Welcome & Introductions: Update on Chronic Lymphocytic Leukemia

Ms. Lizette Figueroa-Rivera:
Hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. We have over 1,000 people participating from across the United States as well as other countries, including Canada, Germany, India, Mexico, the Philippines, and Trinidad. Special thanks to Dr. Jan A. Burger for sharing his time and expertise with us today.

Before we begin, our President and CEO, Louis DeGennaro, will make some remarks.

Dr. Louis DeGennaro:
I'm Dr. Louis DeGennaro, President and CEO of The Leukemia & Lymphoma Society. I'd like to welcome all of the patients, caregivers, and healthcare professionals attending the program today.

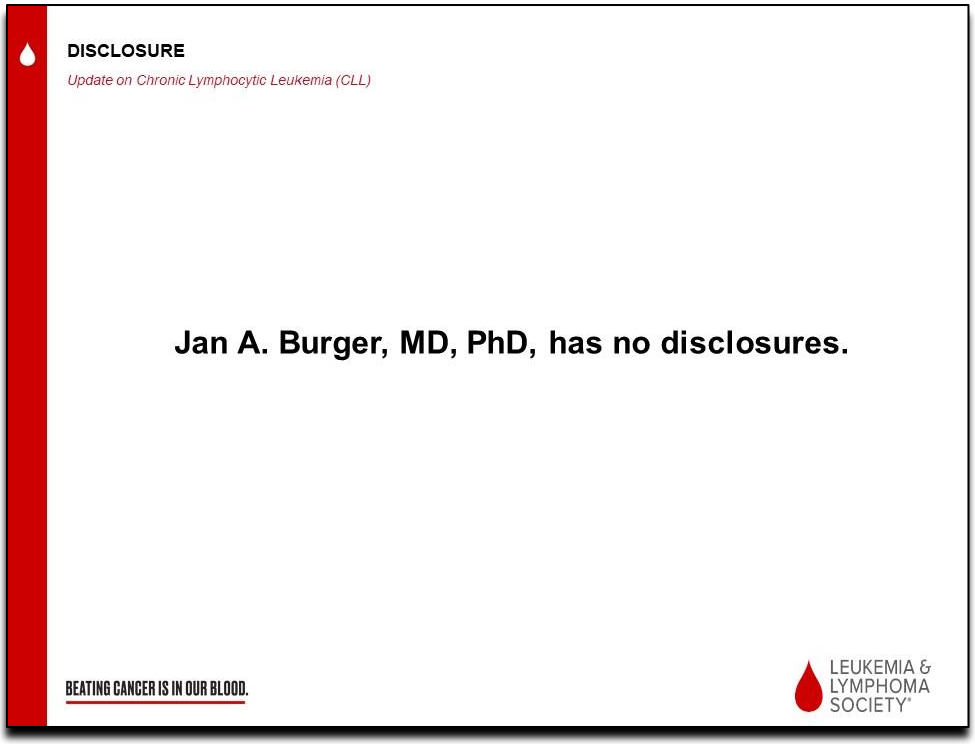
At The Leukemia & Lymphoma Society, our vision is a world without blood cancers. Since we started in 1949, LLS has invested more than $1.2 billion dollars in breakthrough research to advance lifesaving treatments and cures. We've played a pioneering role in funding many of today's most promising advances, including targeted therapies and immunotherapies that have led to increased survival rates and improved the quality of life for many blood cancer patients.

Though LLS is known for funding ground-breaking research, we do so much more. As this program demonstrates, we are the leading source of free blood cancer information, education, and support for patients, survivors, caregivers, families, and healthcare professionals. We also support blood cancer patients in their local communities through our chapters across the country, and we advocate at the state and federal level for policies to ensure that patients have access to quality, affordable, and coordinated care.

We're committed to working tirelessly toward our mission every single day. Today, you'll have the opportunity to learn from esteemed key opinion leaders. They each have volunteered their time, and we appreciate their dedication to supporting our mission, their commitment to caring for patients living with blood cancers. Thank you for joining us.

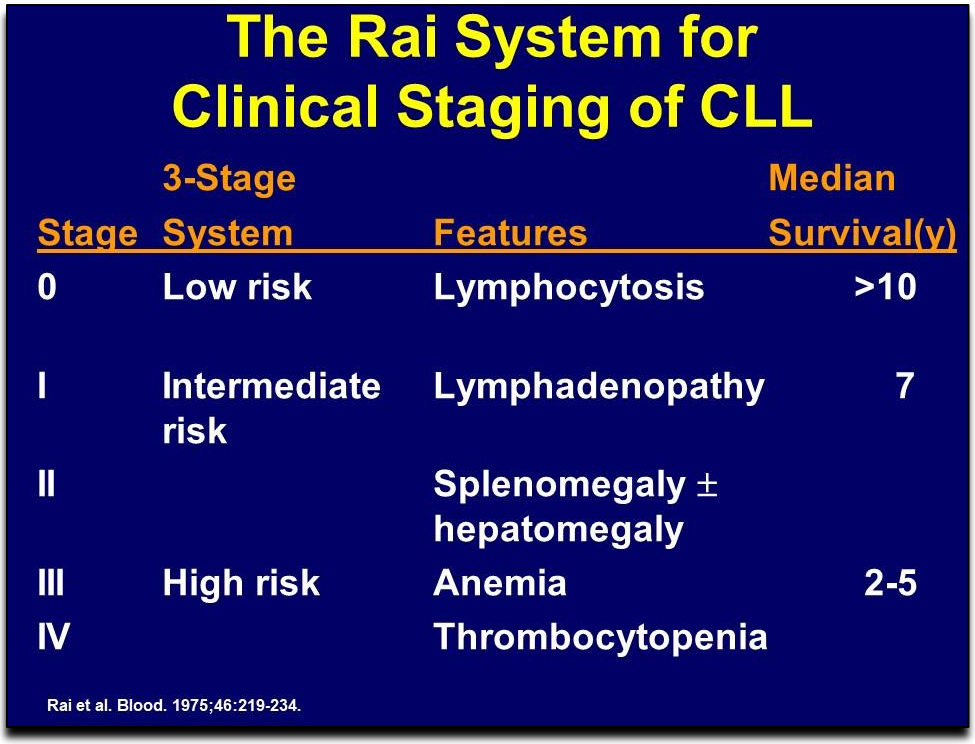
Ms. Lizette Figueroa-Rivera:
Thank you. We would like to acknowledge and thank AbbVie, Genentech and Biogen; and Janssen and Pharmacyclics, an AbbVie company, for support of this program.

I'm now pleased to introduce Dr. Jan A. Burger, Professor, Tenured, Department of Leukemia, Division of Cancer Medicine at the University of Texas MD Anderson Cancer Center in Houston, Texas. On behalf of The Leukemia & Lymphoma Society, thank you for volunteering your time and expertise with us, Dr. Burger. I'm now privileged to turn the program over to you.



Disclosure Slide

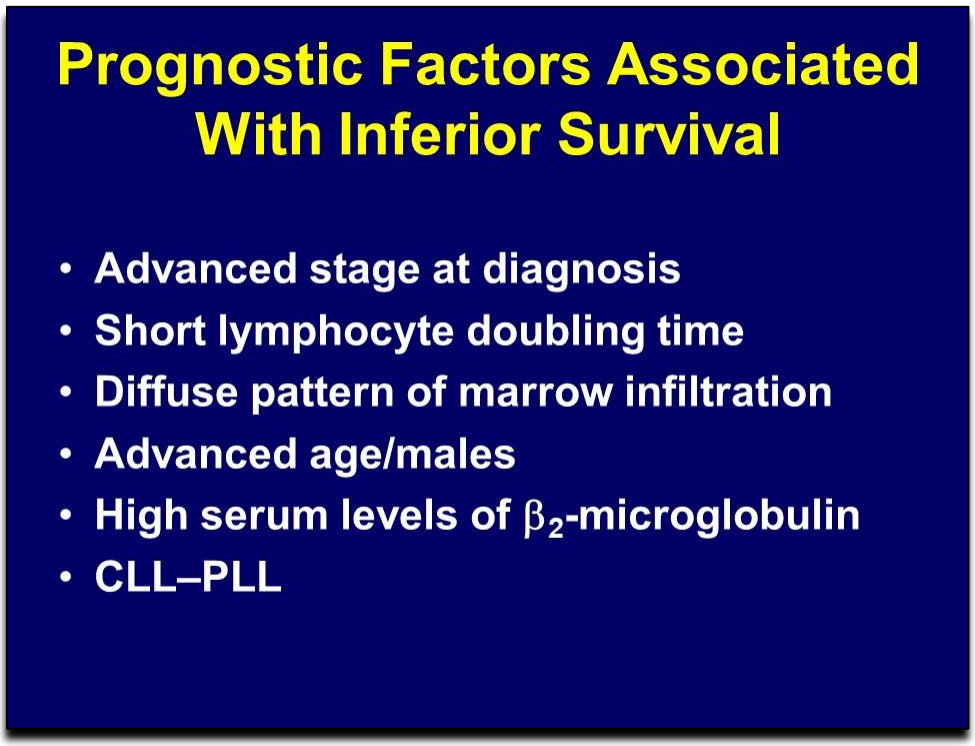
Jan A. Burger, MD, PhD:
Thank you very much, it is very exciting times to discuss CLL and CLL therapy because we've experienced so many changes in CLL therapy over the last 10 years with the addition of new targeted treatments. But, the way I've structured this program is to first give you an overview over the disease, some background about the disease staging and risk factors before talking about the different treatment options and how we approach individualized therapy in CLL these days.



The Rai System for Clinical Staging of CLL

So, as a starting point, I think it is good to bring back a slide about the staging system. That's one of the common questions in the first visits when a newly diagnosed CLL patient comes to see us, which stage. Our patients--many patients are in early stages of the disease. And here, on this slide, you see how the staging system is constructed. We are still using that basically just to distinguish patients at early stages which don't need treatment versus those patients who have advanced stage, stage III and IV, according here to the right, classification where patients then develop anemia, thrombocytopenia in stage III and IV. And that's still kind of a rough guidance towards the question, does a patient need treatment or not?

What you see on the right-hand side is estimated survival. Those are historic numbers, and I think those are no longer accurate. The survival of patients these days, with the added treatment options, is likely to be much better. But, in an historic context, those at the times when we had mostly relied on chemotherapy—those were the survival for patients who had early versus later stages of the disease.



Prognostic Factors Associated With Inferior Survival

Now, in addition to the classical staging, the RAI staging that you looked at, there are additional prognostic markers, which help because most patients, when they come to see us, are early stage patients. And they want to know, what is the perspective for the next years, and is there any way we can tell our patients they are likely to need treatment, or they might have indolent disease for an extended period of time?

And some of the more clinical prognostic markers are listed here on this second slide. Which is--well, how does the patient present? Is the patient at an early stage? Then, that's good prognostic marker. Advanced stage at diagnosis indicates the patient will need to start treatments soon.

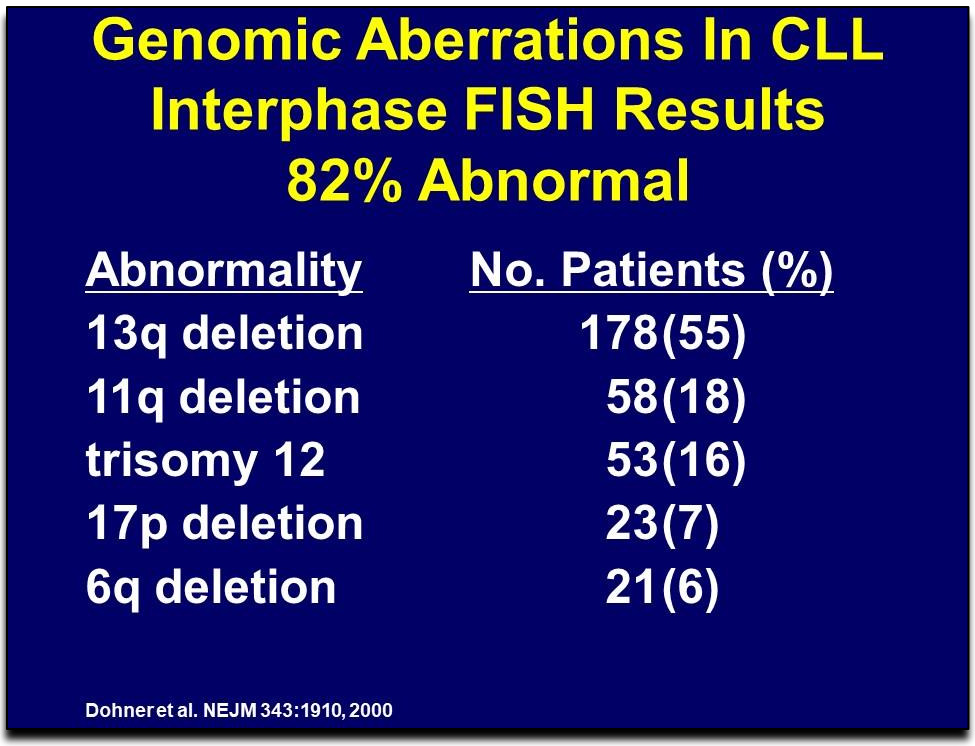
Another classical prognostic marker is the lymphocyte doubling time. And that's something I think patients can actively look at themselves, too. Is there short lymphocyte doubling time? Roughly, short lymphocyte doubling time would be doubling of the white blood cell count or lymphocyte count within 6 months or less. And if that's a trend—just one number usually is not sufficient to fulfill this. But, if that's a trend that continues over longer period of time, that's a sign the disease is active, and it will eventually require therapy.

Diffuse infiltration in the bone marrow—the bone marrow is probably less used these days because we have become very good in testing peripheral blood and that has, at this time, less of a role, in my opinion, to do bone marrow testing. In certain patients, it may still be necessary. But, we're not looking at this diffuse pattern of bone marrow infiltration as much anymore as we used to.

Then, historically male patients, older patients had somewhat poorer outcome than younger, female patients.

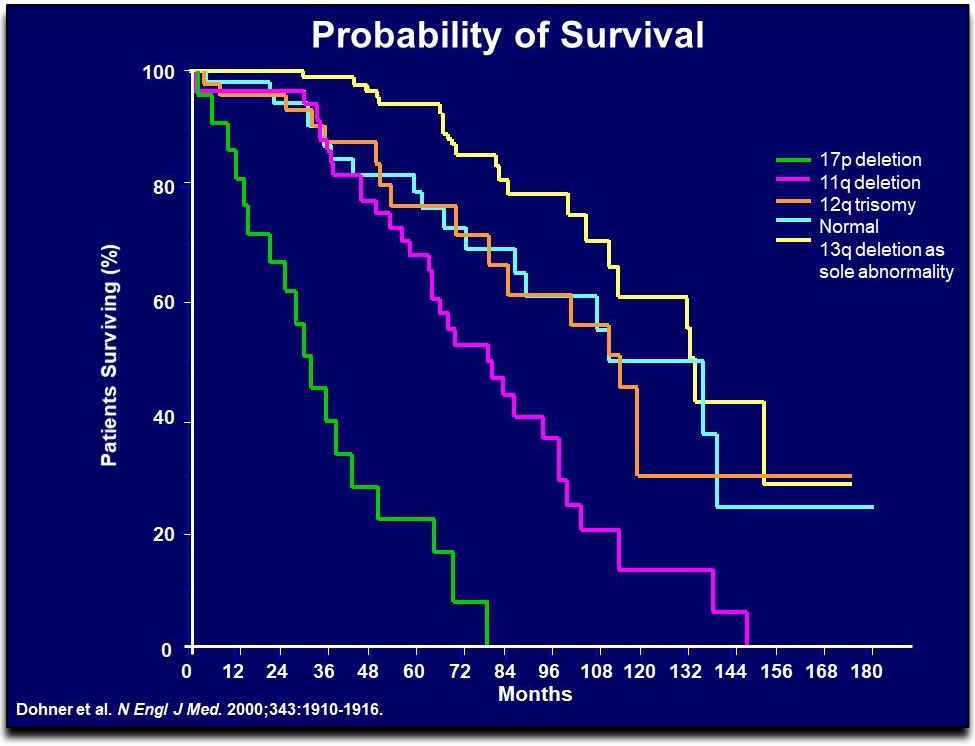
High beta$_2$-microglobulin is another classical marker to look at.

Also, the prolymphocyte count or PLL percentage—those are activated lymphocytes that, under the microscope, have characteristics of activated lymphocytes. If that fraction of prolymphocytes is high—greater than 30 or 40 percent—that's an indicator that the disease likely is more active and more likely to require therapy.



Genomic Aberrations In CLL Interphase FISH Results 82% Abnormal

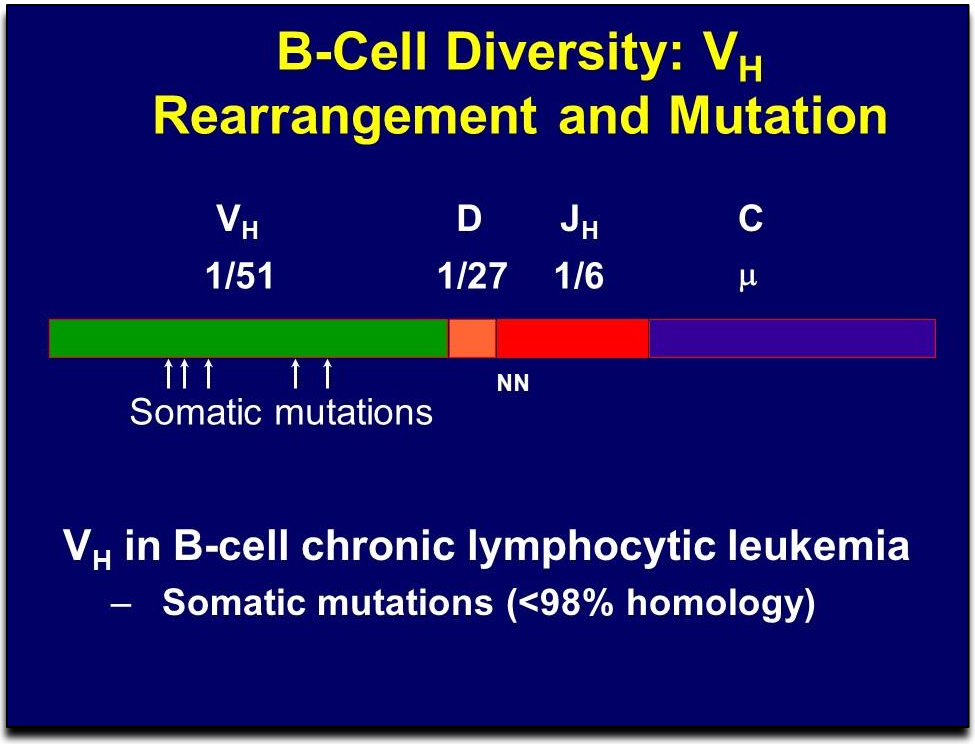
Besides those more clinical prognostic factors, we have additional laboratory testing, and one of the important prognostic markers that is used pretty much in routine practice throughout the US, but also around the world, is the cytogenetic testing. And the way that's done is by using fluorescent probes, which are called FISH probes. And with those, a typical CLL panel is listed here on the left-hand side, which is to detect these abnormalities in the CLL cells where certain chromosomes might have deletions or there might be an additional chromosome, like trisomy 12. And those abnormalities are quite frequent. About 80 percent of our patients will have one of these abnormalities detectable.



Probability of Survival

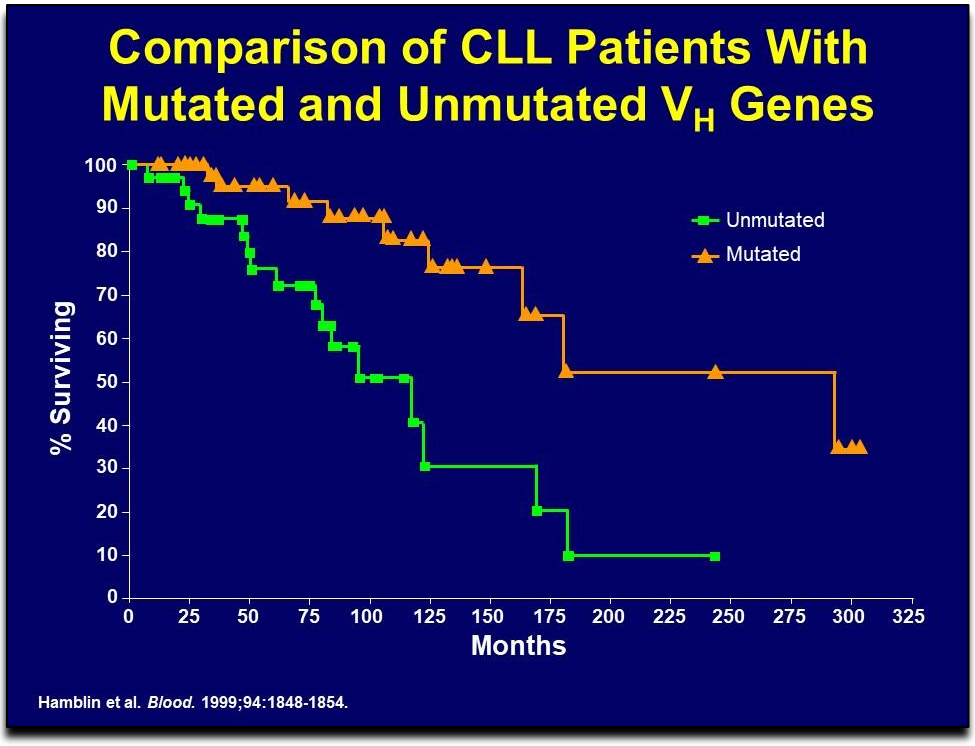
And how they impact the prognosis of CLL patients is shown here on the next slide, where you see, in green, the survival curves of the patients who have a 17p deletion, which is the highest risk feature. You see by this dropping in the curve early on that those patients don't have good survival outcome, and many of the patients will not survive and will die from their disease within a relatively short period of time. And on the other side of the spectrum, in the yellow curve, you see another abnormality, a 13q deletion, which is quite frequent, which is a good prognostic marker.

When you see these curves now, we have to again point out, and you see at the bottom, when this was published, it was in 2000. At that time, we had to rely on chemotherapy for treating these patients because the newer therapies were not yet in use and were not introduced. So, these are survival data based on chemotherapy, and it is well established that, for example, 17p-deleted patients are not responding well to chemotherapy, which explains the survival curves. If we would do, now, survival curves for patients in this new era of the new agents, about which we're going to talk about later, the expectation is that the survival, even for the high-risk patients, is much better. But those data have to be generated proactively, and these curves will eventually be revised and have to be published again over the next 5 to 10 years. And my prediction is that they will look much better for many patients. The survival expectation will be close or similar to age-matched healthy people.



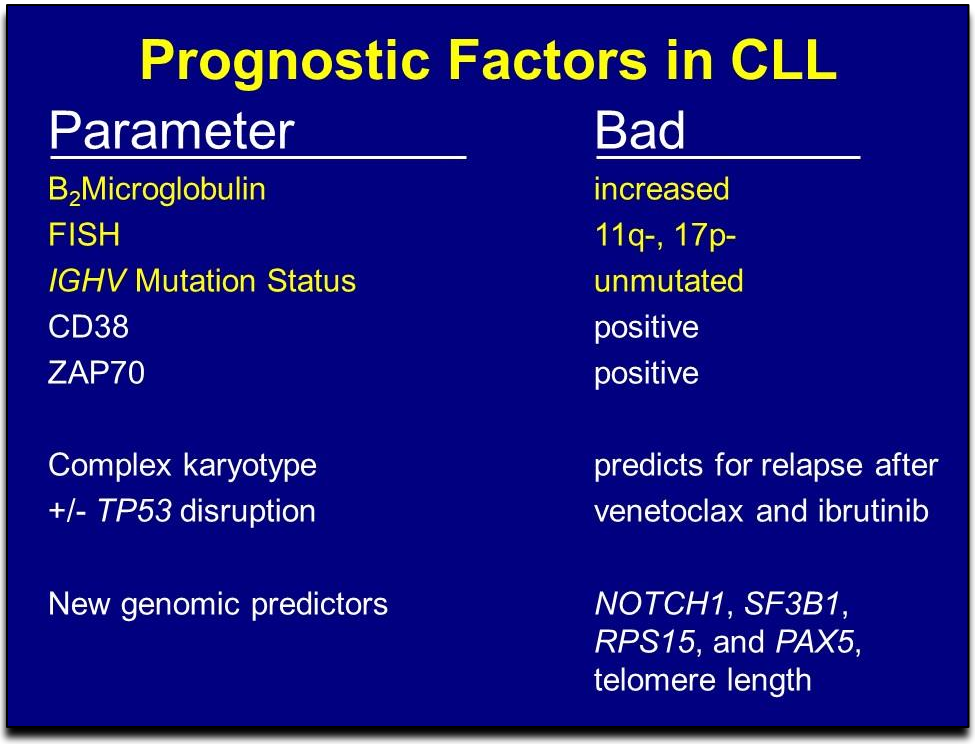
B-Cell Diversity: V_H Rearrangement and Mutation

Now, another prognostic marker that's been talked about a lot and that's in routine clinical use is what is called the mutational status. Is a patient mutated or unmutated? And about half of our patients are mutated or unmutated. And when you talk about that, it is not about these FISH cytogenetics that we just talked about. But it is about mutations in this green area that's shown here on the left-hand side and that is part of a structure that we call the B-cell receptor, which is an important structure on the leukemia cells, on the CLL cells. And some patients have introduced mutations in this area of the B-cell receptor, about half of those patients, and other patients have no mutations in this area whatsoever, and those are called unmutated.



Comparison of CLL Patients With Mutated and Unmutated V_H Genes

And presence or absence of mutations in the B-cell receptor then has important impact also on the prognosis of patients. And patients who are unmutated, who lack these mutations—they have more aggressive disease. They have less good outcome with chemotherapy. And, in contrast, what you see in orange—the survival of patients who are mutated, who have less aggressive and more indolent disease, is better. And, again, trying to make the point here—these are survival data based on use of chemotherapy as backbone for treatment of most of these patients, study which was published in 1999. From studies now with the new agents—and you will see some survival curves later from newer agents—we know that patients who are unmutated, who don't do well with chemotherapy, do much better with the new agents so that these curves also will change when they are updated in the years to come.



Prognostic Factors in CLL

Now, trying to summarize what we've discussed so far, what prognostic factors that will be discussed with patients at diagnosis or at time when treatment is necessary. The beta$_2$-microglobulin is something we are testing. It's not tested everywhere, and it's for clinical trial use; not commonly used. But it is a helpful marker, just across different B-cell malignancies and in CLL too, and they are the cut-off that we are using it for. And it can be helpful, just as a rough guidance, as the disease active is that a patient who's likely to need treatment if the beta$_2$-microglobulin is high. We think that's a helpful marker. But, the more established 2 markers are listed below. We discussed the FISH cytogenetics—11q deletion and especially 17p deletion would be the abnormalities that would indicate higher risk and would indicate those patients who are not good candidates to use chemotherapy.

