my physician is just so happy about my blood counts, but I feel that my quality of life is suffering, even though I am thankful that my treatment seems to be working."

Dr. Matthew S. Davids:
Well, thank you for that important question. This is a challenge for all of us who see patients that we would love to spend more time than we have available, and we do need to see all of our patients. So, it is challenging from our perspective also to spend the type of time that we would like to spend with patients to explore these issues in more detail. So, this will vary quite a bit, based on different practices. In my own practice, I do have a nurse practitioner who is very expert at helping to handle these issues, so I often recruit her help. Some practices may have physician's assistants who can be helpful here. The other resource that I think can be helpful is pharmacists, in particular for a lot of these novel agents, they are prescribed from specialty pharmacies that have a real expertise in the agents, and so sometimes they will actually call to check in with patients on these drugs, and that can be a good way to bounce off certain side effects, and see if they have any recommendations for other options to try to improve them. But, if possible, also to schedule a dedicated appointment with your hematologist or oncologist to discuss side effects. Sometimes that can actually help to focus the visit, rather than just the standard visits that may occur on a particular therapy.

Ms. Lizette Figueroa-Rivera:
Thank you. And we will take the next question from our telephone audience, please.

Operator:
Our next question comes from David, calling from DC. Please state your question.

David from DC:
Here is the scenario. FISH and TP53 tests followed by BR chemotherapy, relapsed after five months, back to 50 to 70K, stable at 50 to 70K for a year. Doctor prescribes ibrutinib, but doctor resists conducting another FISH or TP53 test, and insurance denies coverage for retesting. How important is it to conduct another FISH or TP53 test after post-chemotherapy relapse?
Dr. Matthew S. Davids:
Yes, thank you for that question. So, FISH testing is helpful in a couple of different ways. One way is that if someone is considering chemotherapy-based regimen, compared to ibrutinib, the FISH can be the deciding factor. And so, if the FISH shows the deletion 17p, for example, then clearly the patient should get a novel agent, like Imbruvica/ibrutinib, whereas if the FISH testing does not reveal deletion 17p, then chemotherapy could still be an option. So, in that sense, for this particular scenario, the FISH testing would not be necessary, since the decision has already been made to start on the ibrutinib. However, there is a second area where the FISH testing can be helpful, and that is in terms of the overall prognosis. Because, we know that even in patients doing well on ibrutinib, they may have a shorter progression-free survival when they have the deletion 17p. And, therefore, that might be a scenario where we would consider other therapies, including bone marrow transplant, and that can take time to arrange. So, I think the argument could be made that it is still helpful to recheck the FISH test, even if you know you are going to be starting ibrutinib, or other novel agents, to help inform the prognosis and help to inspire the need to test for bone marrow transplant suitability.

Ms. Lizette Figueroa-Rivera:
Thank you. And our next question comes from our web audience. James asks, "When, approximately, might my complete blood counts show indicators that ibrutinib is improving the out-of-range stats."

Dr. Matthew S. Davids:
That is a little hard to answer without some of the specifics, but I can kind of talk generally about how ibrutinib affects the blood cells. So, one of the things that folks that may be familiar with is that when patients first start on ibrutinib or idelalisib, they often have a rising lymphocyte count for a period of several weeks, or even months. This is what we call a redistribution of the lymphocytes. As the lymph nodes are shrinking, they come into the blood first, and then eventually they die off. And that can, again, take several months to resolve. Also, these drugs targeting the B-cell receptor pathway do not tend to work that quickly on the bone marrow, and so it can take several months, or even a year or longer, until the other counts, like anemia or low platelets, improve. So, typically, for my patients, as long as their counts are headed in the right direction, I stick with the therapy, knowing that it can take time to reach maximal effect.

Ms. Lizette Figueroa-Rivera:
Thank you. And our next question comes from our telephone audience, please.

Operator:
This question comes from Joanne, calling from Georgia. Please state your question.

