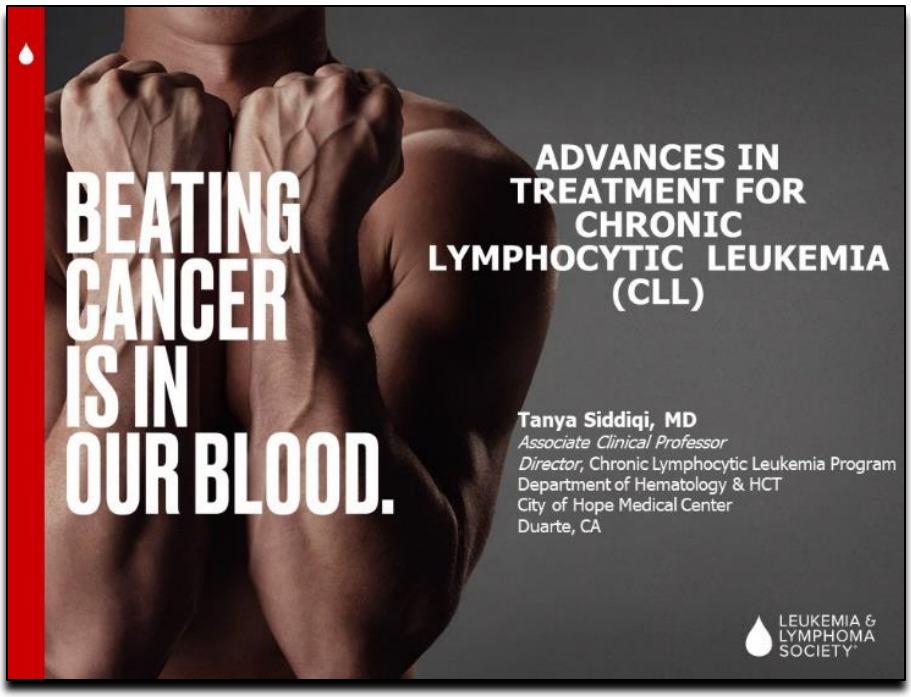


Advances in Treatment for Chronic Lymphocytic Leukemia (CLL)

Operator
Greetings and welcome to Advances in Treatment for Chronic Lymphocytic Leukemia, a live telephone and web education program. It is now my pleasure to introduce your moderator, Ms. Lizette Figueroa-Rivera. Thank you. You may begin.

Ms. Lizette Figueroa-Rivera
Hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. Special thanks to Dr. Tanya Siddiqi, MD for sharing her time and expertise with us today. Before we begin, I would like to introduce Dr. Larry Saltzman, a patient of small cell lymphocytic lymphoma/CLL. Dr. Saltzman will share a few words. Dr. Saltzman, please go ahead.

Welcoming Remarks

Larry Saltzman, MD
Hi. I'm Dr. Larry Saltzman, and I have been a CLL/SLL patient for over 11 years. Fifteen months ago, I had CAR T-cell therapy, and I have been monitored and very sheltered during this pandemic.

During my CLL journey, I have been treated with many of the therapies that you may have heard of: chemotherapy, rituximab (Rituxan®), ibrutinib (Imbruvica®), venetoclax (Venclexta®), and CAR T. I'm followed by MRD, minimal residual disease testing, and I'm happy to say by all accounts I'm clear of CLL. I am proud to say that I've taken the lead with LLS to develop our new LLS National Patient Registry. The LLS National Patient Registry gathers and studies information from patients diagnosed with blood cancers past or present to help researchers better understand outcomes and tailor treatments.

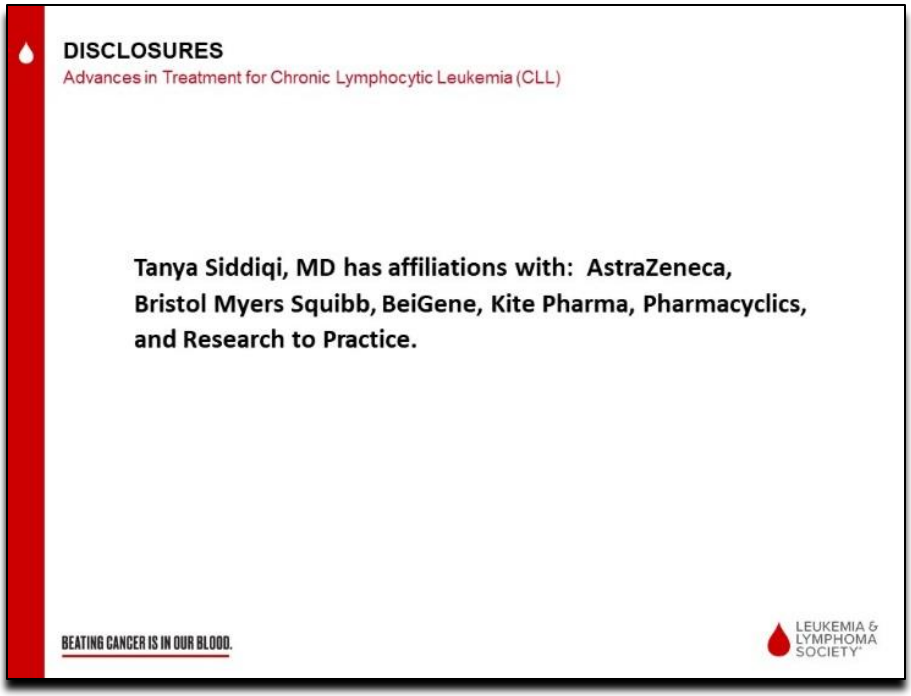
The registry is currently focused on answering important questions about blood cancer patients and COVID-19. This is a unique opportunity for blood cancer patients to join LLS to increase scientific knowledge about how COVID-19 and COVID-19 vaccines affect them. We encourage all blood cancer patients and survivors to become citizen scientists by joining the registry today. Together we will change the future of blood cancer care.

If you are a blood cancer patient, survivor, caregiver in the United States, or know someone who is, LLS needs your help with this research initiative aimed to help shape discoveries that can improve the quality of life and care for people living with blood cancers. Patients and survivors in the United States are invited to join whether or not you have tested positive for COVID and whether or not you plan tobe vaccinated. Joining takes less than 10 minutes and can be done on your mobile device or computer. Your information will be kept anonymous. Your registry abides by HIPAA guidelines to ensure any information you share remains confidential and secure, and there is no cost to you to join the registry.

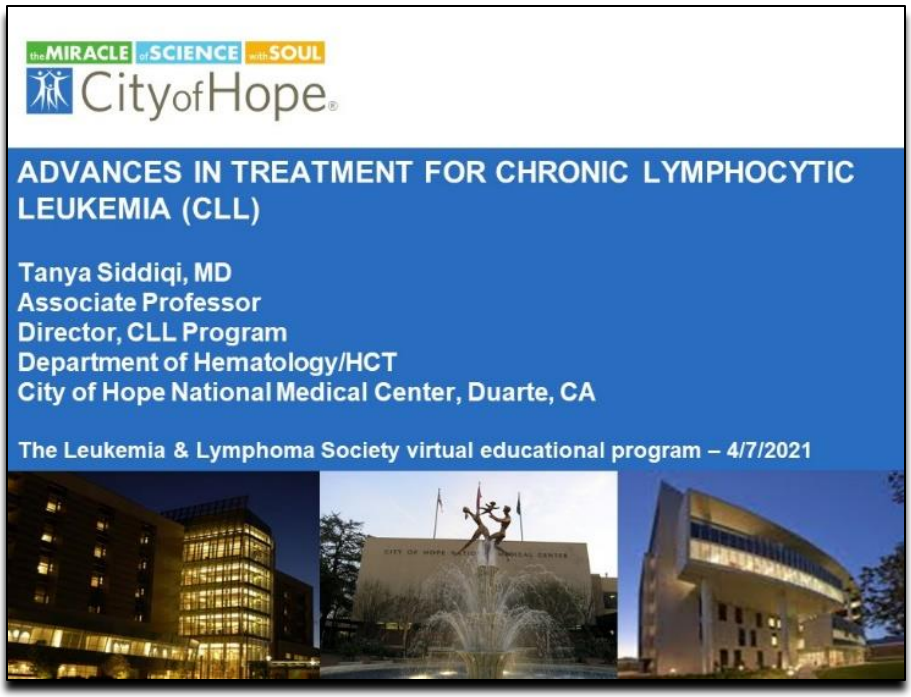
You can join the registry by visiting www.LLS.org/registry or by contacting an Information Specialist at 800-955-4572 for more information. Thanks for joining us today on this program where Dr. Siddiqi will be presenting the latest treatment protocols for CLL and discuss quality-of-life issues. Again, LLS is dedicated to bringing us all the latest information and support. Stay well.

Ms. Lizette Figueroa-Rivera
Thank you, Dr. Saltzman, for your remarks and thank you for joining us as you continue to face your blood cancer diagnosis during this pandemic. We invite you to share the information you heard from Dr. Saltzman about our patient registry and encourage you all to join.

For this program, we would like to acknowledge and thank Genentech and Biogen; Pharmacyclics, an AbbVie Company; and Janssen Biotech for their support.



Disclosures



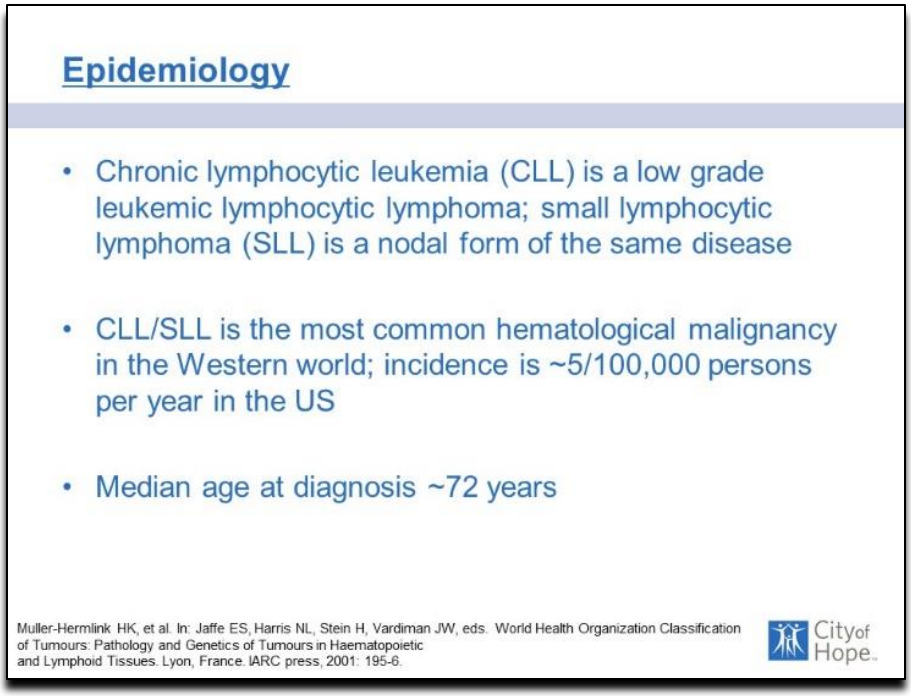
Advances in Treatment for Chronic Lymphocytic Leukemia (CLL)

I am now pleased to introduce Dr. Tanya Siddiqi, MD, Associate Clinical Professor, Director, Chronic Lymphocytic Leukemia Program Department of Hematology and HCT, at City of Hope Medical Center in Duarte, California. On behalf of The Leukemia & Lymphoma Society, thank you for volunteering your time and expertise with us today. Dr. Siddiqi, I am now privileged to turn the program over to you.

Tanya Siddiqi, MD
Thank you, Lizette. It is an honor to be here. Thank you for inviting me to give this talk, and I always preface my talks to patients and caregivers by saying that I tend to give a very scientific talk because that is how we present at scientific meetings and that is how the data is shared. But I will try to explain in words in a little bit more layman's terms some of the stuff, so that you know people who are not as savvy as others in scientific sort of data understanding they can also understand a little bit better. So, hopefully, you will all stay with me through this talk.

Objectives

You know this is just a gist of some of the objectives of what I will go over today. I will start with an introduction of what CLL, in general, is, but the bulk of my talk will be on advances in the treatment paradigm of this disease.



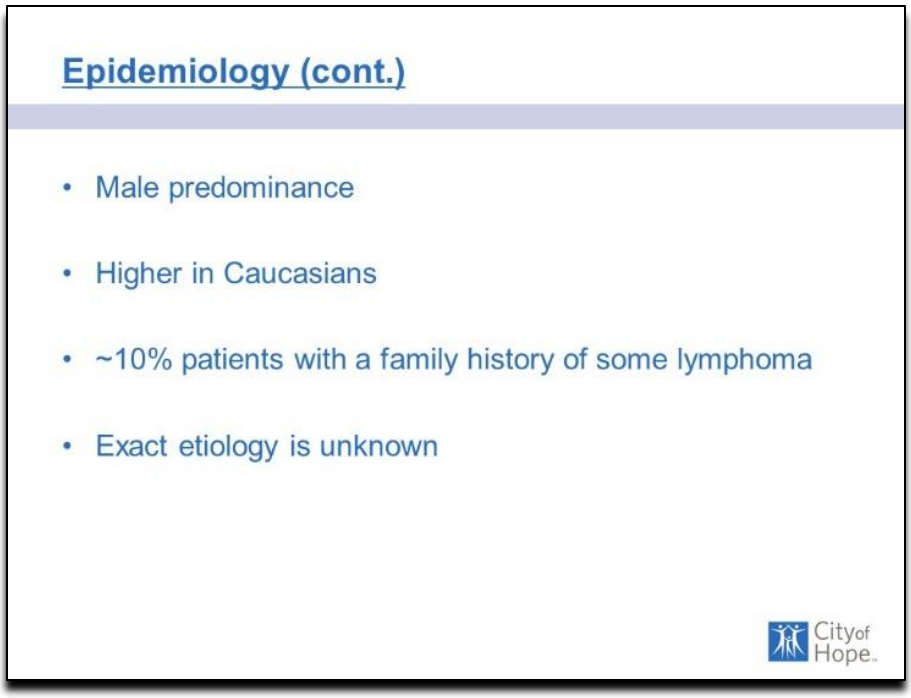
Epidemiology

So, CLL, or chronic lymphocytic leukemia, is generally considered to be a low-grade leukemic lymphocytic lymphoma. And what that means is that you know all of us have white cells to fight infections with, and we all have several different types of white cells in our bodies. One of those white

cells is called lymphocytes, and we all have B lymphocytes or T lymphocytes. The B ones are more common, and in some folks one of these B lymphocyte white cells changes into a cancer for some reason and starts producing many more like itself. And that is called a lymphoma—cancer of lymphocytes.

And in humans, these B lymphocytes lymphoma cancers can be of many different varieties—you know 30, 40, 50 different varieties—and they can range from very slow-growing to very aggressive. And whereas CLL/SLL falls is on the very slow-growing side of things. It is one of the most common hematological malignancies in the Western world, and typically they will be high lymphocyte count or high CLL cells in the blood, which is why it gets the terminology of chronic lymphocytic leukemia. But it really is a lymphoma, and patients who don't have the high white count but only have enlarged lymph nodes with the same disease, that's called small lymphocytic lymphoma. So, it's the same disease. It just depends on where it sort of largely exist. So, about 13%, 14% patients will have pure SLL, but the rest will definitely have CLL and also enlarged lymph cells and enlarged spleen and that kind of thing.

Median age at diagnosis is about 72 years, so it is generally considered to be a disease of older age group. But I have my fair share of patients in their 30s and 40s as well who have this disease already.

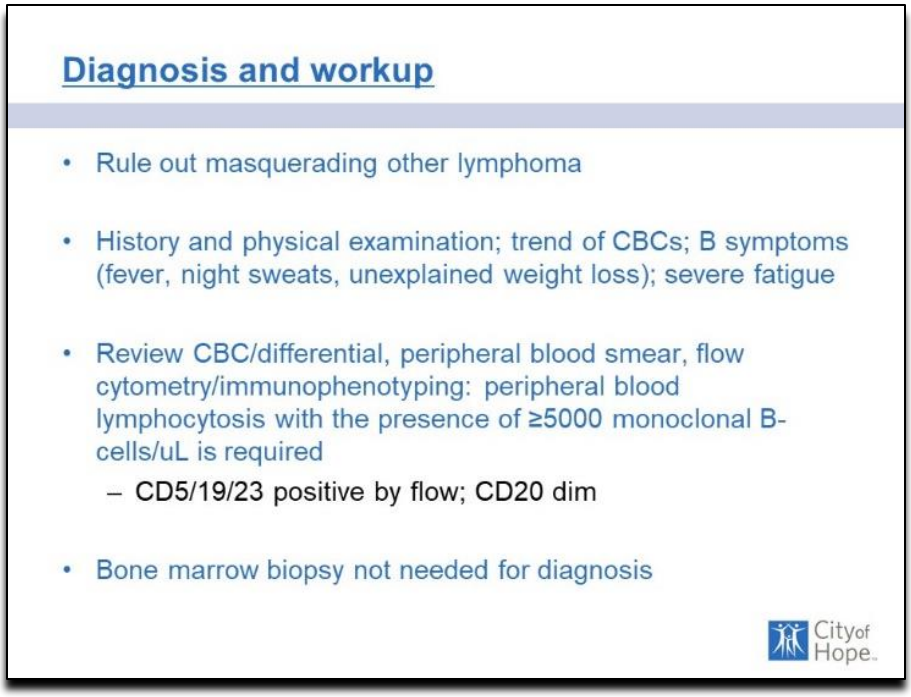


Epidemiology (cont.)

Generally, a little bit of a male predominance higher noticeable in Caucasian populations. About 10% of patients may have some family history of leukemias and lymphomas. We don't think that there is a direct genetic link, but that is also being studied by people like Dr. Jennifer Brown at Dana-Farber, etc. And we don't quite know why people develop CLL and why is it such a common sort of low-grade lymphoma that we see in the Western world.

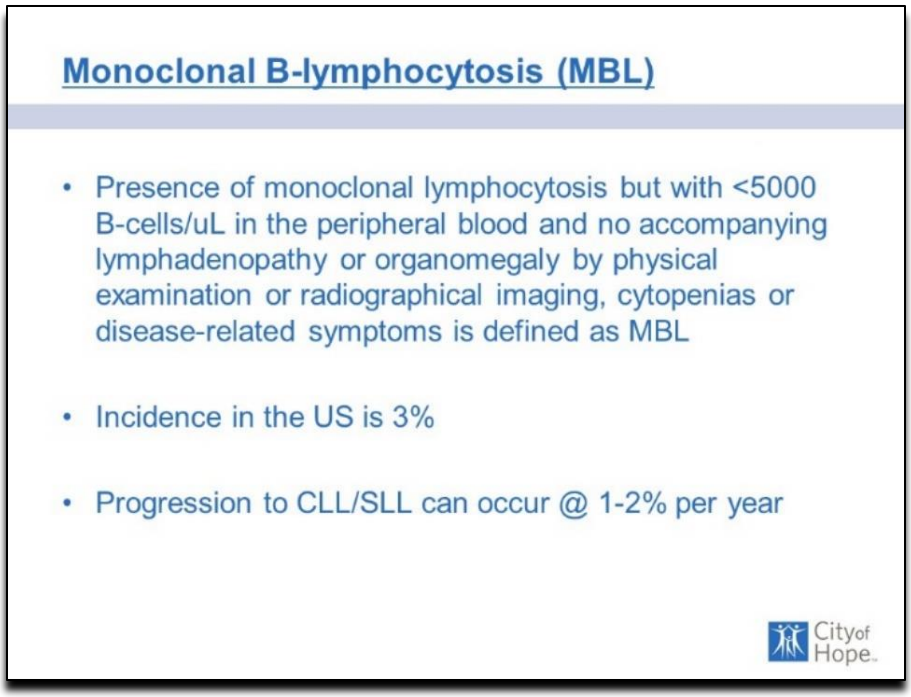
We think that it has to do with just decades of exposures to different things like, pesticides, pollutants, sort of preservatives—all of the P's you can think of. And then just, clearly somebody was in Vietnam got exposed to Agent Orange. That is a direct link or clearly some chemical exposure, specifically of a high intensity for a long duration. Those can sometimes lead to lymphomas down the line, even 30, 40 years later. For instance, kids growing up on farms that were sprayed with DDT like 30, 40, 50 years ago can develop lymphoma decades later because the DNA of those cells

keep getting hit over decades and ultimately become cancer. So, it's not really one reason that we now of.