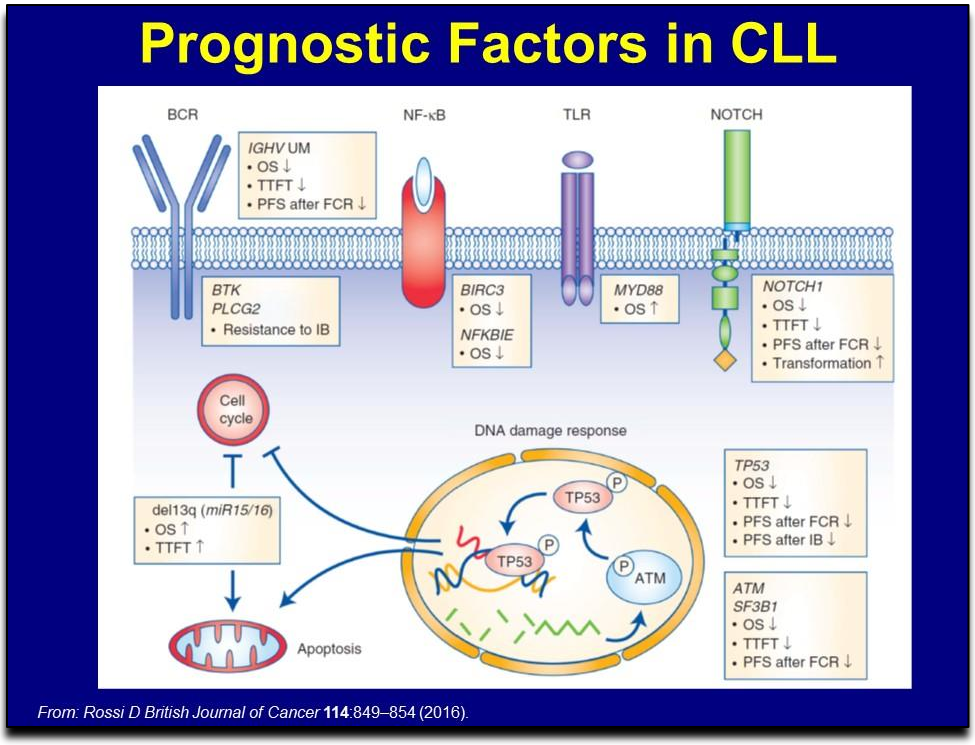
Then, mutational status—we just discussed that as well. And there the indicator for more aggressive disease would be the subset of patients who are unmutated. They don't do well with chemotherapy. They may be respond, but responses are shorter, and those patients would be, in my opinion, better suited for new agents.

Additional markers that have been discussed quite a bit and that may still be offered to many patients are CD38 and ZAP70. Those are two markers, which are tested in an assay that's in a way used as part of the diagnosis called flow cytometry, where antibodies are used to tag molecules on the leukemia cells and make them visible. And if they are present in majority and in a higher frequency of molecules on the leukemia cells, those patients are classified as C38 and ZAP70 positive. That is a negative in terms of prognosis. Those patients have more active disease. But, oftentimes, it coincides with a mutational status. And if somebody's unmutated, those patients are oftentimes then also positive for CD38 and ZAP70. So, those are sometime used as surrogate markers for unmutated status. So, for those patients where this test, for example, cannot be done.

Additional newer markers are listed at the bottom of this slide. There have been discussions. There have been publications about complex karyotype abnormalities in patients who respond but then progress on the novel agents on venetoclax [Venclexta®] and ibrutinib [Imbruvica®]. In that context, this can be helpful. But, it's not something that is offered routinely, and it needs specialized center to do this

kind of chromosome testing. But, it can be helpful in high risk patients who are receiving these new drugs to kind of estimate their risk for responding, but eventually may be progressing on these new agents.

And then, the last point made here are new genomic predictors. And now, with the new technology that's been developed and that's more widely available called next generation sequencing where all the genes can be very precisely analyzed in CLL patients—that's something that's sometimes available, not routinely, but more on a research basis. Additional abnormalities like NOTCH1 mutations have been discovered. But, for daily practice, these are not widely used and are not used for guidelines, or they are more, at this stage, more research tools or more helpful in specific smaller situations.

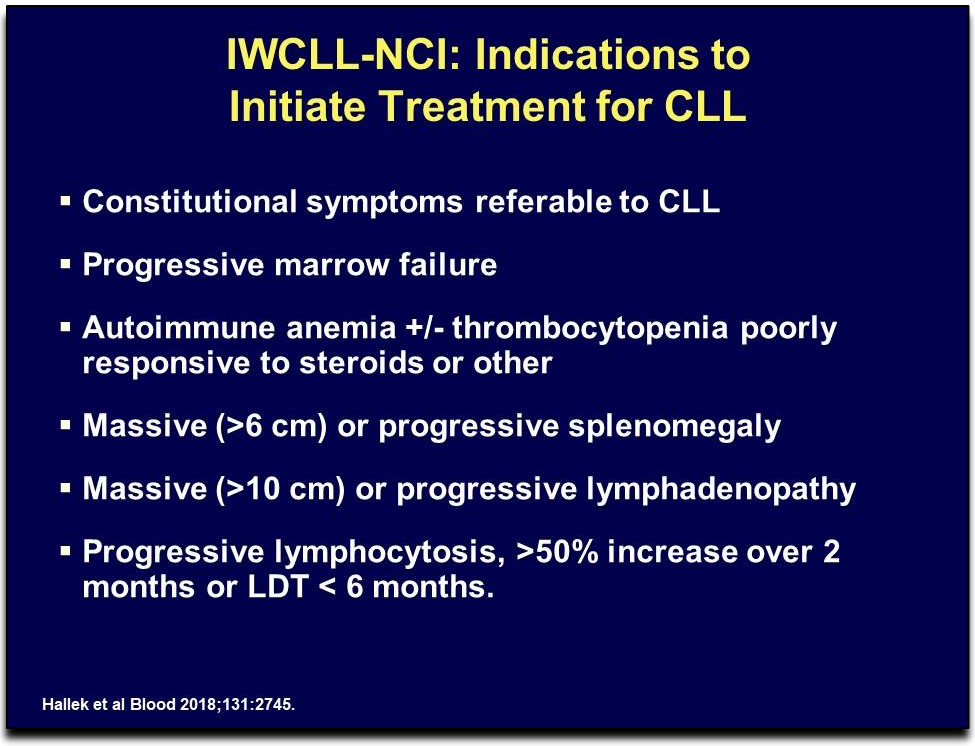


Prognostic Factors in CLL

This slide is putting the risk factors a bit in the context of cell biology, how we are thinking about the leukemia cells, in general, and how leukemia cell operates and how this links to the risk factors. What you can see here, at the top left, is a molecule on the cell surface called the B-cell receptor. And we talked about it earlier. If you have mutations, if you are mutated or unmutated, that has impact on the prognosis. Just as a reminder, unmutated patients were the ones who had more active disease, requiring therapy earlier. And that's linked here to this surface structure of the B-cell receptor. Downstream of the B-cell receptor are other molecules, which can be targets of the new age, like BTK, where ibrutinib is blocking this enzyme. And BTK and PLC gamma-2 are linked, enzymes linked to the B-cell receptor. And they can be mutated in patients who develop resistance to the drug ibrutinib, which we'll talk about later when we come to the clinical data.

Maybe just to highlight—what is the role? What is the importance of 17p deletion or TP53 mutation? Those are regions—TP53, on chromosome 17—which are necessary for DNA damage response. So, if a cell is stressed and is treated with chemotherapy, this molecule helps the cell to repair. And if you have defects, then this is not intact. And that, we think, helps to explain why 17p-deleted patients have inferior outcomes with chemotherapy-based treatment. And the same is true for

ATM, which is on the chromosome 11q. And that's what we pick up with this FISH test that looks for 11q deletion.



IWCLL-NCI: Indications to Initiate Treatment for CLL

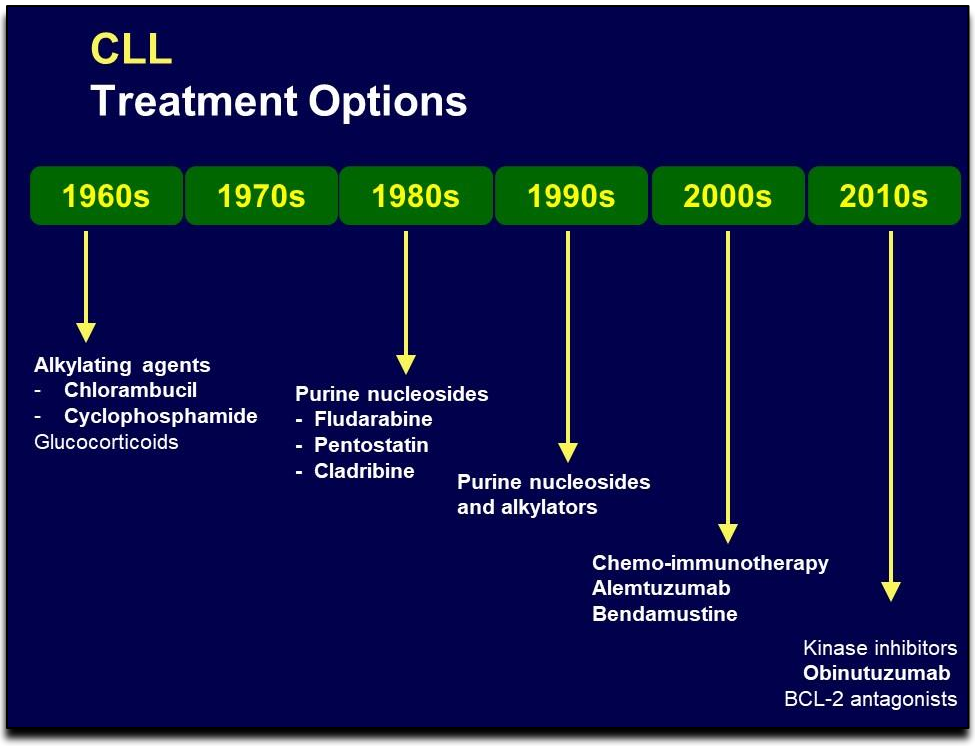
Now, we'll now move on to the question of CLL treatment after covering the risk factors. What is the point when we typically recommend treatment? That's summarized here on this slide, going by the--what we call IWCLL criteria. That's workshop and international consortium, which once in a while make guidelines to help us and update guidance when to, for example, start treatment. And that's summarized here on the slide. A patient who has symptoms from the CLL should be considered for treatments. And those constitutional symptoms oftentimes could be what we call B symptoms, which are night sweats or weight loss attributable to their active CLL. It could be fatigue which is progressing.

But, oftentimes—and most patients, I believe, will start treatment once you see patients moving to the advanced stages of the disease where they have progressive bone marrow failure. How do you know when someone has bone marrow failure? Basically, when the bad cells are crowding out the good cells—the red cells, and the platelets. And patients develop anemia and low platelet counts. When you see that trend, then it is time to focus in on starting treatment and choosing the right treatment for this particular patient.

But, there could be other situations, and those are important to keep in mind as well. If a patient is early stage CLL but develops autoimmune complications—and sometimes this can happen quite rapidly when patients suddenly develop rapidly progressive anemia or thrombocytopenia—always autoimmune cytopenias have to be suspected. And that can be diagnosed in somebody who's otherwise still early stage disease but develops autoimmune complications. Then, treatment needs to be initiated. It could first be steroids. But, oftentimes those patients eventually then need more definite CLL treatment.

How about big lymph nodes, big spleen? That's sometimes also reason to start treatment. But, oftentimes, that goes along with development of anemia and thrombocytopenia. Oftentimes that doesn't happen in isolation, and we talked about this. Short lymphocyte doubling time—if that's a trend that's

observed over an extended period of time, then would also tell us that the patient needs to start treatment.



CLL Treatment Options

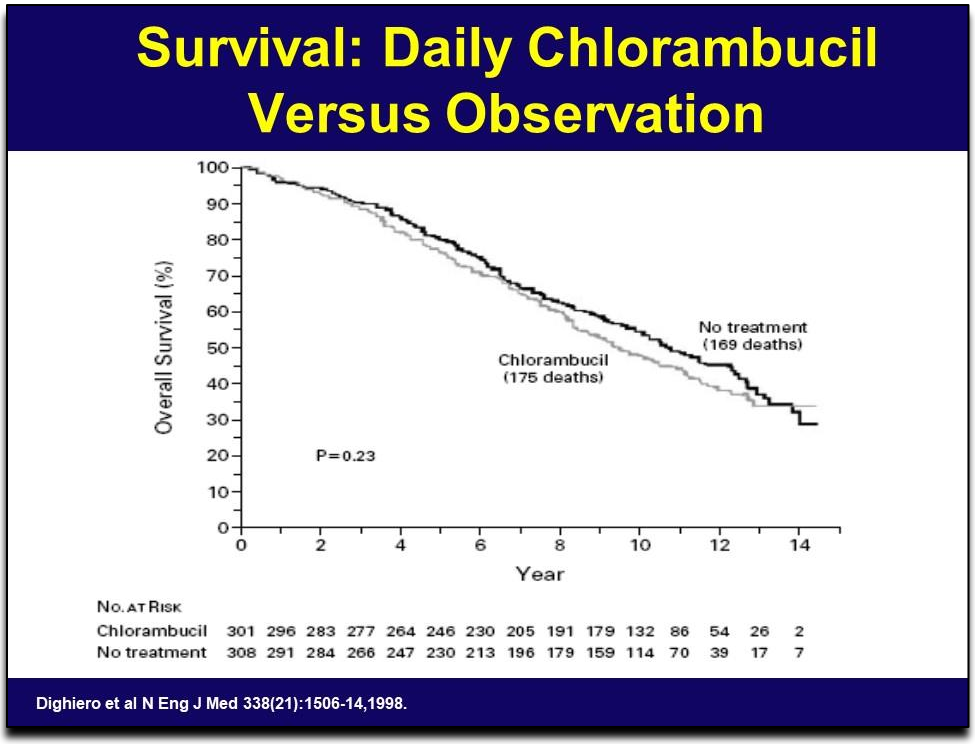
This is an overview, and I said in the beginning, times have become very exciting in the last 10 years because of the new agents. But, maybe just to put it into an historic perspective, where is treatment of CLL coming from, and what has been done over the last decades? If we start on the left-hand side, in the 1950s, 1960s, the cornerstone of treatment was with alkylating agents, and the most widely used agent is chlorambucil [Leukeran®]. That has been a cornerstone for treating CLL, especially in elderly and frail patients other the last decades until very recently. But, now with a lot of studies that we will discuss later, it is used much less frequently and is now shown to be not very useful when compared to new agents. So, that's one of the chemotherapy drugs that's been around. It's an oral agent.

Steroids have been used. And then, there was very little develop until the early 1980s when another group of chemotherapy agents was introduced. That class of agent is called purine nucleoside analogs, and the--one of the most widely used drugs there out of this class has been fludarabine [Fludara®], which you know from the FCR regimen. So, with this development, then investigators started combining alkylator, this drug class with the nucleoside analogs and the prototype regimen that was quite in favor in the 1990s was fludarabine and cyclophosphamide [Cytoxan®].

But then, in the late 1990s, early 2000s, the addition of CD20 antibody, in particular, rituximab [Rituxan®], led to the development of chemo-immunotherapy, which became standard of care in the 2000s. And there are different shades of chemo-immunotherapy. There's the more intensive type of regimen, which is fludarabine, cyclophosphamide, and rituximab. And there are less intensive regimens, for example, bendamustine [Treanda®/Bendeka®], rituximab or chlorambucil with CD20 antibodies.

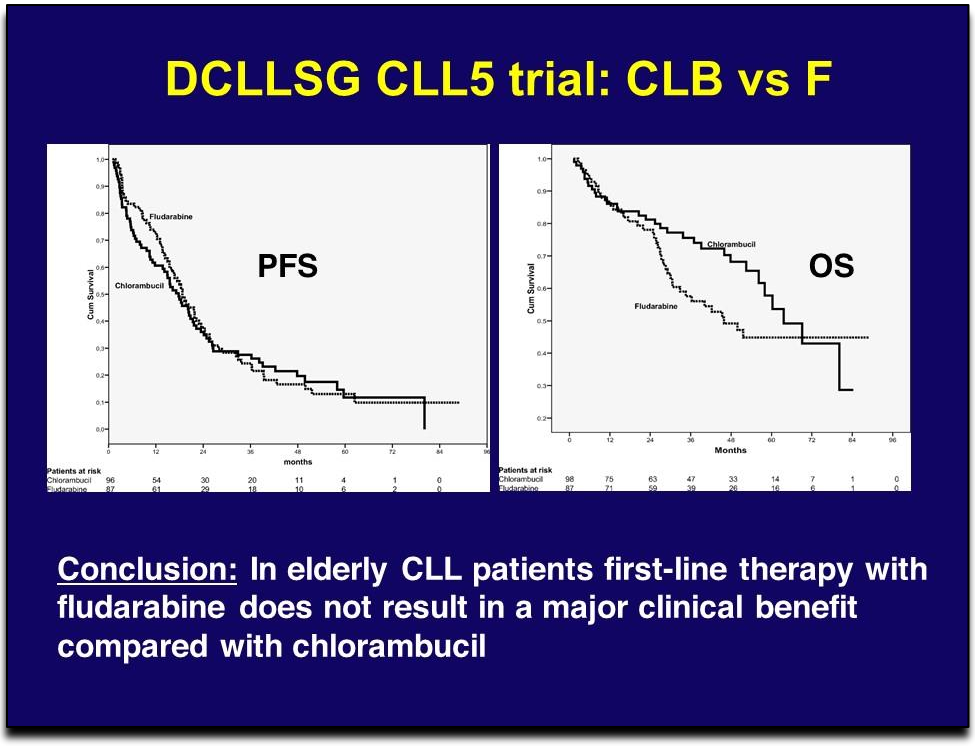
But, really, at the time when these chemo-immunotherapy regimens became standard of care, around 2008, 2010, we had a wave of new exciting drugs coming into early clinical trials and then being fast tracked and approved within a relatively short period of time. Those were the kinase inhibitors, enzyme inhibitors, which block enzymes that have been linked to the B-cell receptor. And those are BTK

inhibitors like ibrutinib or PI3-kinase inhibitors like idelalisib [Zydelig®]. There has been introduction of a new CD20 antibody, which is very active called obinutuzumab [Gazyva®], and the latest addition has been a BCL-2 antagonist, venetoclax. And I will show you the later data about all these new agents and how they compare to the traditional chemotherapy-based treatment.



Survival: Daily Chlorambucil Versus Observation

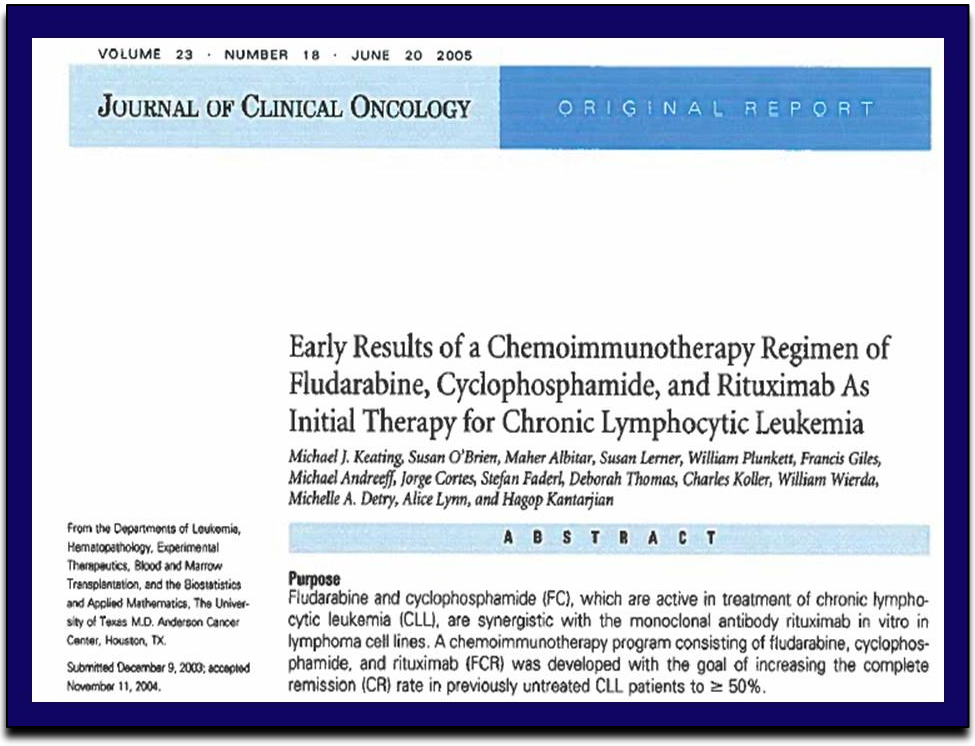
Just to stay with this historic theme, for a long period of time, chlorambucil has been used kind of as a treatment to slow down the disease. But, it was well recognized, and this is one example. It has been recognized that the treatment itself would not prolong life, and that's obviously very disappointing because you could argue, well, if a patient doesn't survive longer on a treatment, you may wonder how active this regimen is. And clearly, here, from this large randomized study, there was no survival benefit. Patients can still benefit in a way from chlorambucil, in terms of their symptoms. But, it's not very satisfying to have a treatment that was standard treatment for decades that does not prolong the overall survival.



DCLLSG CLL5 trial: CLB vs F

But then, we are moving on to the newer treatments, which was fludarabine, and we are obviously wondering, is fludarabine, as a somewhat more intensive chemotherapy approach to treat CLL patients, is that helping patients in terms of survival?

And it was again quite disappointing here in a newer study by the German CLL Study Group, the CLL5 trial, to see, in a randomized fashion comparing fludarabine and chlorambucil that the newer and more intensive treatment may put a few more patients into remission. But, it does not, in a positive way, impact the progression-free survival, and it actually looked somewhat worse for a while in terms of overall survival.



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ORIGINAL REPORT

Early Results of a Chemoimmunotherapy Regimen of Fludarabine, Cyclophosphamide, and Rituximab As Initial Therapy for Chronic Lymphocytic Leukemia

Michael J. Keating, Susan O'Brien, Maher Albitar, Susan Lerner, William Plunkett, Francis Giles, Michael Andreeff, Jorge Cortes, Stefan Faderl, Deborah Thomas, Charles Koller, William Wierda, Michelle A. Detry, Alice Lynn, and Hagop Kantarjian

From the Departments of Leukemia, Hematopathology, Experimental Therapeutics, Blood and Marrow Transplantation, and the Biostatistics and Applied Mathematics, The University of Texas M.D. Anderson Cancer Center, Houston, TX.

Submitted December 9, 2003; accepted November 11, 2004.

ABSTRACT

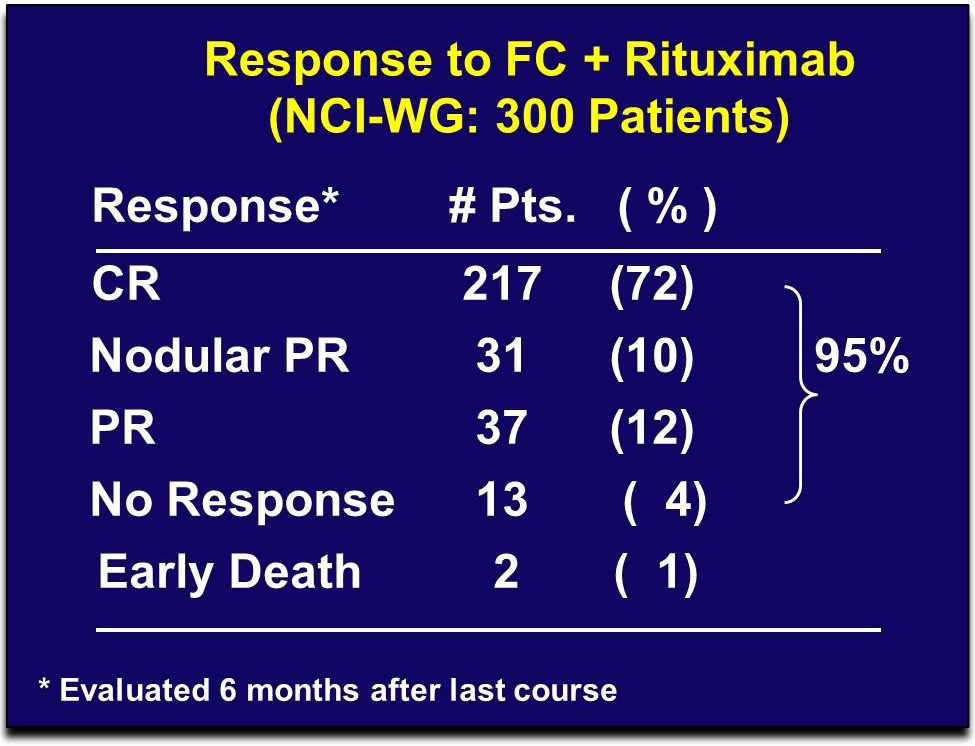
Purpose

Fludarabine and cyclophosphamide (FC), which are active in treatment of chronic lymphocytic leukemia (CLL), are synergistic with the monoclonal antibody rituximab in vitro in lymphoma cell lines. A chemoimmunotherapy program consisting of fludarabine, cyclophosphamide, and rituximab (FCR) was developed with the goal of increasing the complete remission (CR) rate in previously untreated CLL patients to ≥ 50%.

Journal of Clinical Oncology Slide

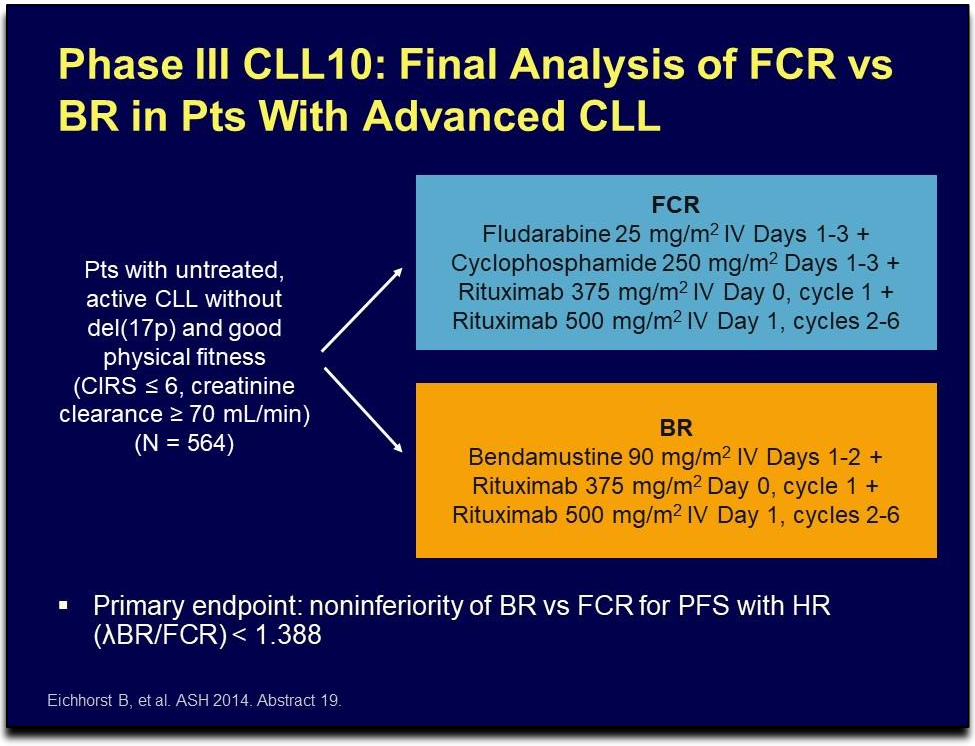
So, not much progress until we started using combinations of chemotherapy with more targeted treatment, which is the CD20 antibody, rituximab.