Joanne:
Yes. I have been on ibrutinib since 2016, and I am doing well with the ibrutinib. I am in a stage I CLL. Is there is a possibility I can go into remission, or what? Can you tell me that?

Dr. Matthew S. Davids:
Right. So, ibrutinib has been developed so far as a drug that needs to be taken continuously. It is interesting now, as we have gotten more experienced with the drug, that patients who have received ibrutinib as a first therapy, about 30% of patients now have been shown to go into a complete remission. However, we do not have experience in what happens with those patients when we stop the drug. My guess is that for most patients, the disease would start to come back fairly quickly after the drug is stopped. So right now, when using ibrutinib as a single drug, we cannot recommend stopping it, based on the data we have. But, again, I think that highlights where the new combination-based approaches are so valuable, because by adding another
drug to the ibrutinib, we may be able to get patients into such a deep remission that we can stop all therapy, and they might be in a great remission at that point.

Ms. Lizette Figueroa-Rivera:
Thank you. And the next question from our web is from Haim. Haim asks, "Can IVIG treatments spike lymphocytic and creatinine counts?"

Dr. Matthew S. Davids:
So, this is an area we did not talk about in the formal program, but I will just mention that CLL patients are at a higher risk than the general population of getting more significant infections. And one of the ways to help reduce that risk for patients who have low levels of their immunoglobulin antibodies, who are having significant infections, is to receive infusions with IVIG, or intravenous immunoglobulin, which is a way to boost up immunity for those patients who are having severe infections. This typically does not cause issues with creatinine or lymphocyte counts. It really works independently of those, and so it is a very safe approach to help reduce infection risk for that group of CLL patients.

Ms. Lizette Figueroa-Rivera:
Thank you. And we will take the next question from our telephone audience, please.

Operator:
This question comes from Thomas, calling from Colorado. Please state your question.

Thomas:
I am a CLL patient, and I have been taking Zydelig®. I did not hear Zydelig mentioned, but wondered what you could tell me about Zydelig?

Dr. Matthew S. Davids:
Sure. So, I have been trying to stick to generic names as much as possible throughout the presentation, but Zydelig is the brand name for idelalisib, so this is a very effective drug for CLL that does have some risks of the immune types of side effect I mentioned, like diarrhea and colitis, or liver inflammation. But for many patients with relapsed CLL, they can do very well on Zydelig therapy for a long period of time. So, it is an important tool that we have for patients.

Ms. Lizette Figueroa-Rivera:
Thank you. And our next question comes from Shirley on the web. She asks, "What do CLL experts feel about their patients getting the new Shingrix vaccine?"

Dr. Matthew S. Davids:
Yes. Thank you for that question. So, another important aspect of the immune dysfunction in CLL patients is that it is critically important that CLL patients receive vaccinations. This includes a yearly flu shot, every five years pneumococcal vaccination, and then historically we were advising patients not to get shingles vaccinations, because the brand available at that time, Zostavax, was a live vaccine, and there was a risk that CLL patients could actually get the infection from the vaccination. So, the patient here is raising the point of a new shingles vaccine that was just recently FDA approved, called Shingrix, which importantly is a killed, or inactivated vaccine, that is safe for CLL patients to take, and as such it is important that CLL patients know about this and get a Shingrix vaccination. It is a two-part series. So, it is something they should ask either their primary care doctor or their oncologist about getting soon.
Ms. Lizette Figueroa-Rivera:
Thank you. And the next question comes from our telephone audience, please.

Operator:
This question comes from Bob, calling from New York. Please state your question.

Bob:
I had ibrutinib for about a year, which caused a heart arrhythmia, and so we stopped it. I have been in remission for the next year since then. What would be my next course of treatment?

