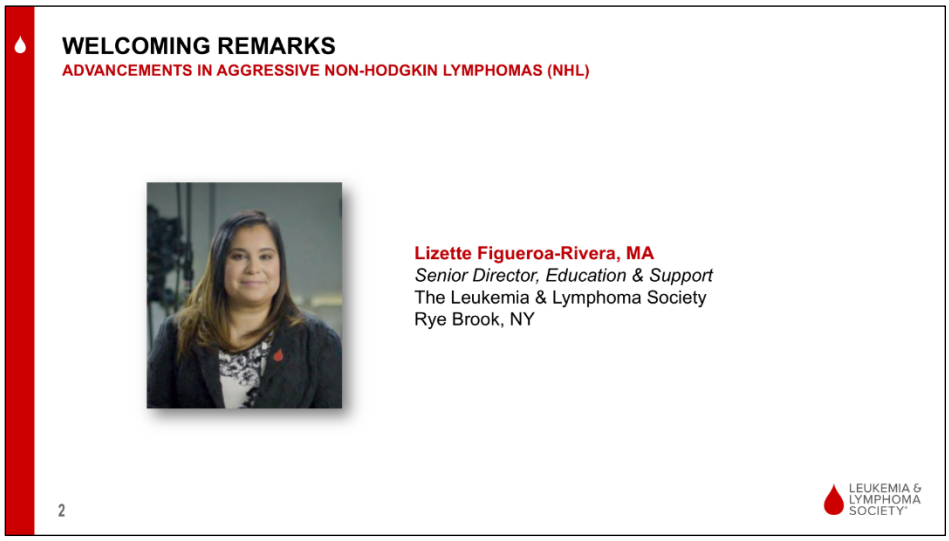
WELCOME AND INTRODUCTION



Lizette Figueroa-Rivera, MA
Hello everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. Special thanks to Dr. Joshua Brody for volunteering his time and expertise with us today. The Leukemia & Lymphoma Society funds leading-edge research for every type of blood cancer.

When it comes to cancer, information is power. For many patients and families, coping with a blood cancer diagnosis can be complicated, stressful, and overwhelming. With so much information available online from so many different sources, it could be challenging to know what is accurate or up to date. LLS is the leader in free information and comprehensive support for blood cancer patients, families, caregivers, and healthcare professionals. From diagnosis and treatment to remission, survivorship, and ongoing wellness, let us be there for you during this time and please continue to let us know what you need.

Following the presentation, we will take questions from the audience. We would like to acknowledge and thank Genentech, Inc. for their support of today's program.

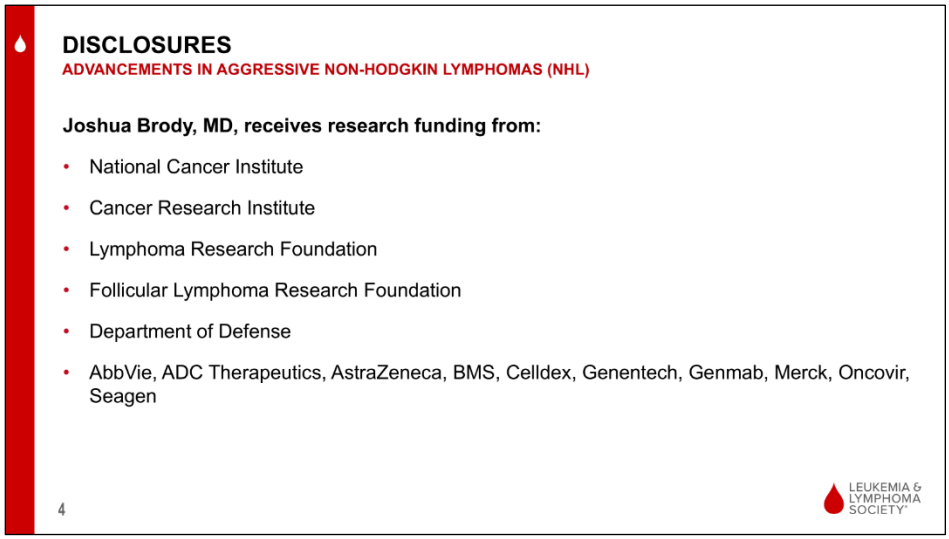
PRESENTATION

Lizette Figueroa-Rivera, MA
I am now pleased to introduce Dr. Brody, Director, Lymphoma Immunotherapy Program at Icahn School of Medicine at Mount Sinai Hess Center for Science and Medicine in New York, New York.

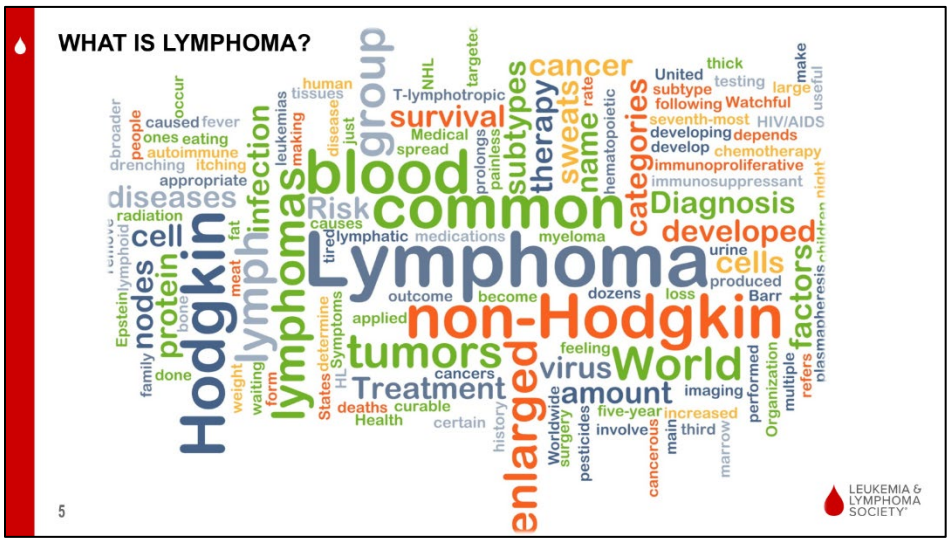
Dr. Brody, I'm now privileged to turn the program over to you.

Joshua Brody, MD
Lizette, thank you so much. This is very exciting. It's a great opportunity. I have to say that both Lizette and I are just profoundly indebted to The Leukemia & Lymphoma Society (LLS) for a lot of types of work they do. They do literally help our patients every day and they help our research every day. They fund some of the research that we do in our lab here to develop novel therapies for patients with lymphomas. We're greatly indebted to them.

Right now on the webcast here, there are literally hundreds of people and it's a difficult thing to set up, so thanks to LLS for all the hard work and the infrastructure that goes into setting that up. Because it's a little bit complicated, hopefully I won't press any of the buttons wrong. We'll be hopeful for that, and hopefully all of you at home or wherever you are, are able to get the web platform working well. If you have any problem with it, you can try to reach out to my 12-year-old nephew who's very good. He does all of my IT for me. He's fantastic. I'll have to get his contact info out afterwards. Hopefully everything moves smoothly.



I first have to mention all of these folks that provide funding for the research that we do, the NCI [National Cancer Institute], and I guess therefore indirectly I'm thanking all of you who are the taxpayers who fund the NCI. And these other various foundations, including these different pharma collaborators who help with a lot of different types of our research providing reagents or providing medicines, et cetera.



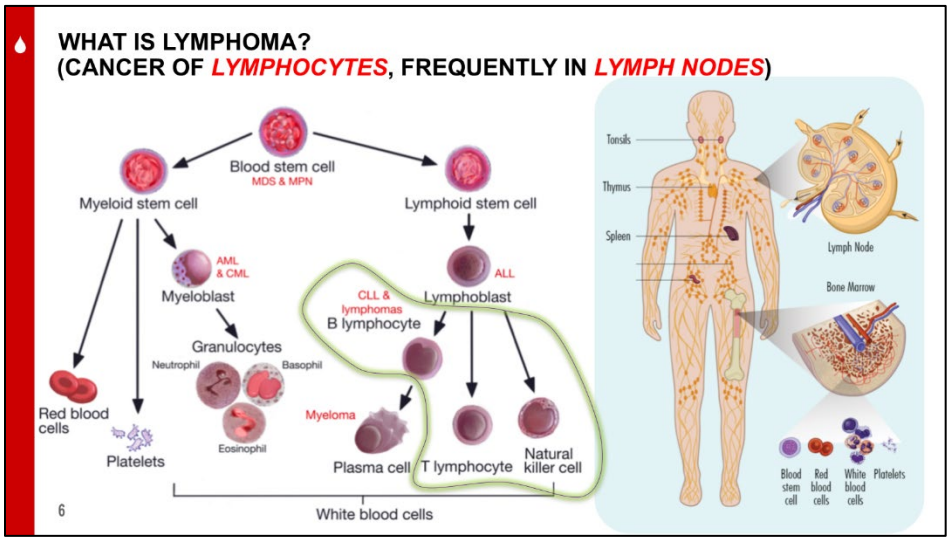
And our goal today is to try to take what is probably sometimes a very confusing subject and try to just make it be a little less cloudy and a little more clear. I know that definitely when people first hear about lymphoma, they hear a barrage of words. It is confusing. I literally have patients stop me mid-sentence and say, "That's too much information. Keep it simple. Please slow it down." The most important thing for making things clear, I think, is to have some dialogue, some back and forth.

WebMD or Dr. Google or whatever, those things are great. They're great sources of information. Sometimes they're sources of misinformation that can make it a little tricky,

so hopefully your actual doctor or this doctor you get for a webcast for a little while can be a bit better because it can be interactive. Ask questions of your doctor when you're seeing your doctor. Please do not be shy to ask questions. Obviously, I'm a New Yorker, so shyness is something that I don't have to deal with as much in my patients. But you have questions in your head, you are doing yourself and your doctor a real service to get those questions out there.

And so we're going to try to exemplify that here today. We have a question-and-answer period at the end, but it would really be great if people are interrupting as we go. There are a couple of ways I think you hopefully see how on the interactive webcast to enter questions and even to be calling them in. Please even interrupt me as we are going. If questions pop up for a bit of information that I'm showing, probably easier to answer those questions in real time while I'm showing the information rather than 30 minutes later. Hey, do you remember 29 minutes ago when you showed that bit? Easy to do it as we go. So, let's do our best to try to make all of this sometimes seemingly complex stuff a bit more clear.

Lymphoma is the fifth most common cancer in America. It's a pretty common cancer. After the big four – lung cancer, colon cancer, breast cancer, prostate cancer – lymphoma is the fifth most common cancer. It's common and yet a lot of confusion. It's just not as clear to folks as those other common cancers, so our goal is to just try to make it a bit more clear with a focus today on aggressive lymphomas.



The first reason I think it's unclear is because people understand breast cancer is a cancer of breast cells. Colon cancer is a cancer of colon cells. Seems real simple. You can picture a colon or a lung in your head. [It is] hard to picture what is lymphoma. Lymphoma is a cancer of lymphocytes, and lymphocytes can live in many places. They can live in lymph nodes, in the blood, in the bone marrow, in the spleen, in other places, but lymphoma is a cancer of lymphocytes. These are some of the many places that lymphocytes can live, but lymphocytes are blood cells. They can go just about anywhere. They can go to the skin, they can go to all of the organs. Lymphoma can show up in any of those places.

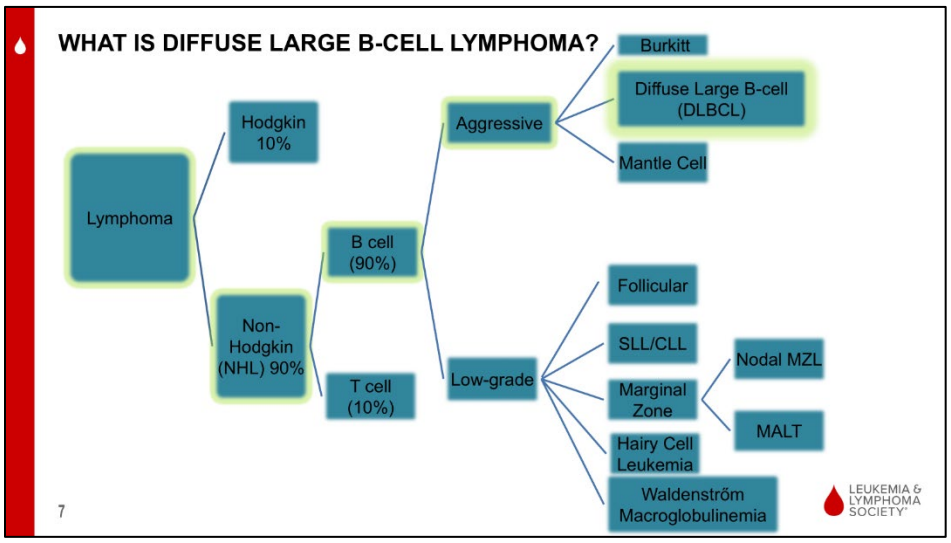
Lymph nodes is one of the most common places that lymphomas show up. We all have lymph nodes. Most our lymph nodes are small. When you don't have a cold or a sore throat, you cannot feel the lymph nodes in your neck. But when you have a cold and those lymph nodes get a little swollen, now you can feel them. We have lymph nodes all the time. If they're getting enlarged, it can be for many, many reasons. One of the reasons could be from lymphoma.

Again, lymphocytes are blood cells, but there are many other types of blood cells that also can become cancers. You probably have sometimes heard, "Oh, lymphoma is a cousin of some of these other leukemias." This is why they are cousins. A normal blood cell starts as a stem cell. These are called blood stem cells, not the stem cells that first make all of your human parts. A blood stem cell can become cancerous. When it does, it can be either a myelodysplastic syndrome (MDS) or a myeloproliferative neoplasm (MPN). You've heard of some of these different types of cancers. If a slightly more mature myeloid blood cell becomes cancer, it becomes acute myeloid leukemia (AML), a common leukemia.

But blood cells also, in addition to becoming myeloid cells, become lymphoid cells. A very young lymphoid cell, we call lymphoblasts. If they become cancer, they become another type of leukemia, acute lymphoid leukemia (ALL), which is more common in young kids and teenagers, but can happen to grownups as well. And then if a slightly more mature lymphocyte becomes a proper B lymphocyte or a T lymphocyte, it can become the lymphomas that we hear about. So, a cancer of a B lymphocyte can become a lymphoma. The ones that we think about and most of the aggressive lymphomas we're going to discuss come from these normal healthy blood cells, B lymphocytes that have developed some cancerous mutations.

We're not going to talk very much today about T lymphomas or natural killer cell lymphomas. They can also be aggressive lymphomas. They're not always aggressive. The goal today is to talk about aggressive lymphomas. But because most of the people calling in or listening at home on the webcast hear about the most common type of aggressive lymphoma, diffuse large B-cell lymphoma, that will be our focus today. But I would like people to feel comfortable asking questions about all types of aggressive lymphomas.

Lizette Figueroa-Rivera, MA
Doctor, Christine asks, "What does aggressive mean? What defines it as aggressive?"



Joshua Brody, MD
Wonderful. I was going to get that here, but I wasn't going to answer it in such a plain way. Let me answer that plainly. Well, it was a well-timed question because this slide is going to differentiate those, but let me just say in English what it means. This differentiation you see between aggressive and what we call low-grade or we sometimes say indolent, that is just a clinical characteristic of the kinetics, of the speed of these lymphomas.

Also, many of these words, we use them in a doctor way and not a regular English way. We think we're saying one thing and people are hearing another. People think aggressive means bad. Oh, I have an aggressive lymphoma. I have a worse prognosis than if I have a low-grade lymphoma. Not actually true. Aggressive lymphomas, the most common ones can be frequently cured, whereas with current therapies, we don't think these low-grade lymphomas are cured.