And the first study that was conducted to look at the benefit of adding CD20 antibody was the FCR regimen in this, what we call FCR300 trial. It was a study which was led by Dr. Keating here at our institution, at MD Anderson.



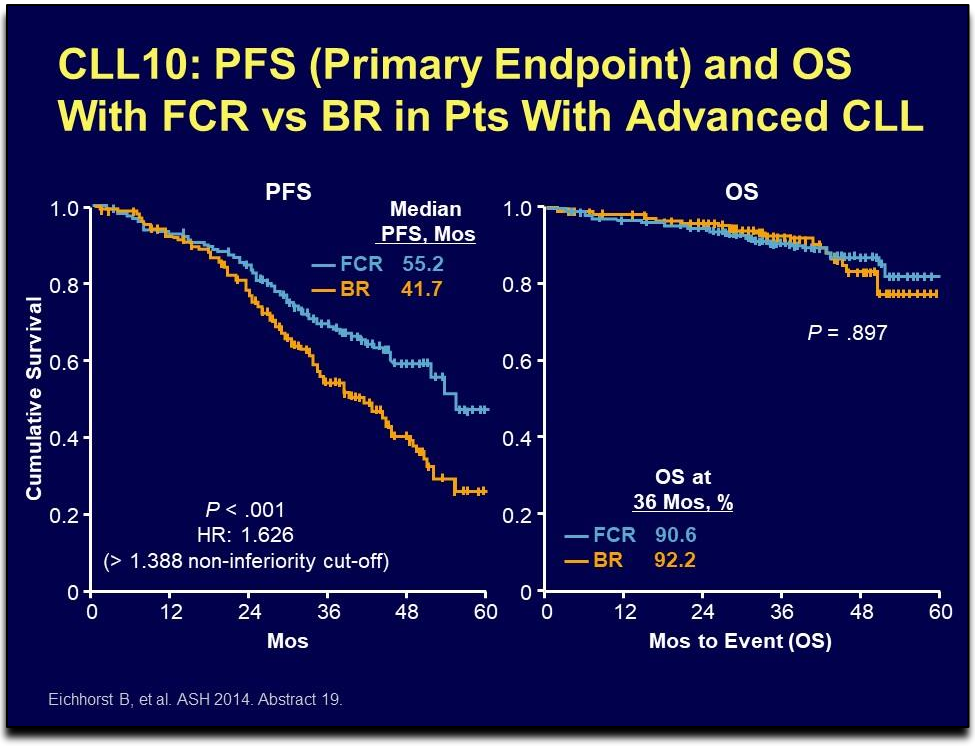
Response to FC + Rituximab (NCI-WG: 300 Patients)

And it enrolled in the early 2000s, 300 patients, which we've now followed for almost 2 decades. And the reason why this study generated so much excitement at that time was that, for the first time, combination chemo-immunotherapy treatment regimen generated a lot of remissions. Majority of patients in this trial achieved complete remissions. Many of them were durable. And over 90 percent of the patients responded to the treatment regimen.



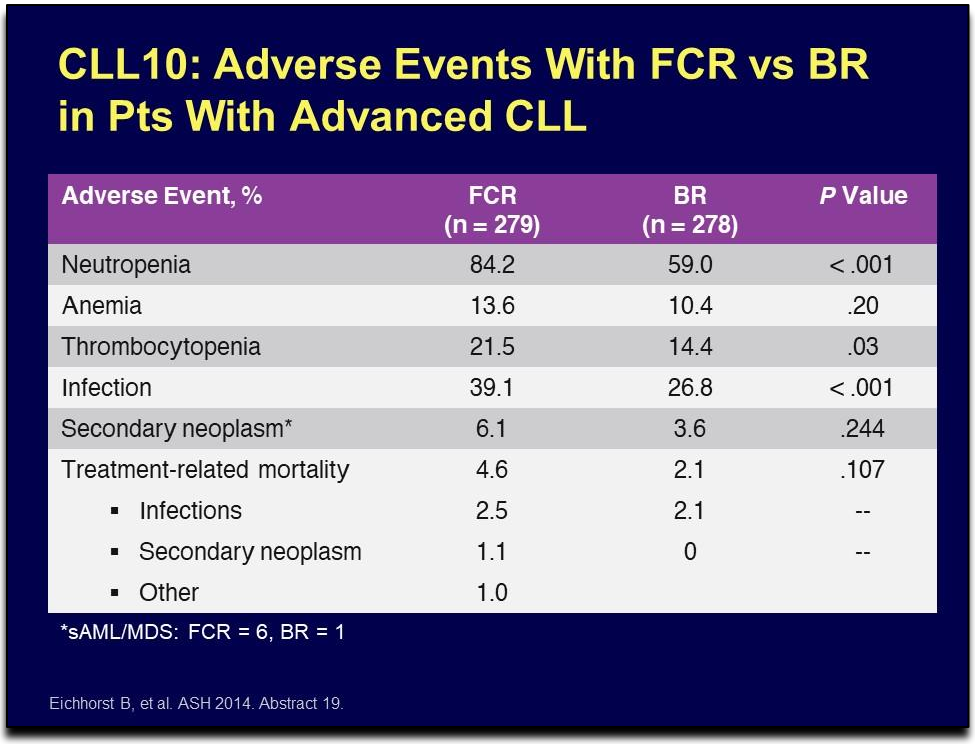
Phase III CLL10: Final Analysis of FCR vs BR in Pts With Advanced CLL

So, with these data, FCR has become one of the options for younger and fit patients, and, at the same time, bendamustine/rituximab was also put forward. And these two regimens dominated, I think, the treatment landscape in the early and mid-2000s, up until probably 2010. And one of the questions that has been debated a lot at that time was, which one was the most suitable regimen subgroup for which patient subgroup? And again, a randomized study, the CLL10 trial, has been informative in terms of telling us what are the pros and cons of each of these regimens. So, patients were randomized to one or the other.



CLL10: PFS (Primary Endpoint) and OS With FCR vs BR in Pts With Advanced CLL

And the outcome of this study is shown here on this next slide, where you see on the left-hand side, the progression-free survival of patients receiving either FCR, which is the blue curve on top, versus bendamustine rituximab. And you see that patients remained in remission for longer if they received FCR. They have a longer progression-free survival. That was probably on an average—maybe longer by about 9 months. It's not a dramatic difference. But, it is a difference indicating that FCR is—there's somewhat more intensive regimen. But, does it impact overall survival? On the right-hand side, you see that this did not lead to a difference in terms of overall survival.



CLL10: Adverse Events With FCR vs BR in Pts With Advanced CLL

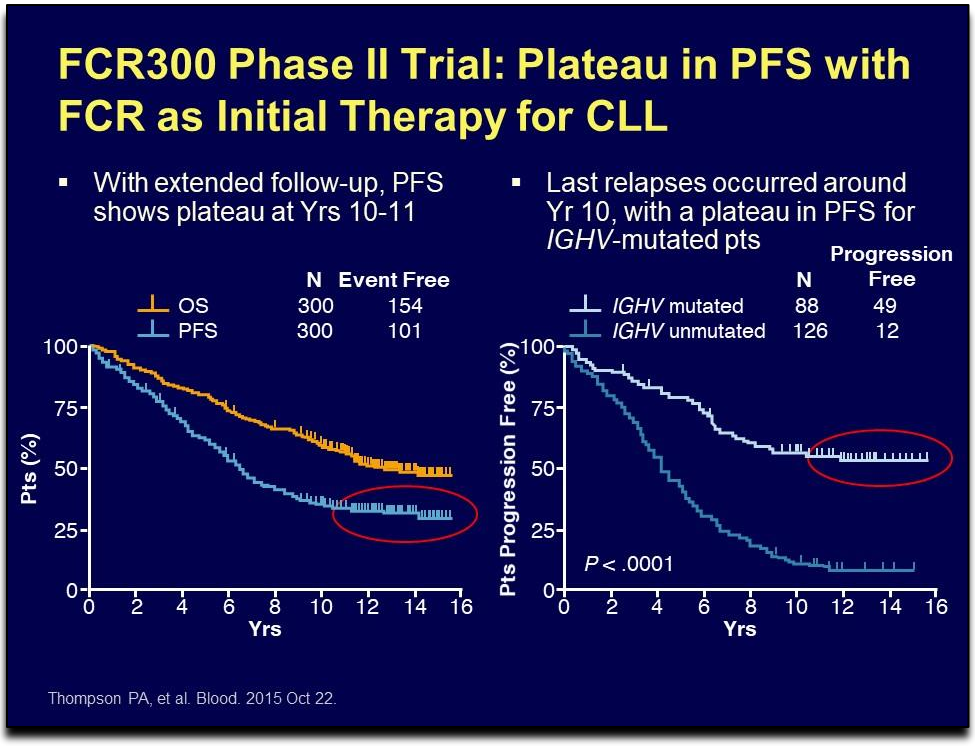
Adverse Event, %	FCR (n = 279)	BR (n = 278)	*P* Value
Neutropenia	84.2	59.0	< .001
Anemia	13.6	10.4	.20
Thrombocytopenia	21.5	14.4	.03
Infection	39.1	26.8	< .001
Secondary neoplasm*	6.1	3.6	.244
Treatment-related mortality	4.6	2.1	.107
▪ Infections	2.5	2.1	--
▪ Secondary neoplasm	1.1	0	--
▪ Other	1.0		

*sAML/MDS: FCR = 6, BR = 1

Eichhorst B, et al. ASH 2014. Abstract 19.

CLL10: Adverse Events With FCR vs BR in Pts With Advanced CLL

And you can also appreciate here on this next slide that the price for the higher activity of FCR is a higher rate of side effects, which is mostly myelosuppression, neutropenia, and that leads to a higher frequency also of infections because those patients treated with this more intensive regimen are more likely to develop infections. What is also, I think, important in the discussions when we may discuss with patients—should we go with a more classical chemotherapy-based approach, or should we go with the novel agents—is this question around secondary neoplasia's, which are in general, secondary AML and MDS. And the frequency seems low. But, it could still affect maybe one in 20 patients treated with FCL suffering a few years later from secondary AML or MDS. And that's situation then which is very complicated to treat and which has a poor outcome.

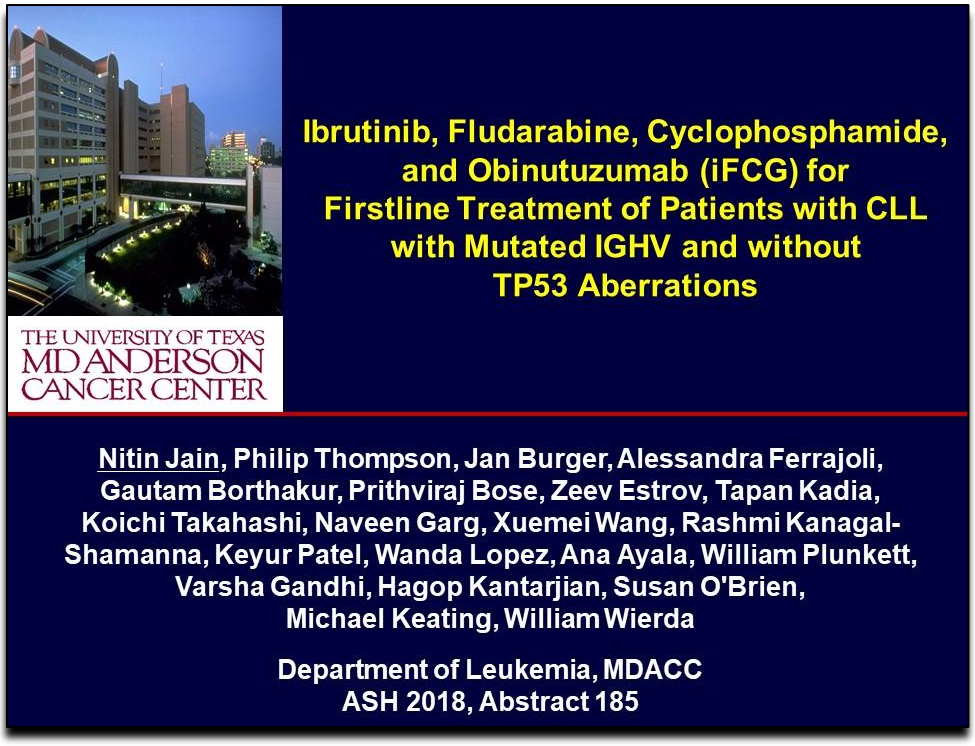


FCR300 Phase II Trial: Plateau in PFS with FCR as Initial Therapy for CLL

Now, we spoke about the long-term outcome of these patients from the FCR300 trial. And, in a way, this has still been instructive over the years. And looking at those data now 15 plus years later, what is interesting about this data set and what is one of the reasons why I would say it is still worse offering this treatment option, in general, to selected patients is based on the survival curves that you are looking at here on the left-hand side, for the entire patient population, and on the right-hand side, for patients treated with FCR, either for patients who are mutated--those are the IGH3-mutated patients, and these are the unmutated patients.

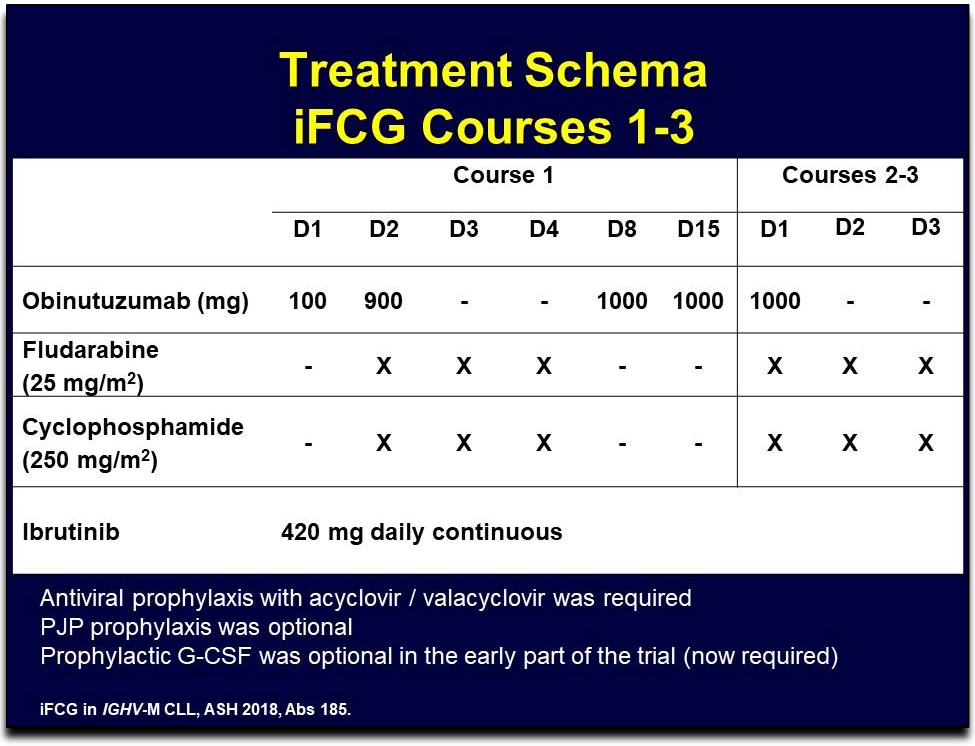
The reasons why we still think there's a value of looking into chemotherapy-based treatment is based on this plateau that you see here in the mutated patients emerging after 8 to 10 years. In the general population, if you think about all patients, that's probably around 30 percent of the patients. But, if you just look at the mutated patients, it's between 50 and 60 percent of the patients. And those are long-term survivors. If patients have not had a relapse of their disease after 8 to 10 years, they are not expected to relapse anymore at this point, and they are, we think, functionally cured. And with those data, we can predict if a patient in this setting and if that's a patient who's mutated—if he goes onto a regimen like this, the odds are in favor that the patient will receive limited period of treatment and then have a very good long-term outcome. But, it is not every patient. It is around 60 percent of the patients.

On the other hand, if patients are unmutated, we see a continuous decline, and we don't see development of this plateau effect with chemo-immunotherapy. And therefore, we believe, for these higher-risk patients, just based on the mutational status, we would not go ahead and recommend chemo-immunotherapy based treatment as one of the options.



Ibrutinib, Fludarabine, Cyclophosphamide, and Obinutuzumab (iFCG) for Firstline Treatment of Patients with CLL with Mutated IGHV and without TP53 Aberrations

Now, what are we doing, and how are we moving forward with these data with this plateau? In the face of new agents and with the desire to reduce the intensity and the amount of chemotherapy that's administered, our group here has developed an alternative program, which is based on FCR, but which is modified now and is called iFCG, which stands for ibrutinib, fludarabine, cyclophosphamide, and obinutuzumab. We think that's an advance over FCR.



Treatment Schema iFCG Courses 1-3

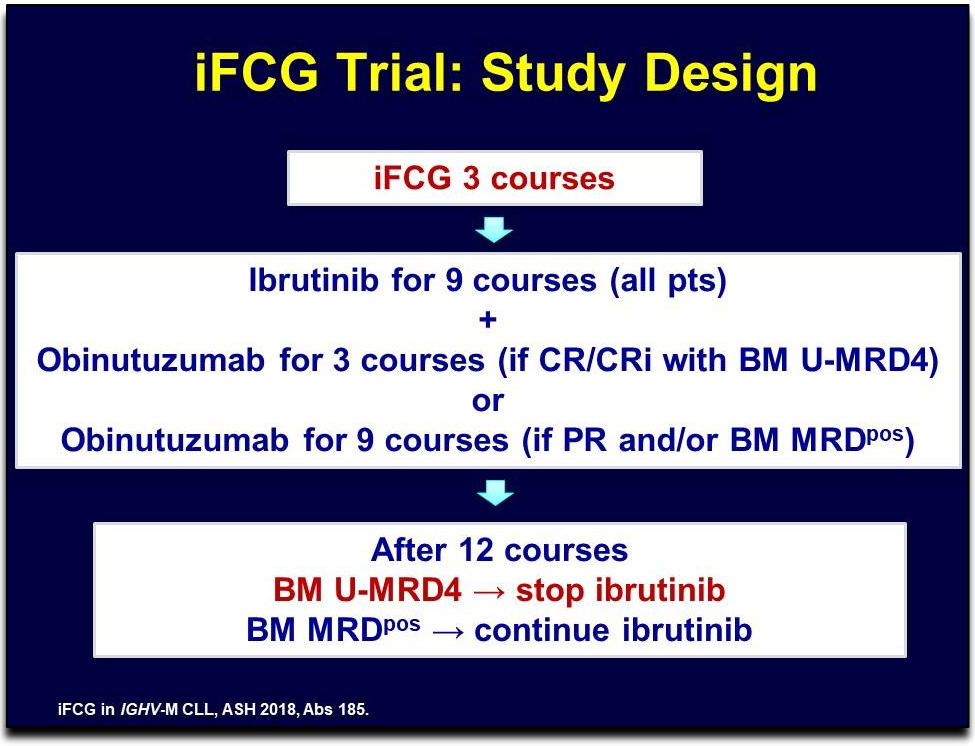
	Course 1						Courses 2-3		
	D1	D2	D3	D4	D8	D15	D1	D2	D3
Obinutuzumab (mg)	100	900	-	-	1000	1000	1000	-	-
Fludarabine ($25\ mg/m^2$)	-	X	X	X	-	-	X	X	X
Cyclophosphamide ($250\ mg/m^2$)	-	X	X	X	-	-	X	X	X
Ibrutinib	420 mg daily continuous								

Antiviral prophylaxis with acyclovir / valacyclovir was required
PJP prophylaxis was optional
Prophylactic G-CSF was optional in the early part of the trial (now required)

iFCG in *IGHV*-M CLL, ASH 2018, Abs 185.

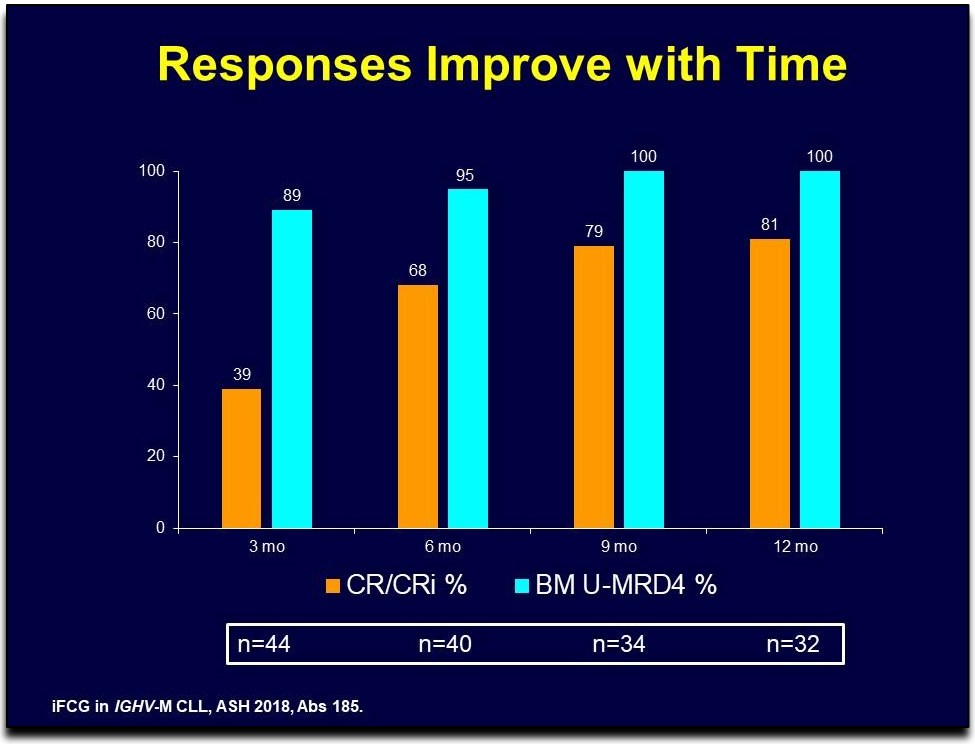
Treatment Schema iFCG Courses 1-3

And the biggest advance is that we are cutting back on the cycles of chemotherapy. Traditionally, with FCR, we would administer up to 6 cycles fludarabine and cyclophosphamide. And with the iFCG regimen, this cut back from 6 to only 3 cycles. Instead of rituximab, we administer obinutuzumab, and we are adding ibrutinib, the kinase inhibitor, about which we're going to talk in more detail later with the ibrutinib trials.



iFCG Trial: Study Design

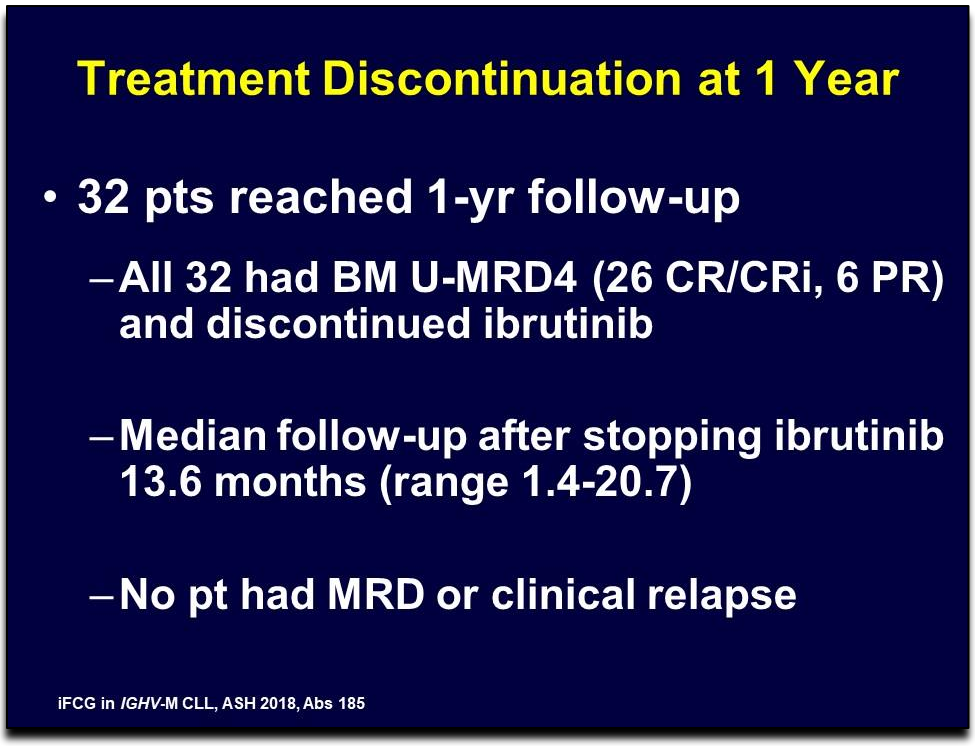
But, this is a continuation of our efforts with FCR. Patients receive 3 cycles of FC, together with the CD20 antibody and ibrutinib and then continue with ibrutinib and the CD20 antibody. And after 12 months of treatment, all patients stop.



Responses Improve with Time

And in the patients that have been treated so far, we had very good success in terms of achieving high levels of complete remissions, which are shown here in orange, over time.

The vast majority of patients achieved complete remissions, and all patients after 9 to 12 months become negative for minimal residual disease in the bone marrow, which in the past, has been a strong predictor for this long-term survival. So, with these data and these data just based on patients enrolled in this trial who are low-risk patients with mutated IGHV, we think there's still value. It is something we would discuss and offer to these patients as an alternative to going straight to one of the new agents.