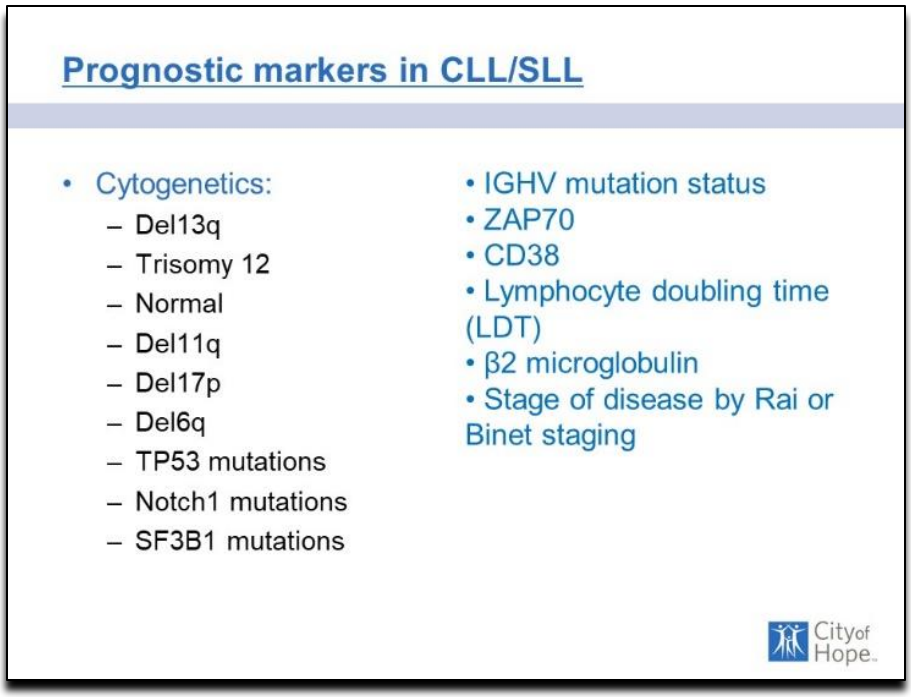
Diagnosis and workup

Regardless, once you have an abnormal white count that's the most common presentation for CLL patients you get referred for, a workup of this. And our job as hematologists is to make sure we're not missing one of the other lymphomas that can be a little bit less common but may require different treatment paradigms. So, we do something called flow cytometry. Usually, we can just do it in the blood because the white count is high, but sometimes we need to do a bone marrow biopsy, especially if we are thinking it's a different lymphoma. And we look for these markers on these elevated white cells or these lymphocytes to show that these are abnormal or cancerous lymphocytes and what type of lymphoma it is. There is an actual pattern that we look for in the lab. And if you have more than 5000 of these monoclonal cancerous B cells per microliter, it generally is called CLL with that pattern CD5/19/23-positive, typically. There can be some atypical features that can have some different markers, but generally speaking that's the pattern we look for.



Monoclonal B-lymphocytosis (MBL)

Of course, patients can present with symptoms or, more commonly, as the disease progresses over years, that's when the symptoms come about. Fatigue that gets fairly severe down the line or what we call B-symptoms fever, night sweats, unexplained weight loss up to 10% even or more. If patients have less than 5000 monoclonal B cells per microliter in their blood, but those cells do look like CLL cells, then it is something called a pre-CLL condition called monoclonal B-lymphocytosis, so very early stage can happen in about 3% of the population in the US. And there can be about a 1% to 2% per year risk of progressing into full-blown or formal CLL/SLL. So, really sometimes we catch it super, super early.

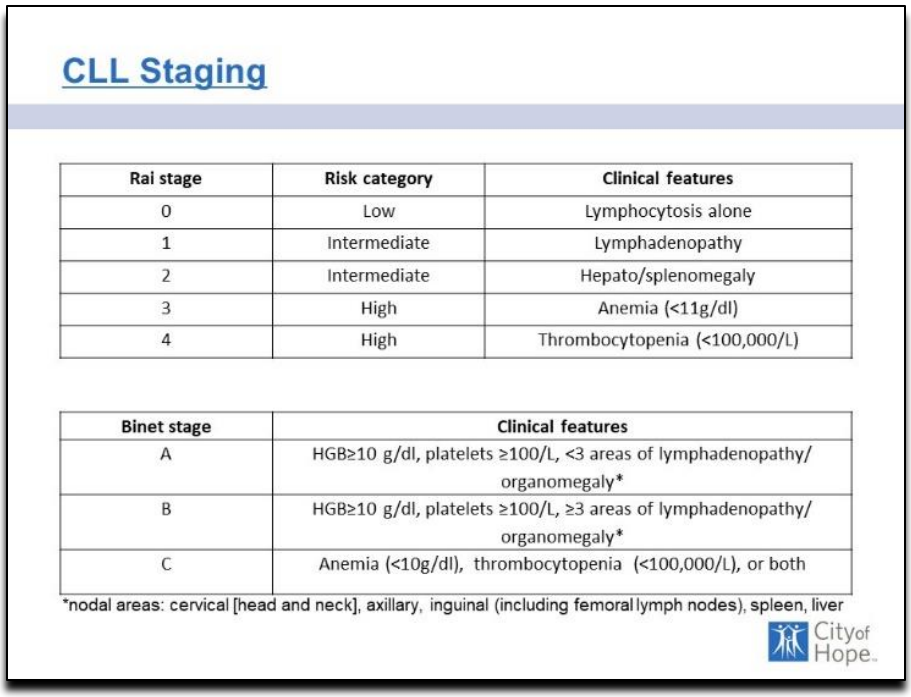


Prognostic markers in CLL/SLL

Nowadays, we look at a lot of prognostic markers. So, on the left column, the cytogenetics and the FISH studies and also mutation analyses for the below or the newer one. The good risk features would be something like del(13q), so chromosome 13 abnormalities. The really poor risk one—the worst one—is del(17p), or chromosome 17 abnormality, or *TP53* mutations, which *TP53* is a tumor suppressor gene that occurs on chromosome 17. So, anything that's aberrant or abnormal with that gives the CLL a poor prognosis. And usually what we mean by that is in the days of chemo we knew that chemo didn't work very well for chromosome 17 patients. But thankfully in the age of novel drugs all of the novel targeted therapies do work very well against chromosome 17 abnormalities as well.

So, actually the prognostication has changed. And it can take a long, long time before people on treatment—novel treatment with chromosome 17 abnormality—will progress or transform. Or, you know, need to change treatment as well, thankfully. In the right column, we have IGHV mutation status, which we use a lot nowadays. ZAP70 and CD38 we don't use much anymore, and then further below we always look at how quickly the lymphocytes in the white count in the peripheral blood or the blood count is going up. So, if it is doubling in less than a year, we know that patients will need treatment soon, especially if it is doubling in less than 6 months.

And then stage of disease by Rai or Binet has to do with how many, not just high white count but also how many lymph nodes are enlarged? Is the spleen enlarged? Is the liver large? Is there anemia? Are the platelets low? Because if there is that much disease in the marrow, you get less and less space for healthy blood to be made. So, the anemia and all of that can get worse over time, and those are all indications for us that we need to treat the patient so that we can set the CLL back enough that all of the counts and all should normalize. And then beta-2 microglobulin is sort of a marker of inflammation, generally speaking. But in CLL it can guide us as to, okay, the beta-2 microglobulin is going up. That means the disease is sort of advancing, but it is kind of nonspecific.



CLL Staging

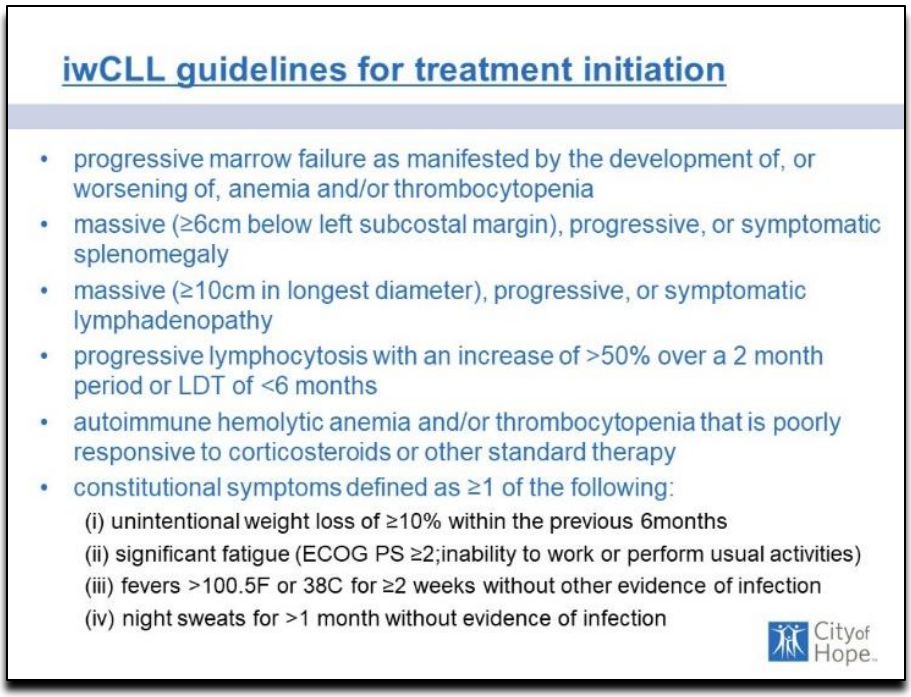
These are just the staging tables. So, Rai stage and Binet stage I won't go over them in detail, but this is what I was telling you. It kind of just tells us how advanced the disease is. A lot of times, people will just have Rai stage 0, meaning just lymphocytosis alone. The white count keeps going up, up, up but there's no other issue. But now that it has doubled from 50 to 100 or 100 to 200 and, like, less than a year I think we need to start treatment sort of a thing. So really stages, isn't really telling us too much

except that okay, how many organs are involved? Or how much anemia or is there anemia or low counts and whatnot as well? So, this tells us how spread or advanced the disease is.

The real crux of the bottom line, the art of treating somebody with CLL is to figure out when do we need to treat a patient. Because as I just told you, it's a slow-growing chronic kind of a cancer and what I didn't tell you is that it really is an incurable disease. We call it an incurable disease thus far although we are actively trying to search for a cure. But because it is an incurable disease and because it grows slowly and people can go many, many years without it even bothering them except for having an abnormal, let's say, white count. Or, you know, just a little bit enlarged lymph nodes that aren't really bothering you. We can actually watch it for a long time before people actually need treatment. And the reason we want to watch it is because first of all, we don't want to use up all of the good treatment early when patients didn't even have any symptoms from the cancer. And secondly, you know each treatment even though the novel treatments, the newer treatments are not chemo and they don't have a lot of side effects like chemo. Did they still have some potential side effects? And if you are the one who is going to get those side effects it can be a very annoying to your quality of life to be on a pill that may not be chemo but that you have horrible joint pain with or some such thing, right?

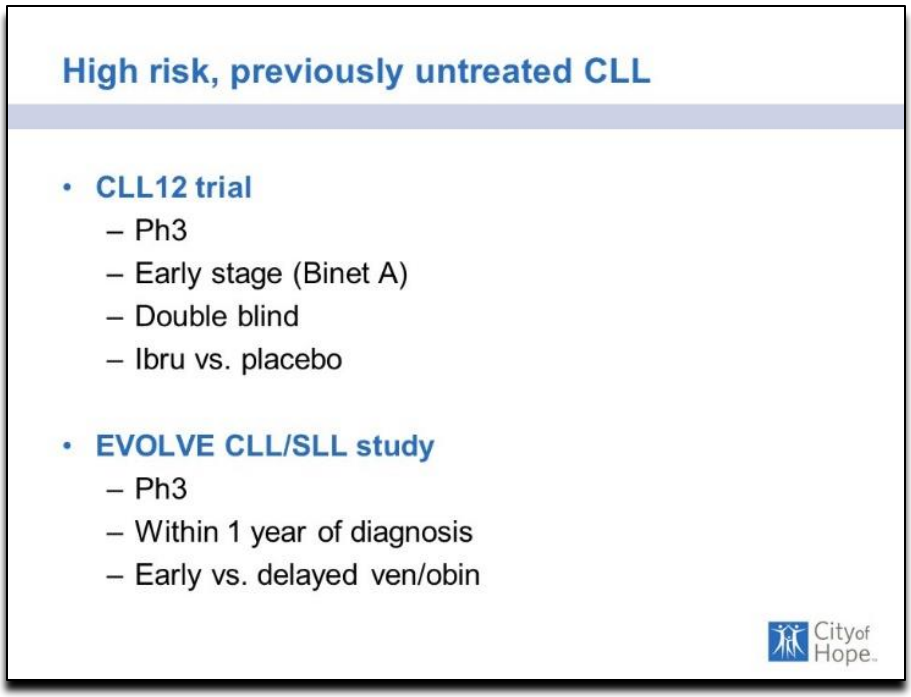
Who Needs Treatment

So, we don't want to put people on treatment that could potentially cause more symptoms than the cancer was actually causing. What's the point of that?



iwCLL Guidelines for Treatment Initiation

So, we would treat ourselves. Okay, our numbers are better. But in the end, who cared if the number was at 50 when you had no symptoms whatsoever, So, I think that is sort of the art, the nuance, the general sort of expertise needed to figure out when does somebody need treatment? You definitely don't want them to get too sick anemic getting, transfusions ending up in the hospital, and when you start treatment. No, you want to start treatment before they get in trouble but not too early so that you don't cause side effects for no reason, potentially. And there is actually a whole guideline that we follow called the iwCLL Guideline, the International Workshop of CLL guidelines that a whole bunch of CLL experts across the world, put together that tells us okay, when we have dropping counts—anemia and all of that. When we have enlarging spleen and enlarging lymph nodes doubling rapidly doubling lymphocytes or some immune effects, like red cells, are breaking down or your platelets are breaking down too fast from an immune attack caused by the CLL. Or if you have just horrible symptoms as the ones shown below in terms of fatigue and weight loss, fevers, etc. Then we say yes, you have got to be treated.



High Risk, Previously Untreated CLL

I'll get to the treatment for people who actually have symptoms for treatment or need indications for treatment, which is our usual go-to sort of pattern that we work on even for clinical trials. Somebody had asked this question early on, so I put it in especially for them. But just to mention that now because we have nonchemo and more targeted therapies out there that are generally better tolerated. There are trials going on in the world. So, the CLL12 trial is a German CLL study group trial that's a phase 3 trial looking at a ibrutinib versus placebo for patients with high-risk CLL, meaning somebody who may have del(17p) or *TP53* mutation at the outset before they have had any other treatment. They have just been diagnosed. They have high-risk disease, but they don't meet the actual criteria for treatment, meaning their lymphocytes are not doubling, they don't have these symptoms, they are not needing treatment per se typically. But what if we treated them early? Would we make a difference in their life span or in how the CLL grows over the years, etc.?

So, as you can imagine, have to follow patients for a long time to see whether you actually benefit them between the two groups, placebo versus ibrutinib. So, that study has actually completed accrual and meaning they are not taking more patients, but now they are just following their patients over the years, sort of speak. The second study, which is actually just starting up in this country in the US, through one of our cooperative groups, is called the EVOLVE study. And that is a phase 3 trial as well, looking at a little bit more time-limited therapies. So, in the previous in CLL12, ibrutinib was basically just continued every day, just like you would take a cholesterol pill every day for the rest of your life. Ibrutinib was continued indefinitely as well.

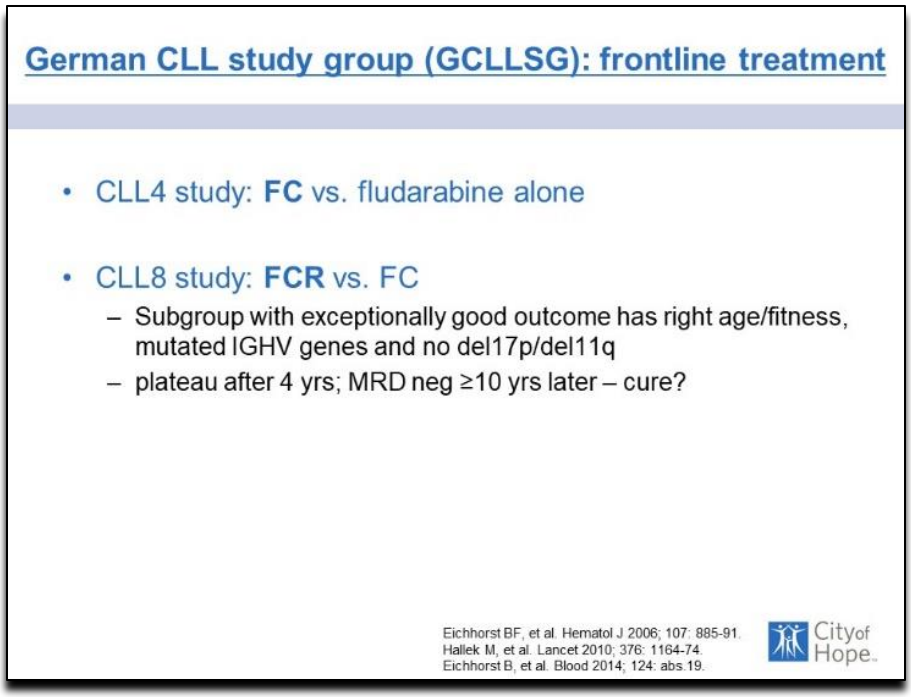
In the EVOLVE study, they are looking at patients who again may have high-risk disease but don't actually meet criteria for needing treatment right away. But they are being randomized or being sort of investigated to see whether they benefit from starting treatment early, meaning within a year of their diagnosis they don't actually meet criteria for needing treatment, but they have high-risk features. And so, what if we give them venetoclax for a year and obinutuzumab (Gazyva®) for 6 months? I will go over these medications in a bit. And so, you just do like 1 year of therapy, and then you stop versus another group of patients who with the same disease pattern who actually wait until they need treatment until they meet criteria for actually needing treatment, which could be 2 years later or whatever. And so, that trial is about to take off, it is going to start enrollment. I don't think it has yet, but it's going to come. And then again, patients will need to be followed for a long period of time.

So, we will know maybe in several years whether it makes sense for patients with high-risk disease to actually wait to be treated. Or should we just jump the gun and soon so that maybe you delay how their CLL will evolve over the subsequent decade? So, going back to patients who actually meet iwCLL criteria for treatment, so people who actually need treatment. How do you decide what is the right treatment or how do I as a physician decide what is the right treatment?