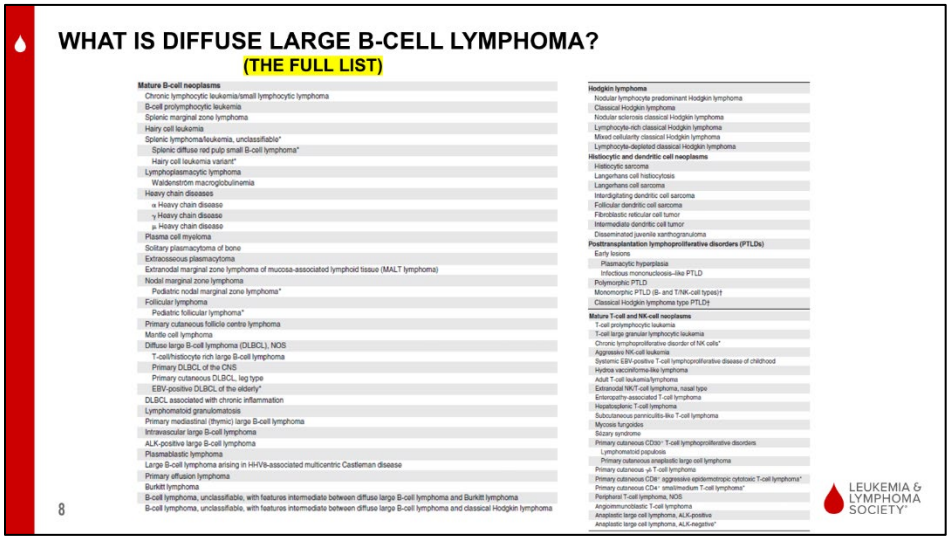
So, aggressive just means that if it were untreated, it would grow at a certain rate. Aggressive lymphomas growing quickly. Low-grade lymphomas growing slowly. Growing at a quicker rate isn't necessarily bad because that fast growth also sometimes makes them more sensitive to the therapies we use, like chemotherapies and some others. Aggressive versus low-grade or indolent just refers to how quickly the thing would grow if we did not treat it. Whereas patients hear the word aggressive and say, "Oh, that means I'm going to die. That means it's got a worse prognosis." Not true, not true, not true. Aggressive just means the rate that it would grow if we did not treat it.

That's a great question. Thank you. Thank you for interrupting me. I just have to say on interrupting questions, if you are thinking of a question on this call with hundreds of people here, there are 11 other people thinking the same question and some of them are just afflicted naturally with shyness. It's not their fault. That's just how they are. If you ask a question, you're doing them a big favor because you're helping them out, and also the first person to ask the question, please excuse the vulgarity, they lubricate the field so everyone else can ask questions. Please, please do. Great question.

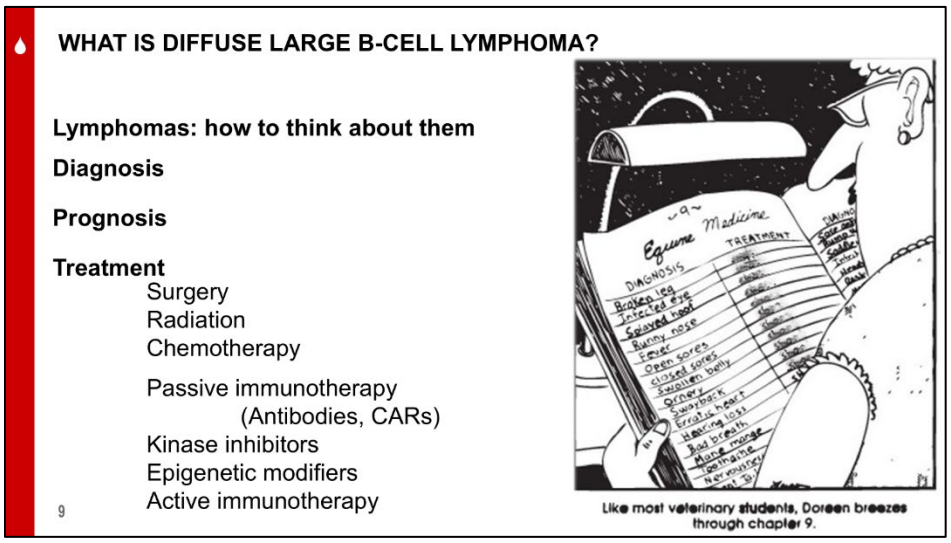
Lymphomas are also confusing because maybe a little bit as opposed to colon cancer or prostate cancer, we really have many very distinct types of lymphomas, which are very different. Different in every way, different in the biology and different in the course of the disease, different in the treatments, very, very different. That makes it confusing. We're not going to talk about all lymphomas today, but we do distinguish non-Hodgkin versus Hodgkin lymphomas. Again, we're not going to explain all of these ones that we're not talking about, but non-Hodgkin lymphomas are the great majority. Ninety percent of lymphomas are non-Hodgkin lymphomas. Ninety percent of those are B-cell non-Hodgkin lymphomas, and those can be split somewhat equally into aggressive versus these low-grade lymphomas, maybe 50/50-ish. [There are] many subtypes within these still, but amongst aggressive lymphomas by far the most common is diffuse large B-cell lymphoma. Probably about 25,000 Americans every year getting diagnosed with diffuse large B-cell lymphoma (DLBCL); so very common.

Here are a few other aggressive ones that we're not going to talk much about, but if folks have questions, please, please interrupt. We might push some of the questions to the end just to keep them all together.

Okay, so we're talking about the diffuse large B-cell lymphoma. It's aggressive because if we didn't treat it, it would grow quickly. What does it mean “grow quickly?” Just pick a common clinical scenario. A person had a painless lump. Let's say it was a lump the size of a golf ball. Pretty big. That golf ball could become an orange or a grapefruit in one month or six weeks or two months, something like that. Whereas low-grade lymphomas would not grow that quickly, a golf ball could become an orange in one year. That's the distinction if we did not treat those things. It's not synonymous with prognosis or bad.



In fact, the list I showed you there was really a simplification. Because really according to all of the experts, there were more than just those 12 types of lymphomas that I showed. There were more than 80 types. Thankfully, we're not going to discuss all of them today and there will not be a quiz on all of these today, but just be aware that we're talking about the more common subsets when I show that simplified list.



Okay, just to try to make them clear, I think that this is a breakdown of how doctors think. Trying to get you into the back room of how doctors assess all of these cancers and lymphomas, but really probably all diseases. How we diagnose them, figure out exactly what type of lymphoma it is or whether it is lymphoma at all. How we prognose them, whether this is a good or a bad prognosis. [How we treat them.] These things with standard therapies do well or do poorly and sometimes affects how we think about treatment. Diagnosis, prognosis, treatment, and we have various tests that we assess for all of these things – diagnosis, prognosis, and treatment.

When we think about diffuse large B-cell lymphoma specifically, we're very lucky because in the old days, this is a Gary Larson cartoon to express I think how we thought about lymphoma in the old days. All these 84 types of lymphomas, we just thought of them all as lymphoma and treated them all the same. This is a terrible Gary Larson cartoon about how veterinary medicine used to work for horse therapies. All horses no matter what the diagnosis all got the same therapy, and I won't tell you the therapy because it was terrible.

Luckily, we are in the era of every different subtype of lymphoma. Almost all of them have distinctions in how we treat the patients, so we're lucky to be in the era where we think [about] fairly personalized medicine [in which a] specific type of lymphoma gets a specific therapy. We're very lucky we were not there 25 years ago for sure. Surgery is sometimes part of the diagnosis to get a biopsy. Occasionally part of the therapy but not usually, and that distinguishes it from other cancers. Again, the common ones, lung cancer, colon cancer, breast cancer, where surgery is usually critical to early-stage disease and part of the therapy.

I mention it here only because every patient just says to their lymphoma doctor when they meet them, "Can't you just cut it out?" That's, again, I think a lack of a basic idea of this is a cancer of blood cells. Blood cells are everywhere. It would be very hard to cut it out. Sometimes because a person sees a golf ball in one spot, they think, "Oh, let's cut that one out." It sometimes is an option, not usually, because underneath that golf ball, there are lots of little sesame seeds somewhere else and we can't cut them all out. We try to think about therapies that treat people systemically.

Radiation, again, is sometimes a part of the therapy for lymphomas. Again, especially when we have these less common, we call limited-stage lymphomas. We'll talk about stage in a little bit. But again, whereas most lymphomas are advanced-stage, that doesn't make them bad. It means they're in multiple places. Luckily, the medicines that we use can still hit all of those places. But on the rare exceptions when we have lymphoma mostly in one place, we can use radiotherapy, and it can be pretty effective. [We sometimes use radiation] by itself and sometimes combine [radiation] with other therapies.

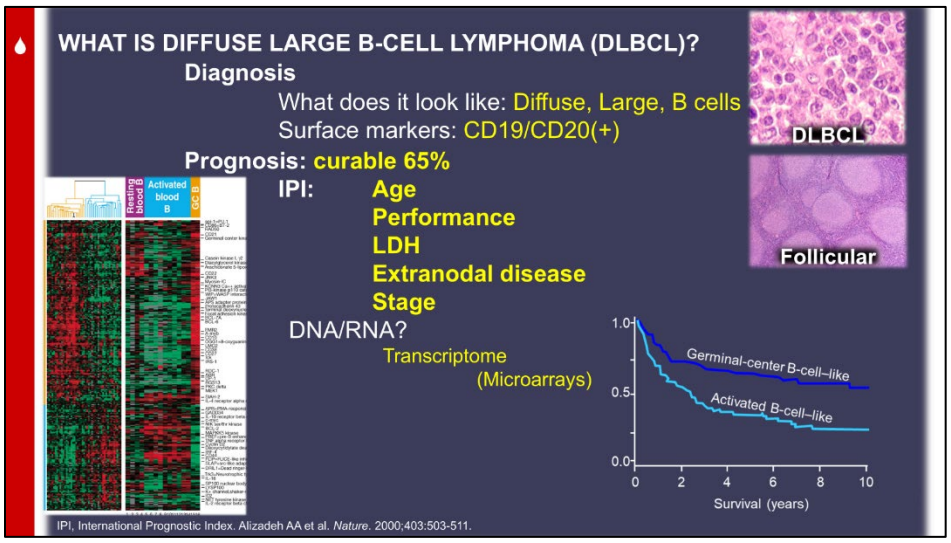
Chemotherapy is still the basis of how we treat most lymphomas and most aggressive lymphomas. People really give a bad rap to chemotherapy because they've seen many movies where it was very toxic. In real life it can be extremely toxic, but we have to first remember there is a huge rainbow of chemotherapies from very gentle to very aggressive. We shouldn't throw away the baby with the bathwater and think of them all as that chemotherapy that your great aunt had and she lost all of her hair and she was very sick. Yeah, there are some very aggressive chemotherapies and there are some very gentle ones. We have to talk about the right therapy for the right person.
So that is still part of therapy for most lymphomas. And the reason is not because we're really married to chemotherapy per se, but, for diffuse large B-cell lymphoma, that's the focus here today. By itself, chemotherapies can cure half or more than half of people. Although we're coming up with more elegant therapies, we wouldn't want to throw that away. Sometimes it's not about [whether we] can get rid of chemo for these common lymphomas, but [rather] how can we improve on top of chemo? Sometimes it is about using less chemo for people with an excellent prognosis.

Passive immunotherapy is a phraseology that I use to refer to immunotherapies that use immune cells or immune molecules, antibodies, chimeric antigen receptor (CAR) T cells that go after a target on lymphoma cells, [and we] call it passive because we are choosing the target CD20, CD19, something on the surface of that molecule. Passive immunotherapies like antibodies, CAR T cells, bispecific antibodies as well.

Kinase inhibitors. People have probably heard of Bruton tyrosine kinase (BTK) inhibitors, which are critically important in some low-grade lymphomas like chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL), but also important for mantle cell lymphoma and maybe have a role in DLBCL.

Epigenetic modifiers. U.S. Food and Drug Administration (FDA)-approved for follicular lymphoma and some promise in other lymphomas. We will talk only a little bit about them.

And then active immunotherapy, I distinguish this from passive immunotherapy. Active immunotherapy is, again, using the immune system but letting the immune system pick the target on the lymphoma cell. This is probably most relevant for Hodgkin lymphoma, where we give anti-PD1 antibodies. Your immune system finds something on that lymphoma cell to attack. We don't tell it to attack CD19 or CD20. We let the immune system choose. We call it active immunotherapy because your immune system is actively deciding who the targets are as opposed to passive immunotherapy.



Again, when we diagnose diffuse large B-cell lymphoma, the first part of diagnosis is [to determine] what does it look like? And although this sounds a bit esoteric, it really isn't. The cells that we see under the microscope when we perform a biopsy of a lymph node look just like what the name sounds like. I put here for contrast diffuse large B-cell lymphoma, but I had to, for contrast, put another lymphoma here, follicular lymphoma. Follicular lymphoma, you see follicles here. You see an architecture. The architecture is all these little follicles, these little grape clusters that we see. Whereas diffuse large B-cell lymphoma, it is diffuse, it lacks architecture. It's just a diffuse sheet of all the same looking cells, so that's what the word diffuse means. It means under the microscope no architecture, all diffusely the same, and that the cells are large. You cannot quite head-to-head the size of these cells, but I'm telling you, they're larger than normal lymphocytes and they're larger than some other lymphoma subtypes. These cells are diffusely spread out. They are large and they are B cells, so diffuse large B-cell lymphoma is a real simple make sense kind of name for us when we're looking at it under the microscope.

How do we distinguish that these are B cells? We look at certain B-cell markers. All of these cells, I couldn't show you on a microscope because it would be much too small, but all these cells have little proteins on their surface. Many, many of them. Some of the most famous [proteins] for B cells are CD19 and CD20. Those are on these lymphoma cells, but they're also on healthy B cells as well, which will hint at a moderate or maybe significant side effect of when we target those things with antibodies or with CAR T cells.

The prognosis overall is a lot better than most other cancers, a lot better than pancreas cancer and lung cancer, et cetera, and certainly a lot better than it was 30 years ago. We think that the majority of DLBCL patients are curable. But when we say these nuanced things, we don't want patients to hear what we didn't say. The majority are curable. Not 100%. We are getting towards that, but we have a long ways to go. Maybe 60%, maybe two-thirds are curable with current modern therapies. That's already good news but not good news for everybody. We still need to improve and try to get that number up towards 100.

And then we have some very simple tricks we can use to try to prognose an individual. Maybe you've heard of this International Prognostic Indicator (IPI). It's a very simple little

calculator tool we can use to estimate if a specific patient has a better or worse prognosis. We have a very silly mnemonic, which is APLES, A-P-L-E-S, misspelled. Dumb mnemonics are always easier to remember, so APLES is dumb because it's misspelled. We look at the **A**ge, whether a person is older or less than 60. Their **P**erformance status. Performance status is if people are doing their normal activities of daily living without too much impairment, they have a good performance status. If people are stuck in bed because they're so sick from their lymphoma, they have a bad performance status. Lactate dehydrogenase (**L**DH) is a blood test that many of you've probably heard of. If it's elevated, that is an adverse prognosticator. Whether patients have disease outside of lymph nodes, **E**xtranodal disease, if someone has disease involvement in their stomach or their bone marrow or their lungs or their liver, those are outside of lymph nodes. And their **S**tage overall.

Again, people hear the word stage, and this is probably one of the worst misconceptions because when we first meet patients, at the end of all the discussion, patients look sometimes a bit abashedly and say, "Doctor, what stage am I?" We will answer their question. But really, I think when a lot of my patients ask, "What stage am I?" they don't really mean what stage am I. They mean, "Am I going to live or am I going to die?" The reason they think that is because for other cancers, stage is a distinction between life and death. If you have stage one breast cancer, you will probably be fine. If you have stage four breast cancer, there's a very real chance you could die from that. And so people had family members with breast cancer or something and equate stage with life or death. That's a misconception for lymphoma. Most of our patients are advanced-stage, stage three or four, and yet still we cure the majority of patients with DLBCL. We answer the question that patients are asking, but we try to, if possible, hear what they really are trying to ask us and then try to answer that question as well. You are at stage three, but still, most patients with stage three – the majority of them are cured thankfully because of advances in therapy.