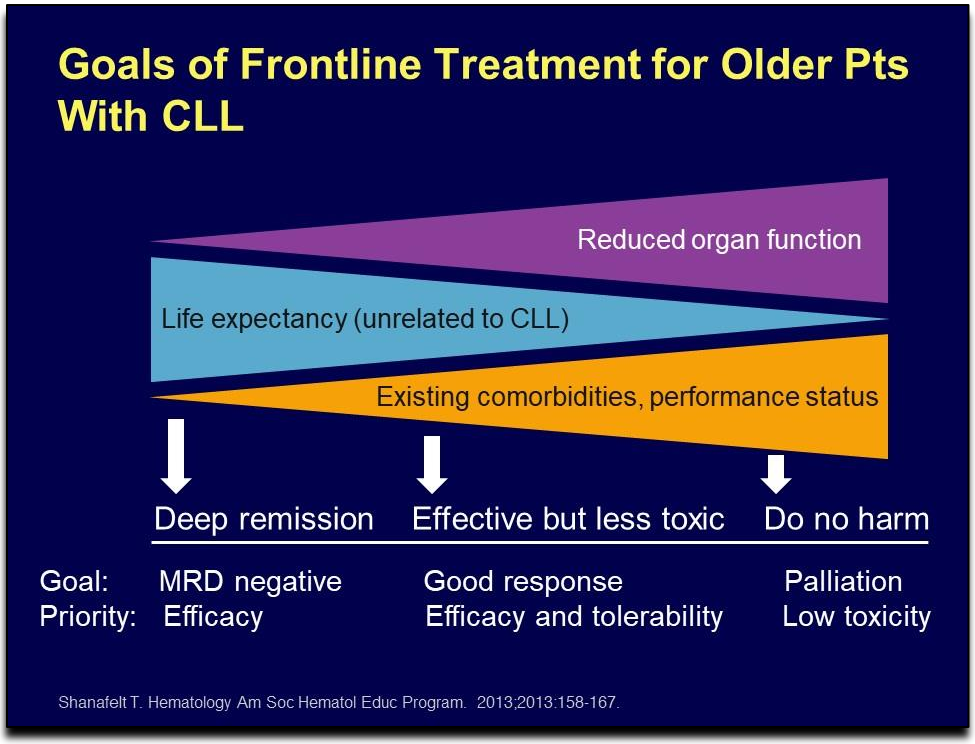
Treatment Discontinuation at 1 Year

We have treated about 40 patients. Many of them have now reached longer follow up and 1-year marks where treatment has been discontinued. All these patients were able to discontinue, and none of the patients have relapsed. But, obviously, this is early in this particular trial. We will update this, and I encourage you all to stay tuned on the long-term results of this trial because our hope is that hopefully, these will be long-term survivor patients. And hopefully--what we are also hoping for is that the rate of secondary problems, secondary AML and MDS, will be low in this patient population because the chemotherapy backbone of the treatment has been cut back from 6 to 3 cycles.

What About Treatment for Older Patients With CLL?

But, discussing FCR, discussing iFCG, these more intensive chemotherapy regimens, we need to keep in mind these are treatment options for rather small subgroup of patients, for the younger, fit patients, which we see, I think, because of selection bias, more frequently here at larger centers.

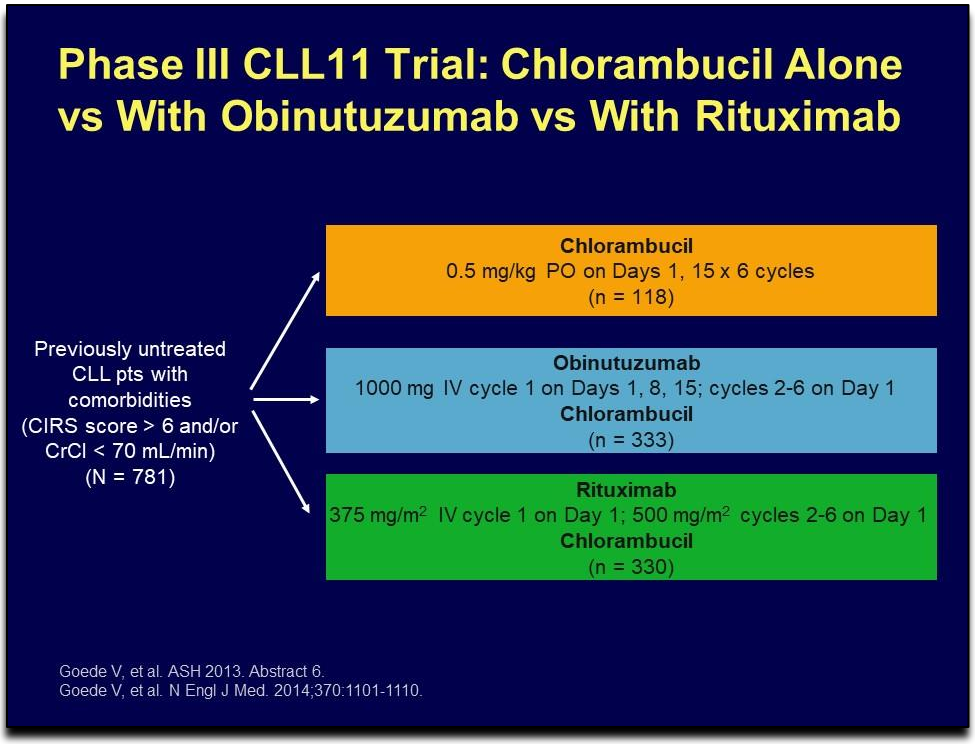
But, the general CLL patient population is a population of patients in their 70s, oftentimes with comorbidities.



Goals of Frontline Treatment for Older Pts With CLL

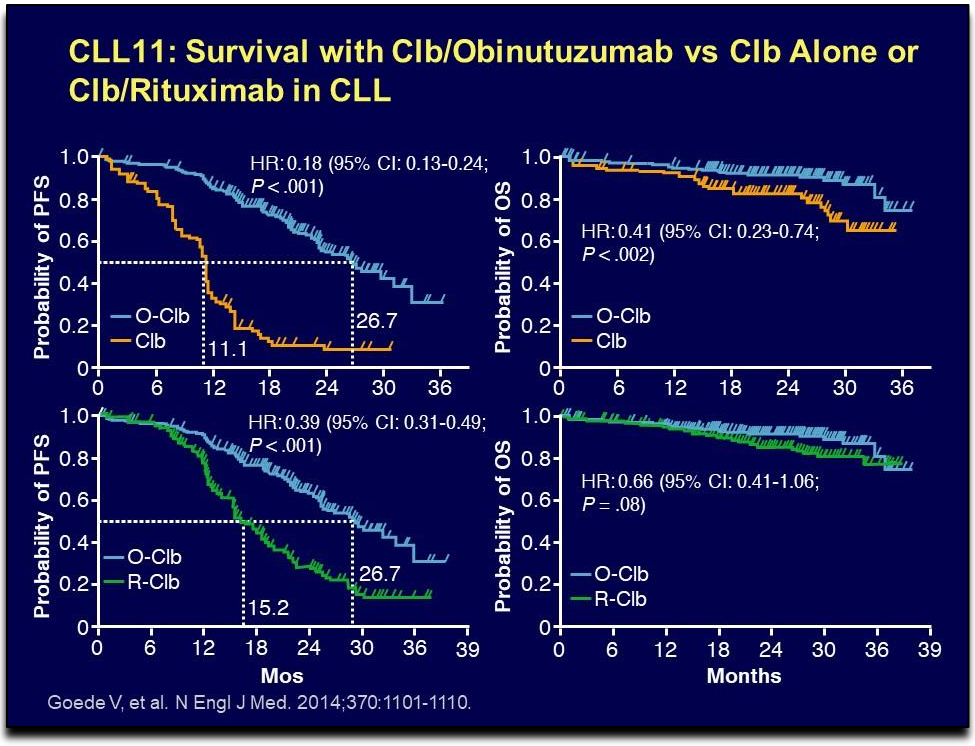
And those patients are not good candidates for intensive chemotherapy, and those patients traditionally have been treated with algorithms that are, in a way, summarized here.

When you look at the right-hand side of this particular slide, where you have an older patient who has additional comorbidities, let's say renal dysfunction or congestive heart failure problems like that, which accumulate as we all age. And because of these comorbidities, the performance status of these patients is not as good as in a CLL patient who is in his or her 50s. And those patients, we know, from experience, do not tolerate FCR-like regimens well, and we don't offer that. So, the goal in these patients is not to go in with intensive chemotherapy regimens and to induce deep remissions. But it is more to maintain the quality of life, to not induce toxicity with our treatments, and not to harm the patient, so that they can continue to live life that provides as good quality of life as possible.



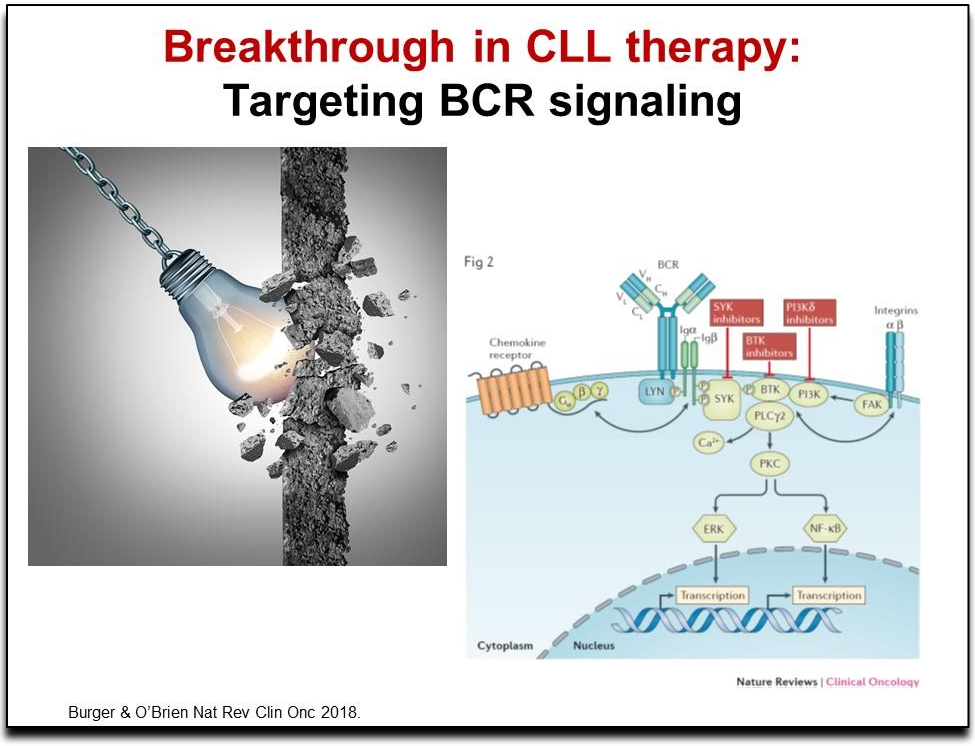
Phase III CLL11 Trial: Chlorambucil Alone vs With Obinutuzumab vs With Rituximab

So, with that in mind, the traditional type of treatment in this patient population has been low-intensity chemotherapy and chlorambucil has been the most widely used drug in the past until we started combining chlorambucil with CD20 antibodies. And here, the CLL11 trial from the German CLL Study Group has been establishing with this trial that if low-dose chemotherapy should be used, it should be combined with these antibodies based on, again, these survival data shown here and just maybe focus on the left-hand side progression-free survival of patients treated with chlorambucil alone on the orange curve in the top left versus chlorambucil together with CD20 antibody, in this case obinutuzumab in the lower left-hand graph. The combination of rituximab versus obinutuzumab combined with chlorambucil.



CLL11: Survival with Clb/Obinutuzumab vs Clb Alone or Clb/Rituximab in CLL

So, these data establishing that, if we use low-intensity chemotherapy, patients do better if a CD20 antibody is added. Rituximab is adding benefit. Obinutuzumab seems to be adding somewhat more benefit, and there was also shown on the right-hand side, some survival benefit. So, this became one of the regimens suitable for elderly CLL patients, populations. But, at the same time, then the new agents became available as clinical trial options and then subsequently also were approved. And this was really, in every regard, in terms of efficacy, but also in terms of FDA and other agencies' approval—it was truly a breakthrough to now being able to target molecules that are important in disease biology. And that's the point the slide is trying to make. We have identified, through these new agents, that these kinases that are related to the B-cell receptor, shown here on the right-hand side, and the downstream kinases, that these are valid and important targets in the CLL disease process.

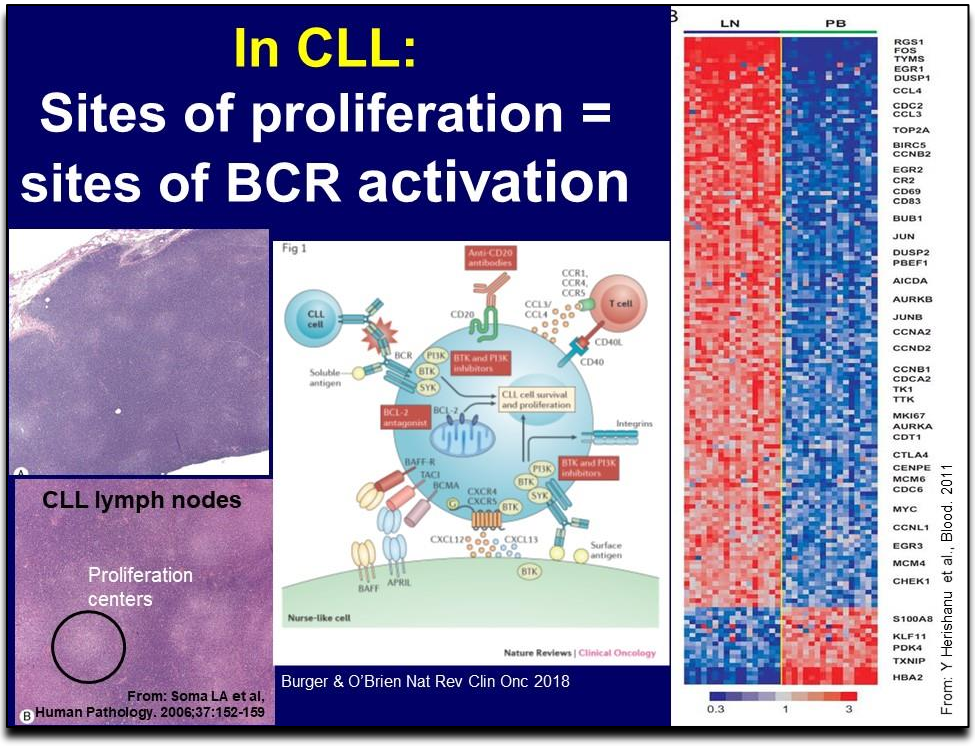


Breakthrough in CLL therapy: Targeting BCR signaling

And now, I'll talk a little bit about how they are related to the CLL disease biology in the next few slides. But, just to stay on this cartoon here on the right-hand side, you see the cell membrane. And in the membrane, you have this structure that is this Y-shaped molecule called B-cell receptor, which recognizes antigens. And when that receptor's activated—and that oftentimes gets activated in CLL—then, it sends and transmits signals into the cell, which then go down to the bottom, into the nucleus of the cell and activates the cell to make it grow and to make it survive and make it divide so that you have more and more of these leukemia cells.

And if we believe in that—and we have strong indication that that's what's happening—then it would become very attractive to block the transmission of these signals into the cell by using molecules that are blocking what we call the signaling cascade downstream of the B-cell receptor. And there are enzymes in the cells that make all this happen. And we have drugs to block these enzymes. The key enzymes that we're going to talk about are spleen tyrosine kinase, or Syk, or Bruton's tyrosine kinase, or BTK, and PI3 kinase isoforms, which are all downstream of the B-cell receptor. We have drugs. There are several drugs proved to block these enzymes and are in clinical use, the most widely used one is the BTK inhibitor, ibrutinib, which, at this point in the US, is probably the most widely used CLL drug to treat most of our CLL patients these days.

Their function is to block the signaling of the B-cell receptor. But, it also blocks—and that's quite interesting and unique to this whole class of agents—it also blocks the signaling and the function of additional molecules, not just the B-cell receptor, but also molecules called integrins and chemokine receptors. Those are molecules which function almost like anchor molecules that keep the CLL cells to stick to lymph nodes, probably also to stick somewhat to the bone marrow, but more to the lymph nodes and make them kind of home to these organs. And if you block these enzymes, then the function of these molecules is compromised, and the cells lose this anchor signal, which then explains something that I will highlight in a couple slides, something that we call redistribution lymphocytosis.



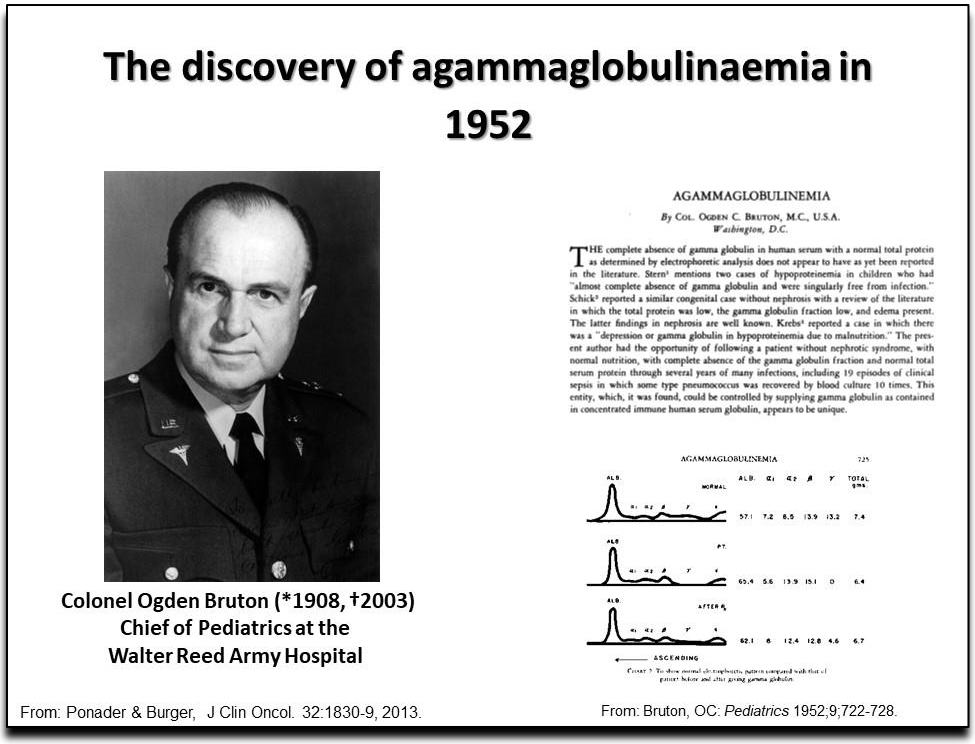
In CLL: Sites of proliferation = sites of BCR activation

On this slide, just to go a little bit deeper into disease biology and how the new agents are more targeted than when we used chemotherapy to treat this disease. What you see here on the left-hand side are sections through lymph nodes from CLL patients when sometimes lymph nodes are retrieved from a patient and then sent to the pathologist and they look at it. They see typically a picture like what is shown here on the left-hand side where you see lymph nodes, pretty homogenous. But then, you see lighter areas within the lymph node, which we call proliferation centers, and there you see CLL cells actually actively growing. And leukemia CLL does not grow anywhere else. It typically grows in the lymph node, in the proliferation centers, but not in the peripheral blood. And it has been puzzling. And just over the last 10 years, it has been dissected out better, what is really happening in these proliferation centers and what makes CLL cells grow in these particular areas.

And the reason is has not been dissected out that well yet—and we just recently made progress—is because it is very complex. You see not just the leukemia cells, which are in this cartoon here in the center shown in the middle, and you see the CLL cells receiving a lot of signals from outside, from other cells or from other molecules, even from other CLL cells. And it apparently needs a lot of these signals, which the cells only can receive in this specialized environment of from the lymph nodes, signals from T lymphocytes, activation of the B-cell receptor, activation of chemokine receptors and so forth. So, it needs this complex interplay of activating signals to make CLL cells grow.

And with these discoveries, one of the questions was, well, if there are so many signals, are they all the same, or is one particular pathway particularly important? And what is shown on the right-hand side is what we call gene expression studies. Those are studies where CLL cells were purified and isolated, either on the left-hand side from lymph nodes, or from the peripheral blood. And you see a marked difference shown here in red where genes are activated. And this activation signal is totally lacking in the peripheral blood where the CLL cells are not growing and proliferating. So, this red has something to do with the growth and the proliferation of the leukemia cells. And if you then analyze which genes are activated, these red genes, what are they actually, and what are they linked to? This is a signature

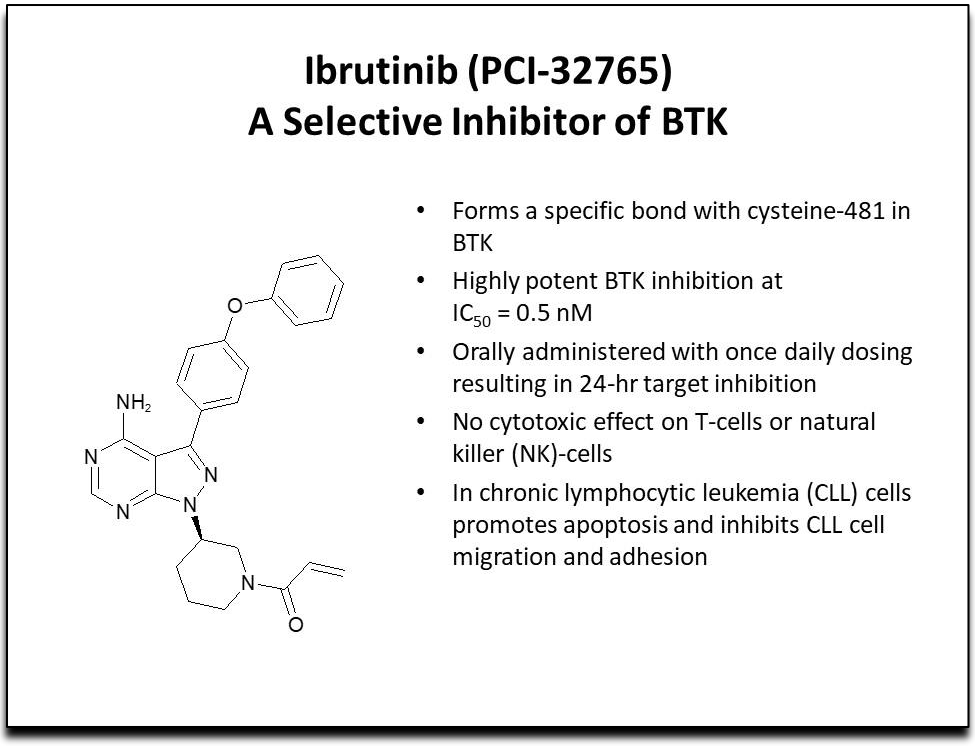
that is very strongly, tightly linked to the B-cell antigen receptor. And for these data and other data along the same lines, I think the conclusion at this point is that the most important event in the lymph nodes that's driving the disease to progress and to grow is coming from the B-cell antigen receptor. And that explains, I think, why the new agents that interfere, shown here in the center, the kinase inhibitor therapies that are blocking B-cell receptor signaling, that they are so successful because they are interfering with something that's very critical to the disease biology.



The discovery of agammaglobulinaemia in 1952

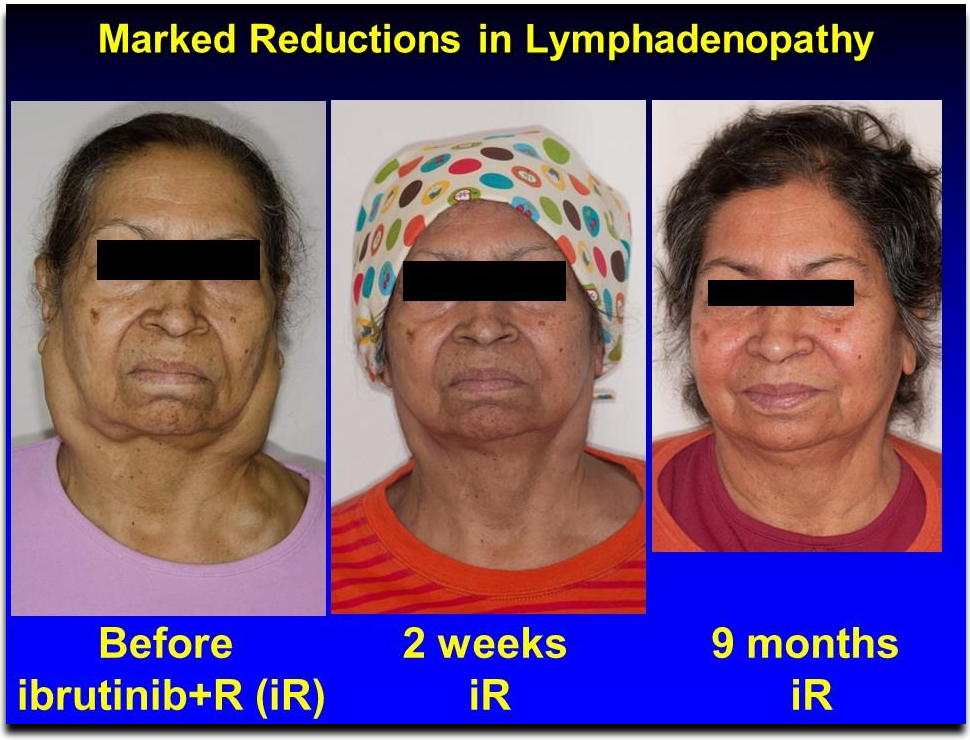
Now, I mentioned earlier that the most widely used--one of these new drugs is the Bruton tyrosine kinase inhibitor, ibrutinib. And you may wonder why this drug has this peculiar name. It goes back to Dr. Bruton, who's shown here on the left-hand side, who was a pediatrician in Washington at the Walter Reed Army Hospital, where he practiced in the 1950s and 1960s, taking care of children from Army personnel. And he described an initial patient in the early 1950s, a child, a boy, at that time, probably 3 or 4 years old, who developed recurrent infections. And he was able to demonstrate—and that's shown here at the bottom on the right-hand side—that this child was lacking what is called gamma globulins. And that is basically a soluble form of the B-cell receptor, immunoglobulins, which are produced by normal B lymphocytes to protect all of us. We all have immunoglobulins. And CLL patients oftentimes have very few immunoglobulins because that's not intact, and that's not properly produced by CLL cells.

But, the link is coming here from these first cases of agammaglobulinemia children who are not able to produce gamma globulins. And later, it was discovered that the basis for this immune deficiency disease is that these children have mutations in the gene that's encoding BTK, the kinase that we talked about. That's the target of ibrutinib. So, there's a genetic link where point mutations in this enzyme lead to deficiency of this enzyme, and those children cannot produce immunoglobulins. And they can be treated, and they have much better outcomes if they are treated IVIG, which some--a few of our patients actually sometimes also get because they have low immunoglobulin levels and sometimes recurrent infections.