Dr. Matthew S. Davids:
That is a fairly typical side effect that we see, is heart issues, and so whether or not we would think to rechallenge with ibrutinib depends on the severity of the issue. So, if it has been a severe heart issue, we may think about switching to a different drug, and typically if we have started with one of the novel drugs, we will switch to a different novel drug for the next treatment. So, options could include idelalisib with rituximab, or venetoclax. If you are using venetoclax in the setting of the 17p deletion, this would be on-label. Right now, if you are using this outside of relapsed deletion 17p, venetoclax would be an off-label use here. But the other consideration would be to try the ibrutinib again, if it was a very mild cardiac issue. It really just depends on the specifics of the situation.

Ms. Lizette Figueroa-Rivera:
Thank you. And the next question from the web, Donna asks, "My sister and I are both in watch and wait. Are there any new research findings regarding familial CLL, a genetic link, typical course of the disease, etcetera?"

Dr. Matthew S. Davids:
So, this is an area that is being actively investigated. There have not been any major developments. I think it is important to note that there is a significant familial association of CLL. It is estimated that patients with CLL have about a five to sevenfold increased risk in their relatives of developing CLL, and that is immediate relatives, like children or siblings. So, we do see cases like this. We are currently doing a study at Dana-Farber, trying to understand which genes may be responsible for genetic variations of CLL. But so far, we do not have any definitive genes that we can test for. But it is possible eventually someday we may find out.

Ms. Lizette Figueroa-Rivera:
Thank you. And the next question from our telephone audience, please.

Operator:
This question comes from Sidel, calling from Florida. Please state your question.

Sidel:
With 11q un-mutation, I have very enlarged lymph nodes, and a very enlarged spleen, but I feel great. Must treatment begin?

Dr. Matthew S. Davids:
So, that is a great question, and I would say not necessarily. So, basically, we monitor for lymph node and spleen size, and we certainly watch closely when they have enlarged, but if the patient continues to feel well, then we do not necessarily need to start treatment. Although I would say that, based on the markers of the 11q
and the unmutated IgHV, it is likely that treatment will be needed soon. So, I would certainly recommend knowing what the treatment options are, kind of having a tentative plan in place for what type of treatment to pursue, and then following very closely with the oncologist. But, based on the description so far, it does not necessarily sound like treatment is indicated right now.

**Ms. Lizette Figueroa-Rivera:**
Thank you. And Patty asks, "Are there any supplements I can take to help boost my immune system and/or help lower my white blood count?"

**Dr. Matthew S. Davids:**
Thanks, Patty. So, the only one that we have data on in CLL is the Polyphenon E, which I showed in one slide in the presentation, and that is one option to consider, based on the data from that Mayo Clinic study. If you look around on the web, you will see a lot of other people trying to sell you other interventions, supplements, vitamins, and nutritional, but if you really try to look at what the data are specifically for CLL patients, you probably will not find much, if any. So, there is really not much else besides the green tea extract Polyphenon that can be recommended on the basis of data.

**Ms. Lizette Figueroa-Rivera:**
Thank you. And the next question comes from the telephone audience, please.

**Operator:**
This question comes from Patricia, calling from Tennessee. Please go ahead with your question.

**Patricia:**
Hello. When and how often is a bone marrow biopsy indicated?

**Dr. Matthew S. Davids:**
That is a great question. So, as I alluded to at the beginning, we do not typically need to get a bone marrow biopsy at the beginning in order to make a diagnosis. But I typically like to get a bone marrow biopsy in a patient who is about to start treatment, because that gives a window into how much disease is present in the bone marrow and gives you a good baseline. And then typically when a patient completes treatment, if it is chemotherapy for example, a couple of months later I like to repeat the bone marrow biopsy, and that gives me a sense for how good a response the patient has had, and that gives a sense for how long that response may last. And then, in patients who have unexplained low blood counts, like anemia or low platelets, that is another scenario where a bone marrow biopsy might be helpful, because sometimes it may be due to infiltration of the CLL cells into the bone marrow, but at other times the CLL disease burden may be low, and patients may be having issues with that autoimmune condition I mentioned before, where the CLL cells can cause destruction of the other blood cells. And that can be sorted out using a bone marrow biopsy test.