How to Pick the Right Treatment?

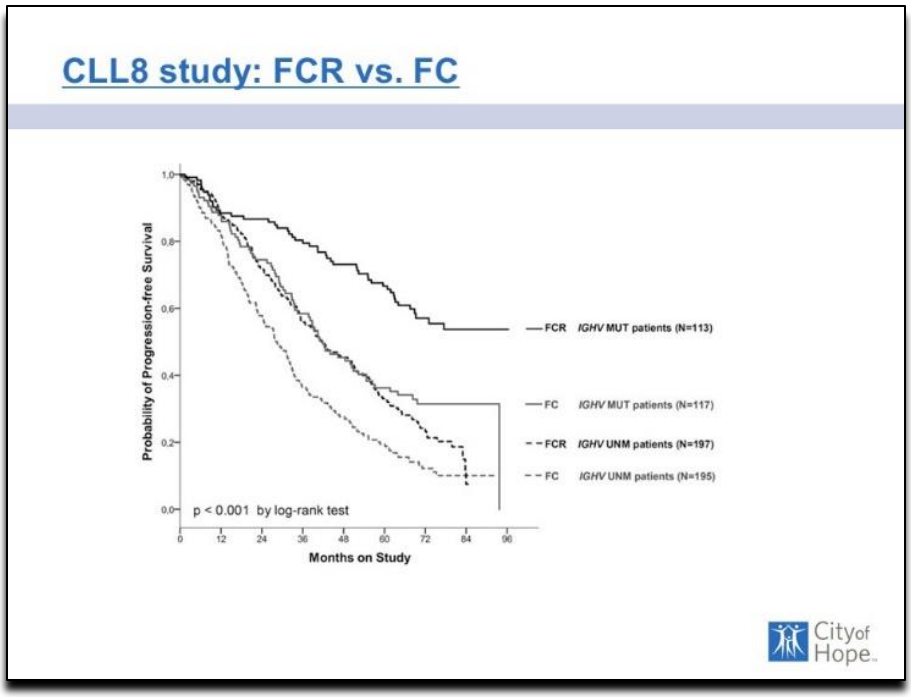
So clearly, just the bulk of disease helps us, meaning how advanced is it? How urgent is it? Do we need to start treatment in the hospital right away or by and large for CLL patients? We can just pick and choose different treatment options in the clinic and start patients off in the clinics. So, we look at a lot of things, like how advanced is the disease by stage? How quickly is the lymphocyte going up and how high it is, whether or not there are features of disease, like chromosome 17 abnormality? How fit is the patient?

I think these two really mattered more when chemotherapy was in discussion. We wouldn't want to do chemotherapy for chromosome 17 abnormalities in patients who are not really very sick to get chemotherapies and then, of course, the patients who have had treatment before. Let's say they had, venetoclax for and obinutuzumab for a year and now they progress again 3 years, 4 years later. Can we do the same treatment or not? And the answer is yes, but those are some of the things we look at to decide which treatment will we want to pick.



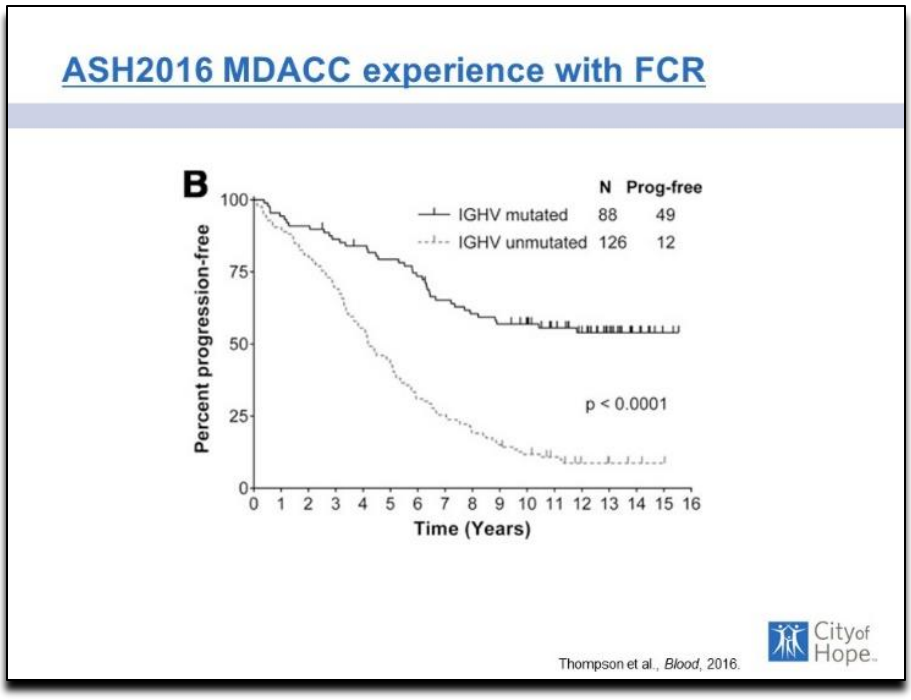
German CLL Study Group (GCLLSG): Frontline Treatment

Going back in history just for a bit, not too detailed, but the German CLL study group is very active under Dr. Michael Hallek in CLL investigations, and they did a lot of the early chemotherapy clinical trials. So, patients who needed treatment for the first time—younger, fitter patients—they showed that, a combination of fludarabine and cyclophosphamide to chemos was better than doing one chemo alone. And then they also showed later in the CLL8 study that adding rituximab infusions, which is an antibody that infuses slowly over several hours, if you add that to the chemo backbone of fludarabine and cyclophosphamide you got even better results with that FCR combination. You all may have heard of FCR.



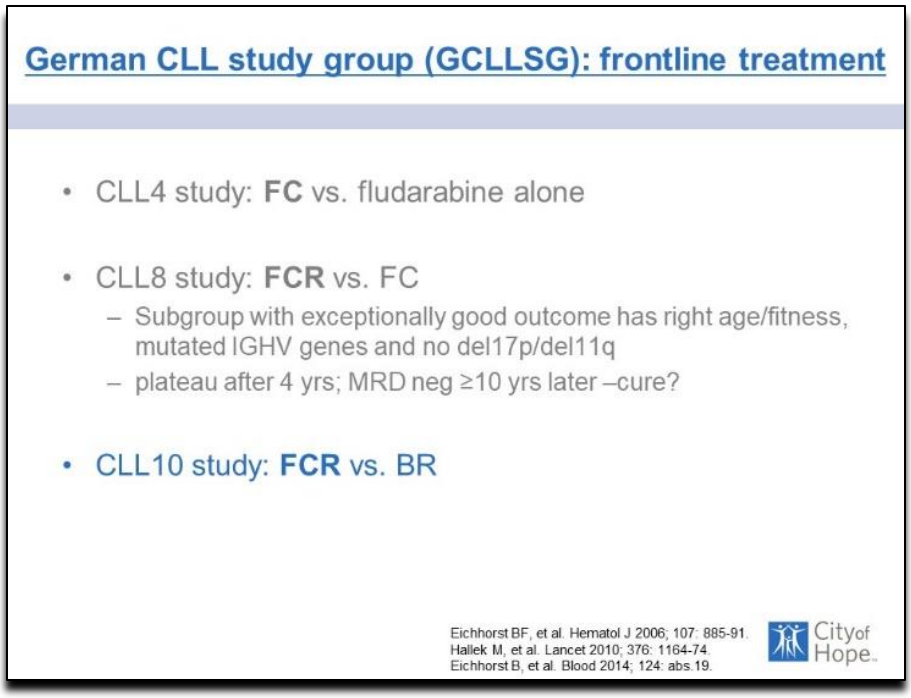
CLL8 Study: FCR vs. FC

And over the decades they found or years, they found that there is a subgroup of patients who were treated with FCR who were younger, fitter, had good risk features of disease, meaning mutated IGHV and no del(17p) or even 11Q. And they happened to do extremely well with no MRD-detectable—minimal residual disease–detectable—relapse of CLL, even more than 10 years out. And the question became, "Can we consider those patients cured if you go more than 10 years in a slow-growing chronic cancer that never comes back, 10 years more than 10 years later. Can we call them cured?"



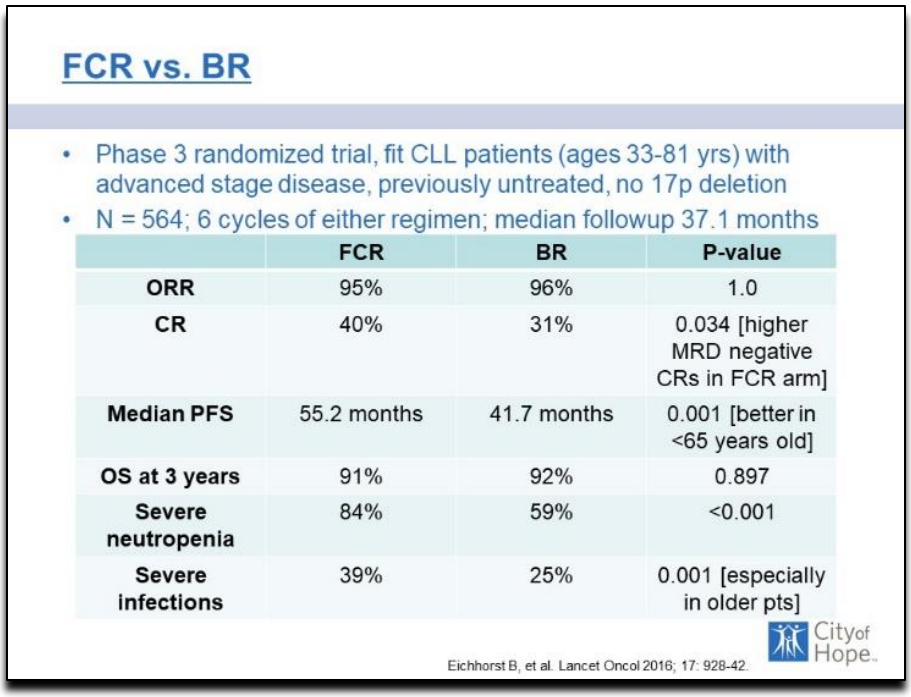
ASH2016 MDACC Experience with FCR

We don't know that. We hope so. I have seen rarely use some of the low-grade lymphomas come back. Like, for instance, had a patient with hairy cell leukemia, which is another low-grade lymphoma, a rarer one, who got chemo 30, 40 years ago and then went in remission. Disease never came back until 30 years later. So, it is certainly possible. But, by and large if you go for more than 10 years without relapsing, hopefully we can call it a cure. And this graph shows on the vertical axis progression-free survival, which means that you know how many patients did not progress with CLL over months on the study, which is the horizontal axis. And then you can see that this line, which is the outermost line where patients who got FCR and had the best risk with IGHV-mutated patients, those patients are above the 50% progression-free survival line as you can imagine—a line in the middle horizontally at 50%.



German CLL Study Group (GCLLSG): Frontline Treatment

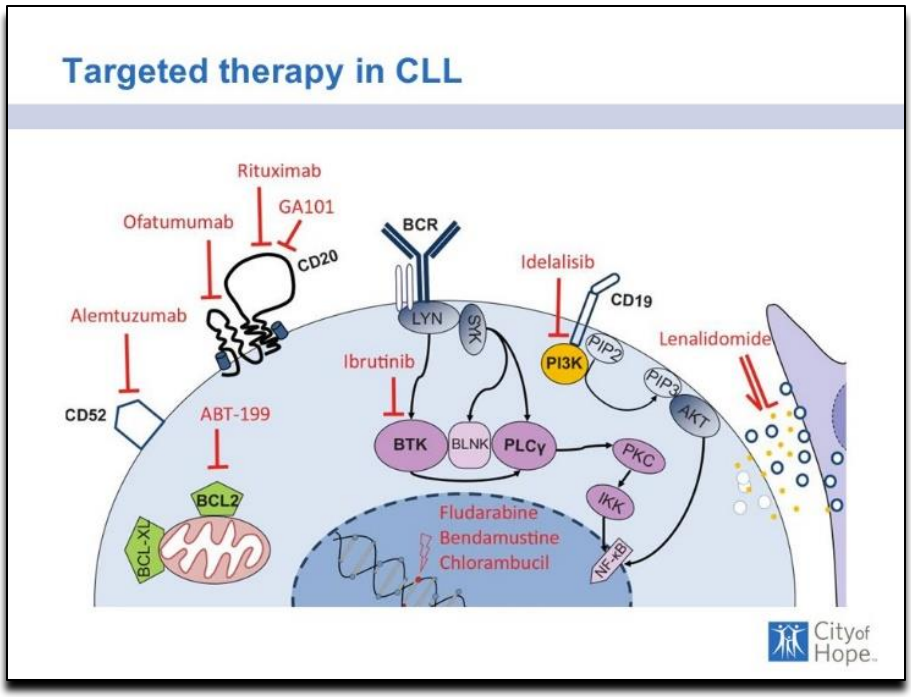
Those patients are plateauing above that several years later and that is the line where we think that if it is this keeps going straight up with no more relapses, maybe those patients are cured. It's a small percentage of patients, but that's the only reason why some people kept giving FCR looking for potential cure in that subset of patients, but there was a lot of side effects and that we have to deal with. So, this is the MD Anderson Cancer Center, who also looked at their own FCR data and showed that they even see this plateau in the IGHV-mutated good risk patients no del(17p) above the 50% progression-free survival, meaning more than half patients would relapse for more than 10 years, and this is well out—10, 15 years—now.



FCT vs. BCR

So, that was encouraging. But because of these side effects of FCR, which had to do with, low counts, even sometimes people developing leukemia, acute leukemia, which is a deadly disease or more commonly just very severe infections and whatnot of very difficult-to-treat type of infections, like fungal infections, etc. So, the Germans then did a comparison of FCR and bendamustine-rituximab, which is a much more commonly used less-toxic sort of a chemo regimen. Some of you may have heard it and they treated a large number of patients with, you know, half and half with FCR and BR. And they found that the response rates were similar. The complete remission rates and the progression-free survival was better for FCR, but the severe neutropenia and severe infections in the bottom two rows, which means the white count being low—very low, dangerously low—was also much higher with FCR than it was for BR. And what they found was that patients above 65 were not seeing this improvement in progression-free survival that the younger patients were seeing because they could not tolerate having to go low white count and infections too much.

So, they weren't seeing the benefit of the CLL not coming back because they were having too many other side effects to deal with. So, in the end, we did a lot of bendamustine and rituximab, because personally I just I think even treating a patient with FCR looking for that 10-year cure in a handful of patients is not worth even one or two patients, dying from some god-forbid severe side effect of FCRs. So, we turn more and more towards targeted therapies.

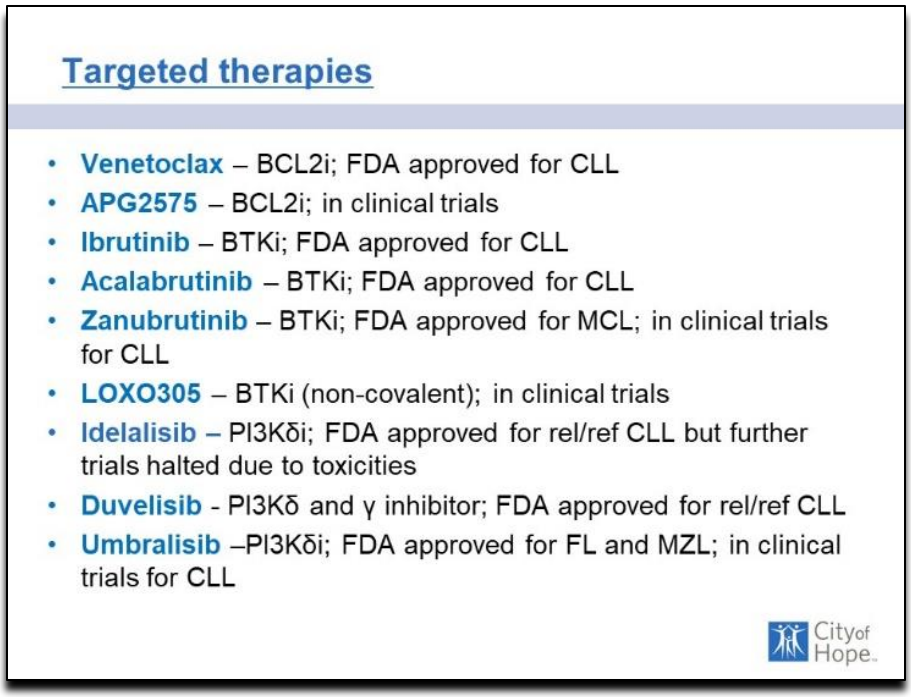


Targeted Therapy in CLL

And you can see in this very sort of simple—it is a very simple diagram—it may look complicated, but it's very simplified. And if you can imagine this as a lymphocyte cell surface, you can see that we have different things targeting the cell membrane on the outside, like rituximab, and you know GA101 is obinutuzumab or Gazyva® as we call it and ofatumumab (Kesimpta®), etc. And then inside the cell there are small molecules—machine parts of the machinery—that keep the cancer cells alive and working and kicking and deviding and growing very actively.

There are very small parts that now we can we have targeted therapies to block. So, BTK is Bruton's tyrosine kinase. We have an inhibitor of against that, the first one being ibrutinib. Now we have acalabrutinib (Calquence®) and zanubrutinib (Brukinsa®), and the next one coming up is LOXO305. So, a lot of exciting stuff where we can actually go in and block even the small parts of the machinery that runs the cells. And then we have other parts of the machinery that are blocked by, PI3K inhibitors and BCL2 inhibitors, like venetoclax, etc.

So, the goal of all of this seeks small targeting new drugs is to go and kill parts of the machinery in the B cells that make up the cancer, which are very important for the running of the cancer. When in the past the chemo would just go in and like explode the whole cell. It was just like it would explode the whole cell. It would also damage a lot of other cells that were sort of in the body that got affected as well, like hair and nails and bone marrow and other things. But these targeted therapies by and large try to target just the B lymphocytes.

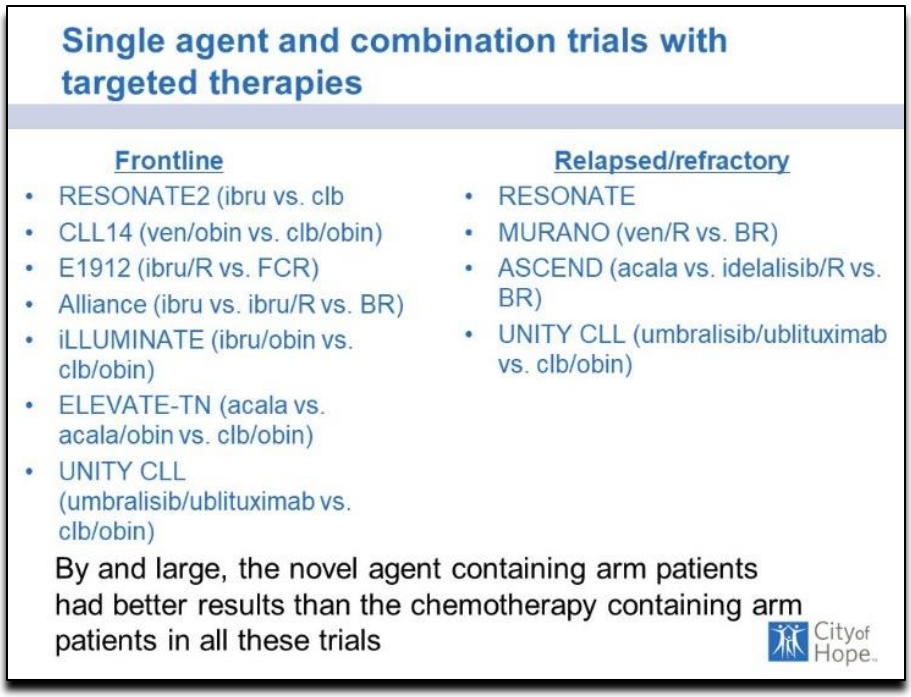


Target Therapies

Now there are a lot of good B lymphocytes as well that can also get targeted, but primarily it is the CLL cells that get targeted and killed by these novel drugs. And so, over the last few years we have seen a whole slew of these small molecule inhibitors targeted therapies that target either BCL2 in the pathway or BTK or PI3K-delta, and a lot of these are already FDA approved as you all may know. Some of them are still in trial, and we will talk about some of these right now.