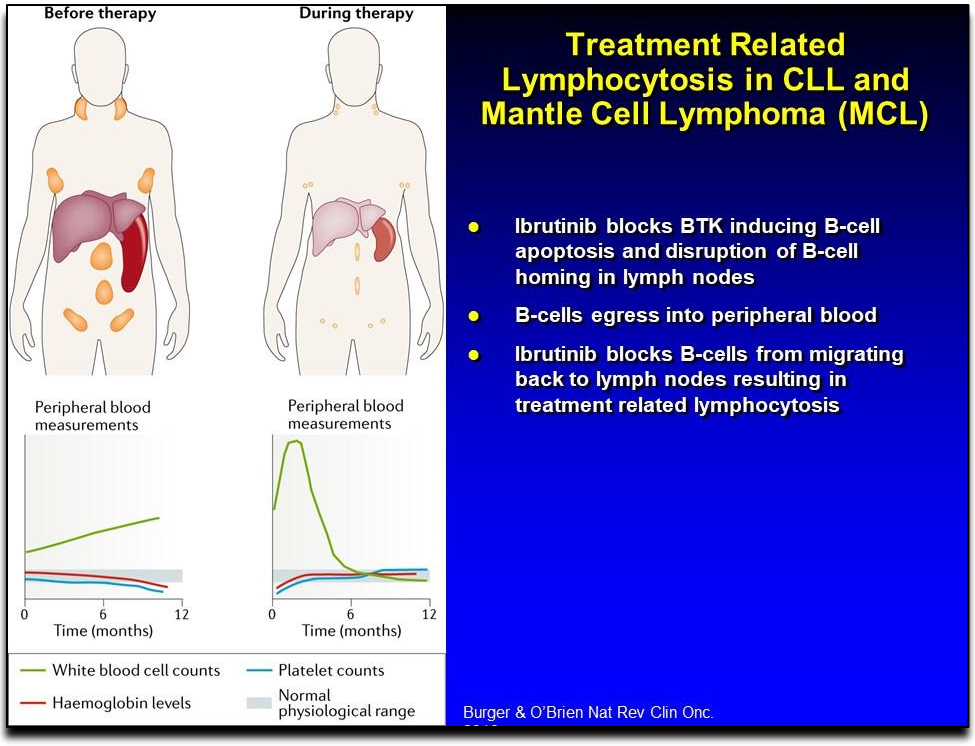
Ibrutinib (PCI-32765) A Selective Inhibitor of BTK

So, with the discovery of the enzyme and these mutations, BTK became a target for drug development, initially with the idea maybe this enzyme could be disabled, and you could help autoimmune diseases like arthritis but maybe also B-cell malignancies. And this cartoon here on the left-hand side shows the molecular structure of ibrutinib, the BTK inhibitor that's now widely used for CLL treatment. It's an oral drug. It's an irreversible inhibitor, which means the drug is taken, distributes in the body of the patient, and attaches to the BTK molecule and doesn't let go from the BTK molecule. It's strongly attached and doesn't come off within 24 hours. And therefore, it can be dosed only once or once a day as a onetime treatment dose.



Marked Reductions in Lymphadenopathy

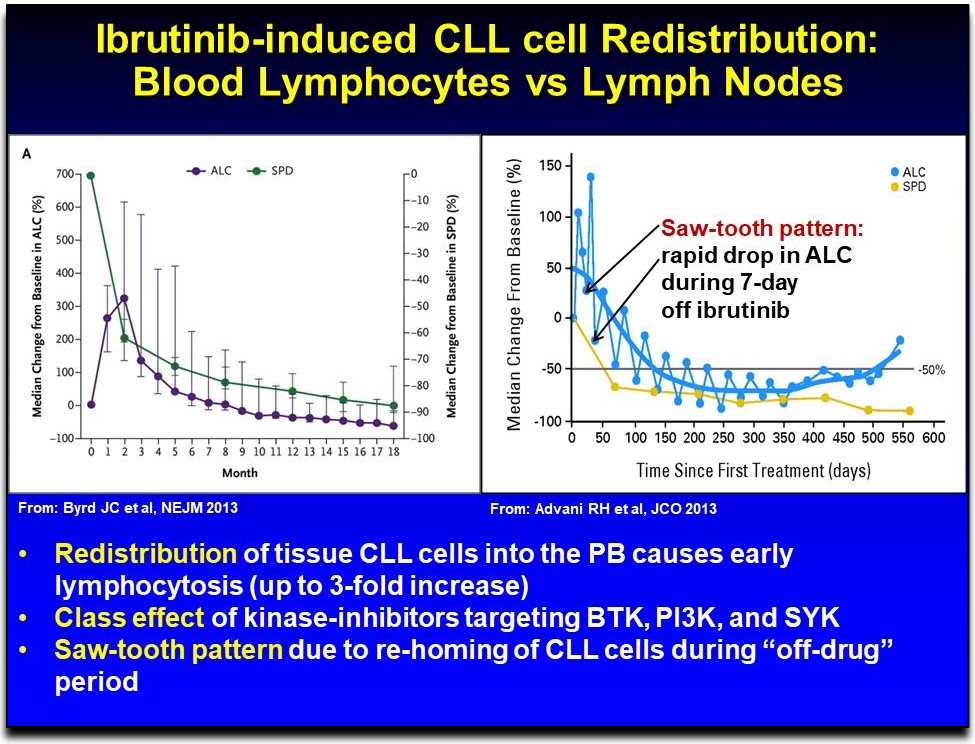
When we started getting this drug into our hands and starting to treat CLL patients with ibrutinib, I think the most striking finding—and this is one of my patients, one of the earliest patients I've treated with ibrutinib is how quickly patients can respond. And what is, I think, the most remarkable finding in the first few days or weeks on treatment with ibrutinib, I think is well demonstrated here by these pictures where, on the left-hand side, you see this female patient with very large, bulky cervical lymph nodes, which were refractory to treatment with chemo-immunotherapy, but which disappeared very quickly within a few days on treatment on ibrutinib. This next picture was taken after 2 weeks. And you see how these large lymph nodes have now largely vanished and melted away. And over time, this pale patient transfusion dependent in the beginning, became transfusion independent and did very well with this treatment. But, really, the striking finding with the targeted kinase inhibitor treatment is that it can so quickly resolve these lymph nodes.



Treatment Related Lymphocytosis in CLL and Mantle Cell Lymphoma (MCL)

And how is that happened? That was one of the questions that was of great interest to us in the very beginning. And what you see here on the left-hand side is a cartoon of the situation before treatment with the kinase inhibitors like ibrutinib. You have patient who has now, like the lady we just saw, big lymph nodes in the different areas: cervical, axillary, inguinal lymph nodes, big spleen. The liver sometimes can be enlarged too. And then, you start treatment, and very quickly, you have resolution of the enlarged lymph nodes, as you just saw in the picture of this patient. And that really happens very quickly. You can expect that to happen within the first week on treatment.

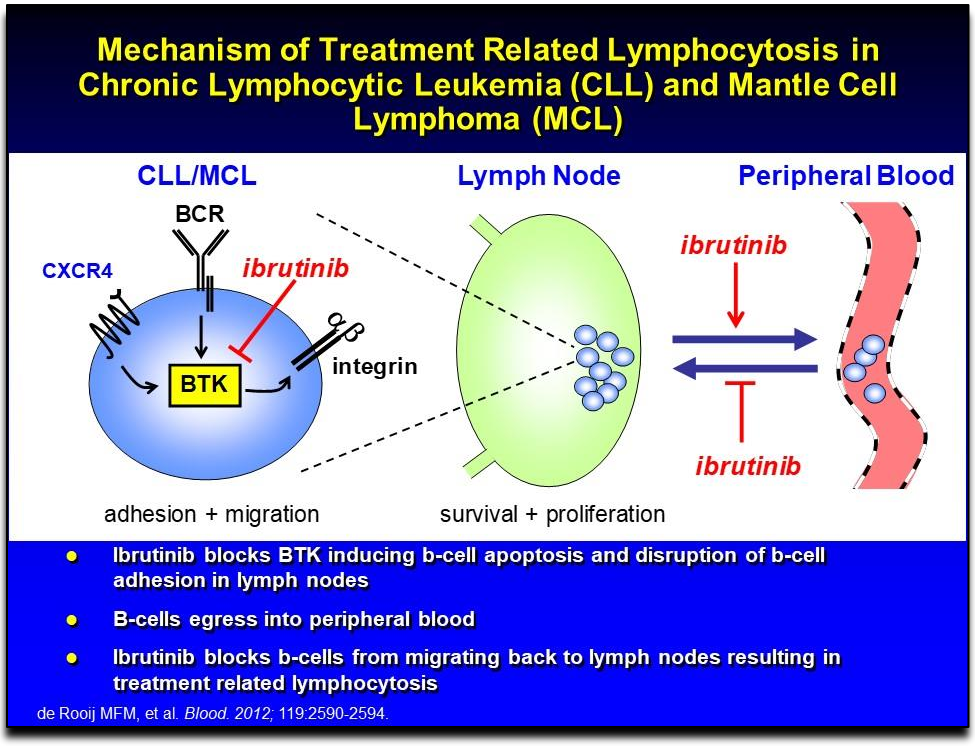
But, what is the reason behind this? Are these cells quickly disappearing because they are killed off? That may be part of it. But, another finding is that the cells are basically mobilized from the lymph nodes into the blood, and you will see an initial increase in leukemia cell counts. And that can be doubling or tripling. So, if you start with a white count of 30,000, you may expect during treatment with, for example, ibrutinib, that the white cell count on the first weeks of treatment actually can go up to levels that are 60,000 or 90,000 or 100,000, due to mobilization of the leukemia cells in the peripheral blood. But, is that something permanent? No, it is not, because in the bloodstream, the leukemia cells are deprived from all the nutrients that the cells normally receive and the lymph nodes. And they will eventually then die. And the peripheral blood and the lymphocyte count and the white cell count, over time, normalizes. And then, patients achieve remissions. But, that needs continuous treatment for an extended period of time, for months, and oftentimes, it takes a year until patients have the best response.



Ibrutinib-induced CLL cell Redistribution: Blood Lymphocytes vs Lymph Nodes

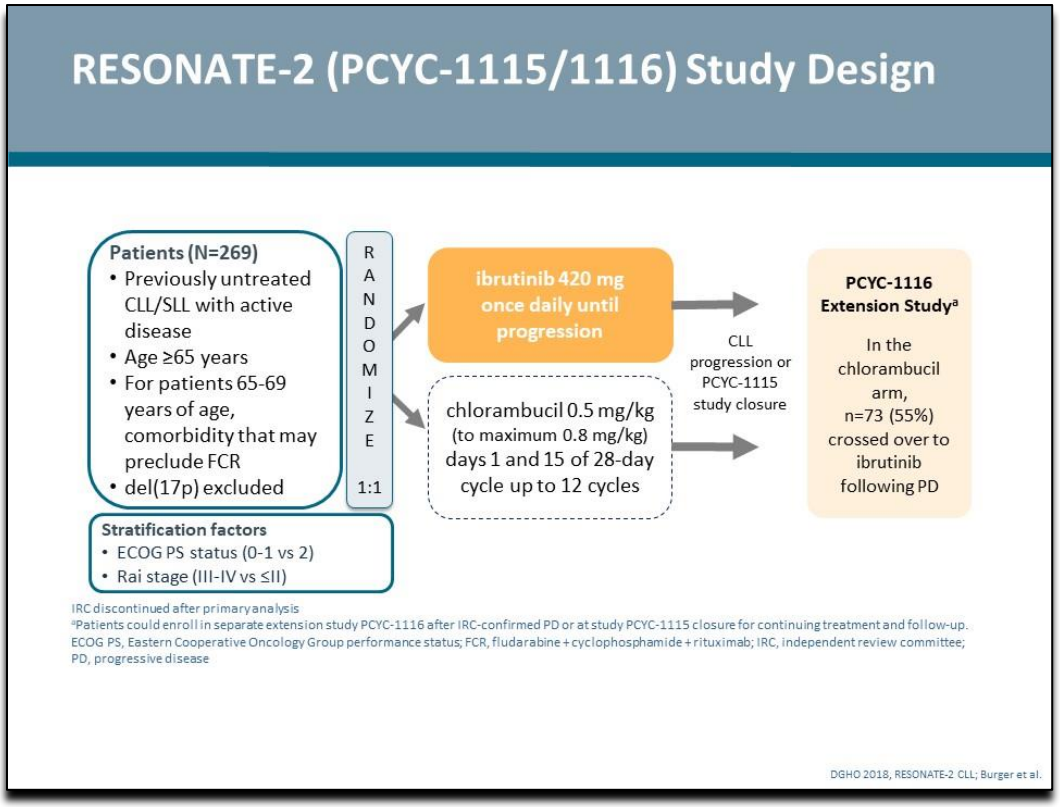
This is a bit more formal data to basically show you the same thing we were just discussing, where you see, on a clinical trial—this is from the first larger clinical trial with ibrutinib in green on the left-hand side, the rapid decline in lymph node sizes over the first weeks on treatment and, at the same time, this purple curve, showing the increase in leukemia cell counts in the beginning, during the first 2 or 3 months on treatment, which then declines. And then, patients have normal lymphocyte counts after 12 to 18 months on treatments.

And if you do intermittent treatment, where you just treat your patients for 3 weeks and then there's a break in treatment, what happens there? That's shown here on the right-hand side. And you see this saw-tooth pattern where the leukemia cell counts go up and down. Whenever patients are on treatment with ibrutinib, the leukemia cell counts go up. And if you take a break from ibrutinib, they go down, because the cells then can go back into the lymph nodes and vanish from the bloodstream. And then, treatment is restarted. The leukemia cell count goes back up. And this goes on and on until eventually, over time, with longer treatment, patients achieve remission.



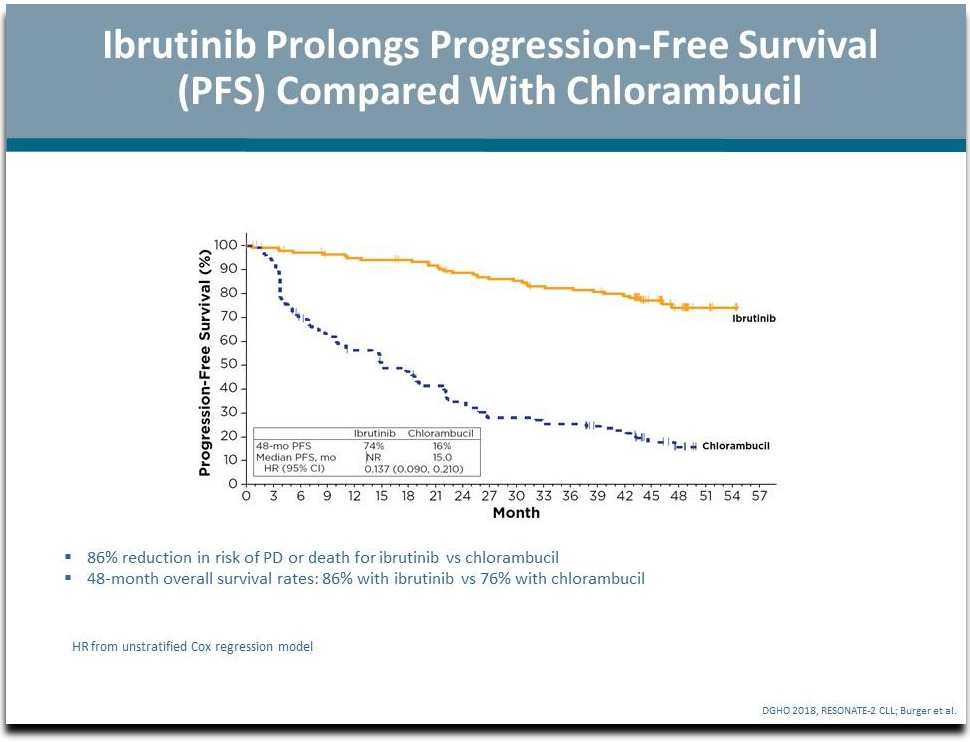
Mechanism of Treatment Related Lymphocytosis in Chronic Lymphocytic Leukemia (CLL) and Mantle Cell Lymphoma (MCL)

So, just to get across this point—how do we think this is all working? On the left-hand side, you see the B-cell receptor. You see these other receptors, the homing receptors, ibrutinib and the other agents, not just ibrutinib, idelalisib and the other BTK or PI3 kinase or spleen tyrosine kinase inhibitors. They are all blocking the B-cell receptor but also these homing receptors. And that results in mobilization, enhanced mobilization of the leukemia cells from the lymph nodes into the blood. Then, you have the higher white counts in the first weeks on treatments. And the cells are trapped in the blood. They cannot go back into the lymph nodes as long as you treat.



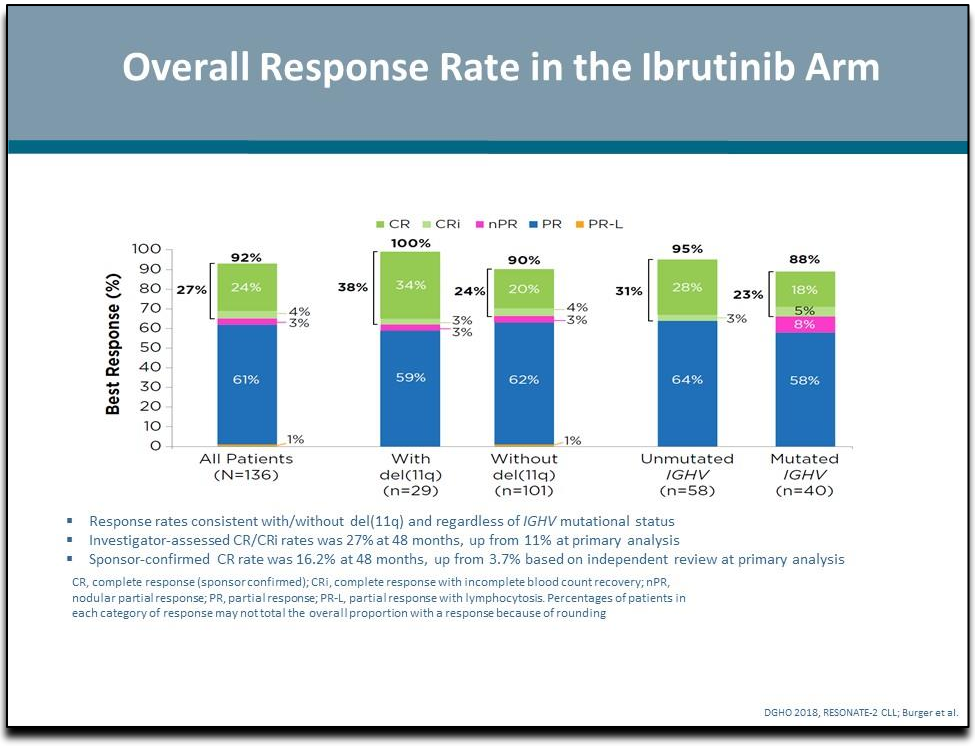
RESONATE-2 (PCYC-1115/1116) Study Design

Now, to the clinical side of things, the different trials that were leading to the approval of the drug—one of them is the RESONATE-2 trial, which is shown here. That's a randomized study comparing ibrutinib and chlorambucil in untreated elderly patients.



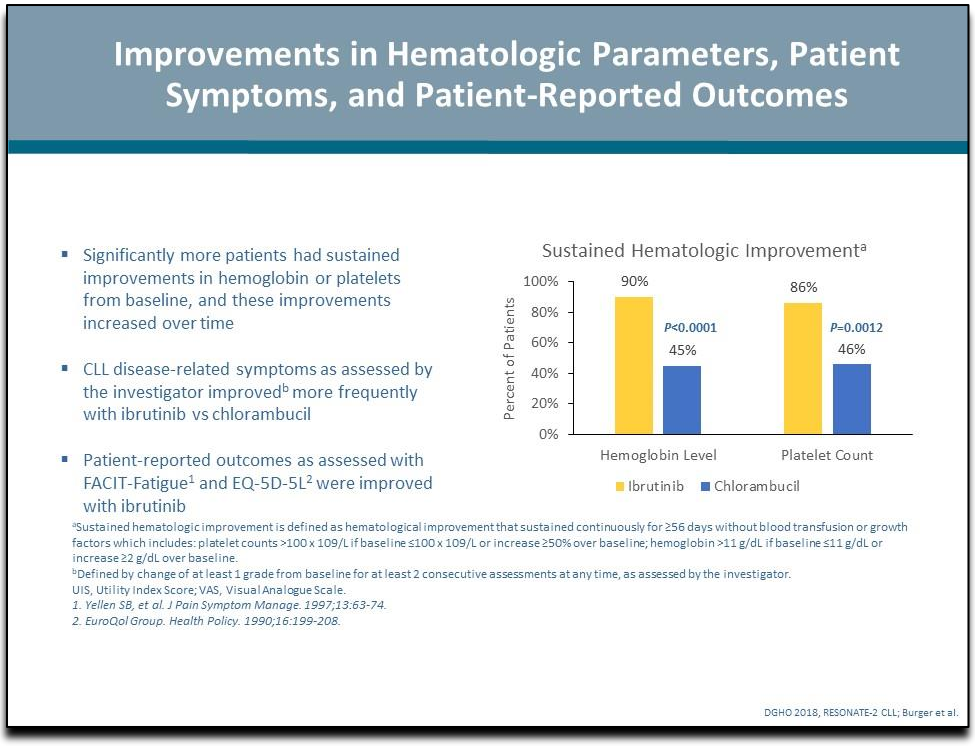
Ibrutinib Prolongs Progression-Free Survival (PFS) Compared With Chlorambucil

That demonstrated a major survival benefit for ibrutinib, shown here—a survival benefit that is durable with this update and that led to frontline approval of the drug.



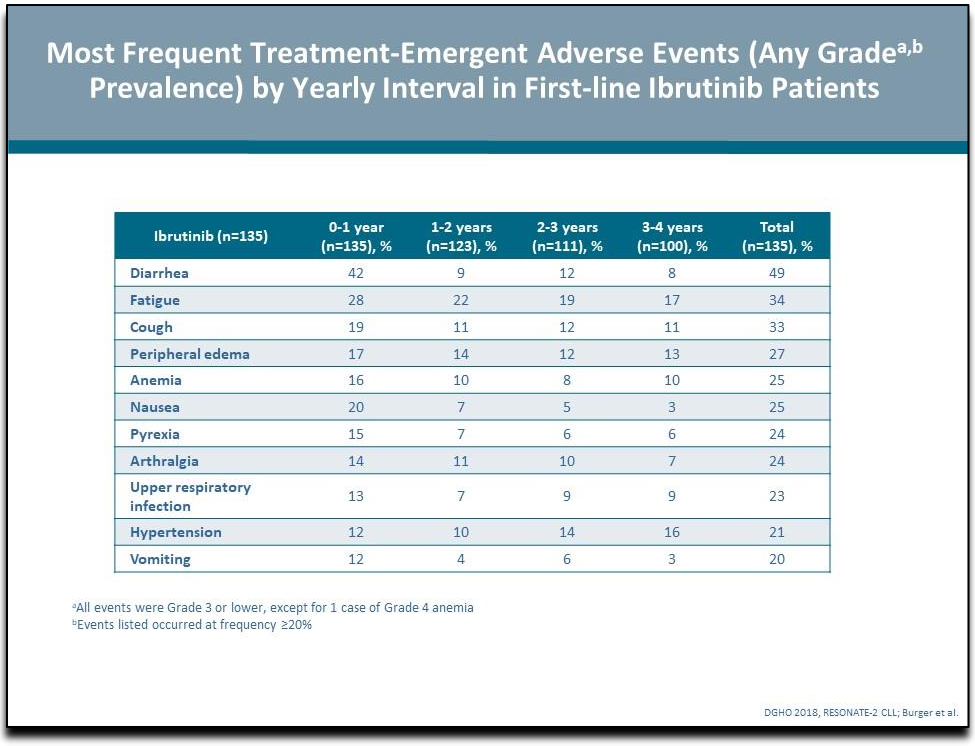
Overall Response Rate in the Ibrutinib Arm

You see here the response rates of all response rates are high. Most patients are responding. More than 90 percent of patients are responding. But, you also see that not all patients have complete responses and complete remissions. There's a majority of patients who have partial remission. And those patients are doing well. But, they still have detectable disease.



Improvements in Hematologic Parameters, Patient Symptoms, and Patient-Reported Outcomes

It improves--treatment with ibrutinib improves red blood cells and platelet counts. And that's shown here. Compared to chlorambucil, the new agents are much better in improving blood counts because they are not myelosuppressive, and therefore patients are doing better, especially if they are anemic or thrombocytopenic, with these agents.



Most Frequent Treatment-Emergent Adverse Events (Any Grade[a,b] Prevalence) by Yearly Interval in First-line Ibrutinib Patients

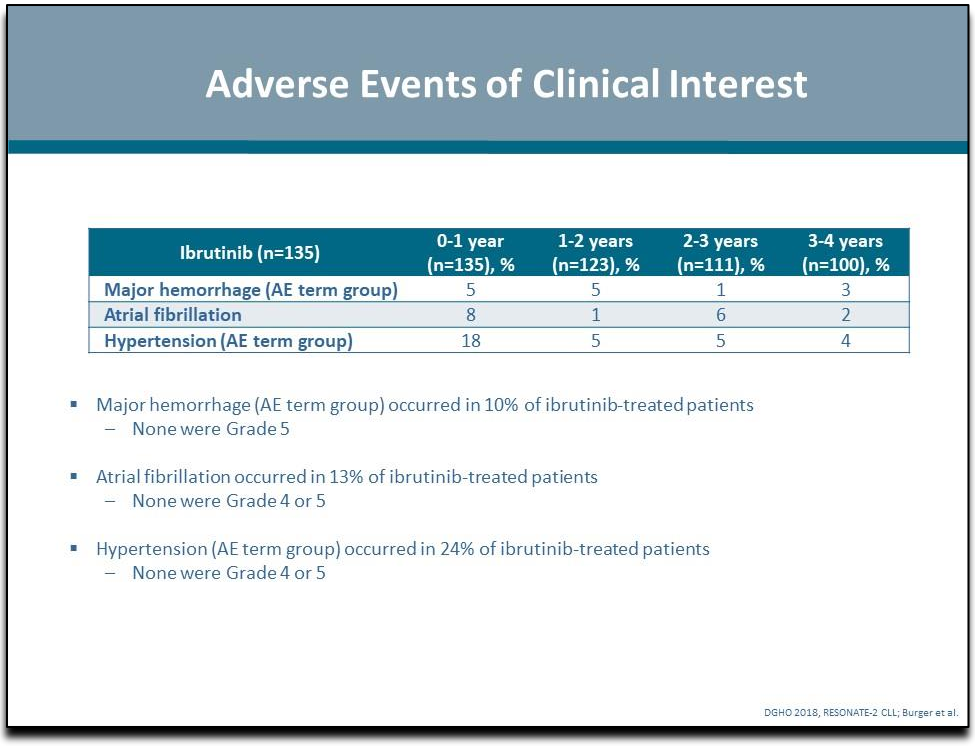
Ibrutinib (n=135)	0-1 year (n=135), %	1-2 years (n=123), %	2-3 years (n=111), %	3-4 years (n=100), %	Total (n=135), %
Diarrhea	42	9	12	8	49
Fatigue	28	22	19	17	34
Cough	19	11	12	11	33
Peripheral edema	17	14	12	13	27
Anemia	16	10	8	10	25
Nausea	20	7	5	3	25
Pyrexia	15	7	6	6	24
Arthralgia	14	11	10	7	24
Upper respiratory infection	13	7	9	9	23
Hypertension	12	10	14	16	21
Vomiting	12	4	6	3	20

[a]All events were Grade 3 or lower, except for 1 case of Grade 4 anemia
[b]Events listed occurred at frequency ≥20%

DGHO 2018, RESONATE-2 CLL; Burger et al.