Just again, very briefly to describe stage without too much nuance, if folks have lymphoma in literally just one spot that we can see on the scans, for example, that could be stage one. Two spots but on the same side of the diaphragm, so both above the diaphragm, stage two. Having lymphoma on both sides of the diaphragm, something in the neck and something in the groin or inguinal region or deep in the abdomen, that would be stage three. Non-contiguous external involvement, for example bone marrow lymphoma, would make a person stage four. And the reason we go through that quickly is because again, the stages don't have a marked prognostic significance. They do have a little significance. That's why you see them here. Patients with stage one do a little bit better than patients with stage four, but it is not the way that it is for other solid tumors like breast cancer, lung cancer, et cetera. So that IPI, we add up these points and people with five positive points do worse than people with zero positive points here, but luckily they still can have good outcomes.

Lizette Figueroa-Rivera, MA
Thank you so much for that distinction. We have a lot of people asking about stage and we also have Leslie asking, "When you say curable, do you mean remission or completely cured?"

Joshua Brody, MD
Great, great, great. Another distinction. I'm sure in the hundreds of people in the audience, there are some lawyers there, so I'm about to offend all of them and say this, I

think when lawyers speak confusingly, they're doing it on purpose. Please forgive me, but that's how I feel. But I think when doctors speak confusingly, it's accidental. We're not trying to be confusing, but we literally speak “doctor” and we speak English and we sometimes forget which one we're speaking. And these words “cure” and “remission” have very specific meanings for us, but people don't always hear the meanings we intend.

So just to put three words in clarity of what doctors mean by them, remission remains that a cancer has decreased significantly, it could be a partial or complete remission. Complete remission means that a cancer is gone to the best of our ability to find it, meaning that a positron emission tomography (PET) scan or computed axial tomography (CAT) scan shows no more cancer, complete remission. It doesn't mean it's cured because CAT scans and PET scans are imperfect and if you had one tiny little bit of cancer left, there's not really a test in the world that can find every last bit. So, we would say you're in complete remission, but it is not a guarantee of cure. It's kind of a step towards a cure because you would need to probably at least be in complete remission to be cured.

And what does cure mean? Cure means that literally it is all gone. And unfortunately therefore you just heard there's no test in the world that we have that can tell someone today "You are cured." But all we have to say someone is cured is statistics. So for example, if diffuse large B-cell lymphoma goes into complete remission and it does not come back in 10 years, it would be almost unheard of for it to come back. And there's a little nuance there still because there are some cases of underlying other lymphomas that could come back later. But diffuse large B-cell lymphoma, if someone is in complete remission for many, many years, we don't think it's likely it will come back.

And now people will say, "How many years?" Okay, if someone hasn't had lymphoma, DLBCL will come back in 10 years. It'll be almost unheard of for it to ever come back. "What about five years?" We sometimes say if someone's in complete remission for five years, they are probably cured. That's a true statement, but probably is not absolutely. If someone has been in complete remission for five years, it is 95% or more, maybe 98% that they are cured. But still, if we guarantee everyone they're cured, we're going to be wrong one or two or three times out of 100. And it's happened to me. I said to people, "You're probably cured." And then a couple of years later, it did come back. The other 98 times I said that we were accurate. So it's imperfect.

And then if someone is in remission for two years with DLBCL, there's a very good chance they're cured but we still need a little more time to say with statistical confidence. So that's a frustrating thing. Complete remission is something we can measure right now and tell you today. Cure is something we can only statistically say to you, "You are 98% likely to be cured, 99%. We cannot always say it with absolute certainty." But we mean the same thing as what you're hearing when we say cured. Good, good. If there are other critical questions, I'll pause. Otherwise, I'm going to keep going.

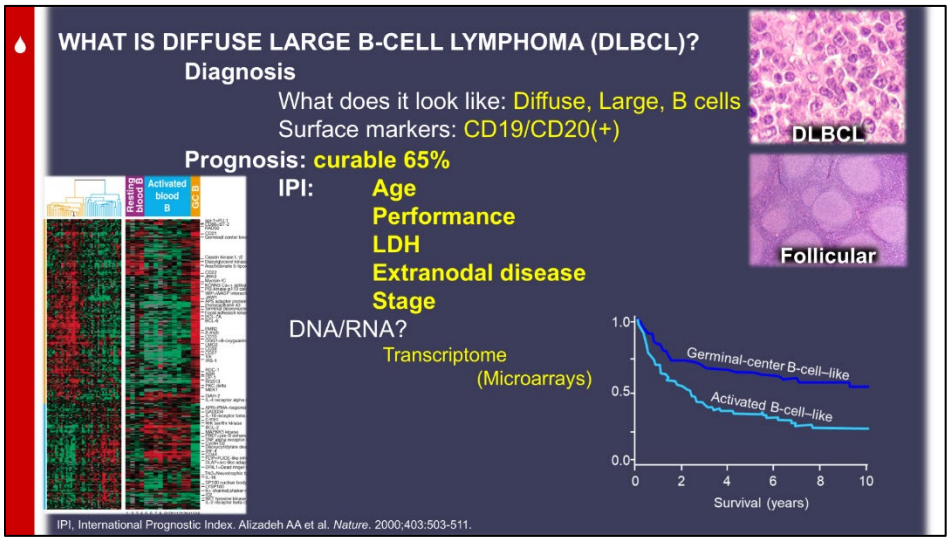
Lizette Figueroa-Rivera, MA
Thank you. Jeanette is actually asking, “What did you say the name of that prognosis test was?”

Joshua Brody, MD
It's right here. IPI, International Prognostic Index, IPI. And you can type “IPI Lymphoma” right into Google and it'll show you how to calculate or type “IPI Lymphoma Calculator” or something like that. And it'll show you these five points and how you add them up. And if someone has been in remission for four years, I wouldn't go starting to calculate your IPI now because it's irrelevant for you. This is really at the time of diagnosis, helps to predict who's going to do well and who's going to do badly. If someone's IPI was five, a higher risk score, but they've been in remission for five years already, they do have a great prognosis now. This is just before the therapy; this is one of our better predictors. Okay, IPI. Good, good question. I'm going to keep going and again, please interrupt me if there are things that I can clarify here.

Lizette Figueroa-Rivera, MA
Just a quick question from Charles, "Is the curable rate and IPI more or less similar for the Burkitt type of lymphoma?"

Joshua Brody, MD
So IPI is specific for DLBCL. It doesn't exactly apply to Burkitt [lymphoma] because IPI is helpful people try to develop IPI-like scores for all the other types of lymphomas. So follicular lymphoma, there's an F-L-I-P-I, FLIPI. For mantle cell lymphoma, there's a MIPI. For Burkitt [lymphoma], we do not quite have a BIPI, per se, but we do have some prognosticators. But IPI is somewhat specific for DLBCL. The same concepts probably are helpful, but an IPI is specific for DLBCL and would not be quite as powerful for Burkitt or any other lymphoma type.

The points of a FLIPI or a MIPI are a little different than the points of IPI. Yeah, good question. Good question. Okay, good. It is getting towards a dialogue, which is exactly what I was hoping for.



Okay. We have other ways that we prognose DLBCL. One of them, it was a cutting-edge way in 2002 when it was first developed and now it was almost old-fashioned. But we literally look at the DNA (deoxyribonucleic acid) and RNA (ribonucleic acid) inside of patients’ lymphoma cells. And we look at the RNA, there are different ways to do that.

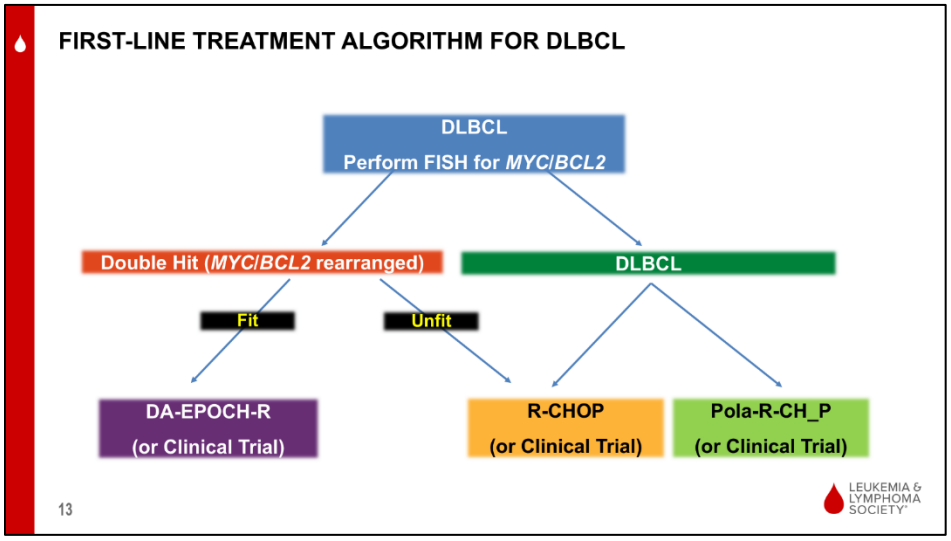
Again, I won't do the basic biology here, but just hear that this is what we do. And when we look at the RNA, we can look at all of the RNA in a lymphoma cell. We call that the transcriptome, and the old technology from the 2000s was called microarrays. And we used that technology to develop, or I should say discern, two types of DLBCL, one we call germinal-center-like or GCB-like, and one called activated B-cell-like, ABC subtype. And because this technology is a bit complex and not available day-to-day, we've made up some surrogates that are similar to this GCB ABC distinction, but much more simple using everyday tools that the pathologists that were looking at your biopsy actually use.

So instead of calling the current surrogates for this GCB and ABC, we call them GCB and non-GCB, but still the same concept is there. This curve I've shown you here is a bit fictitious. It's an over-exaggerated survival curve to say that GCBs do a lot better. In actuality, they only do a little bit better than non-GCB subtype DLBCL, but at least those are words that you will hear. And I'm telling you this is how they were developed. And I won't say too much more about them unless folks have questions.

You can see that this transcriptome test, without trying to explain any of this at all, is a very complicated test where we look at all of these thousands of markers in every lymphoma cell to make the distinction. That's why it's not a day-to-day test. But the concept is there that we can look at the cell of origin of DLBCL and distinguish two types, GC (GCB) and non-GC (non-GCB).

And then I will move beyond how we diagnose and how we prognose DLBCL to how we treat it. This is the oversimplified basics here. For frontline DLBCL, the basis for many, many decades, at least four decades, has been chemotherapy. For the last couple of decades, adding in this anti-CD20 antibody folks have probably heard of called rituximab [Rituxan®]. And then just over the last year or two, maybe adding in an antibody drug conjugate. And I'll explain that more in a bit. So that is the basis today of frontline DLBCL therapy. I'll tell you; we are very lucky that this evolution has been occurring and even luckier that it's still occurring. And I'm telling you now that this standard of care today, 2024, will definitely be different in 2030, probably in 2027, 2028 because with the progress, we're making is quite rapid, thankfully.

As I mentioned, a majority of patients can be cured with this frontline therapy, but not 100%. So some patients will relapse or not respond to that therapy. If patients relapse today, the standards of care may be CAR T cells or sometimes high-dose chemotherapy, we'll talk a bit more about that. And if patients relapse or don't respond to those second-line therapies, one standard of care today is the use of bispecific antibodies or some other therapies that I'll mention as well. But that's the super abbreviated 1, 2, 3, first-line, second-line, third-line therapy for DLBCL.



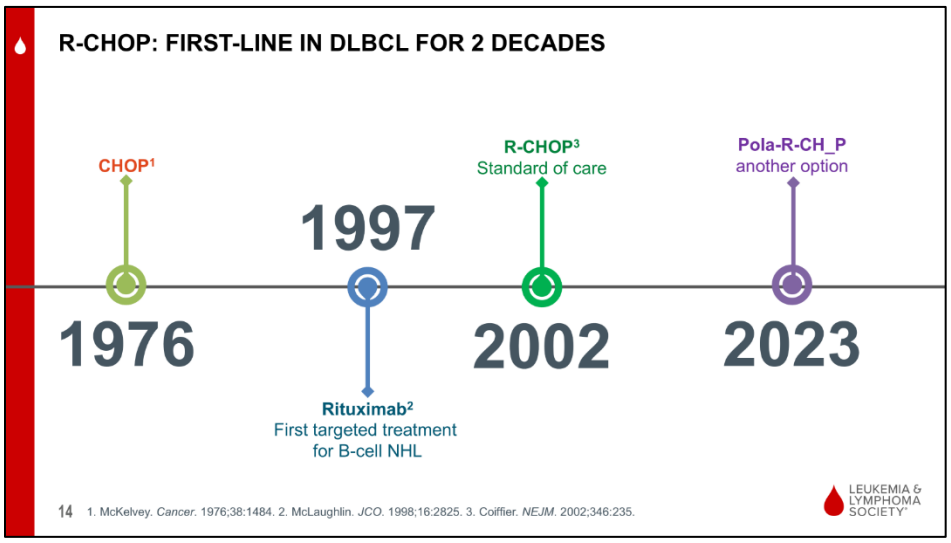
I'll say a bit more about getting into each of these, how we treat frontline DLBCL, first-line DLBCL. Lizette, if there are questions, you'll still interrupt me, I know. This is again an oversimplified algorithm a bit, diffuse large B-cell lymphoma, I did not get into this prognostic fractionation, I just thought we'd do it here. There's a rare-ish subset of DLBCL. Again, the names and semantics of this actually evolve every year, but what we've called this for a couple of decades is double hit DLBCL.

Double hit means that we do another fancy test to assess the DNA and that test is called FISH (fluorescence in situ hybridization) like the animal, fish not like the band Phish, but like the animal fish. And that FISH testing can sometimes show, and this happens in less than 10% of patients, that they have these two genes that are rearranged, actually the chromosomes that they're on are rearranged. Those genes are called *MYC* and *BCL2*. Sometimes we include *BCL6* here, another one you don't have to memorize this, there won't be a quiz on it. But the overall name of this subset of DLBCL is called Double Hit lymphoma or Double Hit DLBCL. Again, it might be 5%, maybe 6%, 7%, 8%, but less than 10% of DLBCLs are like this.

But this, a subtype of DLBCL does have a much worse prognosis with standard therapies. So we have to give something either more or different than standard therapy. And one example is that, if patients are reasonably young and healthy, we give them something a little more aggressive than standard R-CHOP (rituximab [Rituxan®], cyclophosphamide [Cytoxan®], doxorubicin hydrochloride [Adriamycin®], vincristine sulfate (Oncovin®), prednisone), which probably folks have heard of and is still to some degree a standard of care. And you can see that the letters of R-CHOP show up over here as well. But you can see there are even more letters. We sometimes call this dose-adjusted EPOCH (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin plus rituximab), you can see the CHOP letters right here, we added in one more letter E, a medicine called etoposide. You see the R there as well. So this is something that's a little bit more aggressive than R-CHOP. We used it for these more aggressive subtypes of DLBCL. This EPOCH, we were using it even probably more 10 years ago, and we've gotten a bit away from it.