So, I don't have time to go over the trials that led to the approval of some of the listed novel drugs. But I will tell you that when ibrutinib got FDA approved as a single agent, then venetoclax got FDA approved as a single agent. Then idelalisib (Zydelig®) got FDA approved as a single agent, etc. And more and more coming down the pike, the next step becomes, okay, well, by itself, we know these still need to continue indefinitely, and they can control the disease very well. But they will not put patients into a complete remission or into a long-term complete remission where you can actually take a break from the drug or potentially advance the search for the cure that we are looking for.

So, what people started doing, researchers like me and others started doing was to combine these new pills either with each other or with rituximab like antibodies even with chemo in some trials. But I'm not going to go over the chemo trials because, really, we don't do chemo much at all anymore in CLL. But these are some of the trials I have listed here, which you may come across these names of these trials. But you can imagine that everybody is combining every novel drug with each other or with an antibody or something to kind of come up with a more deeper remission so that people can take a break from treatment and enjoy, like, a good quality of life without CLL for many years before treatment is needed again, potentially.



Single Agent and Combination Trials with Targeted Therapies

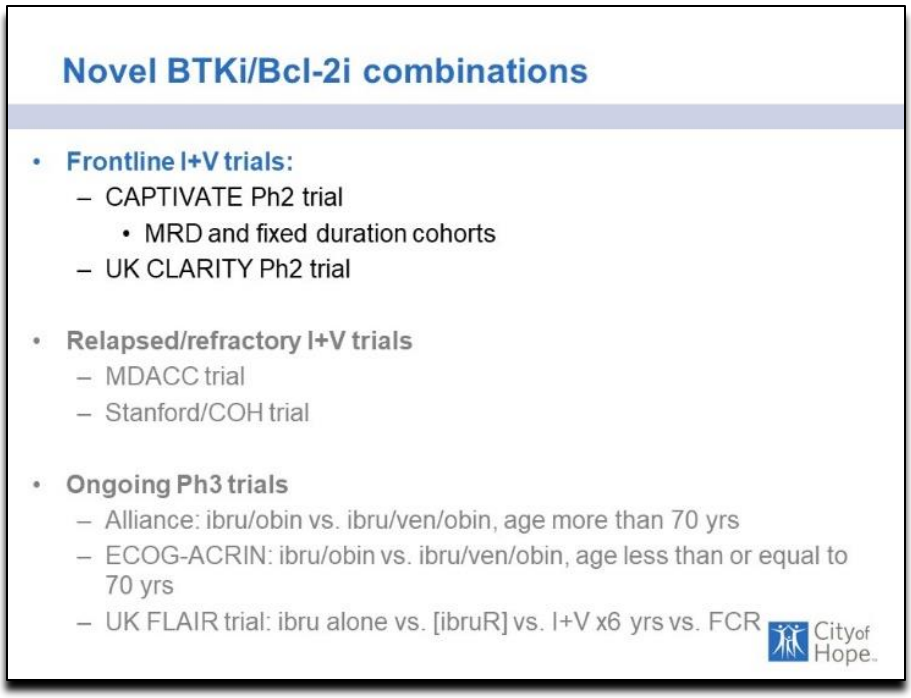
So, in the front-line people have never had treatment before there were originally trials like the RESONATE2 trial, the CLL14 trial that led to FDA approval of venetoclax and obinutuzumab in the front-line settings. So, that's venetoclax for 1 year and obinutuzumab for 6 months and that is one of my favorite sort of regimens to start with. Or it was before COVID hit, I guess I should say. In the era of COVID, in the last 1 year we've used a little bit less of obinutuzumab- and rituximab-type antibodies because they tend to knock out the healthy B cells a little bit more and can put people at a little bit higher risk of sinus infections and pneumonias and whatnot. So, just kind of used it a little bit less also because we didn't want patients coming into clinic too frequently, you know, limit their exposures to other patients and what not.

But now, sort of this year, we are starting to get back on track with more routine treatments, especially as more and more people are getting vaccinated against COVID. So, the E1912 was the one that compared ibrutinib and rituximab against FCR and found that ibrutinib and rituximab does even better than FCR chemotherapy, although we don't have the 10-year data to see if people are getting cured or not, of course. But in terms of responses and progression-free survival and all of that and of course side effects, everything was better with ibrutinib.

The only people who still benefited from FCR as much as ibrutinib—not better but as much as—were people who had mutated IGHV. So, remember those graphs I showed you? Those were the patients who had the plateau beyond 10 years in progression-free survival, so mutated IGHV patients still benefit from FCR, of course. No chromosome 17 either and so but ibrutinib did as well so it is certainly easier to tolerate.

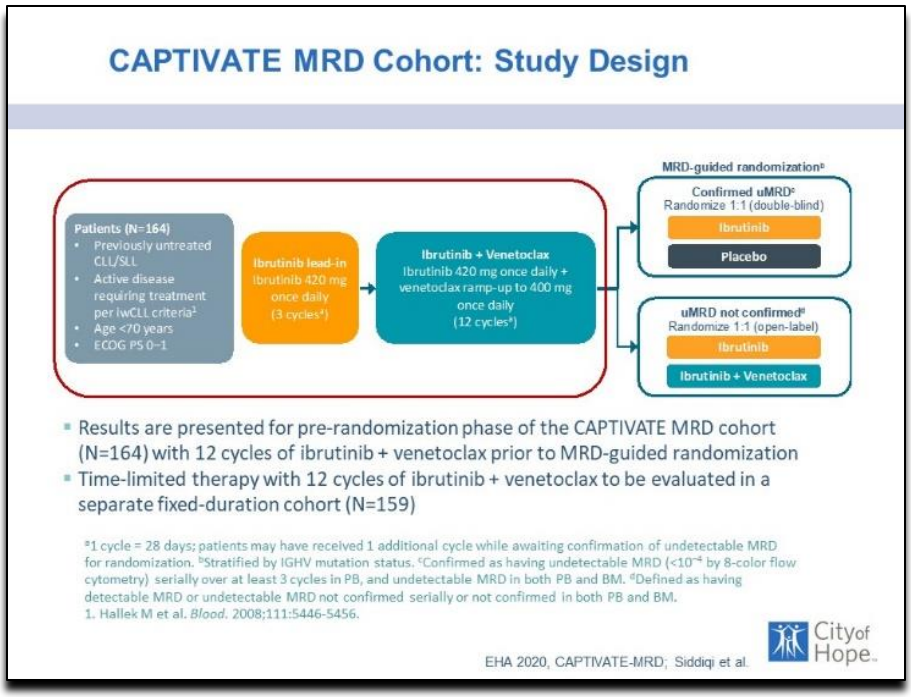
And then the Alliance trial was for a little bit older patients, so they compared the ibrutinib arm versus BR bendamustine-rituximab and found again that ibrutinib did better than BR in pretty much all groups of patients. So, that led us to believe that look, we really don't need to even do BR anymore even for the people with good risk features. We can do ibrutinib, and we may or may not even need rituximab. Just ibrutinib by itself does a very good job, but you have got to stay on it kind of indefinitely, and that is the annoying part.

Then came the iLLUMINATE, ELEVATE, and UNITY trials that looked at further ibrutinib combinations but also acalabrutinib and then umbralisib (Ukoniq®), etc. So, there is more and more stuff coming in the relapsed/refractory setting. The MURANO trial was a big one, which led to approval of venetoclax plus rituximab for people who had had prior treatments, mostly prior chemo actually. And people getting venetoclax and rituximab ended up being a lot better results in terms of progression-free survival and toleration of, you know, tolerability of the treatment compared to bendamustine and rituximab. So, in that trial in the relapse setting, venetoclax is given for 2 years—not 1 year but 2 years—and then rituximab is again given for 6 months at least. And then the ASCEND and UNITY trials again are the relapsed/refractory CLL trials with acalabrutinib and umbralisib etc., respectively. And all of those clearly show that these novel agents do better than chemotherapy. So, those have been extremely promising.



Novel BTKi/Bcl-2i Combinations

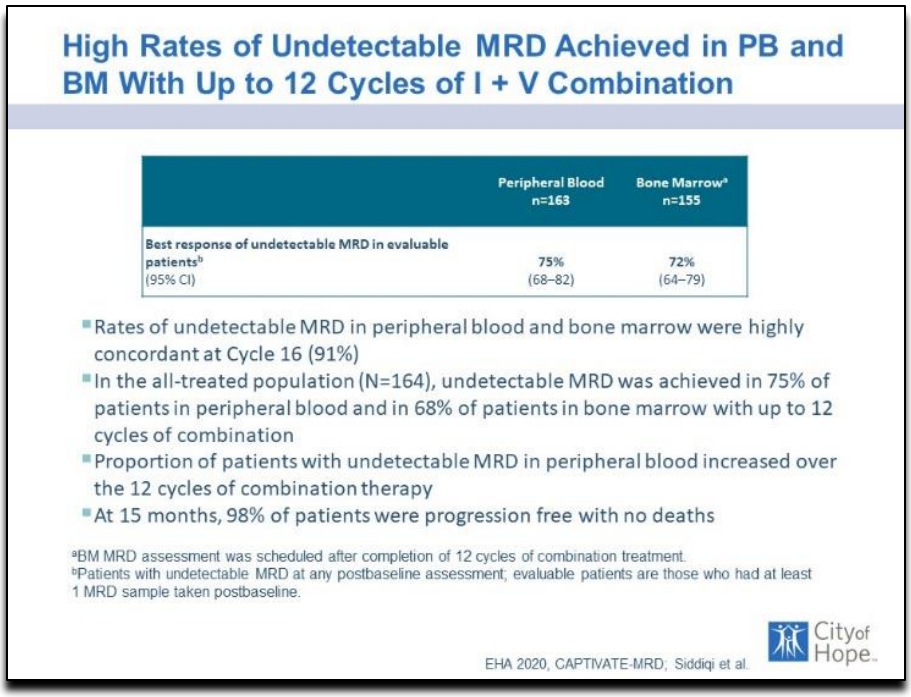
Well, now that we know that small agents do better than chemotherapy, the next generation of trials is actually looking at combining the novel agents with each other. And some of the data that I'm going to show here has to do with ibrutinib plus venetoclax types of combinations—largely, for instance, the CAPTIVATE phase 2 trial and the UK CLARITY phase 2 trial as well.



CAPTIVATE MRD Cohort: Study Design

So, the CAPTIVATE trial had a lot of patients on this as well at City of Hope. And this was a nationwide study—actually an international study–which was basically looking at patients getting both ibrutinib for 3 months followed by addition of venetoclax for a total of 12 months. And at the end of the total of 18 months, people—there were two cohorts. Either everybody stopped, which is the fixed duration cohort, which is not what I am talking about here because we haven't seen the full data for that yet, or the first cohort was what is called the MRD cohort, the minimal residual disease cohort.

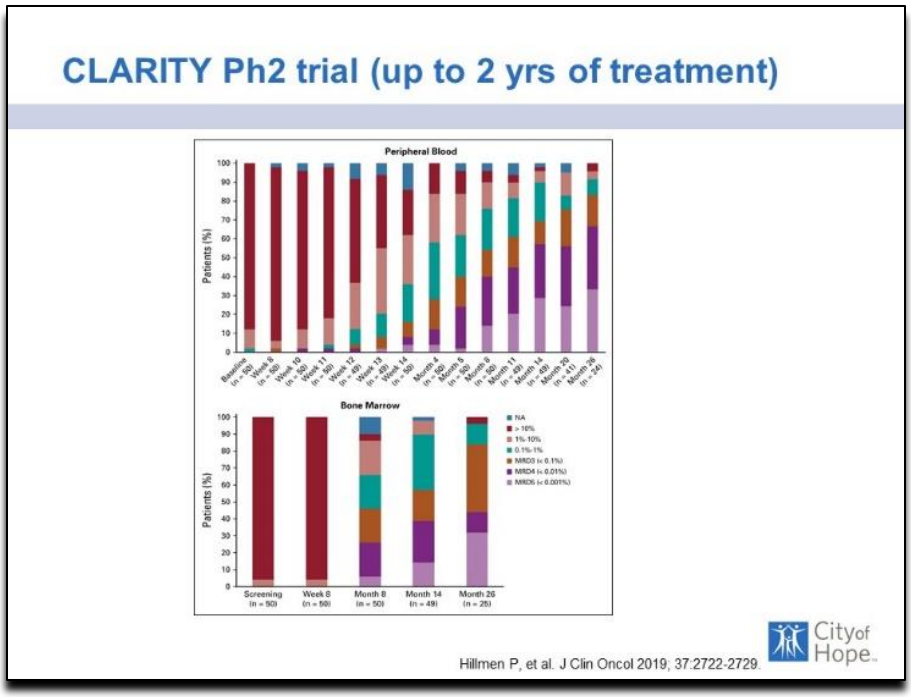
So, at the end of finishing both the year of ibrutinib plus venetoclax people had MRD testing done on the study—very strict MRD testing. They have to be tested two, three times, including once on the bone marrow as well. And if there were clearly MRD negative, meaning undetectable minimal residual disease confirmed on the bone marrow and in three different blood samples, they were allowed to drop the venetoclax and then basically were randomized to continue with just ibrutinib or placebo, but we didn't know which one. So, what the study was studying was that after you do a year and a half of both ibrutinib and venetoclax, do you need maintenance with ibrutinib further down the line or will you not need, any kind of maintenance and you will still have a good long-term response with having done just the two pills together.



High Rates of Undetectable MRD Achieved in PB and BM With Up to 12 Cycles of I + V Combination

Whereas if they couldn't confirm undetectable MRD, let's say the bone marrow is positive but the blood was negative or some such thing. Then we have to see whether you need ibrutinib-alone maintenance or do you need to continue both ibrutinib and the venetoclax? So, this is the MRD cohort of the CAPTIVATE trial that was updated, you know, last year at multiple meetings. I presented it at European Hematology Association meeting, but it was also presented at the American Society of Hematology meeting. And what they found was that when you finish the 12 cycles of the combination I plus V, you have a very high undetectable MRD rate of 75% in the blood and 72% in the marrow.

They found that so the blood and the marrow were pretty similar. And in all of the patients—164 patients—they were able to also see that started checking the MRDs in the blood from cycle 7 onward. And they saw that with each month of treatment, ongoing treatment with I plus V, the MRD got better and better. So, at the end of, a year of combination, the MRD was 75%. I don't know if that would have kept increasing if the doublet was continued for 2 years, let's say. We don't know that. But anyway, so it kept increasing with every month of treatment, and pretty much nobody progressed 98% were progression-free at the end of those combination of ibrutinib plus venetoclax.



CLARITY Ph2 Trial (up to 2 yrs of treatment)

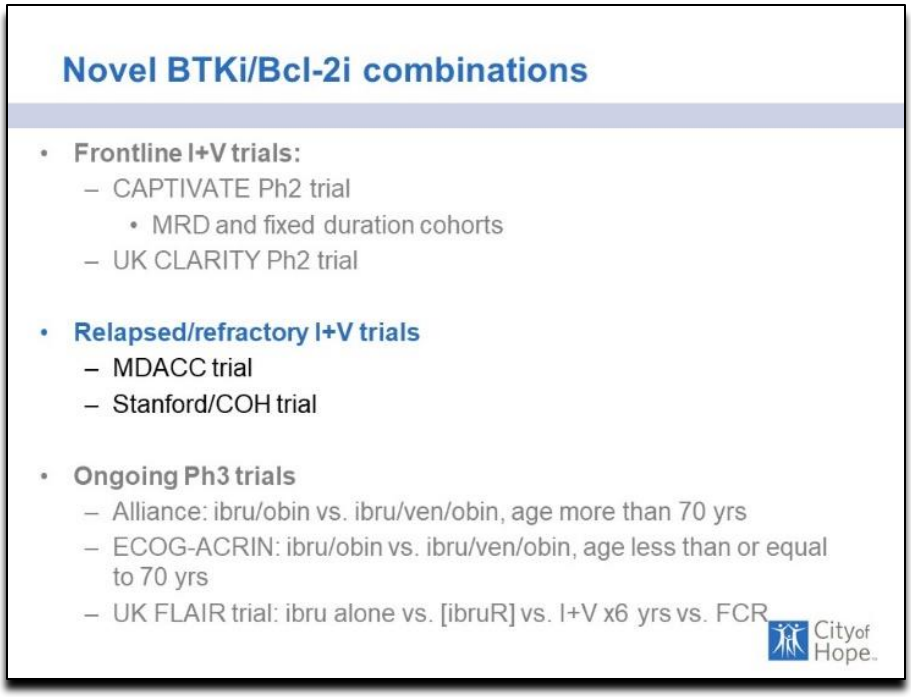
The CLARITY trial and, by the way, the subsequent follow-up, which I don't show here, meaning after they were randomized and after they were started on some kind of maintenance or no maintenance program. The latest data from ASH, American Society of Hematology, in December, showed very early that 1 year after they finished the I plus V combination and then gone to whichever combination of randomization you could think of whether it was just ibrutinib or whether it was placebo or ibrutinib or ibrutinib plus venetoclax, everybody did the same. Like, nobody progressed. Like, it was 95% people did not progress at 1 year after going off of the I plus V combination and going on to one of these you know randomized maintenance programs.

So, 1 year is a short time, of course. If you have such a deep remission that you can't detect residual disease detect very, very few specs of CLL in a very sensitive test that not every center can do. So, you have to send it out to a specific center who can actually do that test. So, it doesn't mean that the disease is cured, unfortunately. It means that our human testing cannot detect MRD or minimal residual disease by a very sensitive test which we developed as a human. But we haven't, you know, there might be still some specs below that level, potentially, and only time will tell if those specs that are left behind will grow into full-blown CLL again or not. So, that longer-term data is still pending, so I don't have those results yet.

On the UK CLARITY trial, they did a similar ibrutinib plus venetoclax trial in the United Kingdom where they did the treatment for 2 years instead of a year or a year and a half. And what they saw was—I'm sorry, this is a bit small—but you can see that these purple bars on the right are increasing. And so, that means that as you get closer to the 2-year mark the undetectable MRD, which is the purple, the light and deeper purple bars—the MRDs are getting better and better, meaning there's more and more people developing undetectable minimal residual disease over time. So, by the end of 2 years it was even better. And I don't know again if it plateaued at that time or could it have continued to become better and better if they continued with I plus V long-term?