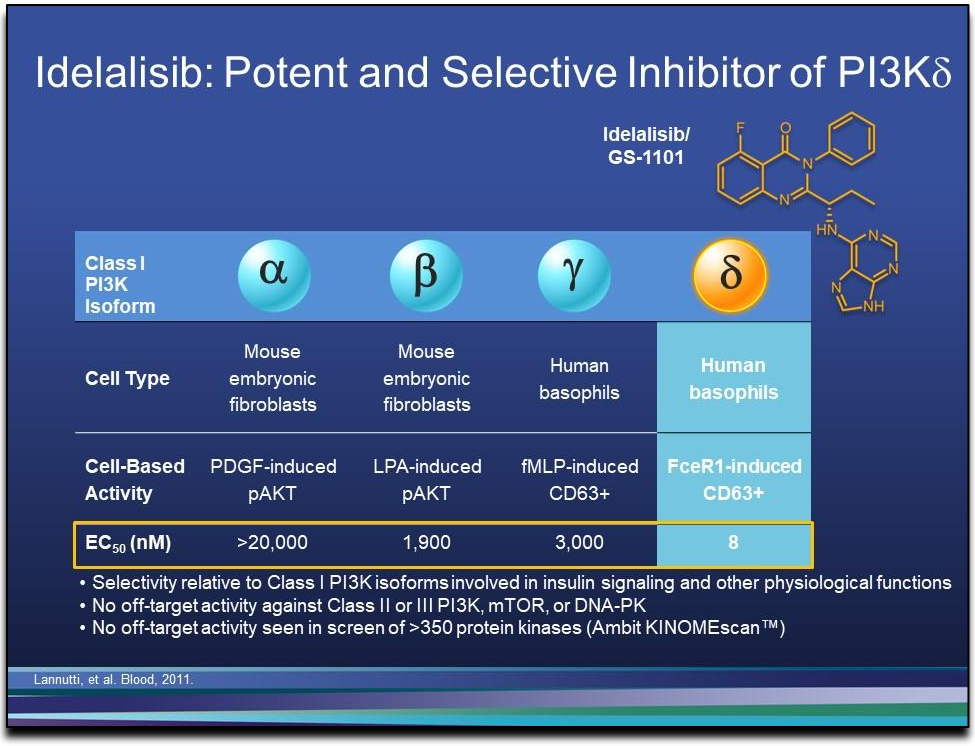
Most Frequent Treatment-Emergent Adverse Events (Any Grade[a,b] Prevalence) by Yearly Interval in First-line Ibrutinib Patients

But, ibrutinib and the other kinase inhibitors are not without side effects either, and some of the side effects are listed here. This is what we are looking at. Patients may have diarrhea early on. But, many of these side effects listed here are transient, and they are more frequent in the first year on treatment. There's nothing really getting worse over time. Most of the side effects are transient in the first months on treatment, and they can be oftentimes managed symptomatically, with maybe the exception of arterial hypertension. That's a signal that continues as patients are on these treatments longer and have to monitored and treated for that.



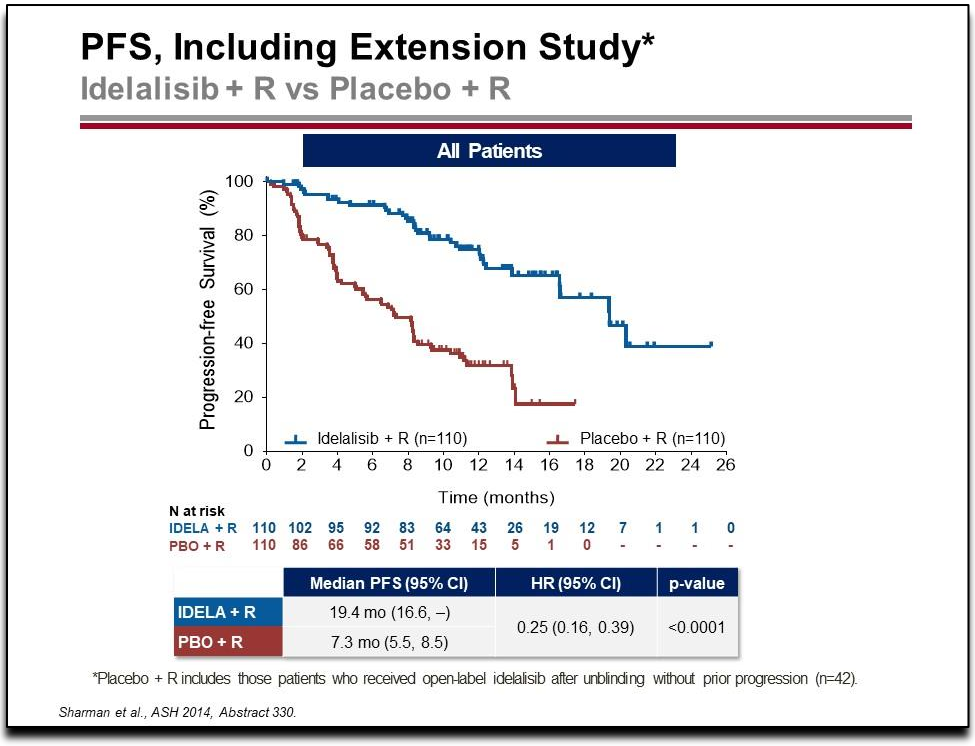
Adverse Events of Clinical Interest

Specific side effects to ibrutinib that need to be monitored and that we need to address—they are not very frequent, but if they happen, they need attention—are bleeding events and atrial fibrillation and arterial hypertension. Atrial fibrillation continuously a signal, but probably a bit more frequent in the first year on treatment. And those are oftentimes treatment related, not in all cases, but in all randomized studies. Atrial fibrillation and bleeding events have been shown to be associated somewhat more frequently with ibrutinib treatments.



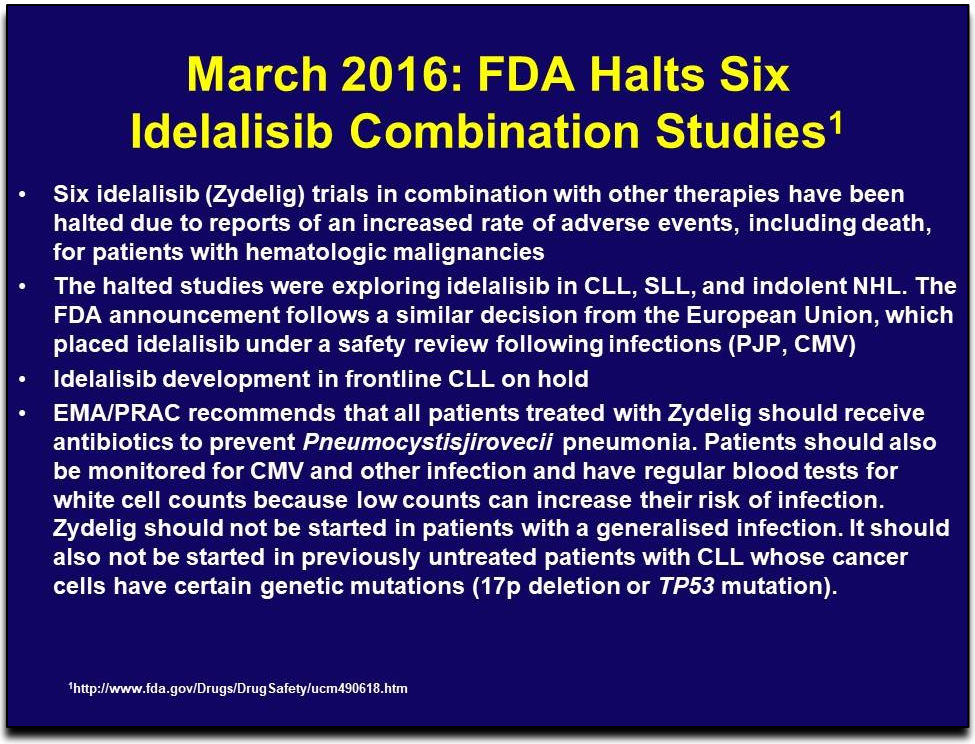
Idelalisib: Potent and Selective Inhibitor of PI3Kδ

What are other treatments besides ibrutinib? One of the drugs that also was developed around the same time is the PI3 kinase inhibitor idelalisib. It is also a kinase inhibitor and an oral agent which blocks this delta form of the PI3 kinase enzyme.



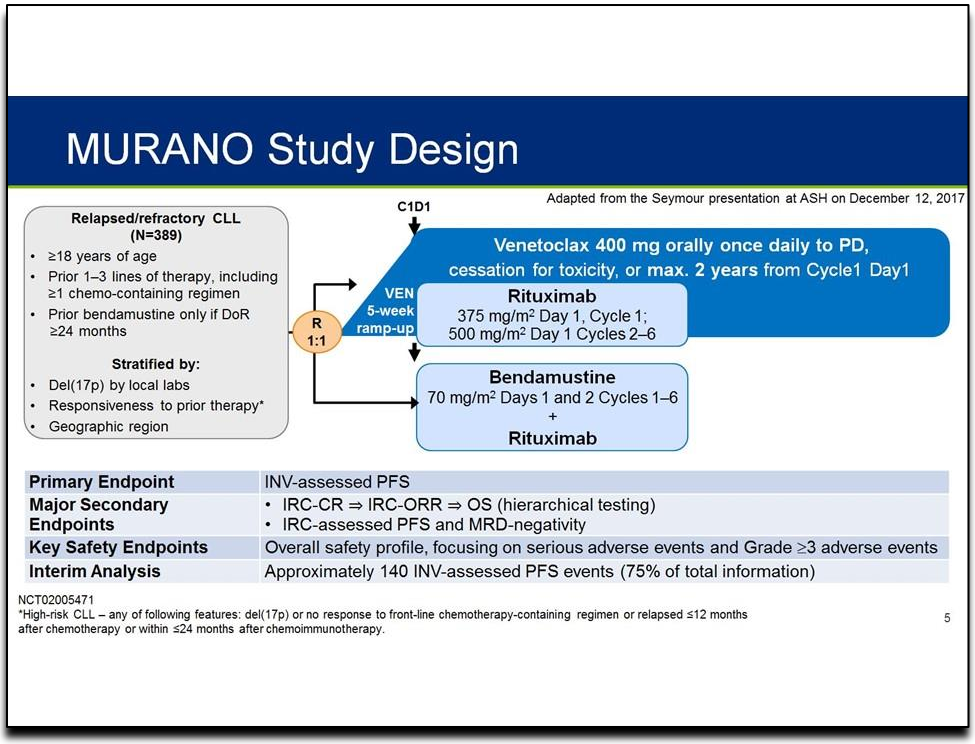
PFS, Including Extension Study*

And it was testing in comparison to rituximab and shown to be more effective in terms of survival, as shown here in this randomized study, and that resulted in the approval for patients with CLL. But, it is not very widely used, and I think one of the reasons is that it is somewhat more complicated to use because of concerns for side effects.



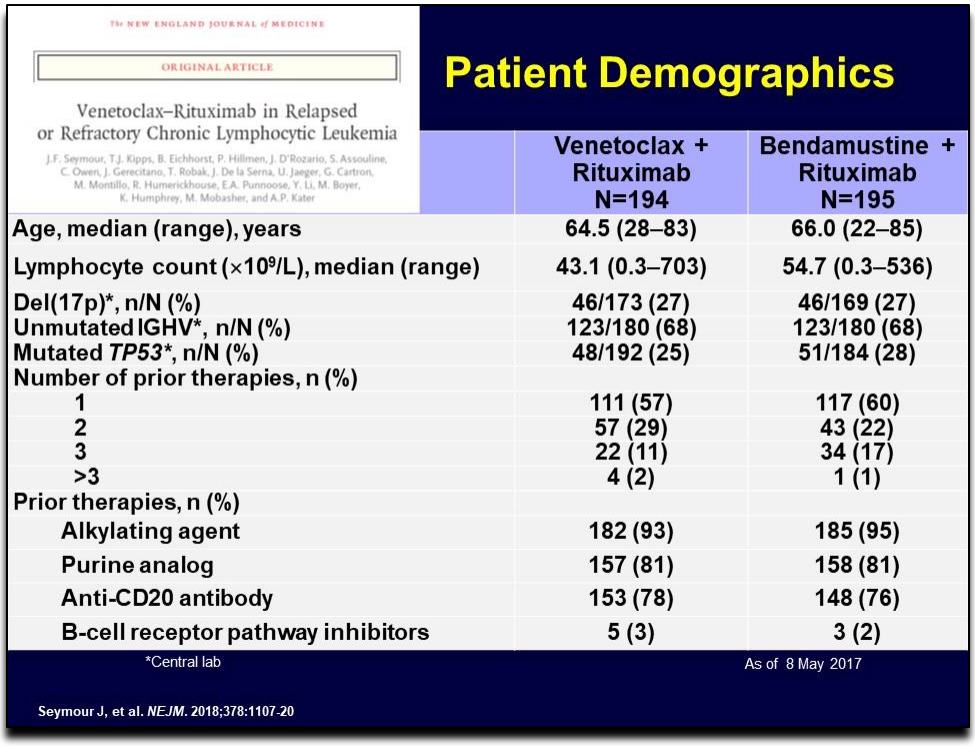
March 2016: FDA Halts Six Idelalisib Combination Studies[1]

And several clinical trials, a while ago, in 2016, were placed on hold because in these studies, idelalisib, the PI3 kinase inhibitor, was somewhat more associated with complications around infections—pneumocystis infections and autoimmune complications like colitis and hepatitis have been a concern. So, patients need to be more closely monitored if they are treated with this particular agent, which overall is perceived, I think, by us as somewhat more complicated and potentially more toxic.



MURANO Study Design

The last agent I wanted to discuss is the PCL2 antagonist, venetoclax. That also has gained a lot of attention in the last maybe 2 or 3 years. One of the biggest studies was a randomized study in relapsed to CLL patients where venetoclax, in combination with rituximab was compared to one of our traditional chemotherapy regimen, bendamustine/rituximab.



THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Venetoclax–Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia

J.F. Seymour, T.J. Kipps, B. Eichhorst, P. Hillmen, J. D'Rozario, S. Assouline, C. Owen, J. Gerecitano, T. Robak, J. De la Serna, U. Jaeger, G. Cartron, M. Montillo, R. Humerickhouse, E.A. Punnoose, Y. Li, M. Boyer, K. Humphrey, M. Mobasher, and A.P. Kater

Patient Demographics

	Venetoclax + Rituximab N=194	Bendamustine + Rituximab N=195
Age, median (range), years	64.5 (28–83)	66.0 (22–85)
Lymphocyte count (×10⁹/L), median (range)	43.1 (0.3–703)	54.7 (0.3–536)
Del(17p)*, n/N (%)	46/173 (27)	46/169 (27)
Unmutated IGHV*, n/N (%)	123/180 (68)	123/180 (68)
Mutated *TP53**, n/N (%)	48/192 (25)	51/184 (28)
Number of prior therapies, n (%)		
1	111 (57)	117 (60)
2	57 (29)	43 (22)
3	22 (11)	34 (17)
>3	4 (2)	1 (1)
Prior therapies, n (%)		
Alkylating agent	182 (93)	185 (95)
Purine analog	157 (81)	158 (81)
Anti-CD20 antibody	153 (78)	148 (76)
B-cell receptor pathway inhibitors	5 (3)	3 (2)

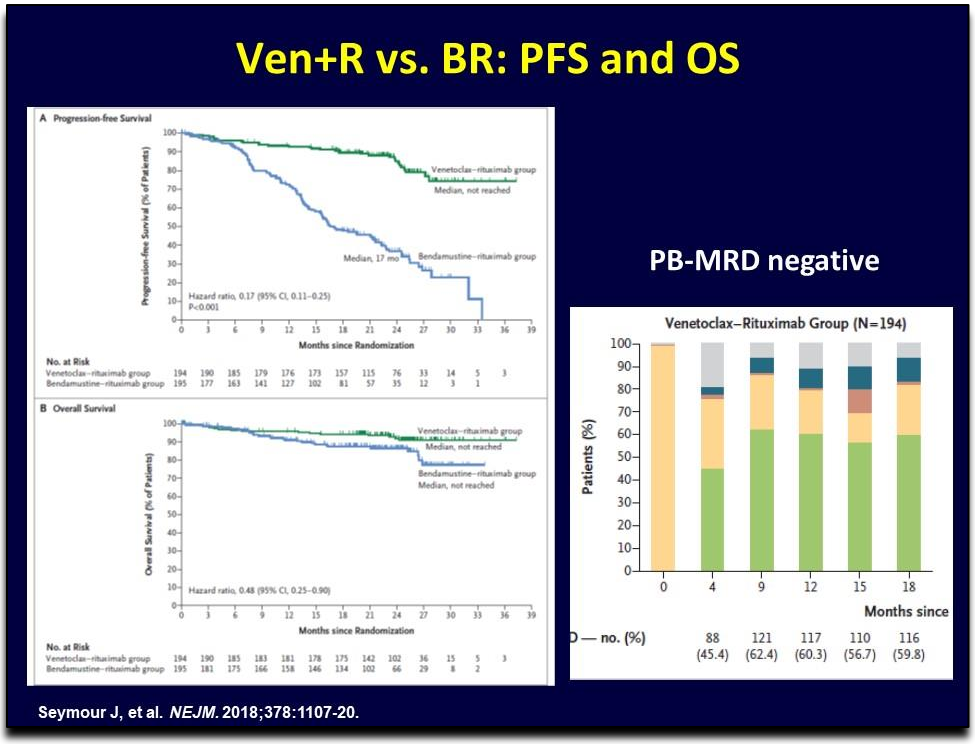
*Central lab

As of 8 May 2017

Seymour J, et al. *NEJM*. 2018;378:1107-20

Patient Demographics

Slide provides additional information.



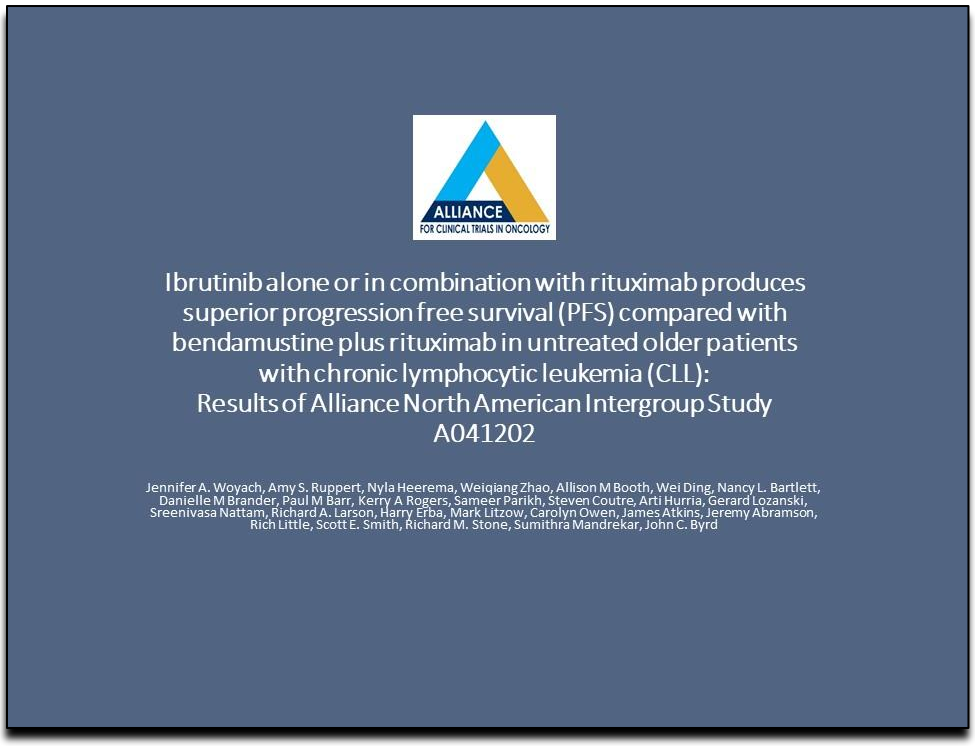
Ven+R vs. BR: PFS and OS

PB-MRD negative

Seymour J, et al. *NEJM*. 2018;378:1107-20.

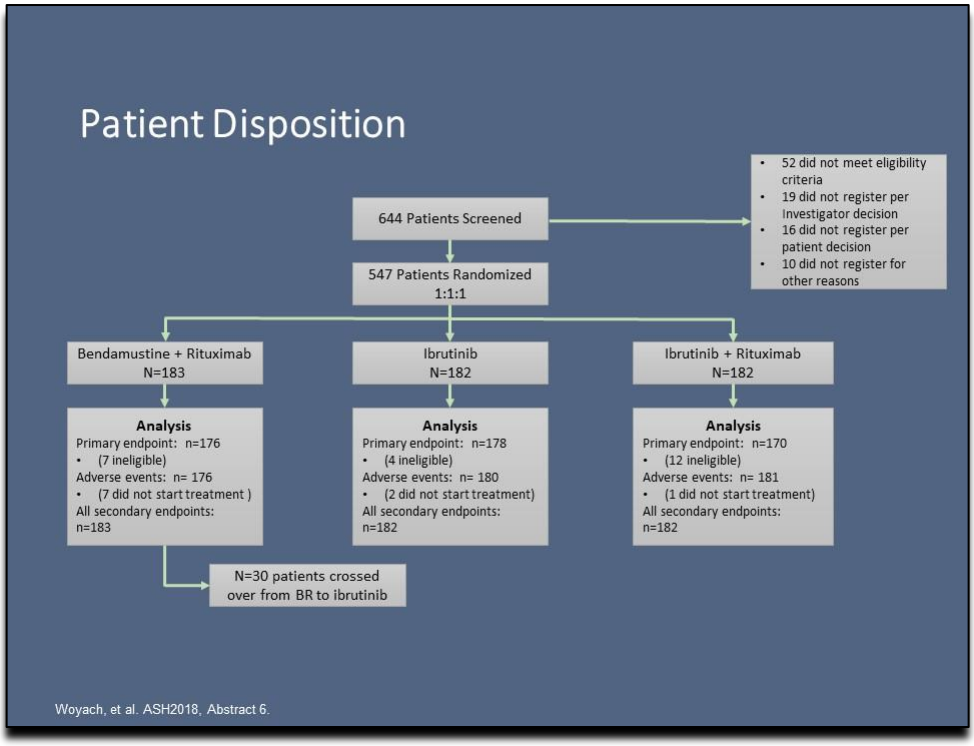
Ven+R vs. BR: PFS and OS

And, in this study, clearly the new agent was doing better, probably best demonstrated, again, by the survival curves, progression-free and overall survival, where you see, again, a big gap between BR and the newer type of approach. And that led to the approval of venetoclax for CLL patients.



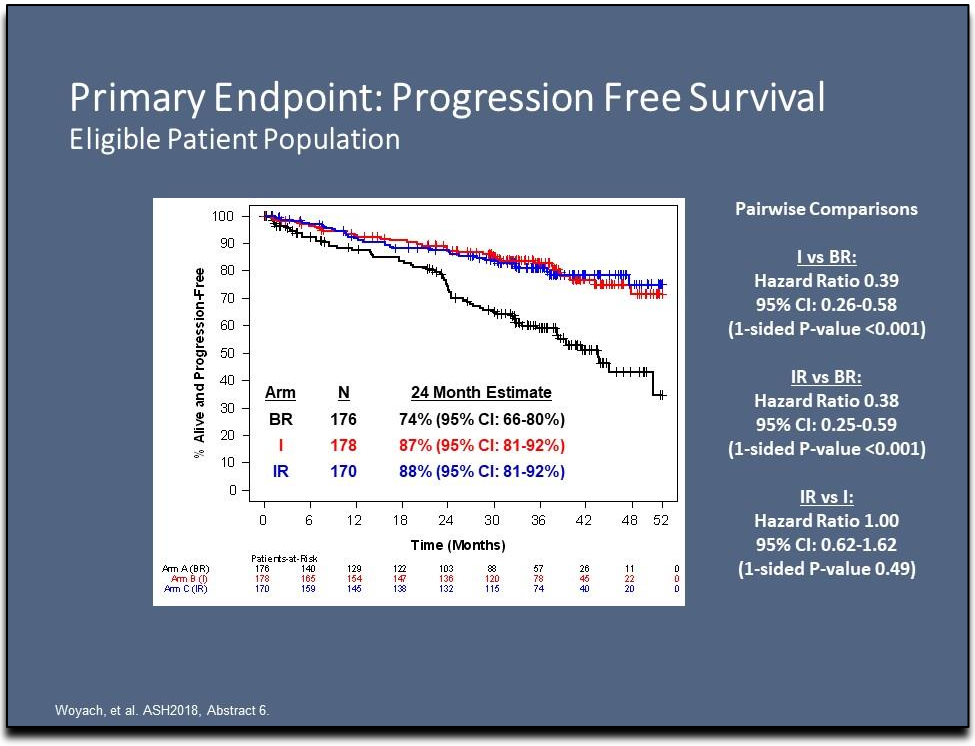
Ibrutinib alone or in combination with rituximab produces superior progression free survival (PFS) compared with bendamustine plus rituximab in untreated older patients with chronic lymphocytic leukemia (CLL): Results of Alliance North American Intergroup Study A041202

Now, the last few slides, I'm going to use maybe another 5 minutes to discuss the latest data of randomized studies, comparing now traditional chemo-immunotherapy versus new agents. There was a study presented at last ASH as well as published comparing ibrutinib, ibrutinib/rituximab with bendamustine and rituximab in untreated patients.