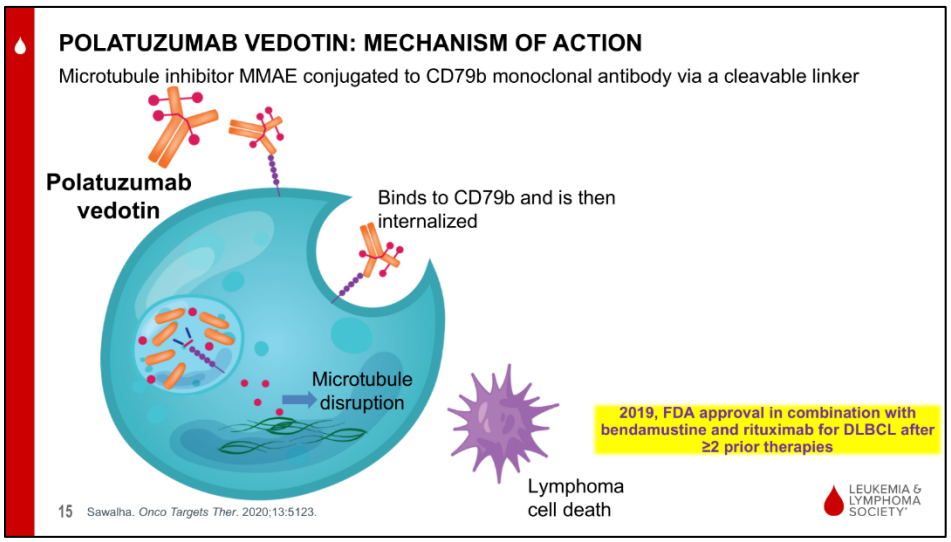
For some types of DLBCL, it's probably more effective and especially for these aggressive double hit lymphomas. So if a patient has double hit lymphoma and is reasonably young or healthy, probably something more than R-CHOP, and this EPOCH is one example. If patients are in their nineties or maybe in their eighties or really terribly unfit because of other comorbidities, bad diabetes, bad chronic obstructive pulmonary disease (COPD), et cetera, and we might not be able to give them EPOCH, we might give them something similar to R-CHOP or hopefully a clinical trial of something better.
For all of these other patients that do not have Double Hit lymphoma – the rest of them DLBCL, and these include those other subtypes that I mentioned before like GCB and non-GC [non-GCB] – they might today in 2024 receive R-CHOP or they might get this other regimen [Pola-R-CHP]. You see, it looks like R-CHOP, but you can see we got rid of the O, and we added this other ingredient called pola, polatuzumab [Polivy®]. So we call this Pola-R-CHP very hard to pronounce because there are no vowels in this second half here. So we're just doing our best, Pola-R-CHP.

And you can see these are all standard options today, 2024. I have to be honest, some of our favorite options are if there's an available clinical trial for frontline DLBCL, these are some of the best options. And again, most of these clinical trials in modern days mean that you'll probably get at least the standard of care, maybe R-CHOP plus something else as well. Not that it will throw away the R-CHOP and just give you an experimental thing. Absolutely will not happen in America in 2024. But most of these trials are taking the standard and adding something else to it. So this is a very oversimplified algorithm of most patients with DLBCL and their basic frontline therapy.



This is a bit of the history of that. As I mentioned, we've been using this CHOP chemotherapy for decades now. Rituximab was developed in the late nineties. It was sort of developed partly by my old boss at Stanford, Dr. Ron Levy, but really a group at Biogen Idec that was allowing this to be developed. And only five years after its development, it was added to CHOP and R-CHOP had a huge benefit on top of CHOP alone, maybe curing 10% more people. That's a huge effect for a pretty simple medicine, rituximab.

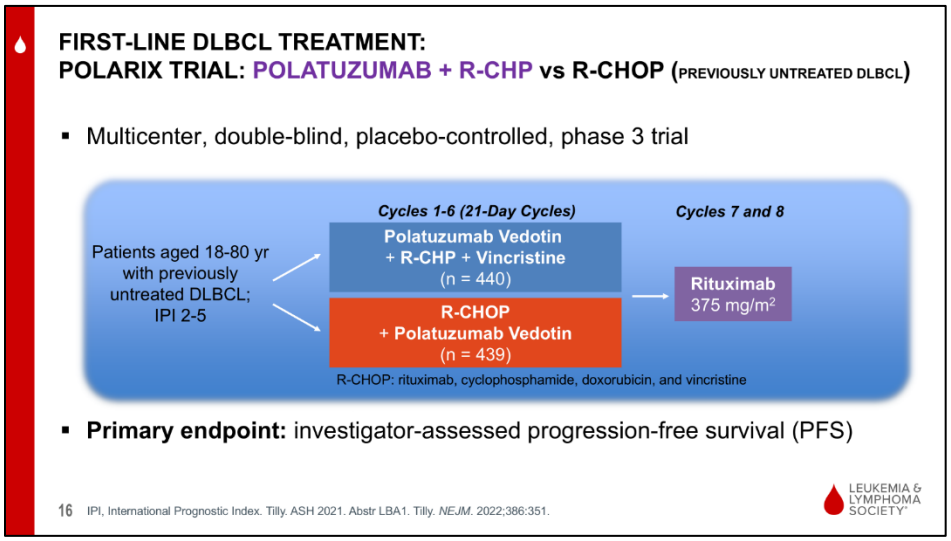
And then just over the last year or two, the new option of adding in this new ingredient, polatuzumab, which I'm going to mention in a moment. So part of the evolution, but I'm telling you we'll have some more marks on the timeline here [of newer frontline therapies] in 2026, 2027, and 2028. We can already see those being developed right now.



I mentioned this polatuzumab vedotin. This is a pretty cool thing. It's a cool concept. This is not the only medicine like this. It is called an antibody drug conjugate (ADC). ADC is sometimes our acronym. Antibody drug conjugate means that this little double hockey stick here, we call that an antibody, and this is our schematic forward because it's sort of molecularly what antibodies look like. Rituximab is an antibody and polatuzumab is another antibody. But the concept here is that this antibody is not just by itself, it is conjugated to a tough type of chemotherapy called MMAE (monomethyl auristatin E). We also call it vedotin.

So this antibody is bound to that chemotherapy, but instead of the chemotherapy flooding into your whole body because it's bound to the antibody, it just gets stuck to lymphoma cells, maybe a few other cells as well, maybe some healthy B cells, and then that chemotherapy gets taken into the lymphoma cells. The pink little chemotherapy circles here, you see get dissociated from the antibody and then can be freed into the lymphoma cell to be toxic just to the lymphoma cell. So this is a pretty elegant way to get chemo just to the lymphoma.

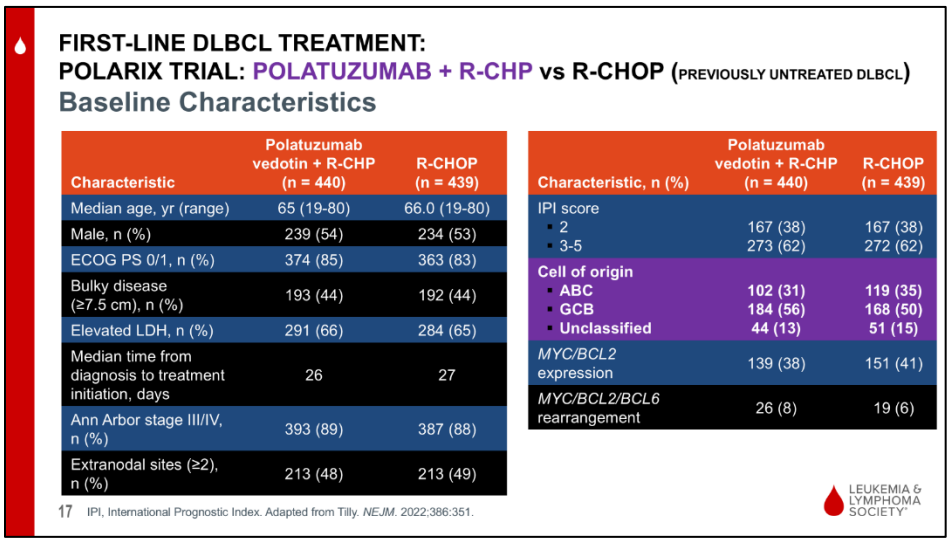
We have a few of these antibody drug conjugates that we use in lymphoma, but this is the one that we've used the most in diffuse large B-cell lymphoma, although there are others as well. So pretty elegant. This medicine has been around for more than 10 years, but just in the last year it became part of standard frontline therapy, and I'll show you how it became part of that standard frontline therapy. I'm going to skip some of the details of the mechanism here of polatuzumab vedotin.



And again, it was approved as a later-line therapy for DLBCL five years ago already, but as a frontline therapy, it was approved now because of this trial, we call the POLARIX trial. Again, [you] don't need to memorize the details. There is not a quiz at the end of this, but I just want to let you guys all see how we basically make these decisions. And I have to say I am a tiny, tiny, tiny cog in the wheel, any of us are of this huge space, which is the development of new therapies for cancers and for lymphoma specifically. There are many, many, many, many parts to that machine, the many clinical research coordinators and all the folks at drug companies that help to develop these therapies and help to perform these trials. The trials are incredibly complicated, but they are

because at the end of it, we want to have some very clear answers. And I have to say, I just speak for myself, I feel very lucky that when people ask me questions, "Hey, is this medicine better than that medicine?" We have this super high level of evidence. Meaning that "I just like this medicine better than that." No, no, no. That's low-level evidence. High-level evidence is "We have tested these things in randomized trials in many, many hundreds of patients." So when we tell you I think that this is better than that, we are saying it for this very simple clear reason, and I'll show you the reasons here.

So this trial was comparing the old standard R-CHOP to the addition of polatuzumab in about 900 patients with frontline DLBCL. The trial was pretty simple; it is just one versus the other. Literally it was a coin toss for every patient. People got randomized to either the standard or the addition of polatuzumab.



FIRST-LINE DLBCL TREATMENT:
POLARIX TRIAL: POLATUZUMAB + R-CHP vs R-CHOP (PREVIOUSLY UNTREATED DLBCL)
Baseline Characteristics

Characteristic	Polatuzumab vedotin + R-CHP (n = 440)	R-CHOP (n = 439)
Median age, yr (range)	65 (19-80)	66.0 (19-80)
Male, n (%)	239 (54)	234 (53)
ECOG PS 0/1, n (%)	374 (85)	363 (83)
Bulky disease (≥7.5 cm), n (%)	193 (44)	192 (44)
Elevated LDH, n (%)	291 (66)	284 (65)
Median time from diagnosis to treatment initiation, days	26	27
Ann Arbor stage III/IV, n (%)	393 (89)	387 (88)
Extranodal sites (≥2), n (%)	213 (48)	213 (49)

Characteristic, n (%)	Polatuzumab vedotin + R-CHP (n = 440)	R-CHOP (n = 439)
IPI score		
▪ 2	167 (38)	167 (38)
▪ 3-5	273 (62)	272 (62)
Cell of origin		
▪ ABC	**102 (31)**	**119 (35)**
▪ GCB	**184 (56)**	**168 (50)**
▪ Unclassified	**44 (13)**	**51 (15)**
MYC/BCL2 expression	139 (38)	151 (41)
MYC/BCL2/BCL6 rearrangement	26 (8)	19 (6)

17 IPI, International Prognostic Index. Adapted from Tilly. *NEJM*. 2022;386:351.

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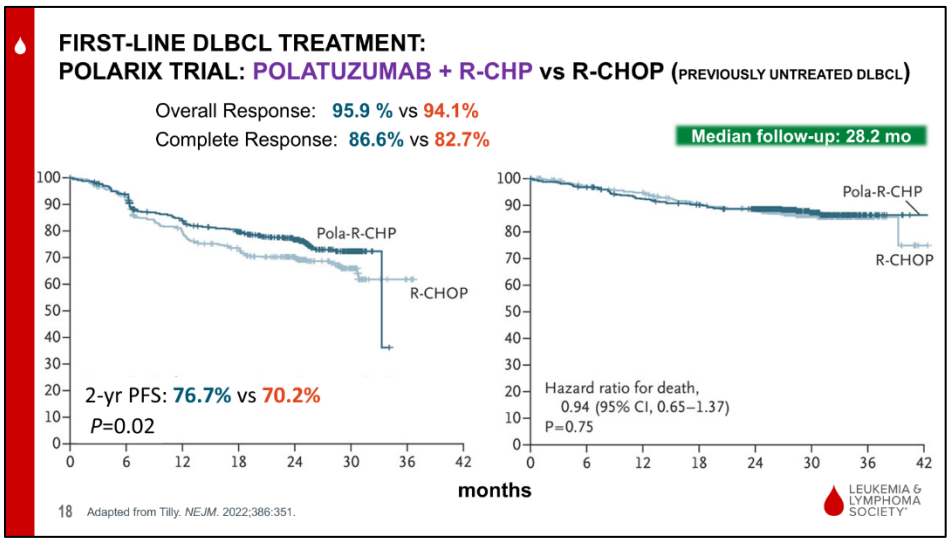
I will not go into the details here. This is just a description of the many, many hundreds of patients in the trial. You can see their average age was in their middle sixties, which is pretty normal for DLBCL. You can see here another mention of their IPI score. So what that is telling you is that these patients were fairly high-risk. I told you IPI of zero is low risk and IPI of five is higher risk. And you can see most of these patients had IPI scores of three to five. And that was intentional because we were trying to develop new therapies for people at the highest risk. Even after these things get FDA-approved, we could still maybe use them for lower-risk patients, but the trial is trying to focus on the people at the highest risk, and it's these IPI 3-, 4-, 5-point patients.

I mentioned this cell of origin thing. I call them GC, GCB, or ABC. I also said we sometimes use the word non-GC as sort of synonymous with ABC. And you can see there were patients here from both groups.

And I mentioned that this super high risk of what we were calling Double Hit lymphomas, I said they were pretty rare. I said that there were 6%, 7%, or 8%, and you can see there were 6%, 7%, or 8% of people in this trial that had those Double Hit lymphomas. So, that's the basic cohort. I can tell you more about it, but it's not critical here.

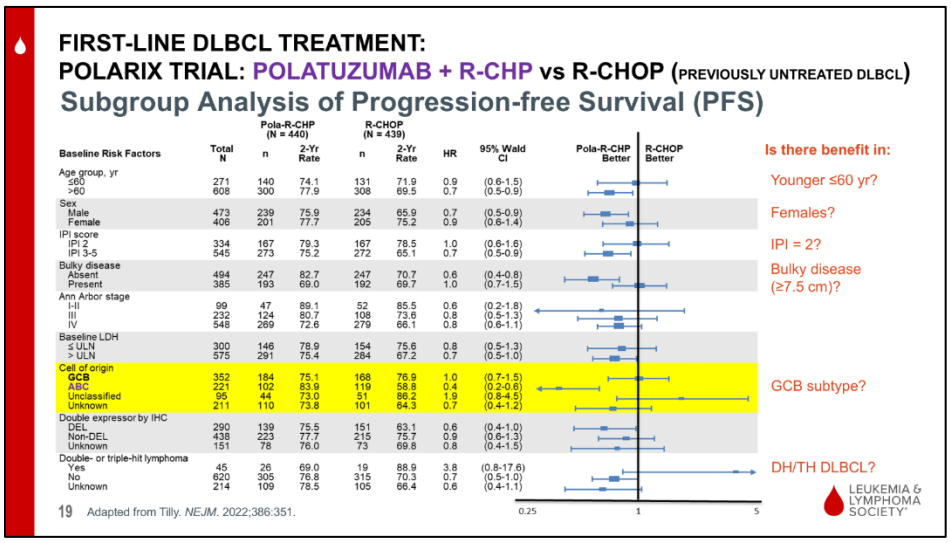


Here's the quick punchline that again in... I don't know if that's blue or slate or whatever that color is there, I'm not great with colors. But overall in the Pola-R-CHP arm, the complete remission rate was a little bit higher. Again, complete remission after therapy, the PET scans looked perfect. It's not synonymous with cure, but it's partway there.

And the complete remission rate was a little bit higher for Pola-R-CHP compared to R-CHOP. More importantly, we followed these patients over time and over the first couple of years, the chance of being in remission was about 6 percent higher, 6-and-a-half percent higher for patients that got Pola-R-CHP. We call these survival curves; we call them Kaplan-Meier curves. I won't get into the details, but you can see that, again, this is how people are staying in remission. This is a progression-free survival curve. And there were more people here on the dark blue curve. I think that's dark blue compared to the gray, I think that's a gray. And again, it's about 6 percent more at two years. So overall it does look like a better medicine by that measurement, and that's the good news. And here's maybe not the bad news, but the lukewarm news – overall, the chance of just being alive (this is the overall survival curve) looked to be about the same whether people got this or got that.

Why are they still alive even if they relapse? Because we have second-line and third-line therapies that are thankfully pretty good. So even if patients relapsed over here at one year, hopefully they got good therapy and could still be alive at 2, and 3, and 4 years. We need a little more follow-up of this trial because maybe these curves will split later on, but we're already about five years into it, you don't see all that data here, and still there is not yet an overall survival benefit. And that really is our purpose is to make patients live. Not just to stay in remission, but to live.