**Ms. Lizette Figueroa-Rivera:**
Thank you. And the next question from Henry states that he is currently on watch and wait, and "My doctor told me because of my age, she will be treating me with Imbruvica. Do the same standards of when to begin treatment apply for patients who will be on Imbruvica as for those who will be treated with chemotherapy? I have heard that for those who are asymptomatic, the doctor will wait until the white blood count is 200,000 to 300,000. Is it advisable to wait that long for patients who are going to be treated on Imbruvica?"
Dr. Matthew S. Davids:
This is a great question, and this is something that we have reviewed in the International Workshop for CLL very recently, and there was discussion about whether we should be changing the criteria to treat the disease, now that we have therapies like ibrutinib, which are a little better tolerated in general than our older chemotherapy regimens. But the consensus of the international experts in CLL from around the world was that we should not change our treatment indications until we have data suggesting there is a benefit to an earlier intervention with ibrutinib. There is that ongoing study, CLL12, which may help to answer that question but, as I said, we do not have results from that study yet. So, as of right now, we would still use the same indications for treatment in starting ibrutinib as we would using chemotherapy. And just to highlight one other point, that we do not use the white blood cell count alone as a marker for treatment, so the white blood cell count can be 200,000 or 300,000, and patients may still not need treatment, as long as they do not meet the other treatment criteria that we listed before.

Ms. Lizette Figueroa-Rivera:
Thank you. And the last question today comes from Ruth. Ruth asks, "How important is sequencing of treatment options to maximize the potential of long-term MRD, which is minimal residual disease, and survival?"

Dr. Matthew S. Davids:
That is a very good question, and we are trying to answer that now with a number of different studies in the field, but I would say right now we do not know how important sequencing is. So, for example, if we started a patient on ibrutinib, and then they later got idelalisib and venetoclax, does that patient do better if they start with venetoclax and then get ibrutinib and then idelalisib, or you can imagine all the different orders. And so, it is a challenging problem to study because we cannot do clinical trials for all these things. We have some initial clues from looking back at how patients have done on the different drugs. But I would say so far, nothing definitive in terms of knowing whether the sequence of administration of the drugs matters. And furthermore, we do not even know whether the combinations of the different drugs will be better than the single drugs themselves. We certainly think so, based on the promising initial data, but I think, again, this highlights the need for ongoing clinical trials and recruiting patients to help explore these cutting-edge approaches and answer these important questions.

Ms. Lizette Figueroa-Rivera:
Well, thank you Ruth for our final question today.
A special thanks, of course, to Dr. Davids for sharing your expertise with us, and for your continued dedication to CLL patients. You and your colleagues' research successes have really made a positive impact on so many peoples' lives. Thank you.

And if we were not able to get to your questions today, please contact an Information Specialist at The Leukemia & Lymphoma Society at 800-955-4572, from 9 a.m to 9 p.m.; that is Eastern time. Or reach us by email at infocenter@lls.org. Information Specialists are available to answer your questions about treatment, including clinical trials, or answer other questions you may have about support, including financial assistance for treatment.
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- **What to ask**: Questions to ask your treatment team: [www.LLS.org/whattoask](http://www.LLS.org/whattoask)

- **Support Resources**: LLS Community, discussion boards, blogs, support groups, financial assistance and more: [www.LLS.org/support](http://www.LLS.org/support)

**Slide 64 – The Leukemia & Lymphoma Society Offers**

Again, we would like to acknowledge and thank AbbVie, Genentech & Biogen, and Pharmacyclics & Janssen Biotech, for support of this program.

Dr. Davids, thank you again for volunteering your time with us today. And on behalf of The Leukemia & Lymphoma Society, thank you all for joining us for this program, and we hope that you will join us in the future as we strive to keep you up to date on the latest advancements for CLL, as well as all blood cancers.
Slide 65 – Thank You for Participating

On behalf of The Leukemia & Lymphoma Society, thank you all for joining us for this program. Take good care.