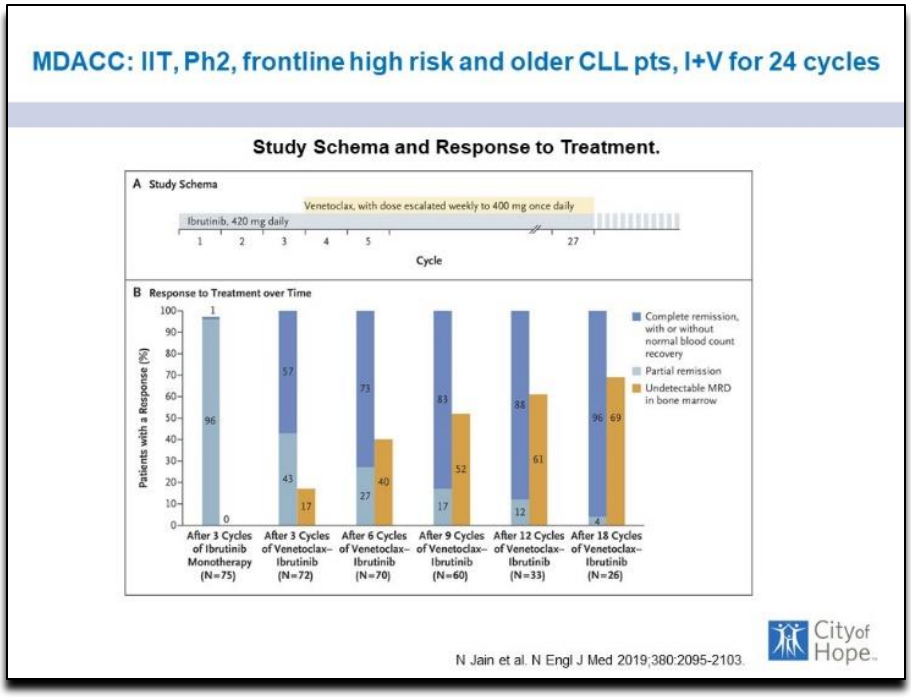
We don't know that. These two are very expensive pills. They do have some side effects, but they were fairly well tolerated put together. You know, sometimes I have had to make an adjustment where I cut down the dose of the venetoclax a little bit, and that helps not get people's white count too low. For instance, sometimes, if people have more diarrhea or joint pain, we cut down the dose of ibrutinib, and

then that helps. So, there is room to kind of make adjustments, but the goal in our minds is to kind of just do this for a year or two so that we can stop treatment and see how well people do for how long without needing treatment at all.



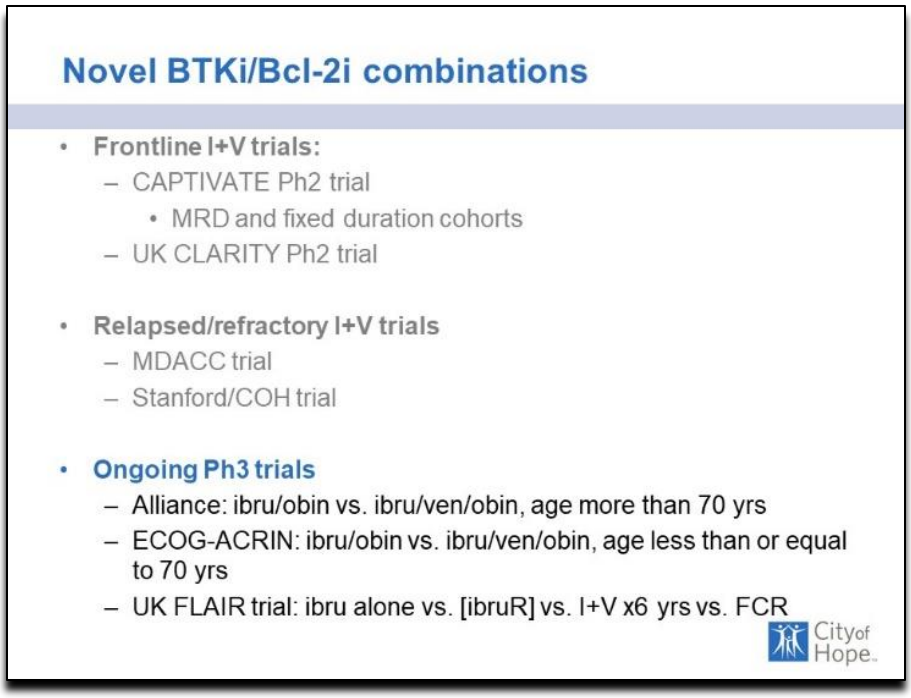
Novel BTKi/Bcl-2i combinations

And then similar trials were done at MD Anderson. We were doing a trial with Stanford.



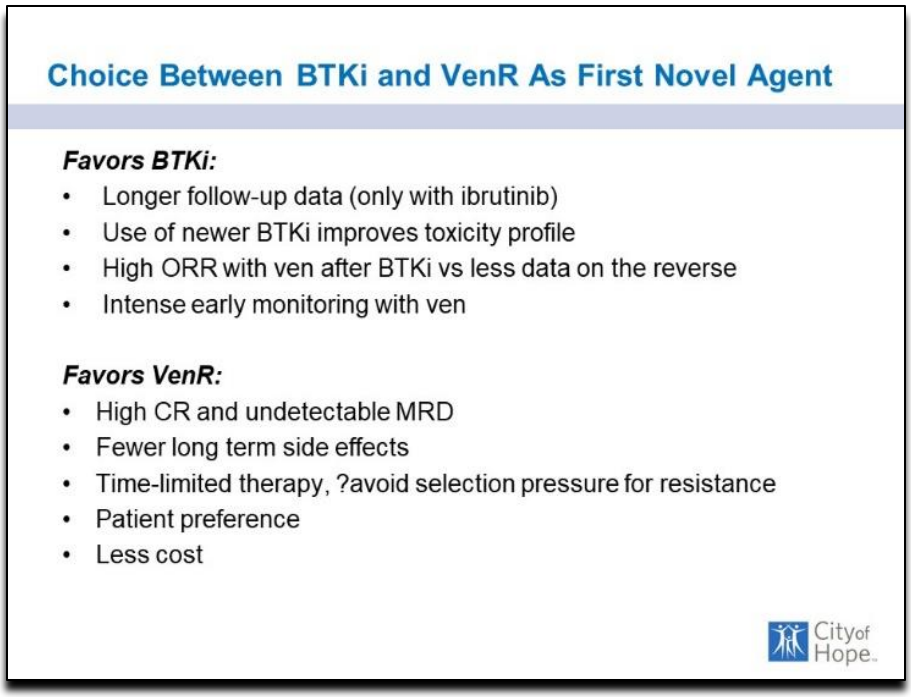
MDACC: IIT, Ph2, Frontline High Risk and Older CLL pts, I+V for 24 Cycles

Looking at ibrutinib plus venetoclax in the relapsed/refractory patient population, and that shows similar results, where the yellow or orange bars are the undetectable minimal residual disease. And those get better and better at a year and a half compared to, you know, after 3 months of combination, for instance.



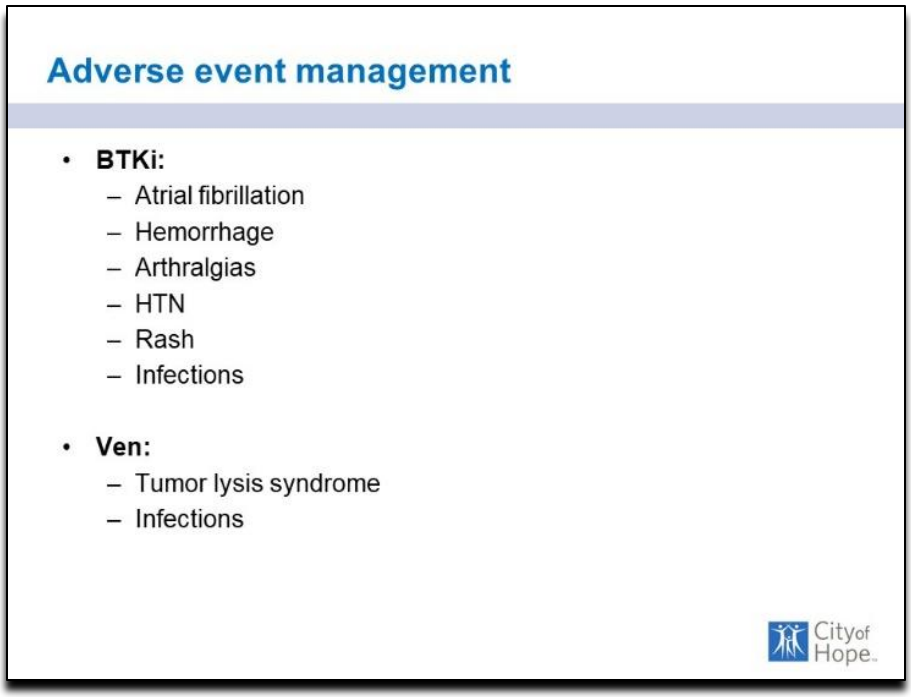
Novel BTKi/Bcl-2i Combinations

And then, finally, we have ongoing phase 3 trials that are now studying whether we can, just get away with ibrutinib plus obinutuzumab combination for a year and a half. Or do we really need to add venetoclax in the mix? And there are two different studies: one for older than 70, one for under 70. At City of Hope I have both studies open. We have put a number of patients on them, and I think the data for that will maybe take another year or two to come out. Obviously, it's a big study, so we will have to wait and see. And in the UK they are also doing some similar combination and comparison studies.



Choice Between BTKi and VenR As First Novel Agent

One of the biggest questions we deal with nowadays is how do we choose between a BTK inhibitor or a venetoclax-based regimen in patients who are needing treatment for the first time with a novel agent. And historically, we have all started with BTK inhibitors, like ibrutinib, first because that was what was available first. And then when people progress on ibrutinib or they are not tolerating ibrutinib, that is when we go on to venetoclax. Nowadays, with the CLL14 trial showing that venetoclax plus obinutuzumab is a great first option, we have seen that people can still respond to a BTK inhibitor very well if we choose to do it after venetoclax. So, we can do it both ways.



Adverse Event Management

I think it works both ways. You just have to as a physician and a patient you have to have the discussion of which one is a better way to go. With first, for instance, if somebody clearly has a lot of heart disease at baseline, you may not want to start with an ibrutinib type of medication because that I can have some side effects of atrial fibrillation, let's say, or irregular heartbeat. Whereas if somebody has kidney weakness, like kidney insufficiency, their kidneys don't work very well. Then you may not want to start with venetoclax because that can sometimes have a tumor lysis effect that can affect the kidneys. Although we watch it very, very closely in the first 5 weeks.

So, there are nuances that we need to deal with. And here are some of the side effects we look for specifically with BTK inhibitors as well as with venetoclax—maybe a little bit more with BTK inhibitors, because that can lead to higher blood pressure over time, maybe a little bit more infections, even rashes, joint pain, and then diarrhea and that sort of stuff. These side effects can sometimes come when patients start treatment. But then in a month or two, patients get use to; or the drug sort of doesn't have all of these side effects anymore. But sometimes they don't go away, and that can be very difficult on the quality of life.

There's about a 10% chance of atrial fibrillation, which is the irregular heartbeat I was talking about. If patients absolutely need to be on their BTK inhibitor, I usually work with a cardiologist and have them optimize the treatment for their atrial fibrillation or their heart medications. And then we can retry the BTK inhibitor, like ibrutinib. Or acalabrutinib will have less side effects of atrial fibrillation simulation actually much less than ibrutinib. So, we can switch to acalabrutinib or we can try ibrutinib at a lower dose, and I have made it work a lot of times that way. Sometimes we've just got to stop and change drugs if it's not, you know, manageable.


Updated Follow-Up of Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Treated with Lisocabtagene Maraleucel in the Phase 1 Monotherapy Cohort of TRANSCEND CLL 004, Including High-Risk and Ibrutinib-Treated Patients

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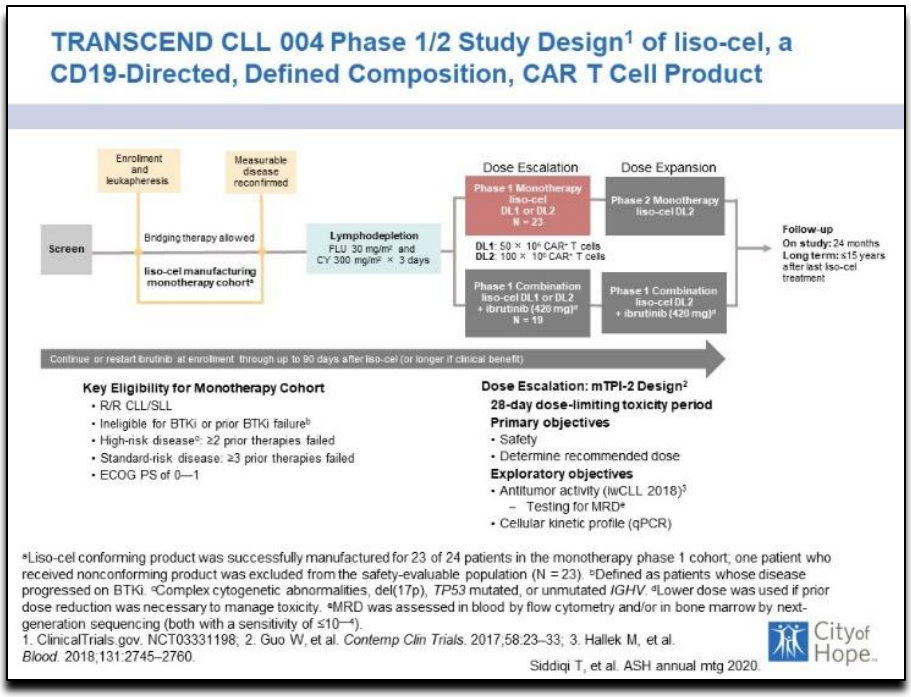
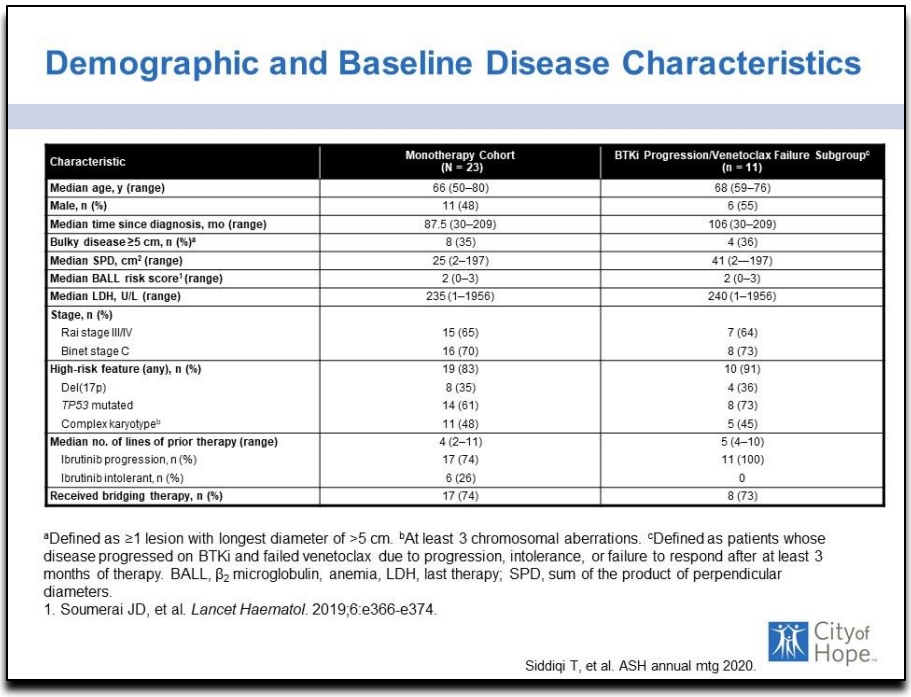
Updated Follow-Up of Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Treated with Lisocabtagene Maraleucel in the Phase 1 Monotherapy Cohort of TRANSCEND CLL 004, Including High-Risk and Ibrutinib-Treated Patients



TRANSCEND CLL 004 Phase 1/2 Study Design1 of liso-cel, a CD19-Directed, Defined Composition, CAR T Cell Product

And then finally I would just talk a little bit about CAR T cells, because I've been heavily involved with the liso-cel, you know, the JUNO CAR T cell trials. So, we have been doing this phase 1 study with the JUNO, Celgene and now BMS companies for their liso-cell product, lisocabtagene maraleucel, which is a CAR T cell that directly attacks B lymphocytes by recognizing and attacking CD19 on those cells, much like rituximab recognizes CD20 on the surface of B cells and attacks B cells by that mechanism. CAR T cells that are currently under production recognize CD19, which is also on B cells. And so, CAR T cells are very challenging in the sense that you have to personally make a product for each and every patient.



Demographic and Baseline Disease Characteristics

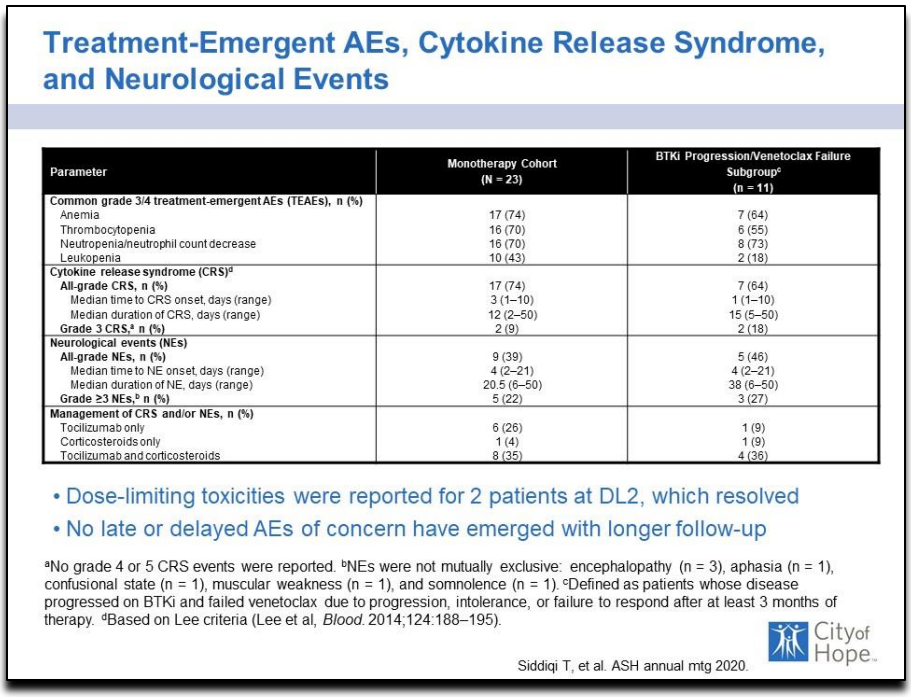
Characteristic	Monotherapy Cohort (N = 23)	BTKi Progression/Venetoclax Failure Subgroup[c] (n = 11)
Median age, y (range)	66 (50–80)	68 (59–76)
Male, n (%)	11 (48)	6 (55)
Median time since diagnosis, mo (range)	87.5 (30–209)	106 (30–209)
Bulky disease ≥5 cm, n (%)[a]	8 (35)	4 (36)
Median SPD, cm² (range)	25 (2–197)	41 (2—197)
Median BALL risk score[1] (range)	2 (0–3)	2 (0–3)
Median LDH, U/L (range)	235 (1–1956)	240 (1–1956)
Stage, n (%)		
Rai stage III/IV	15 (65)	7 (64)
Binet stage C	16 (70)	8 (73)
High-risk feature (any), n (%)	19 (83)	10 (91)
Del(17p)	8 (35)	4 (36)
TP53 mutated	14 (61)	8 (73)
Complex karyotype[b]	11 (48)	5 (45)
Median no. of lines of prior therapy (range)	4 (2–11)	5 (4–10)
Ibrutinib progression, n (%)	17 (74)	11 (100)
Ibrutinib intolerant, n (%)	6 (26)	0
Received bridging therapy, n (%)	17 (74)	8 (73)

[a]Defined as ≥1 lesion with longest diameter of >5 cm. [b]At least 3 chromosomal aberrations. [c]Defined as patients whose disease progressed on BTKi and failed venetoclax due to progression, intolerance, or failure to respond after at least 3 months of therapy. BALL, β_2 microglobulin, anemia, LDH, last therapy; SPD, sum of the product of perpendicular diameters.