So, you can see where this is a victory, a success, but maybe a triple instead of a homerun so far because patients were living similarly with both regimens.

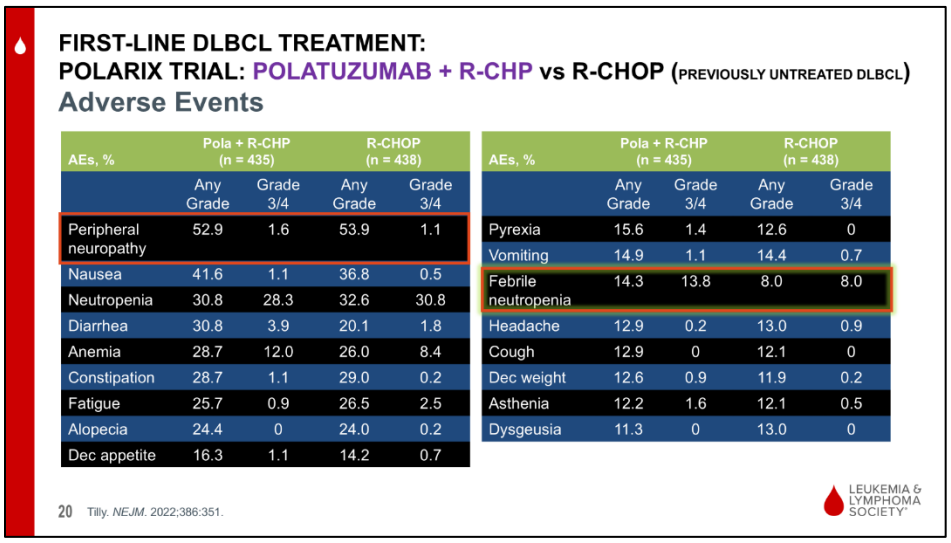


I won't get too much into this, but again, a lot of details go into these studies, and we look at many different subsets of patients. And although overall there was benefit for people getting Pola-R-CHP compared to R-CHOP –I showed you that little 6% benefit – there were some subgroups that got even more benefit. And now this gets into why I mentioned all that biology stuff in the beginning. Patients that have the ABC subtype of DLBCL seem to get a lot more benefit. Being on the left side of this plot shows greater benefit, greater risk reduction if you get Pola-R-CHP. So this is a little curious because this is called a post hoc analysis. We only analyzed these things after the fact, and yet this difference is so large that I think many lymphoma experts have taken this into clinical adoption.

I'll tell you our practice, that we are much more likely to give Pola-R-CHP to someone with ABC subtype or non-GC diffuse large B-cell lymphoma than we are with the other type, GCB subtype, because the benefits seems so much higher. It almost sort of looks like the GCB patients didn't get much benefit with Pola-R-CHP compared to R-CHOP at all. So maybe they're equivalent for the GCB patients.

A lot of nuance here and subtlety. I won't get into all of it, but I'm just showing you how we do, after the fact, looked at these different subgroups and sometimes that can be a strong enough difference to impact our clinical decisions.

Lizette Figueroa-Rivera, MA
Dr. Brody, Charlie has a question, "Does using polatuzumab reduce side effects?"



FIRST-LINE DLBCL TREATMENT:
POLARIX TRIAL: POLATUZUMAB + R-CHP vs R-CHOP (PREVIOUSLY UNTREATED DLBCL)
Adverse Events

AEs, %	Pola + R-CHP (n = 435)		R-CHOP (n = 438)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Peripheral neuropathy	52.9	1.6	53.9	1.1
Nausea	41.6	1.1	36.8	0.5
Neutropenia	30.8	28.3	32.6	30.8
Diarrhea	30.8	3.9	20.1	1.8
Anemia	28.7	12.0	26.0	8.4
Constipation	28.7	1.1	29.0	0.2
Fatigue	25.7	0.9	26.5	2.5
Alopecia	24.4	0	24.0	0.2
Dec appetite	16.3	1.1	14.2	0.7

AEs, %	Pola + R-CHP (n = 435)		R-CHOP (n = 438)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Pyrexia	15.6	1.4	12.6	0
Vomiting	14.9	1.1	14.4	0.7
Febrile neutropenia	14.3	13.8	8.0	8.0
Headache	12.9	0.2	13.0	0.9
Cough	12.9	0	12.1	0
Dec weight	12.6	0.9	11.9	0.2
Asthenia	12.2	1.6	12.1	0.5
Dysgeusia	11.3	0	13.0	0

20 Tilly. *NEJM*. 2022;386:351.

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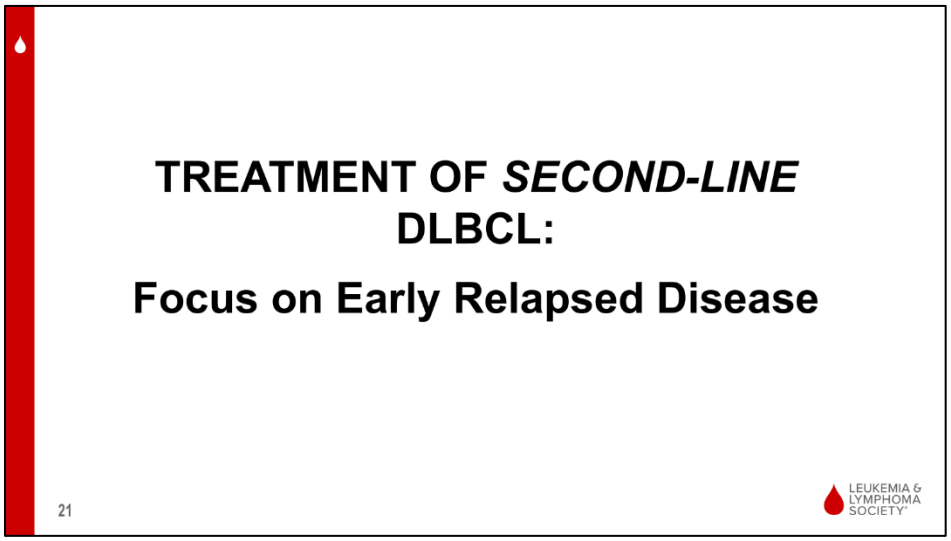
Joshua Brody, MD
Great question. Man, these questions are beautifully well-timed to the slides because here's the side effects slide. I feel like Charlie must be a buddy of mine who knew that this slide was... Anyway. Charlie, here's the answer to your question. And Charlie, because you asked, again 12 other people were thinking the same question.
Polatuzumab is added on top of the R-CHOP. The one difference is we got rid of the O. The O is called vincristine. Don't ask me why vincristine is called the letter O.
And so maybe we could get rid of the vincristine side effects and those can be things like neuropathy, but the polatuzumab does bring its own possible side effects. So overall, the two regimens were pretty close. So here are all of these many side effects, not all of them, but the most important ones I'm showing you and the most common ones.
And we have columns here for anyone that gets the side effect. And this other column called grade 3/4, the people that get the bad, more significant versions of the side effects. We're not going to look at all of these numbers on this page. We're just going to focus on a couple of things.

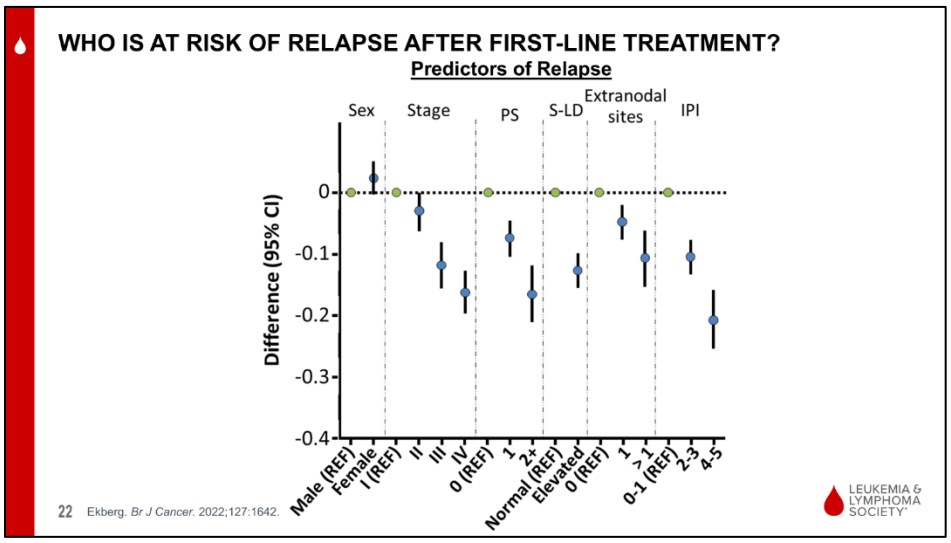
People with Pola-R-CHP versus R-CHOP had about the same amount of neuropathy because we got rid of the vincristine, which can cause neuropathy, but we added in the polatuzumab, which can also cause a bit. So it was about a wash, pretty close to a wash. Similar numbers with Pola-R-CHP and R-CHOP. But we're just going to look at this one side effect, which is for us, the doctors, maybe one of the more concerning ones. Febrile neutropenia means someone had low blood counts, low neutrophils, and they've got a fever. So for us, this is synonymous with an infection, some type of infection, even though we don't know exactly what type. And these febrile neutropenia's land patients in the hospital, hopefully just for a couple of days to get antibiotics and get better and go home, but they can be serious. The punchline here is that there was a bit more febrile neutropenia, about 6% more, you can see 14 versus 8, with Pola-R-CHP compared to R-CHOP. This is actually a little more side effects with Pola-R-CHP, not a lot, 6% moderate difference, and febrile neutropenia not the worst side effect in the world. You go to the hospital, get some antibiotics, most people go home in a couple of days, but it's not nothing. You're going to the hospital.

So my punchline for all of this is Pola-R-CHP is a bit more effective and has a bit more side effects, and therefore, those things all affect who we would recommend it for. If someone's a little younger and healthier and could tolerate the risk of getting an infection, [I'm] a little more likely to give them Pola-R-CHP. If someone has that non-GC subtype, [I'm] a little more likely to give them Pola-R-CHP. If someone is 90 years old or not great health and couldn't tolerate an infection or has that GCP subtype, personally our approach is to give them R-CHOP. That's not a universal standard, but that's one approach, and you can hear how we came up with that reasoning. So hopefully Charlie, I answered your question.

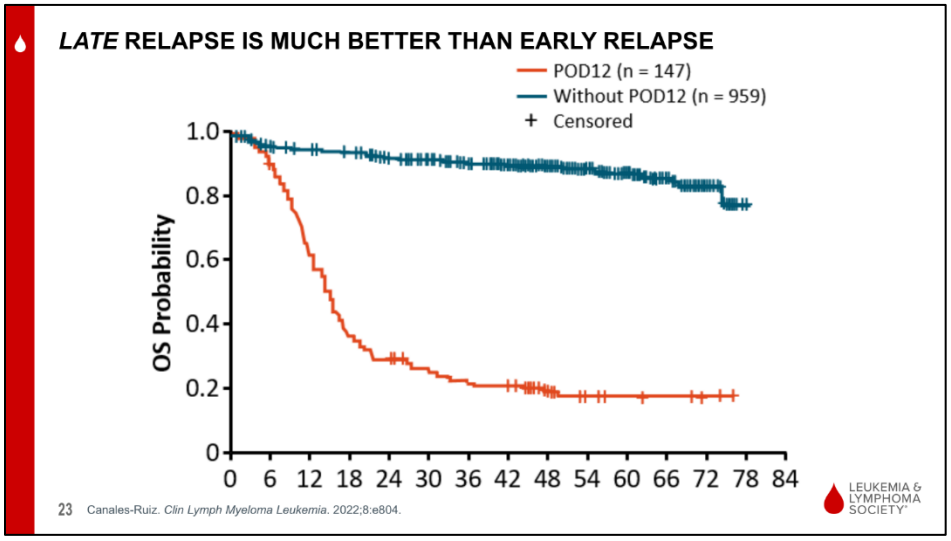


If there's more questions, it's a good time. Otherwise, we're going to move to a quick discussion of second-line DLBCL and how we treat it.

Again, happily, most patients are cured but not all, and some patients do not respond or relapse after that frontline therapy. So we're going to talk about second-line treatment of DLBCL, and we're going to focus on the people who have the early relapses, and the reason is because their outcomes are a bit worse.

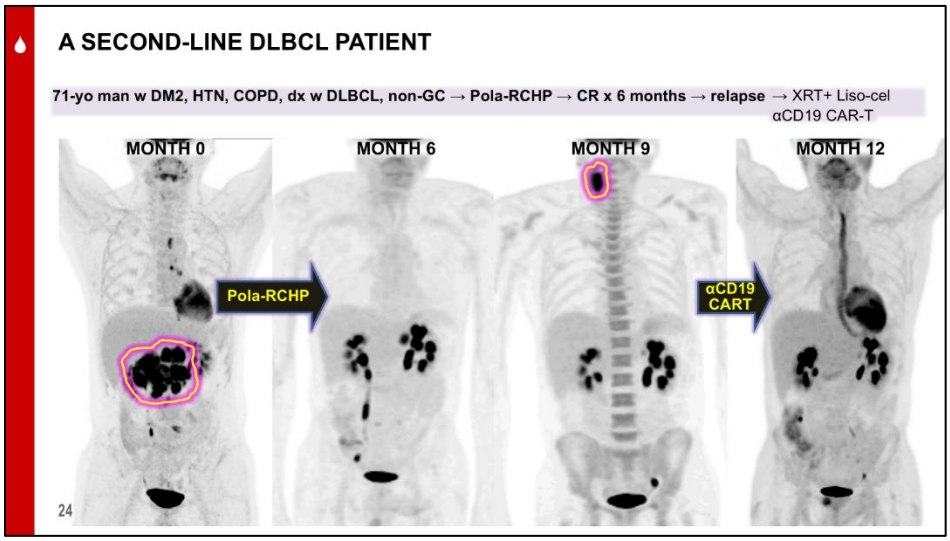


I'm going to first reiterate here that some of these components of that IPI that I mentioned can predict if people are likely to relapse, and here's the overall IPI score. If people have an IPI of two to three, forget the Y axis here, but this is the statistics showing likelihood of staying in remission, so a little less likely. And if they have a higher IPI of 4 or 5, even more likely to have a relapse. These are the components of the IPI. Just having a bad performance status by itself for example, shows a higher risk of relapse. Still, many of these higher IPI patients can be cured, but the risk of relapse is higher.



To show another thing that predicts how patients do overall... These patients that relapse very quickly, this POD12... Again, sorry that we have confusing terminology, but they're not so bad. POD12 means progression of disease within 12 months. If someone gets frontline R-CHOP and they relapse within 12 months, they have a worse outcome overall. This is a retrospective study, so a not perfect study to try to make that point, but you can see in the orange curve here that patients that relapsed early had worse overall survival. This is historical, so hopefully, if we were to redo this study today, this red curve would

actually be a lot better because of the new therapies I'm about to show you. But this is historical. In the '90s and 2000s and 2010s, maybe. If patients relapse quickly, their outcomes were much worse.