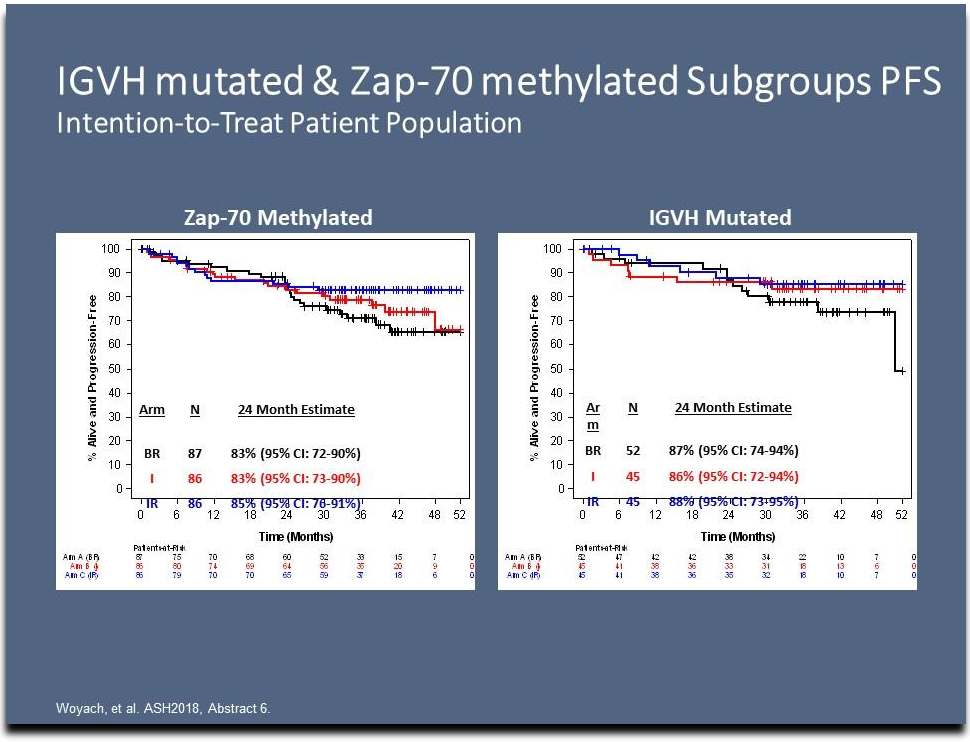
Patient Disposition

Slide provides additional information**.**



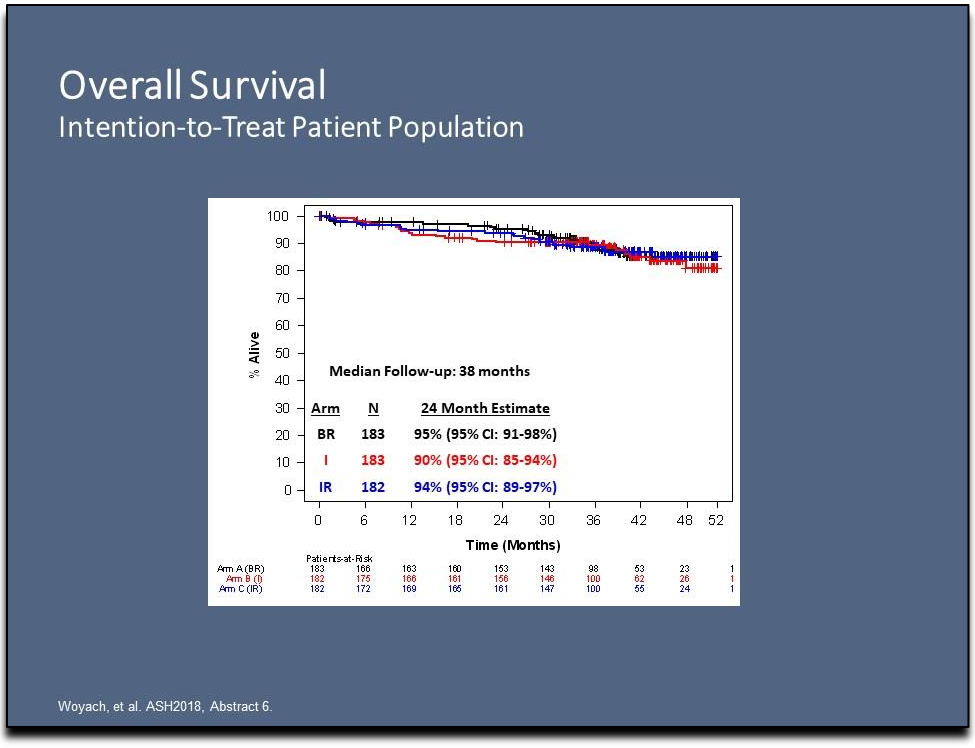
Primary Endpoint: Progression Free Survival Eligible Patient Population

And when you go to the survival data here, you see bendamustine/rituximab is not doing as well in terms of progression-free survival as patients treated with ibrutinib or ibrutinib/rituximab. And it doesn't seem that the addition of rituximab to ibrutinib is adding any survival benefit in this study.



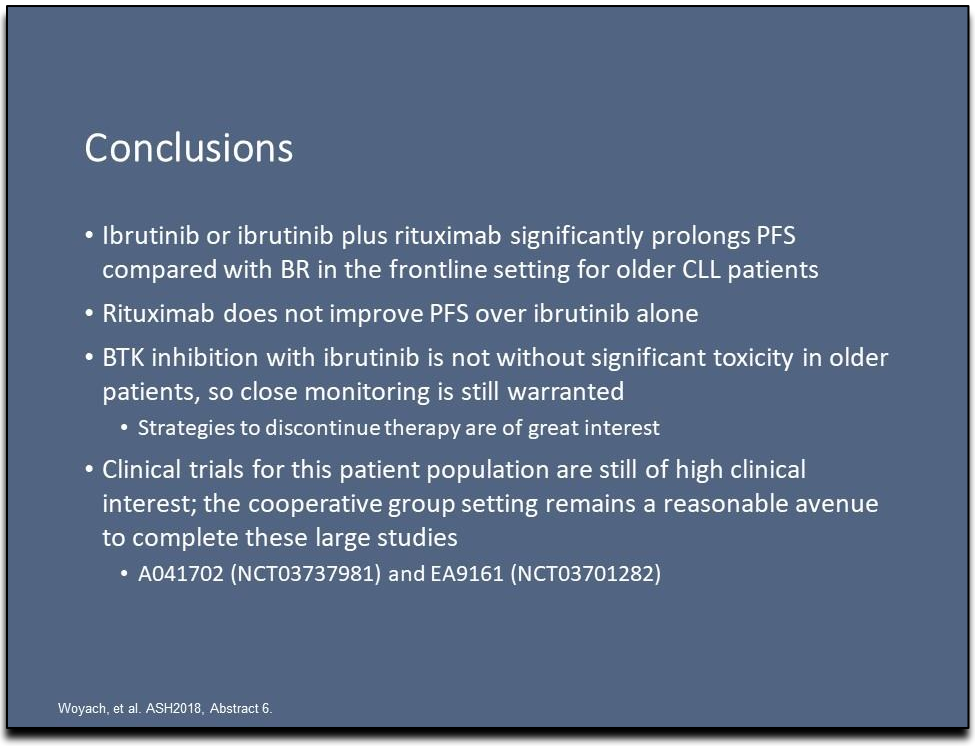
IGVH mutated & Zap-70 methylated Subgroups PFS Intention-to-Treat Patient Population

What is maybe interesting though is that, if you look at the low-risk patients, that bendamustine/rituximab is doing still quite well and the difference is smaller.



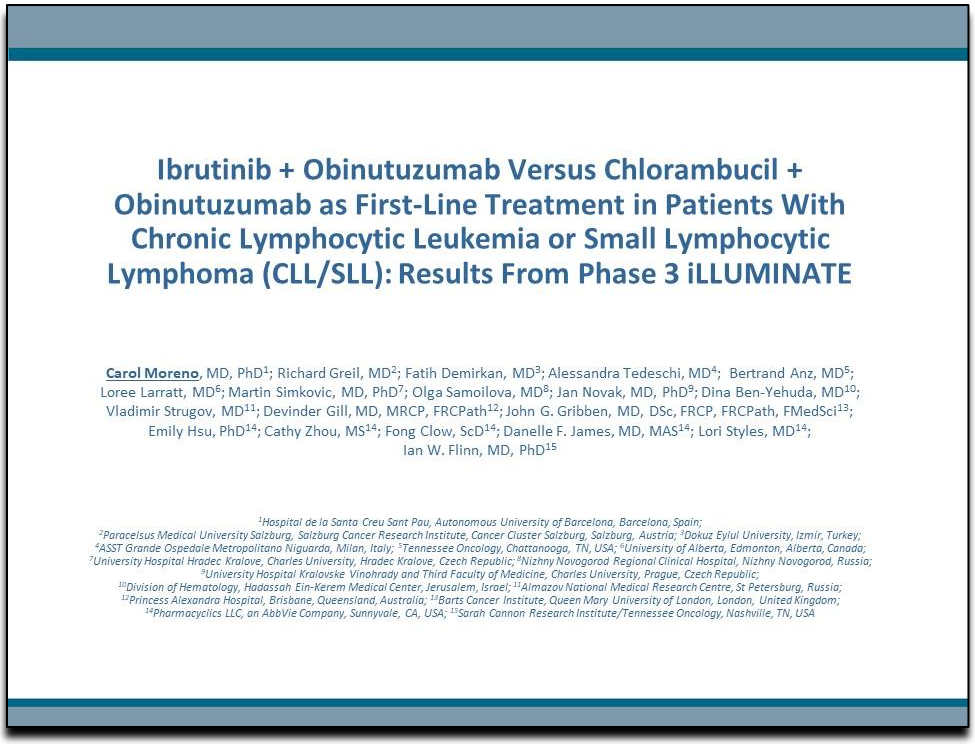
Overall Survival Intention-to-Treat Patient Population

And in terms of overall survival, there was no difference between the different treatment arms.



Conclusions

But, the conclusion, overall, from this randomized study was that, in previously untreated patients, patients treated with a novel agent with ibrutinib were doing better, had better progression-free survival than those treated with bendamustine/rituximab.



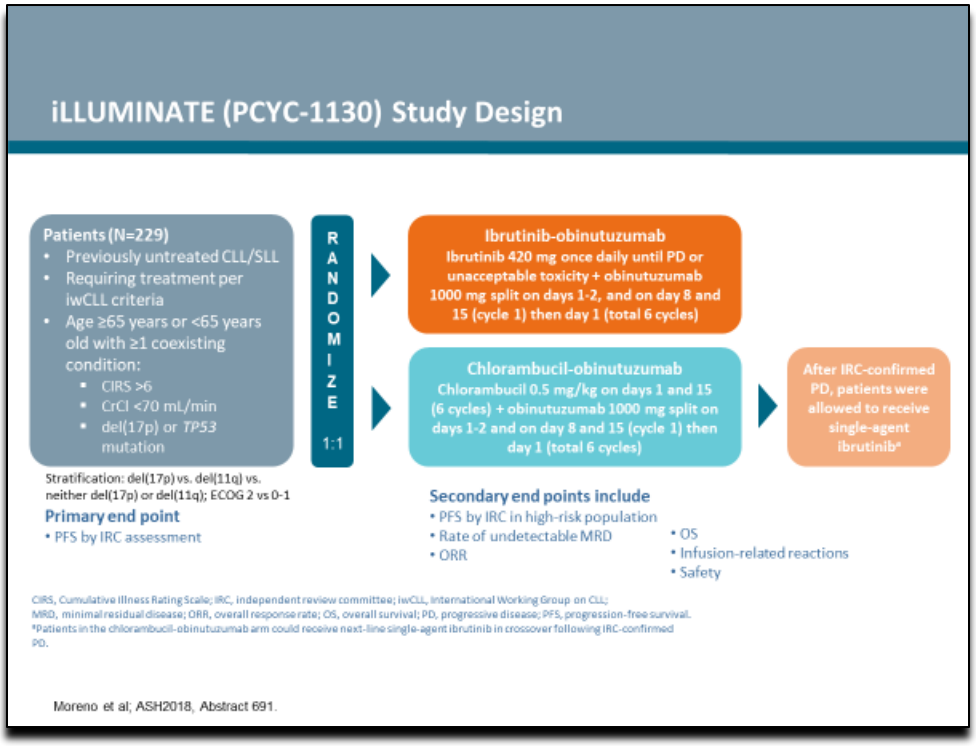
Ibrutinib + Obinutuzumab Versus Chlorambucil + Obinutuzumab as First-Line Treatment in Patients With Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma (CLL/SLL): Results From Phase 3 iLLUMINATE

Carol Moreno, MD, PhD[1]; Richard Greil, MD[2]; Fatih Demirkan, MD[3]; Alessandra Tedeschi, MD[4]; Bertrand Anz, MD[5]; Loree Larratt, MD[6]; Martin Simkovic, MD, PhD[7]; Olga Samoilova, MD[8]; Jan Novak, MD, PhD[9]; Dina Ben-Yehuda, MD[10]; Vladimir Strugov, MD[11]; Devinder Gill, MD, MRCP, FRCPath[12]; John G. Gribben, MD, DSc, FRCP, FRCPath, FMedSci[13]; Emily Hsu, PhD[14]; Cathy Zhou, MS[14]; Fong Clow, ScD[14]; Danelle F. James, MD, MAS[14]; Lori Styles, MD[14]; Ian W. Flinn, MD, PhD[15]

[1]Hospital de la Santa Creu Sant Pau, Autonomous University of Barcelona, Barcelona, Spain; [2]Paracelsus Medical University Salzburg, Salzburg Cancer Research Institute, Cancer Cluster Salzburg, Salzburg, Austria; [3]Dokuz Eylul University, Izmir, Turkey; [4]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [5]Tennessee Oncology, Chattanooga, TN, USA; [6]University of Alberta, Edmonton, Alberta, Canada; [7]University Hospital Hradec Kralove, Charles University, Hradec Kralove, Czech Republic; [8]Nizhny Novogorod Regional Clinical Hospital, Nizhny Novogorod, Russia; [9]University Hospital Kralovske Vinohrady and Third Faculty of Medicine, Charles University, Prague, Czech Republic; [10]Division of Hematology, Hadassah Ein-Kerem Medical Center, Jerusalem, Israel; [11]Almazov National Medical Research Centre, St Petersburg, Russia; [12]Princess Alexandra Hospital, Brisbane, Queensland, Australia; [13]Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; [14]Pharmacyclics LLC, an AbbVie Company, Sunnyvale, CA, USA; [15]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA

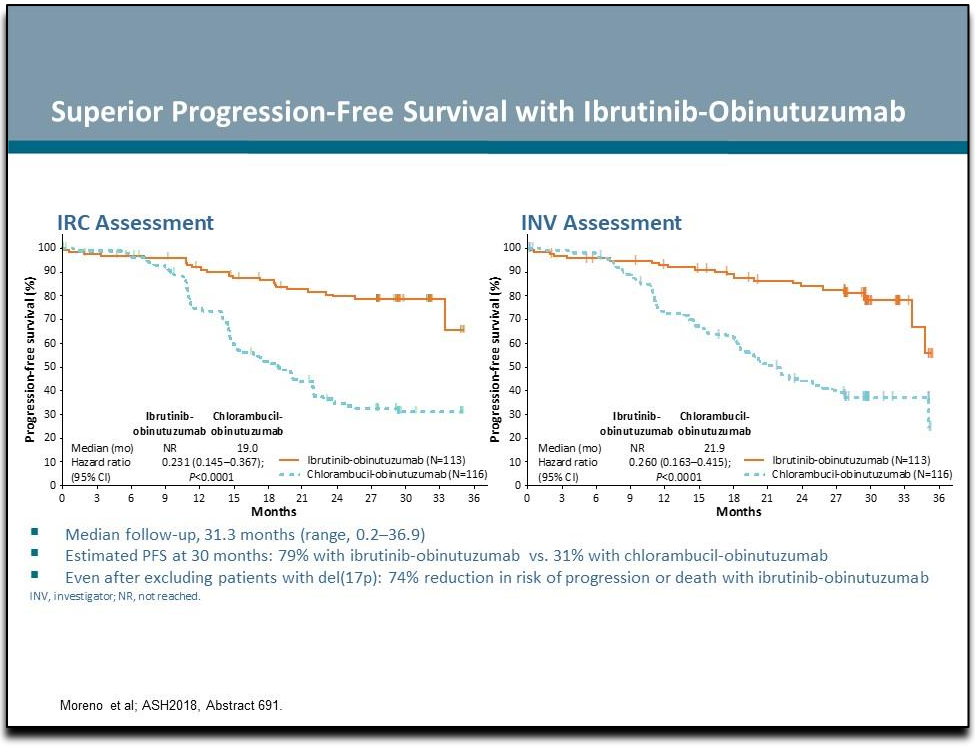
Ibrutinib + Obinutuzumab Versus Chlorambucil + Obinutuzumab as First-Line Treatment in Patients With Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma (CLL/SLL): Results From Phase 3 iLLUMINATE

Along the same lines, the other traditional regimen we discussed for elderly patients is chlorambucil, now with CD20 antibodies, compared to ibrutinib and obinutuzumab. The iLLUMINATE trial where half of the patients were receiving ibrutinib obinutuzumab, the other half chlorambucil/obinutuzumab.



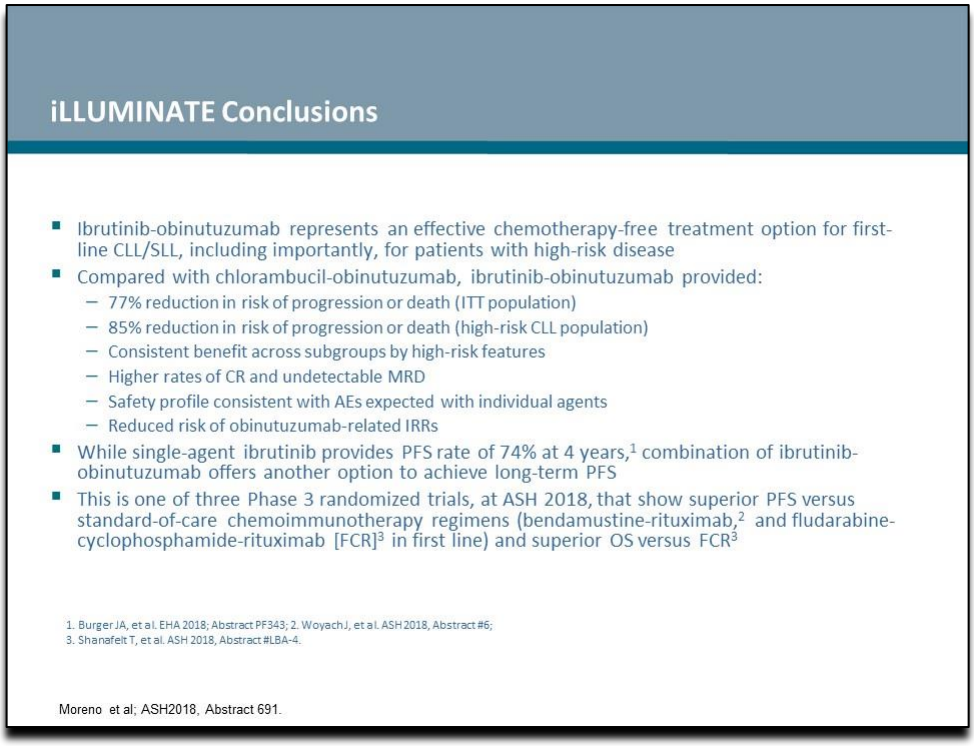
iLLUMINATE (PCYC-1130) Study Design

Slide provides additional information.



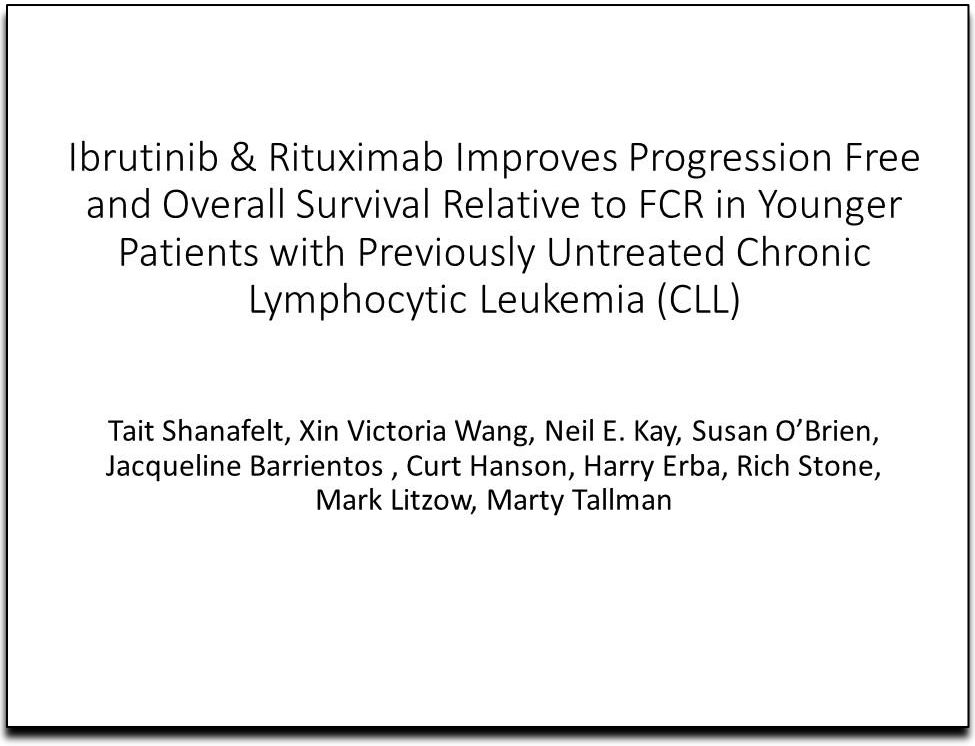
Superior Progression-Free Survival with Ibrutinib-Obinutuzumab

And the same theme here, like in the previous trial, is that the ibrutinib based treatment arm is doing much better than the traditional chlorambucil based treatment.



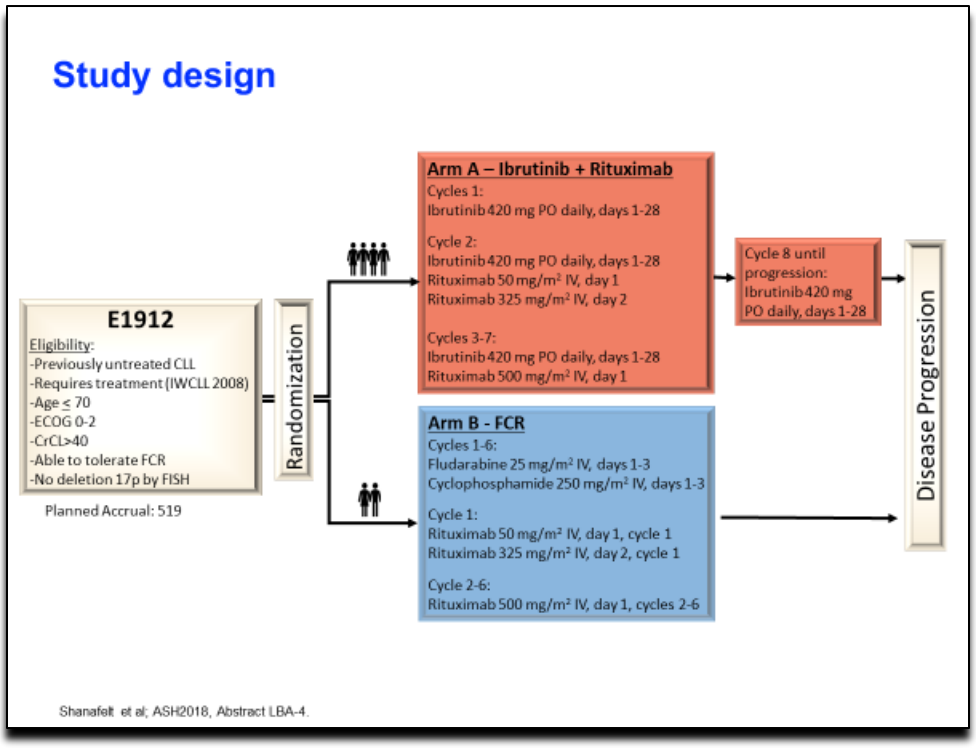
iLLUMINATE Conclusions

Slide provides additional information.



Ibrutinib & Rituximab Improves Progression Free and Overall Survival Relative to FCR in Younger Patients with Previously Untreated Chronic Lymphocytic Leukemia (CLL)

And the last trial to discuss would be this study, which compared our tradition FCR regimen for younger, fit CLL patients with ibrutinib/rituximab.



Study Design

Slide provides additional information.

Patient Characteristics Were Well Balanced

Baseline characteristics		IR n=354	FCR n=175	Total
Median age (y)		58	57	58
Age ≥ 60		41.0%	40.0%	40.6%
Female		33.3%	31.4%	32.7%
ECOG = 0		63.8%	62.3%	63.3%
Rai stage 0		3.1%	5.1%	3.8%
Rai stage I-II		52.8%	53.7%	53.1%
Rai stage III-IV		44.1%	41.1%	43.1%
FISH	11q deletion	22.0%	22.3%	22.2%
	Trisomy 12	19.8%	15.4%	18.3%
	13q deletion	34.2%	33.1%	33.8
B2M >3.5 mg/L		51.9%	48.0%	50.6%
IGHV Unmutated*		75.0%	61.7%	71.1%

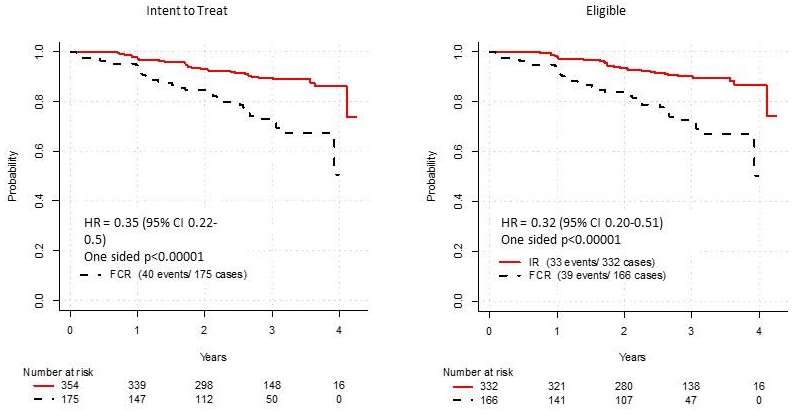
* Tested in 437 (82%) patients

Shanafelt et al; ASH2018, Abstract LBA-4.

Patient Characteristics Were Well Balanced

Here the patient characteristics. You can see, this is a younger patient population.

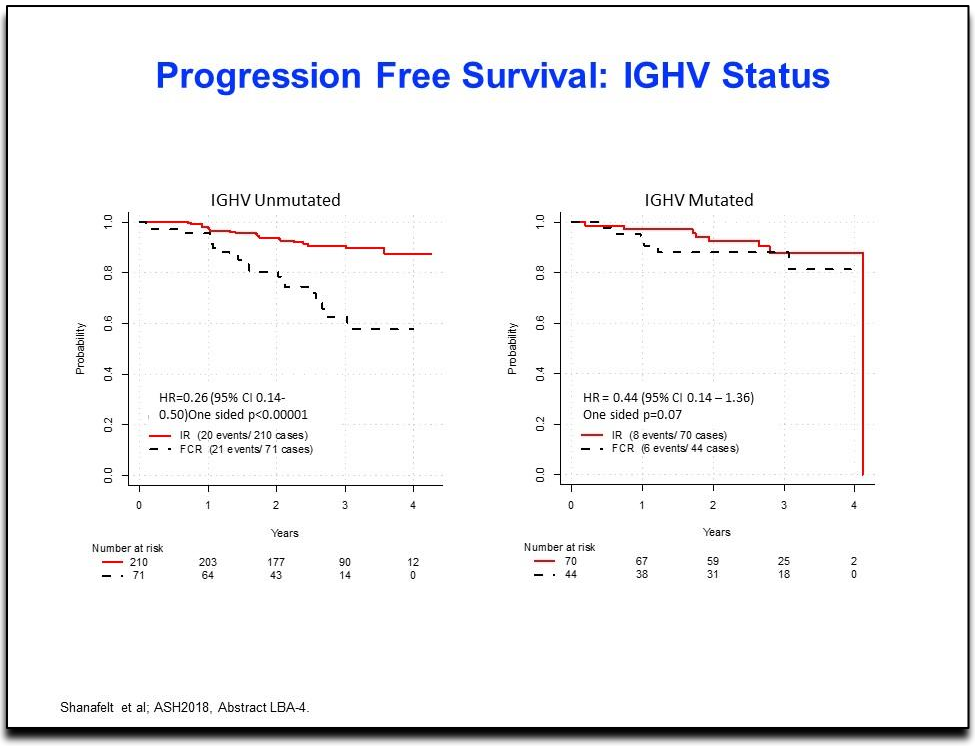
Progression Free Survival



Shanafelt et al; ASH2018, Abstract LBA-4.