1. Soumerai JD, et al. *Lancet Haematol*. 2019;6:e366-e374.

Siddiqi T, et al. ASH annual mtg 2020.

Demographic and Baseline Disease Characteristics
(Additional information)



Treatment-Emergent AEs, Cytokine Release Syndrome, and Neurological Events

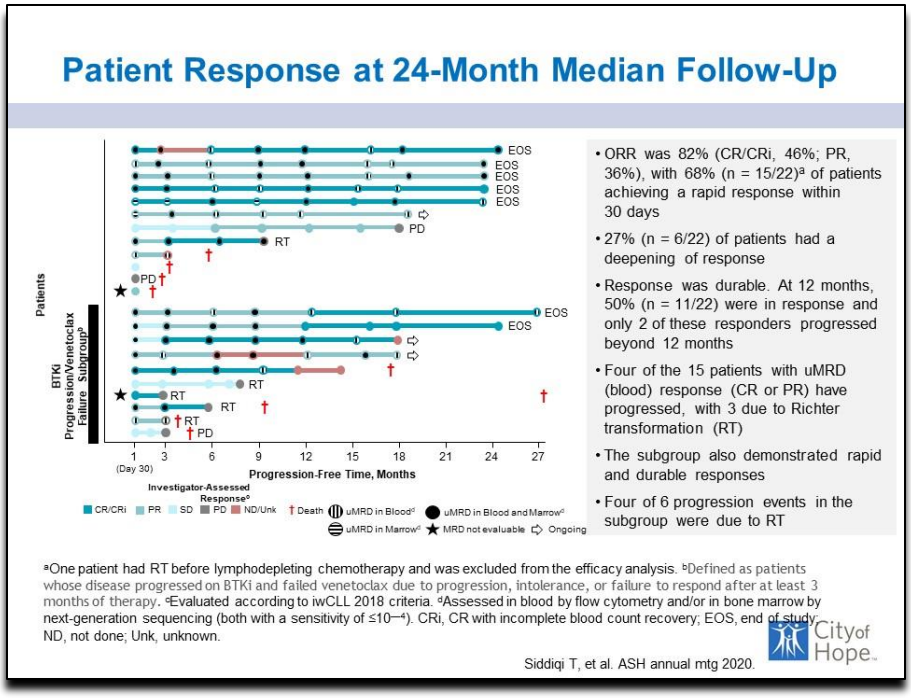
Parameter	Monotherapy Cohort (N = 23)	BTKi Progression/Venetoclax Failure Subgroup[c] (n = 11)
Common grade 3/4 treatment-emergent AEs (TEAEs), n (%)		
Anemia	17 (74)	7 (64)
Thrombocytopenia	16 (70)	6 (55)
Neutropenia/neutrophil count decrease	16 (70)	8 (73)
Leukopenia	10 (43)	2 (18)
Cytokine release syndrome (CRS)[d]		
All-grade CRS, n (%)	17 (74)	7 (64)
Median time to CRS onset, days (range)	3 (1–10)	1 (1–10)
Median duration of CRS, days (range)	12 (2–50)	15 (5–50)
Grade 3 CRS,[a] n (%)	2 (9)	2 (18)
Neurological events (NEs)		
All-grade NEs, n (%)	9 (39)	5 (46)
Median time to NE onset, days (range)	4 (2–21)	4 (2–21)
Median duration of NE, days (range)	20.5 (6–50)	38 (6–50)
Grade ≥3 NEs,[b] n (%)	5 (22)	3 (27)
Management of CRS and/or NEs, n (%)		
Tocilizumab only	6 (26)	1 (9)
Corticosteroids only	1 (4)	1 (9)
Tocilizumab and corticosteroids	8 (35)	4 (36)

- Dose-limiting toxicities were reported for 2 patients at DL2, which resolved
- No late or delayed AEs of concern have emerged with longer follow-up

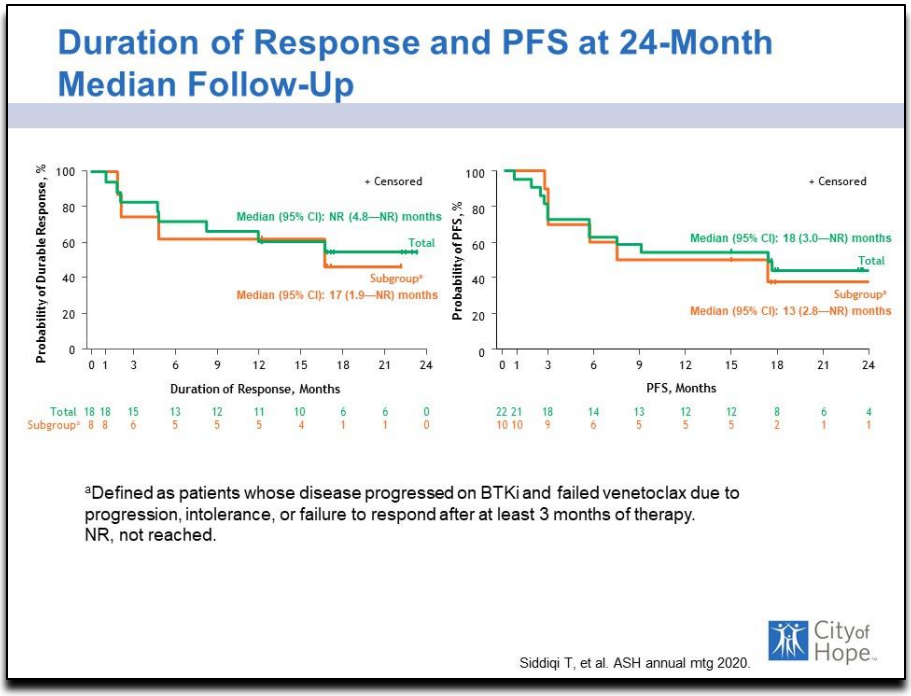
[a]No grade 4 or 5 CRS events were reported. [b]NEs were not mutually exclusive: encephalopathy (n = 3), aphasia (n = 1), confusional state (n = 1), muscular weakness (n = 1), and somnolence (n = 1). [c]Defined as patients whose disease progressed on BTKi and failed venetoclax due to progression, intolerance, or failure to respond after at least 3 months of therapy. [d]Based on Lee criteria (Lee et al, *Blood*. 2014;124:188–195).

Siddiqi T, et al. ASH annual mtg 2020.

Treatment-Emergent AEs, Cytokine Release Syndrome, and Neurological Events
(Additional information)



Patient Response at 24-Month Median Follow-Up
(Additional information)

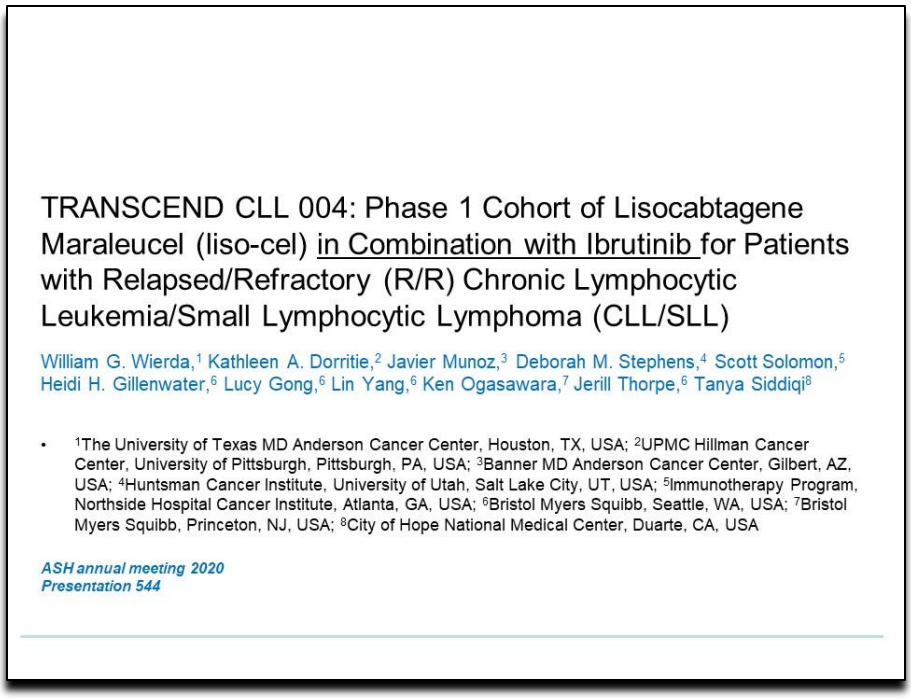


Duration of Response and PFS at 24-Month Median Follow-Up

So, when a patient comes and they are eligible for a study we will take their healthy T lymphocytes, not the B ones. The B ones are where the cancer's coming from, but the T ones from their peripheral blood. And in the lab these cells are manufactured or changed. So that instead of recognizing

infections to fight infections, which is their normal job, they now are trained to fight or look out for and attack the B lymphocytes specifically—more the cancer cells than the healthy ones, but sometimes, , some of the healthy ones also get attacked. And so, it's a production that takes about for Juno CAR T cells it takes about 3 to 4 weeks to make, and there are certain specific side effects that we watch for in the first month of therapy.

But beyond 1 month, technically, people get back on their feet slowly and their counts come back to normal slowly. And so, it's a month of one's life that we kind of ask for to share with us very closely so that we can treat people not just treat people but also manage their side effects very aggressively and very quickly so that they don't become a problem.


TRANSCEND CLL 004: Phase 1 Cohort of Lisocabtagene Maraleucel (liso-cel) in Combination with Ibrutinib for Patients with Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

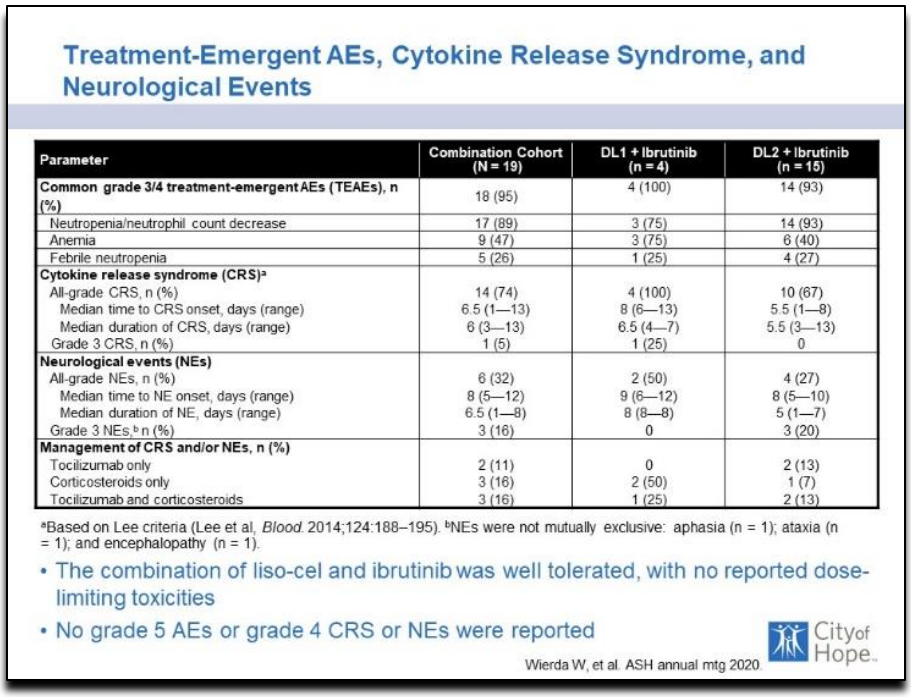
William G. Wierda,[1] Kathleen A. Dorritie,[2] Javier Munoz,[3] Deborah M. Stephens,[4] Scott Solomon,[5] Heidi H. Gillenwater,[6] Lucy Gong,[6] Lin Yang,[6] Ken Ogasawara,[7] Jerill Thorpe,[6] Tanya Siddiqi[8]

- [1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA, USA; [3]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [4]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [5]Immunotherapy Program, Northside Hospital Cancer Institute, Atlanta, GA, USA; [6]Bristol Myers Squibb, Seattle, WA, USA; [7]Bristol Myers Squibb, Princeton, NJ, USA; [8]City of Hope National Medical Center, Duarte, CA, USA

ASH annual meeting 2020
Presentation 544

TRANSCEND CLL 004: Phase 1 Cohort of Lisocabtagene Maraleucel (liso-cel) in Combination with Ibrutinib for Patients with Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

And so, this study, this TRANSCEND CLL 004 trial, is a phase 1/2 study. The phase 1 portion has already been done, so we know which cell does of the two that were tested work well. And so, I have been presenting the phase 1 portion of the study in several meetings, the latest one being the American Society of Hematology in December 2020. And it's basically 23 patients who are part of that phase 1 portion of liso-cel CAR T cells alone by themselves.



Treatment-Emergent AEs, Cytokine Release Syndrome, and Neurological Events

Parameter	Combination Cohort (N = 19)	DL1 + Ibrutinib (n = 4)	DL2 + Ibrutinib (n = 15)
Common grade 3/4 treatment-emergent AEs (TEAEs), n (%)	18 (95)	4 (100)	14 (93)
Neutropenia/neutrophil count decrease	17 (89)	3 (75)	14 (93)
Anemia	9 (47)	3 (75)	6 (40)
Febrile neutropenia	5 (26)	1 (25)	4 (27)
Cytokine release syndrome (CRS)[a]			
All-grade CRS, n (%)	14 (74)	4 (100)	10 (67)
Median time to CRS onset, days (range)	6.5 (1—13)	8 (6—13)	5.5 (1—8)
Median duration of CRS, days (range)	6 (3—13)	6.5 (4—7)	5.5 (3—13)
Grade 3 CRS, n (%)	1 (5)	1 (25)	0
Neurological events (NEs)			
All-grade NEs, n (%)	6 (32)	2 (50)	4 (27)
Median time to NE onset, days (range)	8 (5—12)	9 (6—12)	8 (5—10)
Median duration of NE, days (range)	6.5 (1—8)	8 (8—8)	5 (1—7)
Grade 3 NEs,[b] n (%)	3 (16)	0	3 (20)
Management of CRS and/or NEs, n (%)			
Tocilizumab only	2 (11)	0	2 (13)
Corticosteroids only	3 (16)	2 (50)	1 (7)
Tocilizumab and corticosteroids	3 (16)	1 (25)	2 (13)

[a]Based on Lee criteria (Lee et al, *Blood*. 2014;124:188–195). [b]NEs were not mutually exclusive: aphasia (n = 1); ataxia (n = 1); and encephalopathy (n = 1).

- The combination of liso-cel and ibrutinib was well tolerated, with no reported dose-limiting toxicities
- No grade 5 AEs or grade 4 CRS or NEs were reported

Wierda W, et al. ASH annual mtg 2020.

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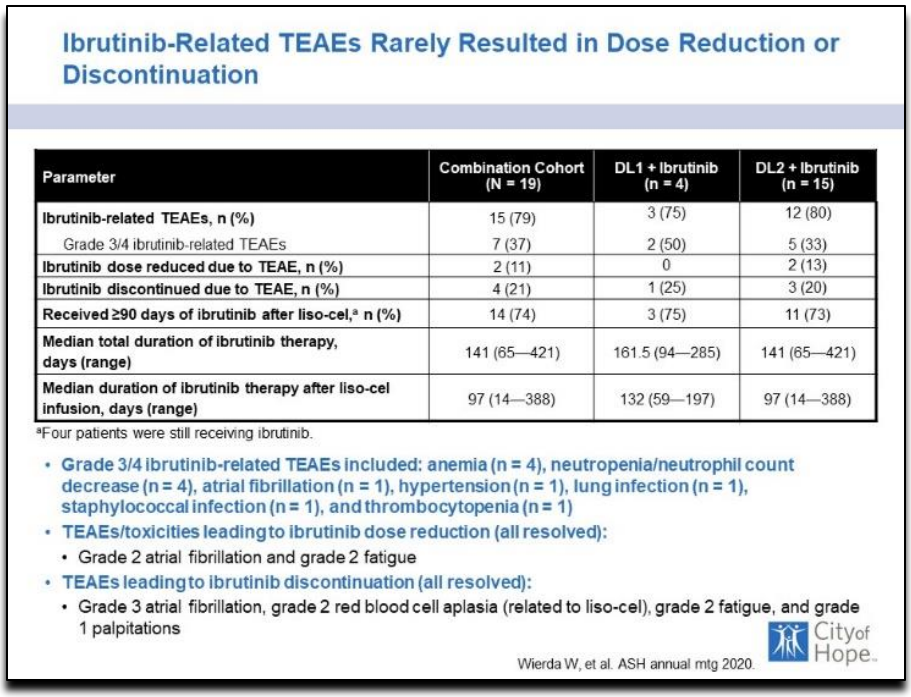
Treatment-Emergent AEs, Cytokine Release Syndrome, and Neurological Events

There is another portion of this study with Dr. Bill Wierda from MD Anderson presented early data on which is combining the liso-cel CAR T cells with ibrutinib, because ibrutinib can sometimes help potentiate the effect of T cells or the CAR T cells and make them even stronger while also reducing the risk of some of the hyperinflammation type of side effects. So, we have seen some very good early data with the combination as well.

So, to be on this trial patients needed to have obviously relapsed CLL, but they all needed to have failed or been exposed to a BTK inhibitor like ibrutinib, and all 23 were exposed to ibrutinib in the past. They need to have two or three total lines of therapy, with one of them obviously being a BTK inhibitor. And again—sorry, it's a little small and complex—but if you look at the middle column, the monotherapy cohort of 23 patients, the median age meaning half were older, half were younger was 66; about half male, half female in that population. Further down, you can see that in the majority of patients had advanced-stage disease, so stage 3 or 4 disease and then the majority of patients, 83%, had high-risk features of some type, whether it was chromosome 17 deletion or mutated *TP53* or complex carrier type.