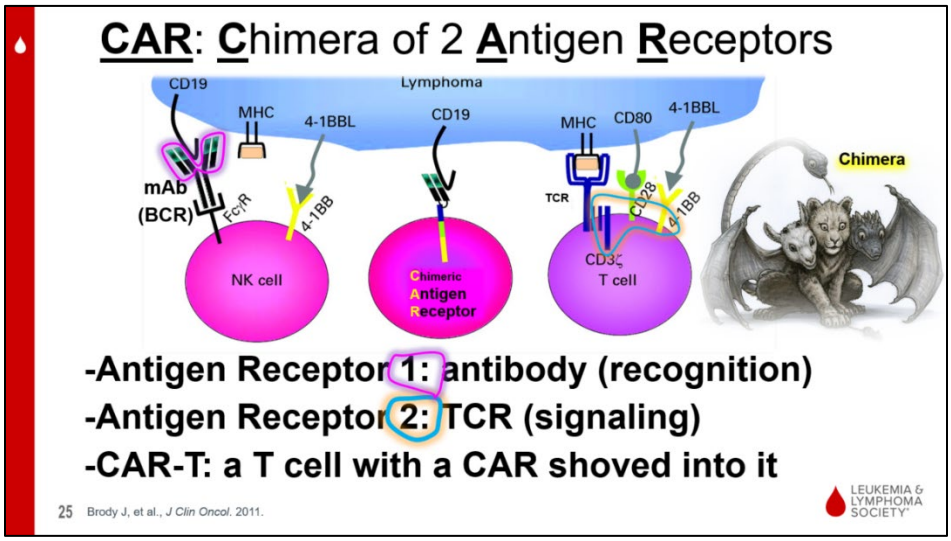


I'm going to show you how we've tried to improve upon that, and I'll start with a quick anecdote. Here's a patient of mine. He's 71. He has diabetes, high blood pressure, and a few other comorbidities. He has this non-GC subtype of DLBCL I mentioned. He got Pola-R-CHP. As I hinted, we give to many folks like this. He had a complete remission. Again, we're writing here in “doctorese,” not English. We're writing in doctor's jargon, but this is how we try to quickly communicate with each other. So now I'm letting you see how it works in the back room. He had a complete remission for 6 months and then he relapsed. Let me show you what that looks like.

These are PET scans, but you do not need to be a radiologist to understand what's happening here. All black is the sugar that we injected during the PET scan, and you have to ignore the sugar that he's peeing out in his bladder here, that's normal, and the sugar in the heart, because that's normal because hearts use a lot of sugar. But almost all of the rest of this black here is his lymphoma. Lots of lymph nodes deep in his abdomen. I'm showing you those here, and he got Pola-R-CHP as I mentioned, and he had a complete remission. All the black you see here is just the bladder and the kidneys. You have to trust me, that's just the kidney peeing at the sugar, both of the kidneys. All of that DLBCL, all that lymphoma in the abdomen, he was in complete remission. So, so far so good.

But three months after that, he quickly relapsed, and now you can see this new golf ball or lemon or whatever it is here in his neck, which is taking up a lot of sugar. These PET scans are pretty easy to understand. You don't need to be a radiologist. You can see that plainly. Then he was treated with this new-ish therapy, this technological wonder called CAR T cells [chimeric antigen receptor T-cell therapy], and he happily went into again complete remission. You'll have to excuse again, the black here is in the heart and the kidneys, in the bladder, and also his esophagus was a little inflamed here because of some side effects and he had some reflux. But you can see this lymphoma, this lemon, disappeared. He went back into complete remission. Now I've known this patient for a

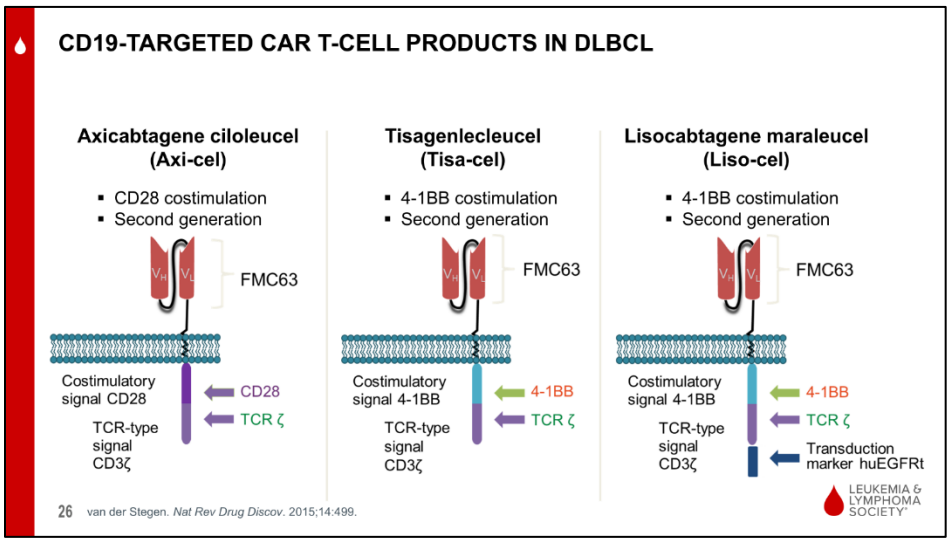
couple more years, and he's still in complete remission. Hopefully he's cured. We won't know that until more time.



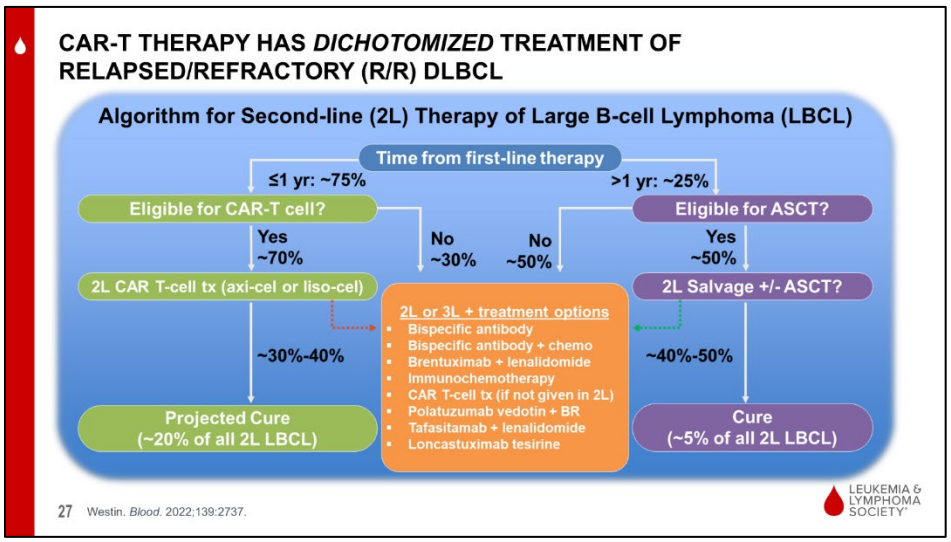
Many of you have heard the word CAR T cells, and many people around the world have heard the word CAR T cell, never quite clear why it's called CAR T cell. I'm going to quickly explain that. CAR stands for a chimeric antigen receptor. Okay, what is a chimeric antigen receptor? First, a chimera is a weird mixture of multiple animals, so we use this word in molecular biology all the time when we mix two molecules together and make a chimera, not of a snake and a kitty cat and a dragon and a bat or whatever that is, but chimeras of molecules. This, but in a molecular way.

What is an antigen receptor? There are two antigen receptors in my body and your bodies. One of them is called the B-cell receptor and we also call it antibody. B-cell receptor, antibodies, same things. Those are synonyms, basically. And antibodies, as you probably have heard of, are great for binding specific parts of another cell. For example, the CD19 protein on a lymphoma cell. An antigen receptor can be a B-cell receptor or a T-cell receptor. That's the other antigen receptor in our bodies. The T-cell receptor has many parts, the T-cell receptor proper and also the signaling parts that we call CD3 or CD28 or 4-1BB. These are all different molecules, all different antigen receptor molecules, and we, the community, the royal we, have made a chimera of these different antigen receptors, so we call that chimeric antigen receptor.

When Dr. Carl June was developing this at UPENN (The University of Pennsylvania) 20 years ago, he was going to call it T bodies instead of CAR T cell. Both cute names, CAR T caught on, and it is because it is a chimera of these two antigen receptor molecules. So that's what a CAR is, and a CAR T cell is a T cell that we put the CAR molecule into. How we do that is a bit fancy. We take T cells out of a person, put this CAR molecule into them, and I will show you a bit here again what those CARs look like.



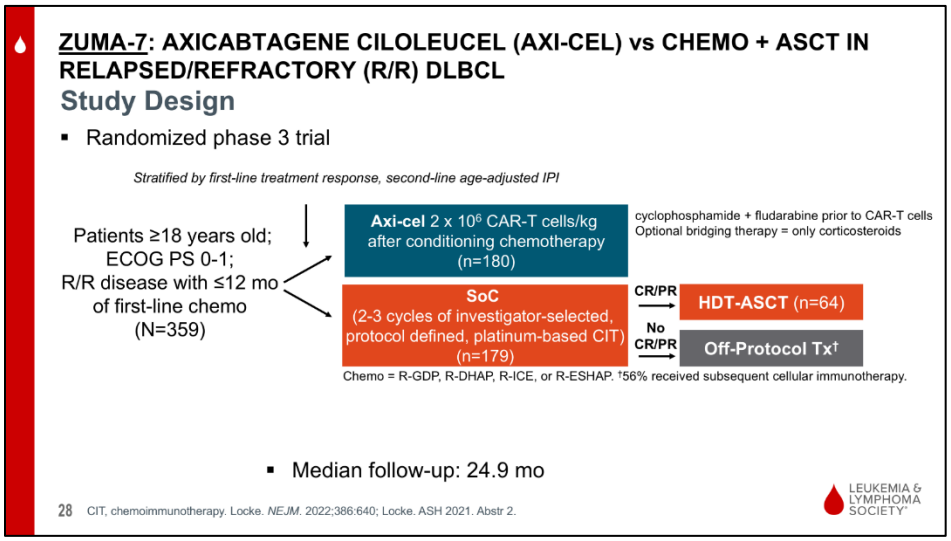
Again, the details here are more than might be needed, but we have three FDA-approved versions of CAR T cells for DLBCL. We have other ones for myeloma, other ones for mantle cell lymphoma. These are the names of them. They are made, respectively, by different companies, Gilead, Kite, Novartis, and BMS Celgene. They're all approved for DLBCL, but two of them are approved for second-line DLBCL. I won't get into the difference here unless folks have questions about them.



Because these have been so promising, and I'll show why in a moment, this has changed the algorithm for how do we think about second-line therapy for DLBCL. And the answer is if a patient relapses very quickly – I told you those folks have worse outcomes in the old days – then if they could be eligible for CAR T cell, just means they're healthy enough to get this slightly tricky therapy, and probably more than 70% of people are probably eligible for CAR T cells. If you are 95 and have bad, bad COPD and bad heart, maybe you're not eligible for CAR T cells, but most people are. If someone relapses quickly and is eligible for CAR T-cell therapy, we try to get them CAR T cells as their second-line

therapy, and probably cure a good fraction of these relapsing patients with those CAR T cells.

If patients relapse later, they relapse 3 years after R-CHOP or 5 years after R-CHOP, we go down a different path on the algorithm maybe including stem cell transplant. I'm not going to emphasize this half of it today because again, the majority of patients are on this left side of the page and it is the more important update because it's the new thing over the past few years, so I'm going to talk a bit more about that. If folks have questions with anything on this page, we can talk about it.



If folks do not get CAR T cells in the second line or if they relapse afterwards, here I'm just hinting. There are still many things in the third line, and we'll talk about that a bit later as well. Again, I won't go into the details-

Lizette Figueroa-Rivera, MA
Dr. Brody, John is asking, "Why is CAR T not offered from the beginning?"

Joshua Brody, MD
John, I was told there would be no hard questions at today's meeting, so here's the quick answer to that. The first answer is because R-CHOP and Pola-R-CHP cure a majority of patients and, number one, are a lot quicker to get than CAR T cells, which takes many, many weeks to make for a patient. Three weeks to make it, but also a couple of weeks to set it up, probably. With frontline DLBCL, we can't wait around that long, usually, number one.

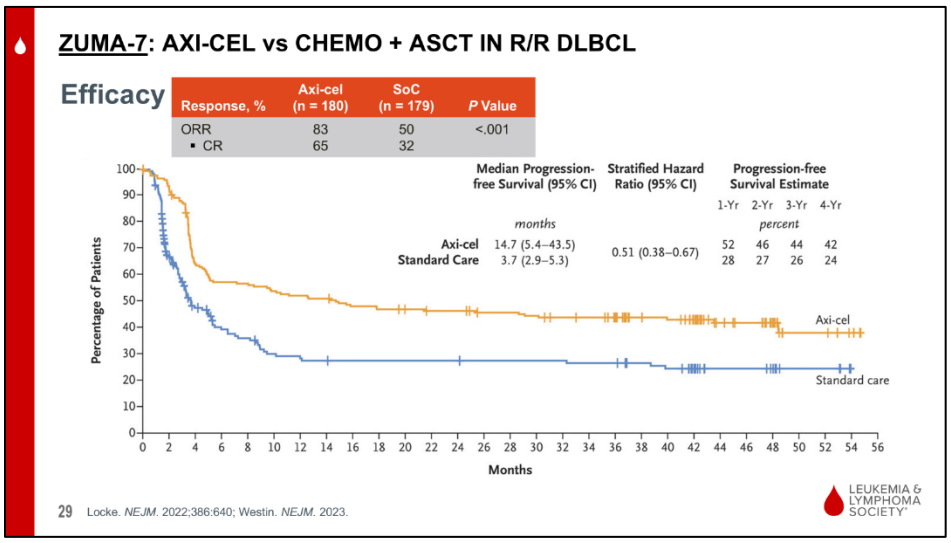
Number two, there might be some consideration for giving chemo and CAR T cells, but that's a little tricky because if you were going to be cured with chemotherapy alone, what I didn't quite get to yet is that CAR T cells, as miraculously elegant as they sound, and they are miraculous, they still have very significant side effects. If someone was going to be cured, let's say you were in the 65% of people that were going to be cured with R-CHOP, and people may be thinking, "Oh, R-CHOP has bad side effects." Moderate, bad for some people, pretty mild for a lot of people. If you were already going to be cured

with that, why would we add another therapy on top of that, which may or may not increase the cure chance but would almost definitely increase the risks and side effects? So the quick answer is because CAR T cells do have a bunch of side effects, which I'm going to get to in a bit, so you're not getting something for nothing, you're getting something for a cost, and the cost is side effects. Number two, it is very difficult to get CAR T cell in a timely way, and diffuse large B-cell normally needs to be treated pretty quickly. Those are two of the answers.

There are some ongoing trials of trying to get CAR T cells for some of the highest-risk patients with DLBCL as part of frontline therapy, maybe not instead of chemo, but maybe after just a little bit of chemo to tide patients over while the CAR Ts are being prepared. Those are most of the answers. But John, I will say that we're going to mention in a bit another immunotherapy similar to CAR T, a little bit different, called bispecific antibodies, and those, as opposed to these CAR T cells, are, we say, off-the-shelf. They're available instantly, and those are being now incorporated into frontline DLBCL therapy. We are trying to improve frontline therapies with immunotherapies, but CAR T cell has been logistically very tough to even make it into a second-line therapy and very, very tough to try to get into a frontline therapy.

I kind of answered the question. I may have gone over a bit of it quickly, but I'm happy to field more questions about it. Good, good question. If there are more there, I'll pause or I'll keep going.