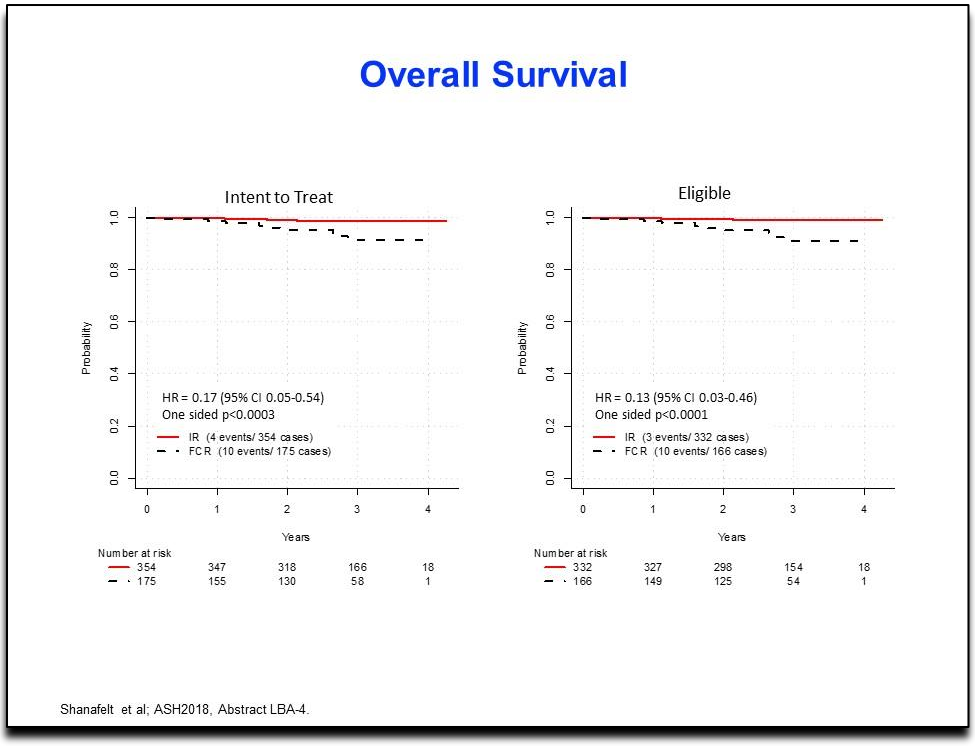
Progression Free Survival

And the theme continues that the new targeted agents are doing better in terms of progression-free trial. Here, the top curves are ibrutinib/rituximab, and the FCR-treated patients have shorter progression-free survival.



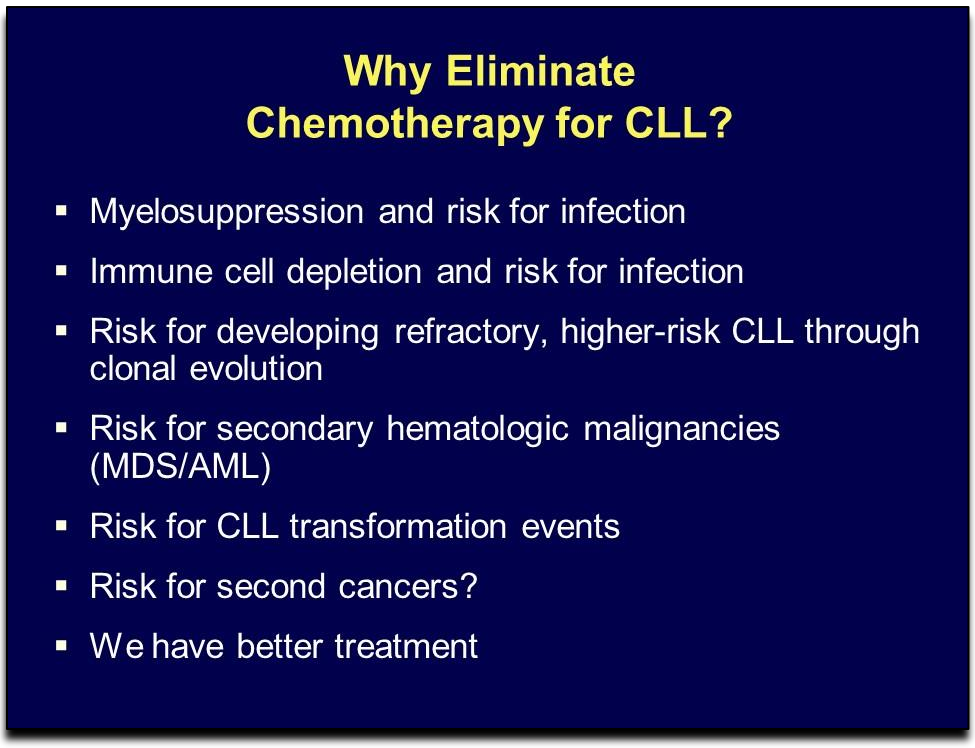
Progression Free Survival: IGHV Status

Although, we must also say that the difference is much smaller in the low-risk patients.



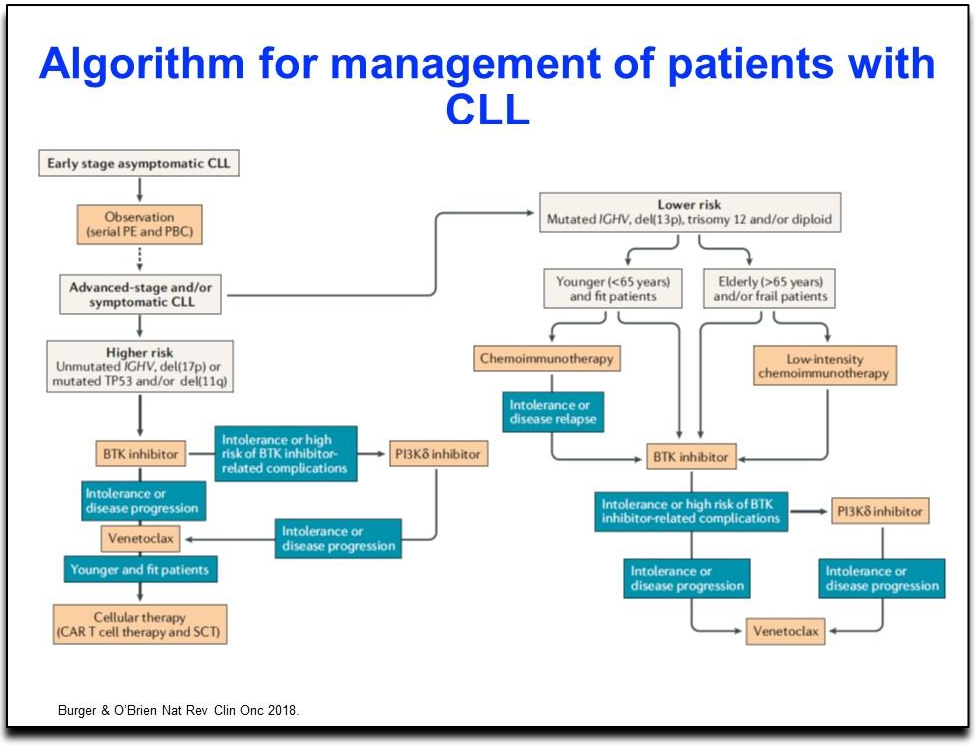
Overall Survival

But, there was also a statistically significant overall survival benefit if patients were treated with the ibrutinib based regimen.



Why Eliminate Chemotherapy for CLL?

So, the trend, in my opinion, in my view, is that we are using, these days, much less chemotherapy. There might be a role for a very small subset of CLL patients for chemotherapy-based treatment. But, overall, the trend is that most patients will be treated more and more with the novel agents. And the reasons why this is, for our patients, a good trend—that's summarized here. We have with the new agents less myelosuppression, less risk for infection. We have less compromise of the immune system with the new agents. Although there are still issues, even with the new agents, there's less risk for developing these problematic secondary cancers, secondary AML and secondary MDS. There's probably—even though it's not formally proven—there's probably less risk for transformation. And with the randomized studies, I think we have good reason to say, for most patients, we now have better treatment, and we should move away from the chemotherapy-based approaches.



Algorithm for management of patients with CLL

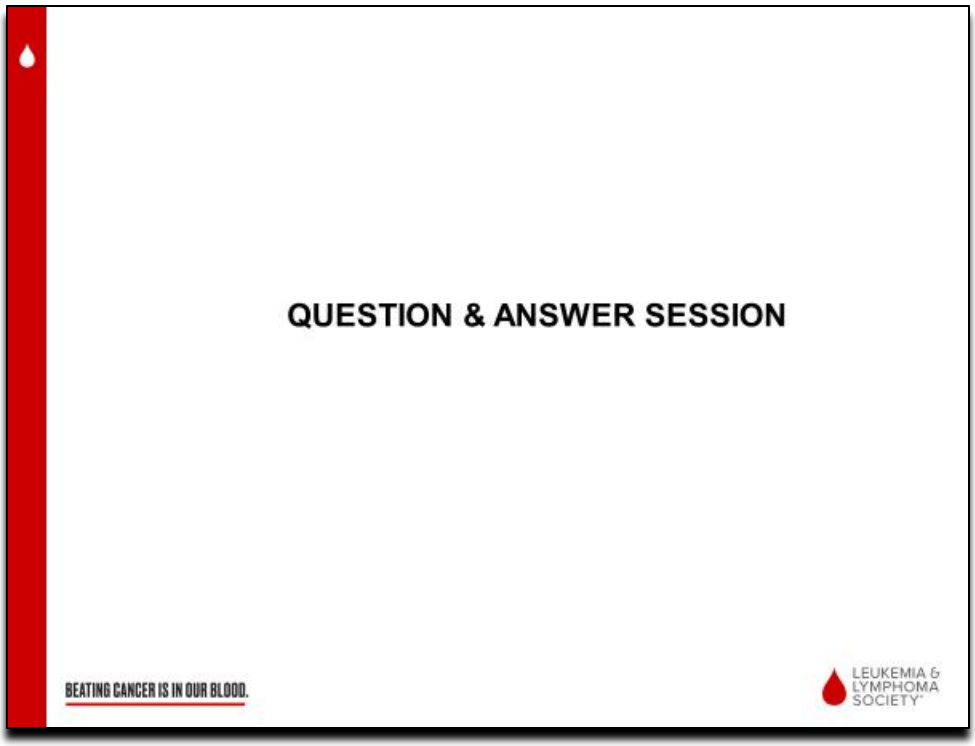
Last slide here showing kind of a treatment guidelines that we used if we treat the patients outside of clinical studies. If patients are early stage, we would manage them with observation. And if a patient then needs treatment, we would distinguish high- versus low-risk patients. For the high-risk patients who are unmutated and/or 17p or 11q deleted, we would go straight to new agents at this time. Ibrutinib, BTK inhibitor is the one which is most widely and which is used and which is approved in the frontline setting. So, that would be the first choice. But, patients can be intolerant or can have problems over time with these agents and then may sometimes move on to PI3 kinase inhibitors, or they could go to venetoclax based treatment. And sometimes if they are younger, need stem cell transplant. But, this is high-risk patients.

The low-risk patients would be still distinguished between younger and elderly patients. And traditionally, for the younger patients, we use chemo-immunotherapy. They're still based on this long-term survival outcome that we discussed with plateau of FCR. There's still a possibility of using chemo-immunotherapy if somebody doesn't want to go on a kinase inhibitor or has problems with it during long-term treatment. You could still get good outcome. But, the desire would be to reduce the amount of chemotherapy, like what we are using in the iFCG regimen, or you could go, based on the randomized study, straight to the kinase inhibitor for these patients and also for the elderly patients. So, I think the

trend is to use more the kinase inhibitors in this patient population, based mostly also on this recent data.

Thank you!

With that, I would like to conclude. I thank you very much for your attention.



Q&A
And I look forward to our discussion over the next 20 minutes or so.

Ms. Lizette Figueroa-Rivera:
Thank you so much, Dr. Burger, for your very informative presentation. It's now time for our question and answer portion of our program.

Ms. Lizette Figueroa-Rivera:
Thank you. And Doctor, along the same lines as treatment, Ronald is asking: Will CLL be cured by the combination of venetoclax and ibrutinib? Your thoughts on that?

Jan A. Burger, MD, PhD:
We don't have the data. I think we are hoping that some patients may be cured. But, you've seen the data with FCR. It took us about 15 years of follow up to come to the conclusion that maybe 50, 60 percent of the mutated patients, a subset of patients, are potentially cured by FCR. And it's going to take about the same amount of time to come to the same conclusion with these new trials. So, there is hope. But, I doubt every patient is going to be cured by this combination. But, those studies are early, and we just have follow up of probably 1 or 2 years at this point. So, you need to stay tuned. The hope is there. I think it is justified. But, we're not sure at this stage.

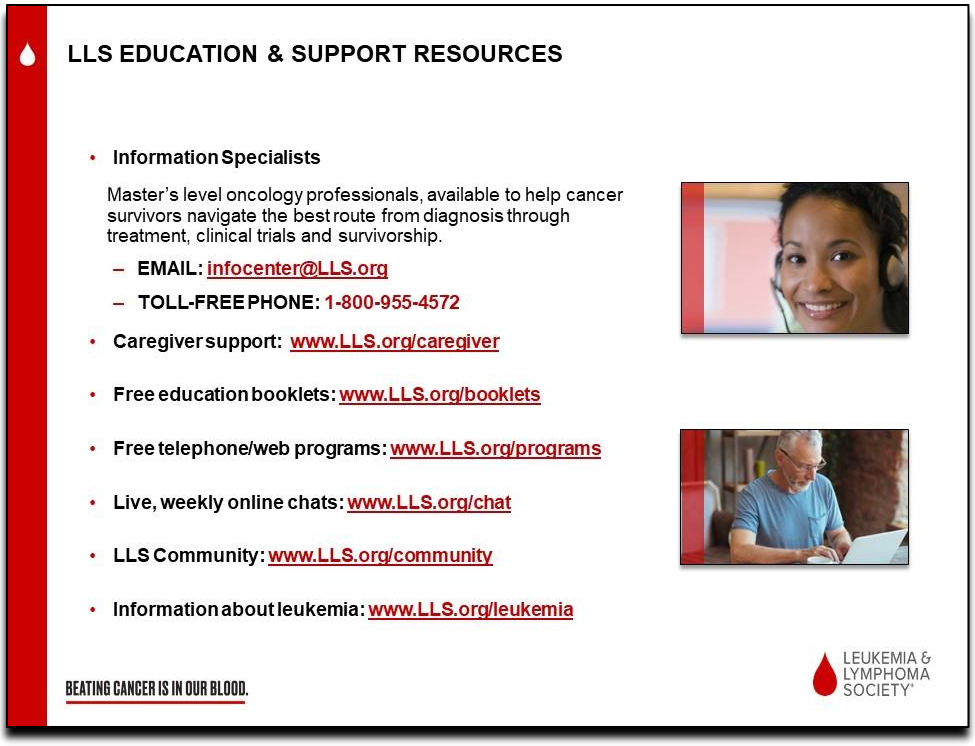
Ms. Lizette Figueroa-Rivera:
And I think also, talking about cure, Carolyn is asking: When you have CLL, does it always come back? I've been off chemo for 5 years now.

Jan A. Burger, MD, PhD:
I know where this question is coming from, because if you read a textbook or many discussions, we still say CLL, in general, is an incurable disease. And I think there's good reasons for hope that this is changing. But, to validate that, we need long-term follow up on the different programs. And maybe not for every patient the goal should be cure. I think, in general, for the younger patients, it would be really desirable to have a curative regimen, probably for everybody. But, we don't want intensive regimen probably in elderly patients where quality of life is very important too. And for that reason, it's not a straightforward answer. It doesn't always come back.

But, with the kinase inhibitors, which we are now using so much, we don't really cure the disease. For example, if you treat with ibrutinib by itself, even after 3 or 5 years, there's usually still some disease left. And if those patients stop, they might eventually relapse and potentially then could be treated with the same agent again. So, for most patients we say yes, this is a disease, at this stage, most patients may not be cured, and we just control the disease, and we can do that by maintaining the quality of life, and cure is not always the focus of discussions. And in many of these treatment situations, for other patients where we treat more intensively like with ibrutinib venetoclax combinations, for example, there we want to get patients into deep remissions. And we hope some of them will be cured.

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

Operator:
Thank you. Our next question is from the line of William in Pennsylvania. William, please proceed with your question.



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William:
I'm currently on 200 milligrams of Venclexta® each day, along with 6 cycles of Rituxan®. I've had 5 cycles of Rituxan® already. But, I can only tolerate approximately 200 milligrams of the Venclexta®. Would that be sufficient, going forward, to be able to stabilize the condition I have?

Jan A. Burger, MD, PhD:
I think so. I mean, that's something we experience quite a lot. Venetoclax, Venclexta® has been around now a few years, and we've been using it increasingly and building up our experience with it. But, from my practice, I know many patients cannot tolerate the 400 milligrams because it is a bit more myelosuppressive, and then, oftentimes other blood counts would suffer too much and patients may become anemic or neutropenic, if they are on higher doses.

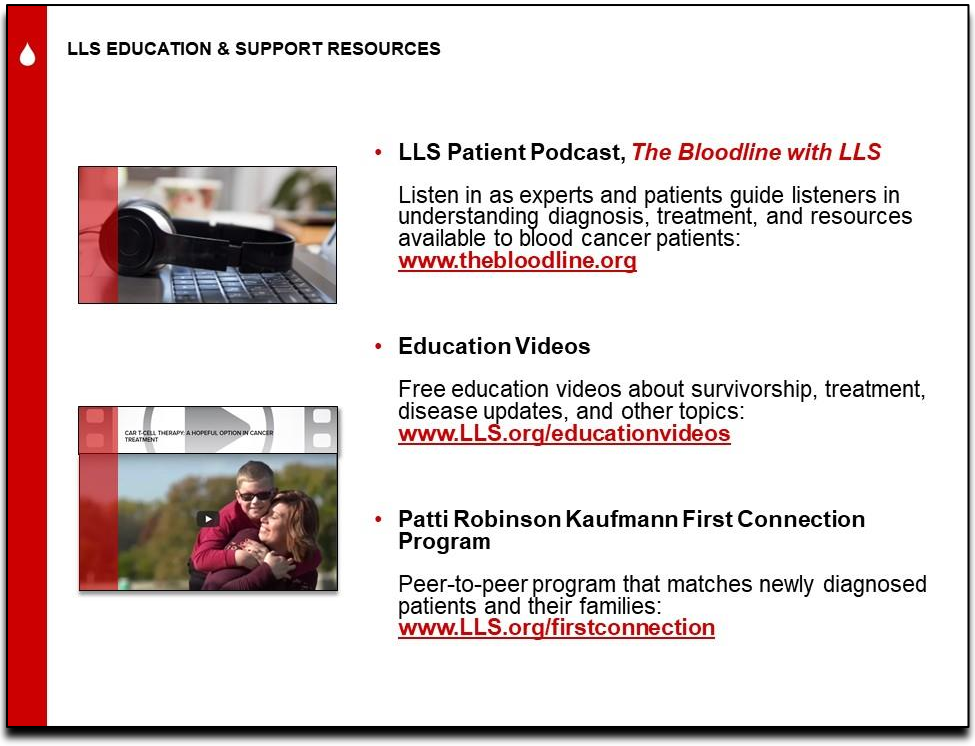
So, for many patients, the lower doses are just fine. It is just then a matter of your hematologist and your oncologist controlling, making sure the disease is going away and monitoring where the trend is.

Sometimes we do blood testing for residual disease. And there, you can quantify how many CLL cells are left. And you do that over the time, over months. You can monitor that every 3 or 6 months and just look at the trend. And if the trend is positive where the CLL cells go away or stay away, then if the low dose is just fine. If you see, however, over time, the disease starts eventually coming back, then obviously, there was a response, but then, either disease has become resistant, or maybe the dose that you are on is not sufficient. So, it is a question of monitoring where the CLL, where your disease is headed on the particular dose of drug and monitoring that over time. And that's what I would suggest you discuss with your oncologist.

Ms. Lizette Figueroa-Rivera:
Thank you. And we have many questions on CAR T-cell therapy. And Aaron is asking: Do you think the T-cell therapy that has been in the news will be something that will be an option for people not participating in a trial any time soon?

Jan A. Burger, MD, PhD:
It has received an enormous amount of publicity. This is, in my opinion, not justified by the data because in CLL, we now recognize that CAR T-cell therapy is, at this stage, not as effective as in other cancers, especially not as effective as in T lymphoblastic leukemia. And it is also quite a toxic type of treatment, which requires very close monitoring—oftentimes in the intensive care unit—for signs of tumor lysis, but also for neurologic side effects. So, for that reason, it is, at this stage, something that is only recommended in terms of clinical trials for patients who have failed the other established treatment options.

In theory, it is a very attractive tool that--and there's a lot of effort to develop and make this treatment option more effective and safer. But, at this stage, I would not recommend patients getting CAR T-cell therapy for CLL outside of clinical trials.



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Ms. Lizette Figueroa-Rivera:

Thank you. And Eva is asking a very timely question about recommendations for CLL patients in regards to the measles, with the rise of measles across the country right now.

Jan A. Burger, MD, PhD:
We have not encountered that. I think what you could state about that situation is, as CLL patients, as you all know, have compromised immune system. Vaccination status should be discussed with a primary care physicians. And if something needs to be vaccinated, then that should be done. But, I have not seen, in my practice, any patients with CLL getting measles. We still have good vaccinations throughout the general population. But, the rise is a concern, speaks to the fact that maybe vaccination is not always pursued.

But, what can CLL patients do proactively? Discuss their vaccine status with their oncologist or with their primary care physicians. But, I would not worry too much about it. Obviously, what we say, in general, if somebody has CLL, they should be aware of their compromised immune system. Even if they are in

remission, on treatment, or after treatment, their immune system will not always be 100 percent in comparable to a healthy person. So, if somebody, obviously, is sick or if somebody is suspected or has measles, stay away from those persons until that illness has resolved.

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

Operator:
Thank you. The line is open for Gloria from Arizona. Please proceed with your question.

Gloria:
Yes. Good morning, or good afternoon. I have problems with my nails getting fungus underneath my nails, and they try to split in half. I don't know what would be good to try to avoid this. And I guess it must be the Imbruvica® that I'm taking, because I never had this problem before. What can I do to help resolve this or make it better?

Jan A. Burger, MD, PhD:
Yeah. That's a thing that comes up once in a while. So, we didn't pay attention to that in the first few years using ibrutinib because we were so excited how it helps with the CLL and how it helps patients who were not doing well on chemotherapy. But now, treating more and more patients with Imbruvica, we realize nail changes are one of the side effects affecting not too many, but some patients. And it can be disturbing. But, I personally haven't seen a patient really discontinue because of that, because usually patients were able to manage that. It is not so much the infection. It is more that the structure of the nail changes. And maybe in some people like yourself, it is somewhat a setup to then develop other things. I would probably talk to your primary care doctor or podiatrist about how to best conservatively manage that and see, for 6 or 12 months, if it's manageable, if you can get that under control. And if that's not the case, then talk to your oncologist about pros and cons of maybe looking at a different treatment. But, ibrutinib, on the other hand, has so many pros towards your leukemia that I would be initially a bit hesitant to say that should be a reason to immediately go toward a different type of treatment.

Ms. Lizette Figueroa-Rivera:
Thank you. And Doctor, Anna is asking: Are there studies suggesting that there may be a genetic predisposition to CLL?

Jan A. Burger, MD, PhD:
It is sometimes running in families. But, that's a rare exception, certainly less than 10 percent of patients have a family history. So, most patients, if they are wondering, are their children at higher risk for developing CLL, I tell them it is an exception and usually children of CLL patients don't have to worry about this. But, as everybody gets older, usually children from CLL patients also have CBCs done. So, it would be picked up early, and maybe there could be somewhat alertness. But, if that's a question on somebody's mind, it is good to look into the family history, see if there has been relatives who have CLL. And there are efforts to figure out why it sometimes runs in families. But, it's really an exception, and most patients don't have a family history.

Ms. Lizette Figueroa-Rivera:
Thank you. And Paul is asking: I'm taking strong doses of green tea extract and curcumin. What do we know about its effects or benefits for CLL?

Jan A. Burger, MD, PhD:
There has been interest and there has been some studies done to look at those two natural compounds and how that impacts CLL. And many patients who are--especially if they are on observation, try this with the hope that it's going to slow down the disease progress. But, larger studies have been somewhat--showing somewhat discouraging results. And it hasn't really made it into bigger, larger studies because the efficacy, if there is an effect, is not very big. So, when I see patients and they are

saying, "We are taking green tea or cumin," I don't discourage that. But, I also point out to those patients that it does not always prevent disease progression. And I would not have too much of hope for these natural products. On the other hand, I'm not aware of any downsides of taking that. So, I don't really actively discourage that.

Ms. Lizette Figueroa-Rivera:
Thank you. And our last question from today comes from Elizabeth. Elizabeth is asking: How long can I continue not to have any symptoms? It's been 11 years since I was diagnosed.

Jan A. Burger, MD, PhD:
That's a great question. We know from like long-term follow up of patients that about 30 percent of patients, 3 out of 10 patients, throughout their lifetime will never require therapy. So, it's a good sign if you have not had disease progression for 10 years. That makes it likely that you will not progress throughout your lifetime. Although, it depends on your age too. So, if you are still young, then there might still be a possibility that the disease will eventually progress. But, overall, in all CLL patients, there is a subset, which is sizable, which is 30 percent of patients, who will throughout their lifetime never require any therapy for CLL.

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Ms. Lizette Figueroa-Rivera:
Well, thank you for your question, Elizabeth, which was our final question today. And a special thanks to Dr. Burger for sharing his expertise with us and for his continued dedication to our blood cancer patients.

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Ms. Lizette Figueroa-Rivera:
If you weren't able to get your question in today, please contact an Information Specialist at

The Leukemia & Lymphoma Society at 1-800-955-4572. And we're available from 9 AM to 9 PM Eastern time, or you can reach us by email at infocenter@lls.org.

Information Specialists are available to answer your questions about treatment, including clinical trials or answer other questions that you might have about support, including financial assistance for treatment. Again, we'd like to acknowledge and thank AbbVie, Genentech and Biogen: and Janssen and Pharmacyclics, an AbbVie company, for support of this program.

Thank You

Dr. Burger, thank you, again, for volunteering your time with us today, and, on behalf of The Leukemia & Lymphoma Society, thank you all for joining us for this program. And we hope that you will join us in the future as we strive to keep you up to date on the latest advancements for all blood cancers. Take good care.