Ibrutinib-Related TEAEs Rarely Resulted in Dose Reduction or Discontinuation

Parameter	Combination Cohort (N = 19)	DL1 + Ibrutinib (n = 4)	DL2 + Ibrutinib (n = 15)
Ibrutinib-related TEAEs, n (%)	15 (79)	3 (75)	12 (80)
Grade 3/4 ibrutinib-related TEAEs	7 (37)	2 (50)	5 (33)
Ibrutinib dose reduced due to TEAE, n (%)	2 (11)	0	2 (13)
Ibrutinib discontinued due to TEAE, n (%)	4 (21)	1 (25)	3 (20)
Received ≥90 days of ibrutinib after liso-cel,[a] n (%)	14 (74)	3 (75)	11 (73)
Median total duration of ibrutinib therapy, days (range)	141 (65—421)	161.5 (94—285)	141 (65—421)
Median duration of ibrutinib therapy after liso-cel infusion, days (range)	97 (14—388)	132 (59—197)	97 (14—388)

[a]Four patients were still receiving ibrutinib.

- Grade 3/4 ibrutinib-related TEAEs included: anemia (n = 4), neutropenia/neutrophil count decrease (n = 4), atrial fibrillation (n = 1), hypertension (n = 1), lung infection (n = 1), staphylococcal infection (n = 1), and thrombocytopenia (n = 1)
- TEAEs/toxicities leading to ibrutinib dose reduction (all resolved):
  - Grade 2 atrial fibrillation and grade 2 fatigue
- TEAEs leading to ibrutinib discontinuation (all resolved):
  - Grade 3 atrial fibrillation, grade 2 red blood cell aplasia (related to liso-cel), grade 2 fatigue, and grade 1 palpitations

Wierda W, et al. ASH annual mtg 2020.

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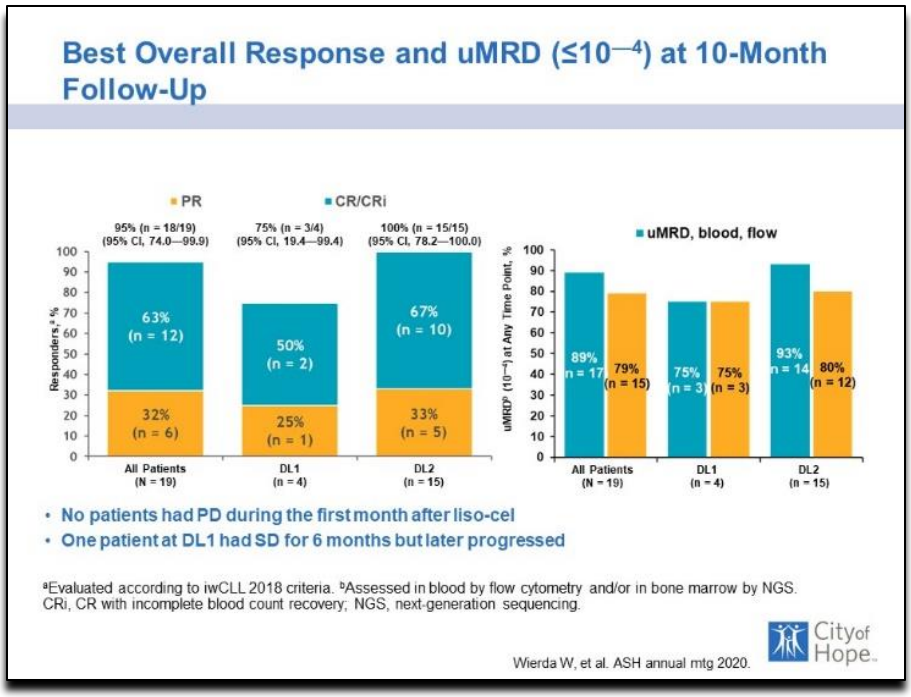
Ibrutinib-Related TEAEs Rarely Resulted in Dose Reduction or Discontinuation

All of them had had prior ibrutinib, and median number of prior lines of therapy was four. So, a lot of them had had at least four treatments prior to coming to CAR T cells, and then the majority had progressed on not just ibrutinib. But there were 11 patients in the right-hand column, 11 patients who had progressed not just on ibrutinib but also venetoclax. So, 11 of the 23 were those even worse-acting CLL patients who had progressed already on ibrutinib as well as venetoclax. And so, you're going to start thinking, okay, we are running out of options now what do we do next. And so one of the some of the side effects we look for with CAR T cells in that first 2, 3 weeks after CAR T-cell infusion is cytokine release syndrome, which is a type of hyperinflammation in the body, as the T cells fight the B cells. And then also sometimes they can be a quirky side effect of neurotoxicity or just confusion or pretty severe kind of just altered mental state for a few days until we give them steroids, and that kind of passes.

We don't know exactly why that happens, but it is probably because these CAR T cells, which are the patient's own cells in a way they kind of get in everywhere and create inflammation in different places, like even in the spinal fluid around the brain and things like that. So, everybody doesn't get that. Only two people out of the 23 had grade 3 cytokine release syndrome, and nobody had grade 4, which is a very severe form of inflammation. And only five patients out of the 23 had grade 3 or 4 neurotoxicity or this confusion that I talked about in a more severe or aggressive presentation.

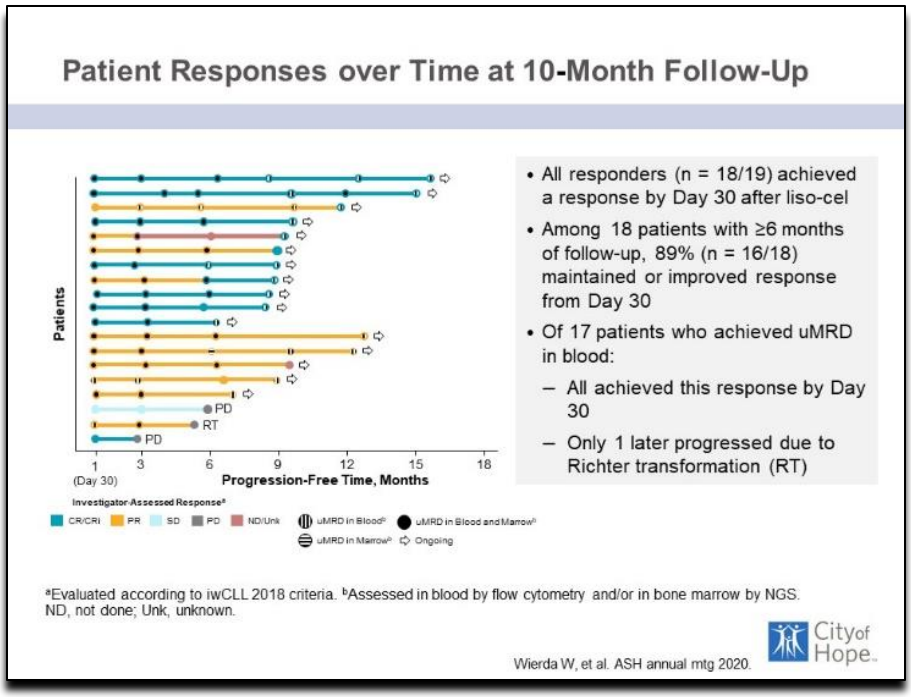


Best Overall Response and uMRD (≤10—4) at 10-Month Follow-Up

So, generally speaking, it was very well tolerated in terms of the cytokine release syndrome and the neurotoxicity side effects of CAR T cells. And there were no delayed or late adverse events in this group of 23 patients, who the majority of whom we have now followed for 2 years at least. And this plot kind of shows each individual of the 23 patients the lower panel of the group of patients who have failed both ibrutinib and venetoclax. And you can see even in that there are some patients who are now beyond 2 years without relapsing, which is great.

There are some people who relapse and unfortunately relapse with Richter's transformation. About four or five patients did that, and that is just a side effect of CLL, especially in people who have more of the poorest features of chromosome 17 type of disease. But by and large, the majority of patients had achieved a very good remission with 60%, 70% undetectable minimal residual disease as early as 1 month after CAR T cells. And you can see in the top panel a lot of patients maintained their response over time, even out to 2 years and longer now. So, it is promising.

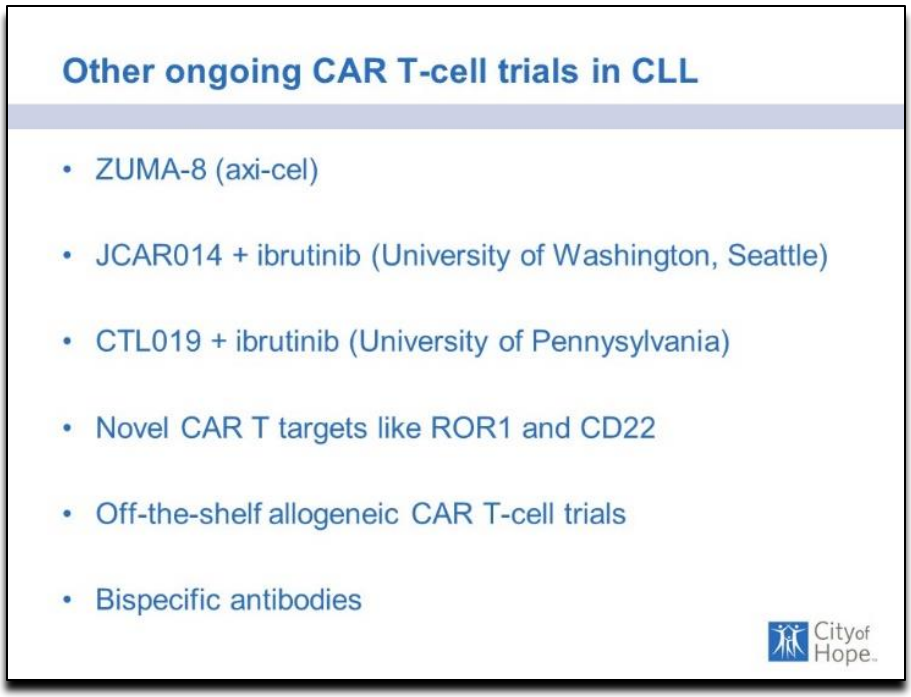
We still have some ways to go. We have enrolled in the phase 2 portion a lot more patients. I will skip this just because it was very preliminary data, but what I will say is that patients who had undetectable minimal residual disease after the 65%, 70% patients who had undetectable MRD after CAR T cells on this trial were the ones who seem to have the longest progression-free survival without even meeting the 50% PFS yet. So, it's very encouraging for those patients, and it is encouraging that the majority of patients had a very rapid and deep response with undetectable MRD. So, the phase 2 portion I was talking about has now completed enrollment of 100 or so patients, and the combination trial with ibrutinib, which is this one that I just put up on the screen. And that cohort is still enrolling, so we have space for more patients who would meet criteria for liso-cel plus ibrutinib, which is also showing very good responses. And again I just showed the side effects.



Patient Responses over Time at 10-Month Follow-Up

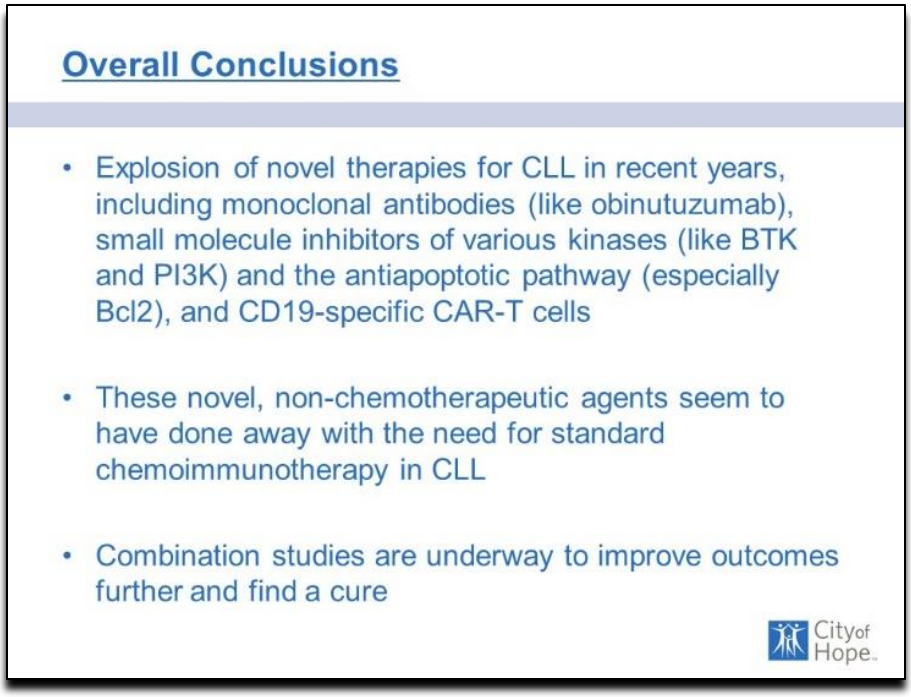
Only one patient in this group had grade 3 cytokine release syndrome or hyperinflation, or only 3% had grade 3 neurotoxicity. There were no grade 4 or severe inflammation or neurotoxicity-type side effects, and this is just showing some more side effects of anemia and whatnot. And the reason why we see anemia and platelets at low counts is because everybody before getting their CAR T cells get 3 days of fludarabine and cyclophosphamide chemo, just 3 days. One time it is not repeated monthly or anything like that, and the reason is because the CAR T cells in order to go in and be successful to expanding and growing in number in the patient's body they need to have certain competitive T cells out of the way and cytokine. And fludarabine and cyclophosphamide does that very well, so that is why everybody needs to get 3 days of FC.

With the combination of ibrutinib and liso-cel you can see that in all patients, 63% were already in complete remission and 89% patients already out of the 19 had undetectable minimal residual disease. So, it's very, very promising. And what we need to see is over time they have been followed for about 15 months out the first few patients. So, we certainly need longer-term data and longer follow-ups but less with just transformation in the combination. Thus far, one had Richter transformation. So, maybe that will be an advantage as well.



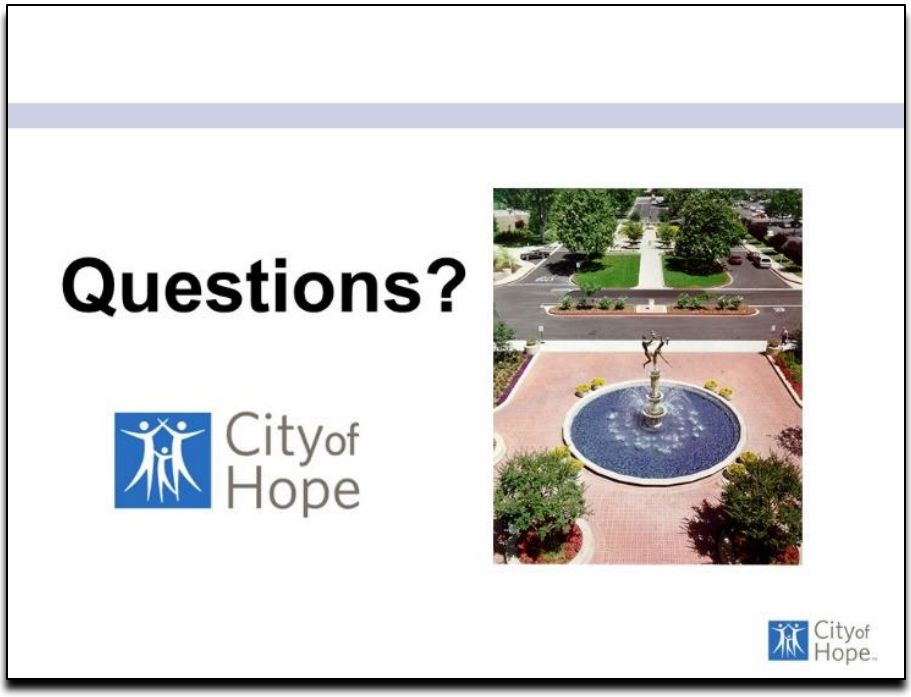
Other Ongoing CAR T-cell Trials in CLL

There are many CAR T cell trials ongoing in the country with different combinations, mostly with ibrutinib, but also different targets other than CD19. ROR1, CD22 and other specific antibodies, which are not CAR T cells, but many other technological advances in the field of CLL, which is why I am hopeful that we can honestly say that there is a cure available even though currently, as of today, I can't say that.



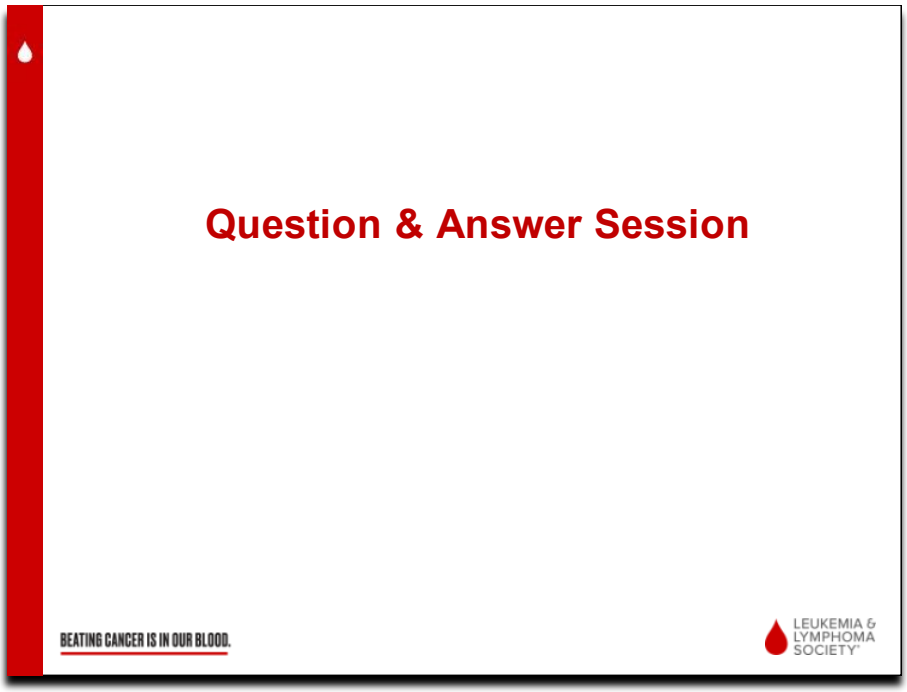
Overall Conclusions

So, overall conclusions. There is an explosion of novel therapies we just saw and combination treatments are now being tried. CAR T cells are being tried, and we are trying to find the cure.



Questions?

And with that, I will hand over back to Lizette. Thank you for your attention.



Question & Answer Session

Ms. Lizette Figueroa-Rivera
Thank you so much, Dr. Siddiqi, for your very informative presentation. It is now time for the question-and-answer portion of our program. So, for everyone's benefit, please keep your questions general in nature without many personal details.

And we will take the first question from our web participants. Dr. Doon is asking what is the current data regarding patients and the COVID vaccination?

Tanya Siddiqi, MD
So, very relevant question. I, as a group, as the CLL community of physicians we have been encouraging our patients to get the COVID vaccine. But I do caution my patients that patients with B cell lymphomas, B lymphocytes, lymphomas of any sort—especially CLL—they just do not have a normal immune system. So, even if your CLL is currently in remission, even if you are not on any treatment, your B cells inherently will not work 100%. And because they can't work 100% they will never have a full response to any vaccine like the general population will.

So, I got the Pfizer vaccine myself, second dose was early January. I feel like I got a 95% response like the data suggest. I know that CLL patients will get a lower response, but I tell patients that any response is better than zero, so any protection is better than zero. But we know that the amount of response will be less if you are especially on things like Rituxan® or even ibrutinib-type medications. But again, even if it's a 20% response it's better than zero. So, any protection might help prevent very severe COVID infections that end people up in the hospital, and so that would be a great advantage.