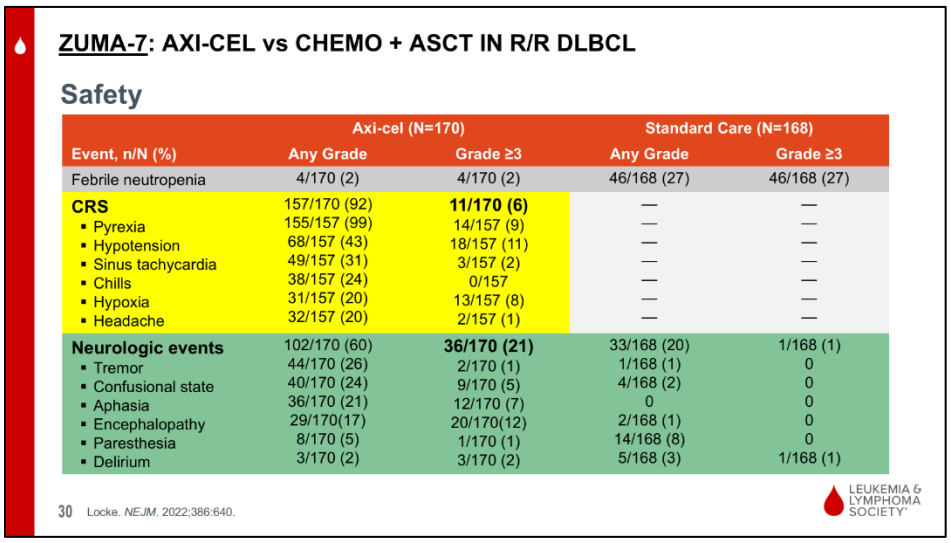
I'm going to mention how we made CAR T cells become part of second-line therapy, which was already a big advance. They were already part of third-line therapy for eight years already, but now, in the last three years, have become part of second-line therapy. We did this large trial of giving people either standard of care, which used to be more chemo... This is for second-line if, let's say, R-CHOP has failed. Patients relapsed six months after R-CHOP. Their options were, again, 50/50, get more chemo and maybe we say high-dose therapy and autologous stem cell transplant. We have to put all the doctor words here because we can't fit all the English words onto a page. We sometimes call this BMT [bone marrow transplant] or auto transplant. That was the standard of care for 20 years: so half the people got that and the other half the people got CAR T cells. This trial was called the ZUMA-7 trial, a big trial of 350 people.



Here's the punchline of that. This is called progression-free survival, and you can see that the people in orange, I think, here that got the CAR T cells were much less likely to progress than the folks that got the chemo plus or minus stem cell transplant. That was, overall, a huge win. In addition to being less likely to progress, that's what this chart is showing, actually there was an overall survival benefit.

This is the gold standard of clinical trials and progress in cancer, and lymphomas especially, that if you got CAR T cells you were more likely to be alive 2 years and 3 years and 4 years later if you were on this orange curve, if you got the CAR T cells, instead of standard of care. That's a huge benefit, and that is what pushed the FDA to approve CAR T cells as second-line therapy.

John could ask, "Hey, can we try to do this trial for frontline again?" It would be near to impossible, and just take my word on that for the moment, because of some of the logistic things I hinted at, and I can mention again. So this was a huge success. For patients that relapse early, this is part of what made second-line CAR T cell our recommendation for DLBCL patients that relapse within the first 12 months after their frontline therapy.



ZUMA-7: AXI-CEL vs CHEMO + ASCT IN R/R DLBCL

Safety

	Axi-cel (N=170)		Standard Care (N=168)	
Event, n/N (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Febrile neutropenia	4/170 (2)	4/170 (2)	46/168 (27)	46/168 (27)
CRS	157/170 (92)	**11/170 (6)**	—	—
▪ Pyrexia	155/157 (99)	14/157 (9)	—	—
▪ Hypotension	68/157 (43)	18/157 (11)	—	—
▪ Sinus tachycardia	49/157 (31)	3/157 (2)	—	—
▪ Chills	38/157 (24)	0/157	—	—
▪ Hypoxia	31/157 (20)	13/157 (8)	—	—
▪ Headache	32/157 (20)	2/157 (1)	—	—
Neurologic events	102/170 (60)	**36/170 (21)**	33/168 (20)	1/168 (1)
▪ Tremor	44/170 (26)	2/170 (1)	1/168 (1)	0
▪ Confusional state	40/170 (24)	9/170 (5)	4/168 (2)	0
▪ Aphasia	36/170 (21)	12/170 (7)	0	0
▪ Encephalopathy	29/170(17)	20/170(12)	2/168 (1)	0
▪ Paresthesia	8/170 (5)	1/170 (1)	14/168 (8)	0
▪ Delirium	3/170 (2)	3/170 (2)	5/168 (3)	1/168 (1)

30 Locke. *NEJM*. 2022;386:640.

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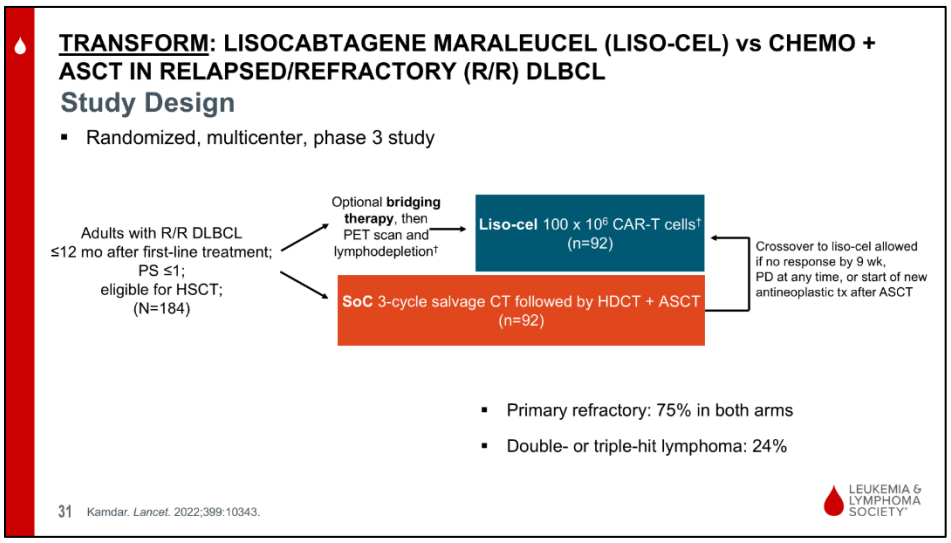
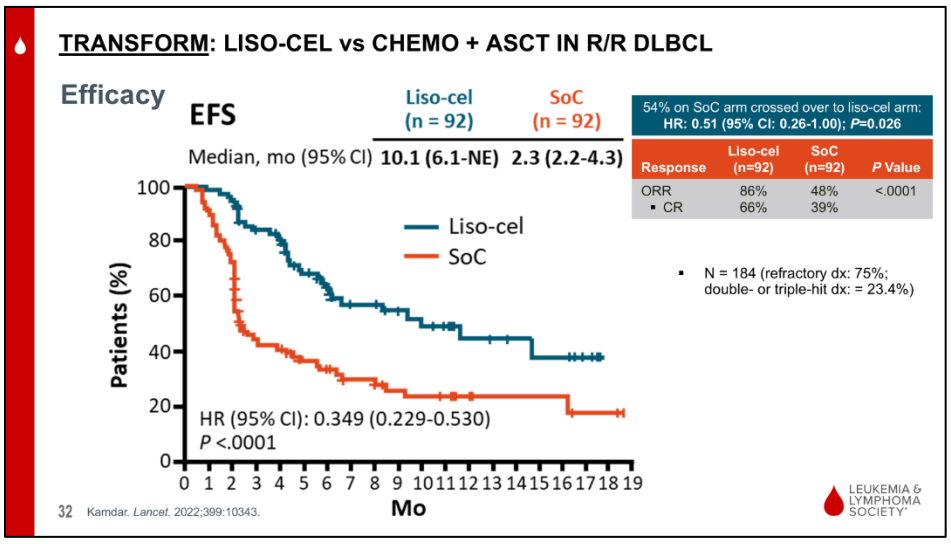
John and everybody, I hinted that CAR T cells still have toxicities, and here are some very specific toxicities that are unique to CAR T cells or specific for them. One is called cytokine release syndrome (CRS), which involves fever and sometimes low blood pressure. Lots of patients got some of this side effect. You can see 92% got some of it, but let's skip that and look at the patients that had high-grade cytokine release syndrome, and you see that again, 6 out of 100 people. High-grade pretty much means it landed you in the intensive care unit. Super scary. So 6% of people were in the intensive care unit because of cytokine release syndrome.

Then this other side effect I won't talk too much about, we sometimes call ICANS (immune effector cell-associated neurotoxicity syndrome) or just neurologic side effects. CAR T cells, in a complicated way, can make people go crazy. It can make them hallucinate, it can make them confused, it can even make them obtunded, unable to wake them up. Those high-grade neurologic side effects happened in more than one-fifth of patients getting CAR T cells here. That all sounds scary. The good news is these things were almost always quite transient. They last for two days, three days, sometimes less. We have good therapies for some of these things, but it can be very scary. And again, landing in the intensive care unit is a dangerous thing. Not everyone that goes to the ICU always comes out of the ICU.

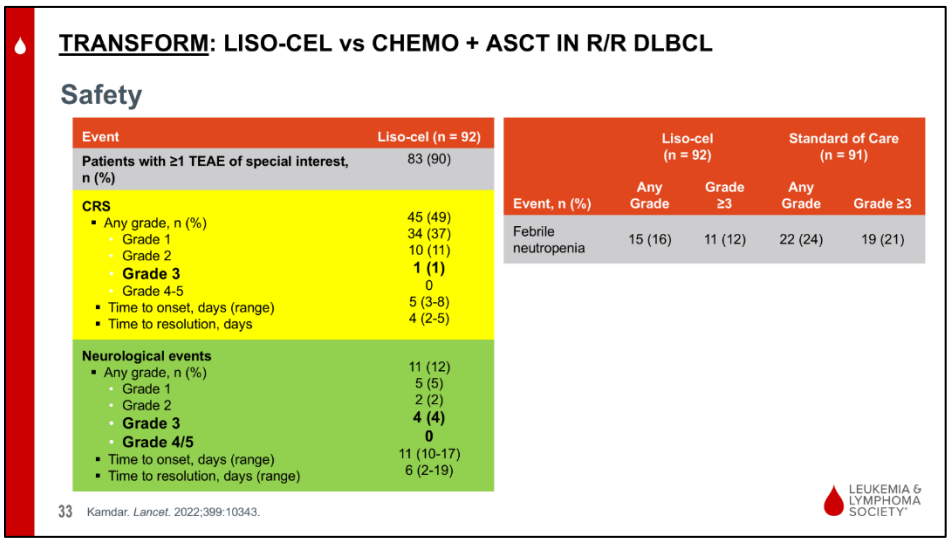
This is to John. Another answer to the question. These things do have side effects. You might even say that these side effects are still less than the alternative, less than stem cell transplant, which is tough therapy and can have a lot of side effects, but they're not nothing overall. I won't go too much more into this, but again, CAR T cells have side effects. The standard-approach therapy, high-dose therapy transplant, also has side effects. I won't go into them. Overall people say, "Doc, which is safer, CAR T cells or auto transplant?" They're different. It's not just one is safer than the other, but overall, I would say CAR T cells are safer than autologous transplant, overall. That's a broad statement and my opinion, but overall, I would rather get CAR T cell than auto transplant. We would call this trial a real win-win. More effective and maybe a bit safer than the old standard of care.



I'm going to mention one other trial, kind of similar, by using the other CAR T cell that I mentioned. Instead of axi-cel, this one is called liso-cel, made by a different company. They're both great CAR T-cell therapies. This trial, instead of called ZUMA-7, is called TRANSFORM. Again, half of the people got CAR T cells, half of them got the standard chemo plus autologous transplant.

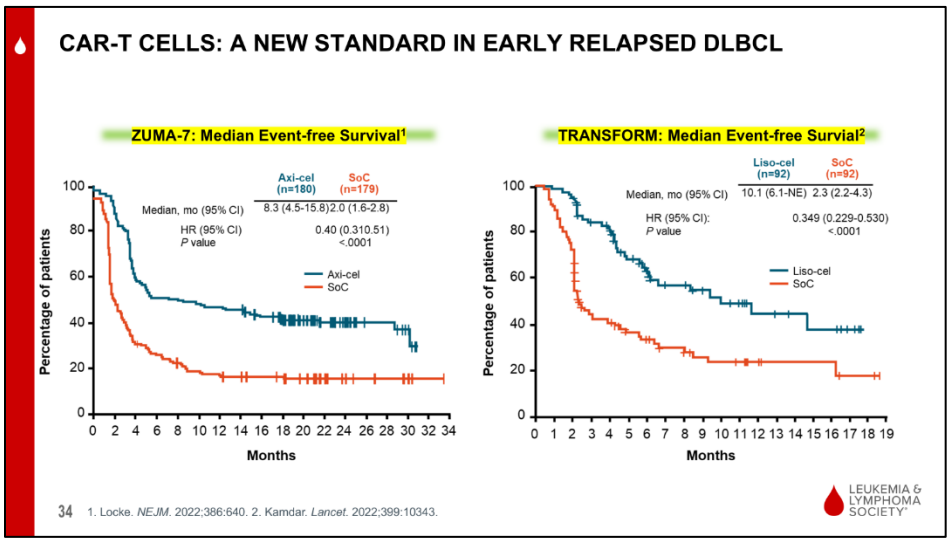


The quick punchline is very similar. The patients that got CAR T were more likely to be in remission than the ones that got chemo and auto transplant. So, this CAR T cell was also FDA approved for second-line therapy. Again, almost about two years ago now.

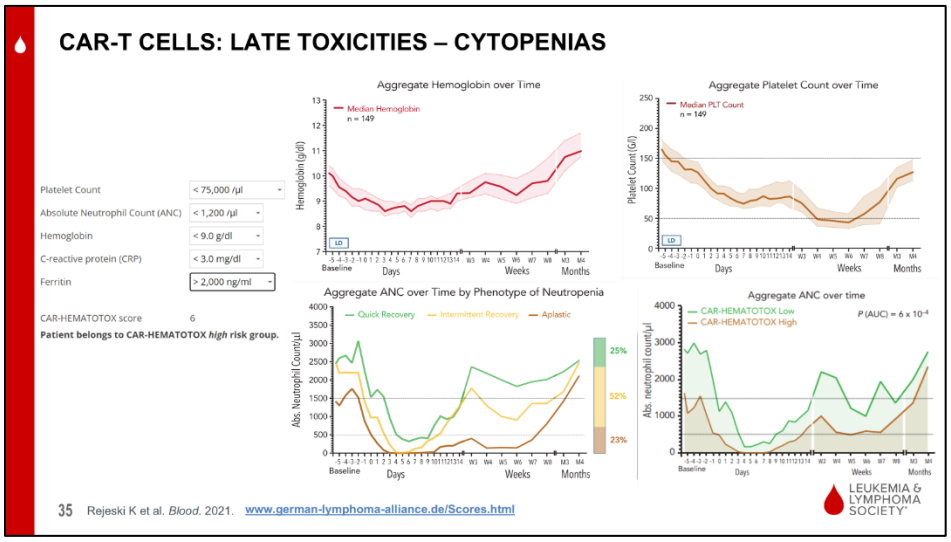


Again, these side effects that I mentioned were there, as well. The cytokine release syndrome, some of them high-grade but not too many, and those neurologic side effects. But at a glance, it does look like there were fewer of those high-grade side effects with this liso-cel compared to axi-cel.

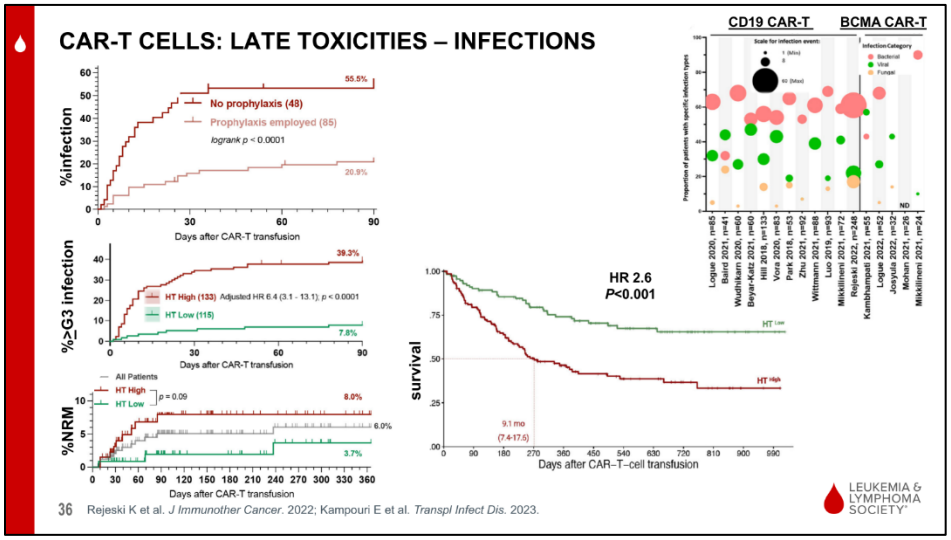
We will frequently get the question, "Dr. Brody, which one's better, axi-cel or liso-cel?" We don't know because we have not compared them directly against each other, and these two trials were a little different, so it's hard to say, "The number 4 is less than the number 20, so it must be safer." But overall, probably our feeling is that liso-cel does have a little less of these high-grade side effects. That's our belief, even though we haven't compared them head-to-head and maybe have some data that axi-cel might be a little bit more potent because we saw that overall survival benefit. But again, that's a soft statement because we have not compared them head-to-head. They're both very good. At the end of the day, we choose axi-cel for some patients and liso-cel for other patients, and it's a nuanced discussion of which one is right for which patient. Not a simple statement.