We don't have a good way of checking immunity development or immune response development, commercially that's available. We are trying to do a study now with the University of Washington where we are collecting blood samples at different time points from CLL patients who have had the COVID shots and sending them to the University of Washington so they can check in their lab on a research basis whether any antibodies have been developed against specifically the vaccine. We don't have results yet. We just started the study, and so we won't know until the end of the year probably. But I think that that will be very welcome information for everybody.

Ms. Lizette Figueroa-Rivera
Thank you, doctor. And also, on LLS.org/coronavirus, we continue to provide information and update this site with vaccine information. Can we please take the next question from the telephone audience, please?

Operator
Our question comes from Martha calling from Texas. Please go ahead.

Martha
Yes. My immune system has crashed twice in the past, and I have CLL. I want to know, I have been told to take the Johnson & Johnson vaccine only, and I am treating within IVIG octagam, and I'm going to do the vaccine hopefully next week after treatment on Friday the 9th. Can you tell me, I'm so afraid it's going to crash again. Mercury poisoning and other toxicities created the others.

Tanya Siddiqi, MD
Right. So, as far as I am aware, any of these vaccines will be good or okay for CLL patients. I've certainly had most of my patients get the Moderna, Pfizer vaccines thus far because J&J is just newer. I think that there is no risk of the vaccine causing or interfering with your CLL. That I am not worried about at all. There's just no way they can sort of interact.

I think the reverse or the opposite is true, which is what I said that people with CLL just won't mount a full response to the vaccine, so you may not get full protection. But again, you may get some protection. And that might be a good thing to actually protect you against a severe COVID infection down the line. There's no sort of reason why the vaccine would mess with your immune system or

make it worse. It just doesn't work that way. The flip is true, where your immune system won't allow the vaccine to work very well because the immune system is inherently weak, as you suggested. So, I think you should be fine.

Ms. Lizette Figueroa-Rivera
Thank you. And our next question is coming from the web audience. Gary is asking when is treatment not considered chemo?

Tanya Siddiqi, MD
So, I know that everybody says you're scheduled for your chemo, and you are here for chemo when people even come in for, let's say, rituximab- or obinutuzumab-type of infusions. Antibody infusions. It is just an easier term to say chemo pills rather than targeted therapy pills, but chemo strictly when I say none of these treatments are chemo that means they are not like fludarabine or cyclophosphamide or bendamustine. Like in the chemicals, since the way that these medicines are made they are not chemo that is going to go in and attack all parts of your body—like a bomb going off in your body—rather than targeting very specific parts of the B-cells system. So, anytime you talk about ibrutinib and venetoclax, rituximab or obinutuzumab to me, these are all nonchemo targeted therapy agents.

Ms. Lizette Figueroa-Rivera
Thank you, doctor, and we will take the next question from the telephone audience, please.

Operator
Our next question comes from Cynthia calling from New York. Please state your question.

Cynthia
Yes, I just wanted to verify CLL for around 20 years with no treatment, and I would very much like to keep it that way. And going back to what you said before about the vaccine, I am very concerned about if indeed the vaccine will affect my present condition, which is very good.

Tanya Siddiqi, MD
Right, bottom line, the vaccine works. So any vaccine, including COVID vaccines, they work by making your body think that there is an infection that it needs to attack. And so, the B cells get revved up to kind of make immunity or antibodies against that particular infection—in this case, COVID-19. The white count potentially may go up temporarily, but it then goes back down, much like if you get a cold or flu or something. The white count might go up, and your lymph nodes might enlarge, but then everything settles back down once you are back to normal.

I have had a lot of patients get the COVID vaccine already. Some of them have their white count go up and then come down, but the majority didn't. So, it's not going to affect the CLL necessarily. Do you know what I mean? It's not really going to affect the growth of your CLL or anything. If anything, there may be a transient effect on your count.

Ms. Lizette Figueroa-Rivera
Thank you. And the next question is about 17P deletion. Actually, we have two questions about the 17P deletion. Andrea asks if there's anything to help with this deletion, and then we have a question from Julian. And Julian is asking if you are initially diagnosed with CLL, and you don't have the 17 deletions is it possible that this deletion can occur later in the disease progression?

Tanya Siddiqi, MD
Right, yes. So, the answer to the second question is yes. And that is why we always recommend that anytime a new treatment is being started, or there is disease progressing in a different pattern like faster, or a treatment is being changed like, let's say, one is going from ibrutinib to venetoclax because something is not working right and it's been more than 6 months since the last FISH test or the last genetics were checked, I definitely recommend rechecking the cytogenetics or the FISH study to see

whether there has been any acquired new changes to the CLL genetics, including acquiring chromosome 17 abnormality as time goes on.

We used to see that a lot more with chemo. Like, chemo would sometimes affect the cells in a way that they would then acquire new genetic changes when this disease came back, but we are still learning about the novel agents. So, hopefully, less evolution to chromosome 17 but CLL itself can as it grows it can acquire new genetic changes so it can happen.

The first question had to do with whether we can do anything about the 17P deletion. The answer is no. Like, we can't fix it or change it, but the treatment that we have now, like the novel treatments, do help manage and put the disease even in remission nicely for some period of time. So, but when the disease comes back theoretically, you will still have the 17P deletion. So, we can't really make it go away for good technically, but our new treatments work much better against 17P deletion than the old chemos ever did.

Ms. Lizette Figueroa-Rivera
Thank you. And the next question is coming from Joel. Joel is asking, “Is there ever a time or situation that you stop taking the targeted medication and go back to watch and wait?”

Tanya Siddiqi, MD
Yes. That is the goal for all of us to that is why we are doing these combination trials because we want to find a combination where you can actually stop taking the targeted therapy for a while and maybe go 3, 4, 5 years without, you know, needing treatment, get a break, do watch and wait, watch the disease slowly come back. And then when it needs treatment again then you go on to treatment again.

So, those are some of the studies we are doing now, and there is some data to suggest, like, venetoclax in the front-line setting you can combine with 6 months of obinutuzumab. And then venetoclax can stop at 1 year or in the relapse setting venetoclax can stop at 2 years if you combine it with rituximab for 6 months. So, there are different things that can be done.

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

Operator
Our next question comes from Patricia calling from Tennessee. Please state your question.

Patricia
Hello. Referring to the immune system, does IVIG benefit the immune system? Is it worth getting IV infusions monthly and how is it possible the lady can have 20 years of no treatment?

Tanya Siddiqi, MD
So, there are some people who have very good risk features of their CLL, like chromosome 13 abnormality, mutated IgVH, like, just very good risk disease features where the white count just stays stuck in the teens or the 20s and never really goes up. And people can go a long time—10, 15, 20 years even—if it goes up slowly to 100, 200. It goes up over 10 years to 100, like, that is something we can just watch. So, it's not saying that her disease is not visible. It's just that she never needed treatment because it really wasn't bothering her and I think that sometimes that can happen, that is not unheard of.

As far as your first question was concerned about the IVIG, we definitely recommend it to people who have recurrent or serious infections. And you may or may not need to do it every month for the rest of your life. But if you have had some serious, like, hospitalizations, sepsis events, whatever because your immune system is weak, then IVIG really helps boost that up temporarily. That’s why you need to do it repeatedly. So, yes, it's a very good way to protect yourself from a severe life-threatening infection.

Ms. Lizette Figueroa-Rivera
Thank you. And the next question is about side effect management. Nicole asked, “Do you have any advice for managing side effects of fatigue and diarrhea from daily venetoclax?”

Tanya Siddiqi, MD
I have cut the dose from 400 to 300 successfully in some patients. Diarrhea kind of depends how bad it is, but of course, Imodium. Some people take Imodium or Lomotil regularly. That can sort of help. Fatigue, unfortunately, we don't have.... I mean, if the dose reduction helps, that's great. Otherwise, think about a treatment break if the disease is sort of in a very good place—don't have anything specific for the fatigue. They may want to check thyroid and B12 and make sure not deficient in iron and things like that, which can also cause a lot of fatigue, and those are easy to replace.

Ms. Lizette Figueroa-Rivera
Thank you. And Brad is also asking, “Are there ways to manage night sweats?”

Tanya Siddiqi, MD
Just the treatment, treatment of CLL should manage the night sweats, I think. You make the CLL go away, the night sweats generally go away.

Ms. Lizette Figueroa-Rivera
Sure. And then we have Marsha asking about cramping and muscle spasms.

Tanya Siddiqi, MD
With ibrutinib specifically?

Ms. Lizette Figueroa-Rivera
Yes, Imbruvica®, yes.

Tanya Siddiqi, MD
Yeah, unfortunately, that is a known side effect. I have had success reducing the dose a little bit, just a smidge down by one level. I have had some success with patients taking magnesium for the cramping. Keep the extremities warm, stretching, things like that. And definitely hydrating very well, keep the water levels up. But sometimes, they just need to reduce the dose of the ibrutinib.

Ms. Lizette Figueroa-Rivera
Thank you. We will take the next question from the telephone audience.

Operator
Our next question comes from Gary calling from Pennsylvania. Please state your question.

Gary
Hi. I am asking for my husband, Gary. He has been on ibrutinib, and I don't know the correct name Calquence®, and he has experienced hematomas’ side effects. Is that common?

Tanya Siddiqi, MD
It's not common, but it is a known side effect. And that is a very serious side effect because that indicates bleeding under the skin are in the muscle and collections of blood that are not just bruises but actual collections of blood under the skin. And if it's in the muscle it's very painful. Is he also on aspirin or some other blood thinner? Typically that is when I have seen it, is somebody is also on a blood thinner for something else. Then the combination becomes a little too much. One thing that can be done I have done successfully is reduce the dose of the ibrutinib or the Calquence®, but it can be changed to venetoclax. That would be even safer because venetoclax does not cause bleeding as a side effect.

Ms. Lizette Figueroa-Rivera
Thank you. And Claudia is asking if you think allogeneic CAR T will play a role for CLL to allow easier access to CAR T treatments.

Tanya Siddiqi, MD
That would be awesome. I think the studies are just underway for allogeneic CAR T cells in everybody in all lymphomas. So, allogeneic means that it's not the patient's own T cells that we then have to manufacture, but they are really just off the shelf. There were healthy donors who donated T cells. And the T cells are then manufactured to target, let's say, CD19 or whatever the target is on the B-cell lymphoma. And then so you just have these T cells sitting around that you can grab and give to a patient without wasting time manufacturing, and so those side effects are still being teased out.

There is a question of whether or not people can get rejection type of side effects because they are not a patient's own T cells, but I don't think I've seen that yet in the early phase trials. But again we are waiting on more data. But that would certainly be much more convenient if we could make it happen, yup.

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

Operator
Our next question comes from Mayer calling from Pennsylvania. Please state your question.

Mayer
Yes, hello. I have been on ibrutinib for 5 years, 5 and a half years. My numbers are absolutely normal and have been for the 5 years. Is there any chance of getting off ibrutinib? I don't have any side effects from it at all.

Tanya Siddiqi, MD
That's great. So, I can tell you that I have had people come off of it 3, 4, 5 years down the line for some kind of side effect or the other, or they got an infection, or they had to go to surgery and had to stop ibrutinib for a while and never restarted it. It is, unfortunately, the CLL in those cases did come back within a year, 9 months, 12 months, something like that, and we feel like it's not worth stopping the ibrutinib for that short a period of time if you are otherwise tolerating it well.

The only time where I would say you may be better off and be able to stay off of the ibrutinib longer is if they tested your minimal residual disease test and that was undetectable. Then you may go even longer without needing treatment again, but typically ibrutinib by itself may not give you that undetectable MRD. So, yes, if you need to take a break. But just know that you will probably need treatment again within a year, and whether that is worth it or not, I don't know.

Ms. Lizette Figueroa-Rivera
Thank you for the questions, and our next question comes from Christine. Christine is asking, “What do you know about the use of supplements or diets that can help CLL patients?”

Tanya Siddiqi, MD
I don't have a robust knowledge of that. I do like to tell patients to stick to a balanced healthy diet and not do any extreme dieting or cutting out something entirely or starting something entirely and just sticking with that. So, it is sort of a balanced program is a good program. And secondly, exercising is good for the immune system. So, a reasonable amount of exercise each week is actually a very good thing for the immune system and to keep your body strong for any treatments we throw at it.

And then lastly, as far as supplements are concerned, you know, vitamins and all are okay to a reasonable extent, but herbal stuff doesn't go well with some of these novel targeted therapies. So, if you were going to be on ibrutinib, Calquence®, venetoclax those types of novel treatments, we would

not want you to be on any herbal medications because they interact badly together and may cause more toxicity or take away the benefits and may even cause liver issues and whatnot. So, just be aware of that. Make sure your doctor knows what you are taking, even the nonprescription stuff, when you start any of these novel treatments because they do interact badly sometimes.

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

Operator
Our next question comes from Judith calling from New Jersey. Please state your question.

Judith
Yes. I was just wondering if there is a problem with maybe going to another hospital just to get a second opinion when you have CLL?

Tanya Siddiqi, MD
That is a very good idea. In fact, we generally recommend; or a lot of patient groups that I know CLL society, the LLS, etc. I think people recommend getting a second opinion from a CLL-specific expert because, as you see, there's a lot of data—a lot of new stuff that's out there that maybe the community oncologist who also treats, you know, breast cancer, colon cancer, other things may not keep up with. And I think for your own health and options—treatment options—it's a good idea to get an opinion from a CLL expert at a big center near you. They don't have to be your primary oncologist but I think that if they can advise your primary oncologist on treatment options. I think that would be very good for you as a patient.

Ms. Lizette Figueroa-Rivera
Yes, thank you. And yes, LLS does recommend second opinions. And as Dr. Siddiqi mentioned, many of your doctors will also assist you in getting that second opinion. Next question. Dr. Siddiqi, Christine is asking, “Does erythropoietin cause the CLL to advance more quickly? I read that Procrit® (epoetin alfa) can make tumors grow faster.

Tanya Siddiqi, MD
No, it doesn't because the pathway is totally separate. Erythropoietin helps us make more red cells. Erythropoietin comes from the kidney, and it affects the bone marrow in helping it make more red cells. There have been some adverse reactions in patients with cancers, more so having to do with blood clots and things like that. So, I don't think you know if somebody has, say, kidney failure and they are on dialysis, they will normally get erythropoietin. Otherwise, they become too anemic. And that is fine, but I don't think it affects CLL directly to be honest.

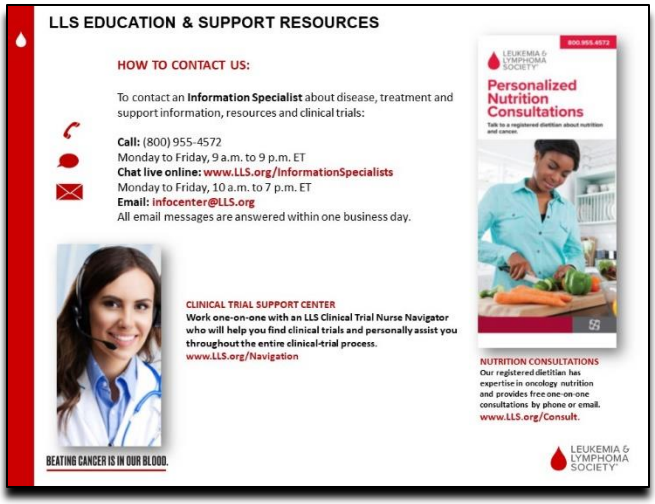
Ms. Lizette Figueroa-Rivera
Thank you. And our next question. Michael is asking, “Does the likelihood of required treatment increase as the patient ages? I am 70, and I haven't needed treatment for about 10 years. Just curious if I can expect that will become necessary because of age?”

Tanya Siddiqi, MD
No, no. I think it's the biology of the disease itself and the genetics and things like that that dictate how fast the disease will grow. I don't think age necessarily will be the only thing that plays a role. So, hopefully—you never need treatment. That will be great.

Ms. Lizette Figueroa-Rivera
Yes. And our last question today. Cindy is asking, “I understand there are different types of CLL. Should my oncologist have tested for the specific types at diagnosis?”

Tanya Siddiqi, MD
So, the types have to do, I think, with the genetics, which is what we were talking about. The FISH studies, the IGHV mutation, just to name a couple, when it comes to big centers, people come to me for an opinion. I will do all of that because then I can prognosticate their CLL better. I can tell them, look, you have chromosome 13 abnormality mutated IGHV. I think your disease will not move very fast. You may not need treatment for a long, long time if ever. Or you have chromosome 17 abnormality or unmutated IGHV, and so you may need treatment within the next 2, 3 years, and we definitely should avoid chemo.

So, it just makes the conversation a little bit more in-depth, but it doesn't tell me that you need treatment now. So, if they didn't do it at diagnosis that's fine, as long as they diagnosed the CLL properly. You should definitely get those genetics test done before any treatment is initiated so that you know what the original CLL looked like before treatment. And that I think would be more important.



LLS Education & Support Resources

Ms. Lizette Figueroa-Rivera
Well, thank you for your question, which was our final question today, and a special thank you to Dr. Siddiqi for sharing your expertise with us and for your continued dedication to our blood cancer patients. Now, if you were not able....

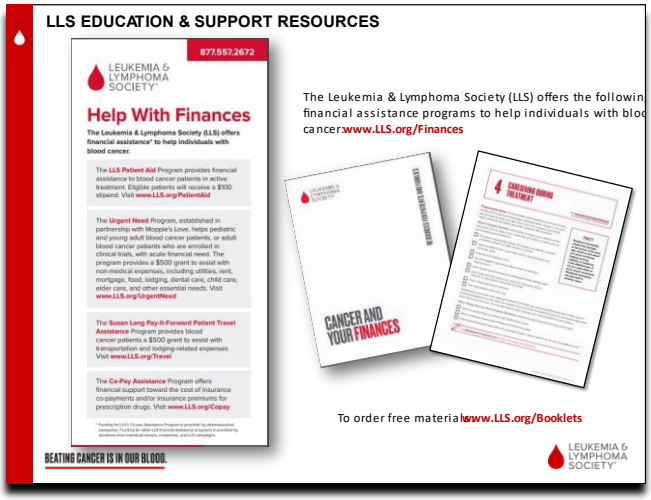
Tanya Siddiqi, MD
Thank you for having me.

LLS Education & Support Resources

Ms. Lizette Figueroa-Rivera
Of course. Thank you, especially during this time when we are still, dealing with the COVID-19 pandemic, so we appreciate you. Thank you.

If we were not able to get to your question today, you can contact an Information Specialist at The Leukemia & Lymphoma Society, at 1-800-955-4572, from 9 AM to 9 PM Eastern Time, or you can reach us by email at www.LLS.org/ContactUs. I know Al was asking about finding clinical trials and our Information Specialists may assist you as well as provide information about our Clinical Trial Support Center where Nurse Navigators provide patients with personalized clinical trial searches.

The LLS co-pay program has funding for CLL patients. Please visit LLS.org/Copay for more information. Now our co-pay program not only covers medical insurance premiums, treatment-related co-pays, and prescription medication related to treatment, but it now also covers co-pays for select labs, scans, and tests. Again, LLS.org/Copay visit or call toll-free at 877-557-2672.



LLS Education & Support Resource

Again we would like to acknowledge and thank Genentech and Biogen, Pharmacyclics, an AbbVie Company, and Janssen Biotech for their support.

Thank You

Again, Dr. Siddiqi, thank you for volunteering your time with us today, and on behalf of The Leukemia & Lymphoma Society, thank you all for joining us for this program. Please let us know what you need from us during this time and take good care.