Again, here's those two things side by side. You can see great benefits with CAR T cells as opposed to the old standard of care, stem cell transplant.

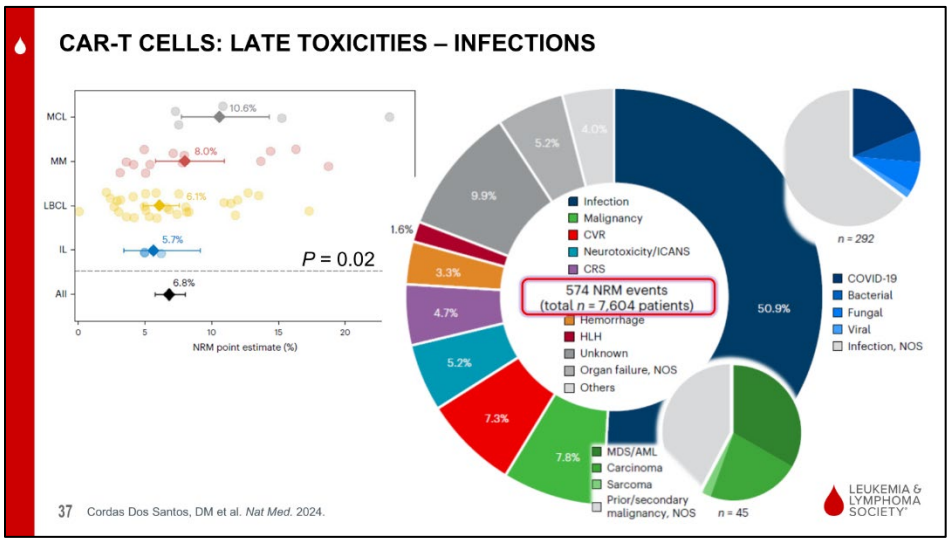


As I mentioned, there are these side effects of CAR T cells, but the side effects I mentioned were the early side effects. You get them five days, 10 days after CAR T cells. These are some later side effects. I won't go into detail here, but the obvious thing is that people can get low blood counts either days or sometimes even many, many weeks or even months after CAR T-cell therapy. Sometimes we can add up the amount of low blood counts people have and predict who's going to get them. We have some scores, another calculator you can find on the internet, to predict who's going to be likely to have these low blood counts. This score, this calculator you can find, is called HEMATOTOX score. The likelihood of having hematological toxicity, HEMATOTOX score.



To emphasize here that there are late side effects beyond the first few weeks from CAR T cells, and low blood counts and infections resulting from that is one of them. So again, even though some people could be cured with CAR T-cell therapy –and this is also getting back to John's questions – some of these side effects can be a bit cumulative. Even the patients that do not have their lymphoma recur can still die of other things, and the most common thing here was infections.

This has been tough because over the last few years, we had people dying of COVID, whether they had therapy or even if they didn't, especially here in New York. But patients that got CAR T-cell therapies had higher risks of infections than patients that don't, and especially patients with prolonged low blood counts had higher risk of infection. I'm only showing that those risks are real, and they happen later. I'm not going to talk more about the details of them. I won't get into the specifics, but these are side effects that we worry about. I'm going to skip the details of this data for the sake of time.

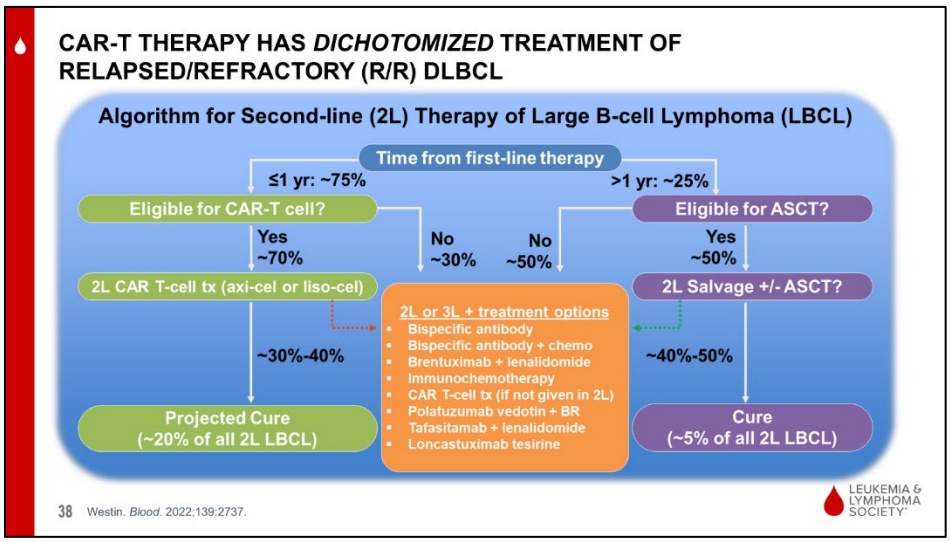


These scary letters here, NRM, non-relapse mortality, people that died but did not have their lymphoma relapse. Again, that can happen. More than half of them occurred because of infection. Blue is infection, and this can occur many months later. I'm emphasizing that infections can happen, even long after the CAR T cells. I'm not saying this to scare people, I'm saying this because it's actionable. We sometimes have to watch these folks closely for many, many months, and sometimes we have to give them antibiotics, even preventative prophylactic antibiotics, to prevent some of these infections. That is general advice, not specific advice, and I won't go into more detail on this data because we're running a little long.

Lizette Figueroa-Rivera, MA
Doctor, are these side effects also the same type of side effects that mantle cell lymphoma patients face when they're getting CAR T-cell therapy? We have a lot of mantle cell lymphoma patients on the line today.

Joshua Brody, MD
Yes. In fact, I have one little bit here about mantle cell lymphoma. You can see on the top left here, that the answer is absolutely yes. These CAR T side effects, the early ones like the neurological side effects and the late ones like infections, happen with... You can see LBCL, it's DLBCL, the common lymphoma we're talking about. There were even a bit more of them with mantle cell lymphoma. Again, CAR T cells are awesomely effective for mantle cell lymphoma, probably the most potent anti-lymphoma medicine for mantle cell lymphoma. But these side effects are significant, so it's not for everybody with mantle cell lymphoma.

This is real hard because we want to both brag about how great they are but also be very honest about some real risks. If some patients are dying from these side effects, the great majority are not, but we still want to list them with it. The purpose is not to scare people, but to give them all the information and again, hint that they may require close observation from their doctors even for months after the CAR T cells. So mantle cell [lymphoma patients listed on the slide] had a few more of these problems than DLBCL patients, 10.6 here instead of 6.1. So yes, same sorts of side effects from mantle cell [lymphoma patients], in slightly different proportions. Good, good, good question.


CAR-T THERAPY HAS *DICHOTOMIZED* TREATMENT OF RELAPSED/REFRACTORY (R/R) DLBCL
Algorithm for Second-line (2L) Therapy of Large B-cell Lymphoma (LBCL)
Time from first-line therapy
≤1 yr: ~75%
>1 yr: ~25%
Eligible for CAR-T cell?
Eligible for ASCT?
Yes ~70%
No ~30%
No ~50%
Yes ~50%
2L CAR T-cell tx (axi-cel or liso-cel)
2L Salvage +/- ASCT?
2L or 3L + treatment options
Bispecific antibody
Bispecific antibody + chemo
Brentuximab + lenalidomide
Immunochemotherapy
CAR T-cell tx (if not given in 2L)
Polatuzumab vedotin + BR
Tafasitamab + lenalidomide
Loncastuximab tesirine
~30%-40%
~40%-50%
Projected Cure (~20% of all 2L LBCL)
Cure (~5% of all 2L LBCL)
38 Westin. Blood. 2022;139:2737.
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TREATMENT OF ≥ THIRD-LINE DLBCL
39
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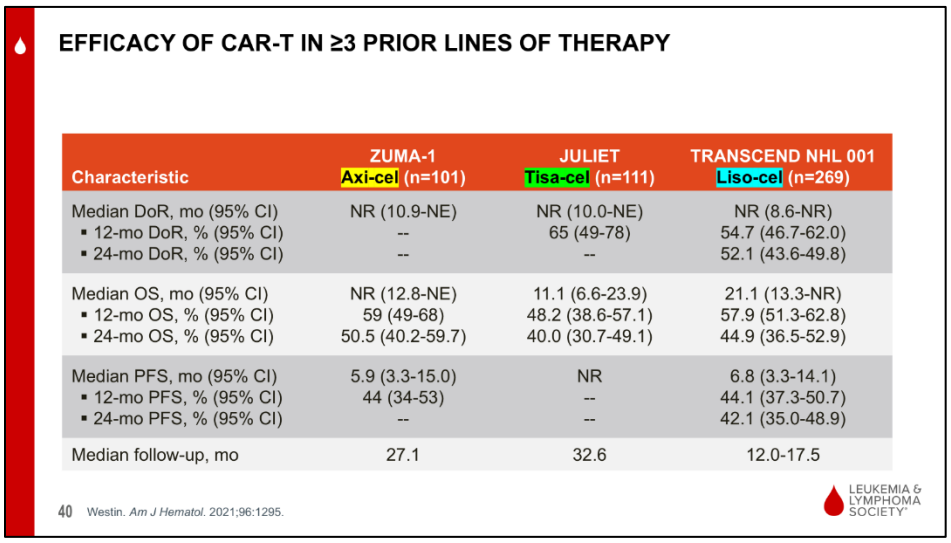

EFFICACY OF CAR-T IN ≥3 PRIOR LINES OF THERAPY

Characteristic	ZUMA-1 Axi-cel (n=101)	JULIET Tisa-cel (n=111)	TRANSCEND NHL 001 Liso-cel (n=269)
Median DoR, mo (95% CI)	NR (10.9-NE)	NR (10.0-NE)	NR (8.6-NR)
▪ 12-mo DoR, % (95% CI)	--	65 (49-78)	54.7 (46.7-62.0)
▪ 24-mo DoR, % (95% CI)	--	--	52.1 (43.6-49.8)
Median OS, mo (95% CI)	NR (12.8-NE)	11.1 (6.6-23.9)	21.1 (13.3-NR)
▪ 12-mo OS, % (95% CI)	59 (49-68)	48.2 (38.6-57.1)	57.9 (51.3-62.8)
▪ 24-mo OS, % (95% CI)	50.5 (40.2-59.7)	40.0 (30.7-49.1)	44.9 (36.5-52.9)
Median PFS, mo (95% CI)	5.9 (3.3-15.0)	NR	6.8 (3.3-14.1)
▪ 12-mo PFS, % (95% CI)	44 (34-53)	--	44.1 (37.3-50.7)
▪ 24-mo PFS, % (95% CI)	--	--	42.1 (35.0-48.9)
Median follow-up, mo	27.1	32.6	12.0-17.5

40 Westin. *Am J Hematol.* 2021;96:1295.

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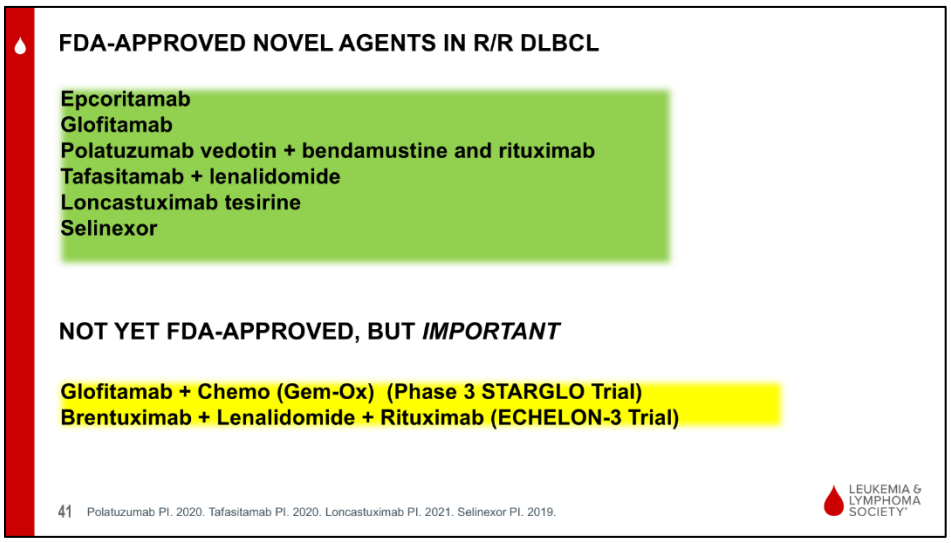
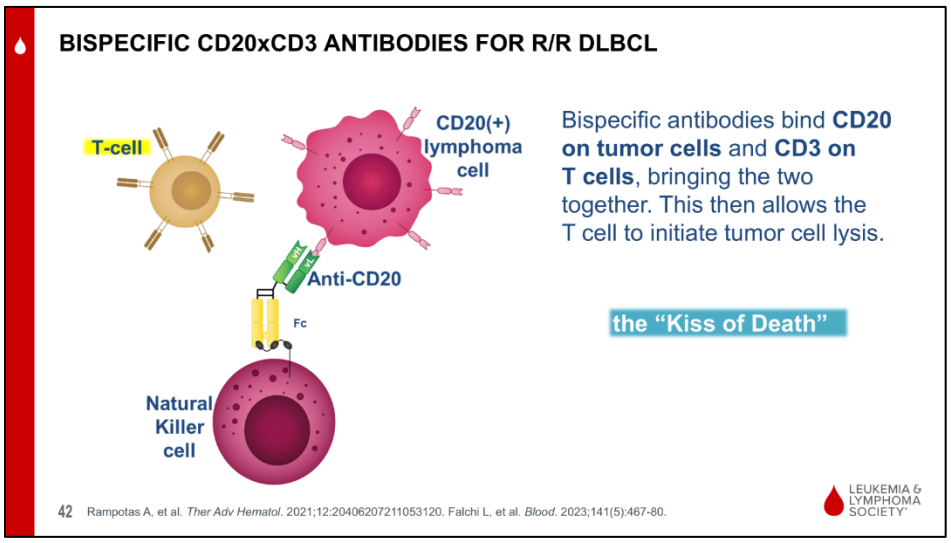
I won't say more about second-line therapy in this algorithm, and I'll just give a couple quick hints about third-line therapy, and that way, hopefully, we'll have enough time for more questions at the end. Again, CAR T cells can be used in second-line, but they're also FDA approved in third-line. These were three big trials to show, from the different types of CAR T cells, the results in third-line DLBCL therapy when the first two lines of therapy had been insufficient. The quick punchline you can see here across the board is that a good proportion of patients were alive and doing well, or at least pretty well, two years after these third-line CAR T-cell therapies ([that is, about] half of patients).

I don't want to oversimplify this, but the point is here, this is back when we developed CAR T, when there was no other great third-line therapies for many of these patients, and some of these patients got CAR T as third-line therapy, some of them got it as 8th-line, 12th-line therapy. [They had received] many, many prior lines of chemotherapy. Some of these patients were in a very tough way, and yet still these CAR T cells were able to give prolonged survival for many of them and probably cure for a significant fraction of them. Hard to say what that exact fraction is, maybe it's 35%, maybe it's 40%. This is why we were happy to try to move CAR T cell to become a second-line therapy.



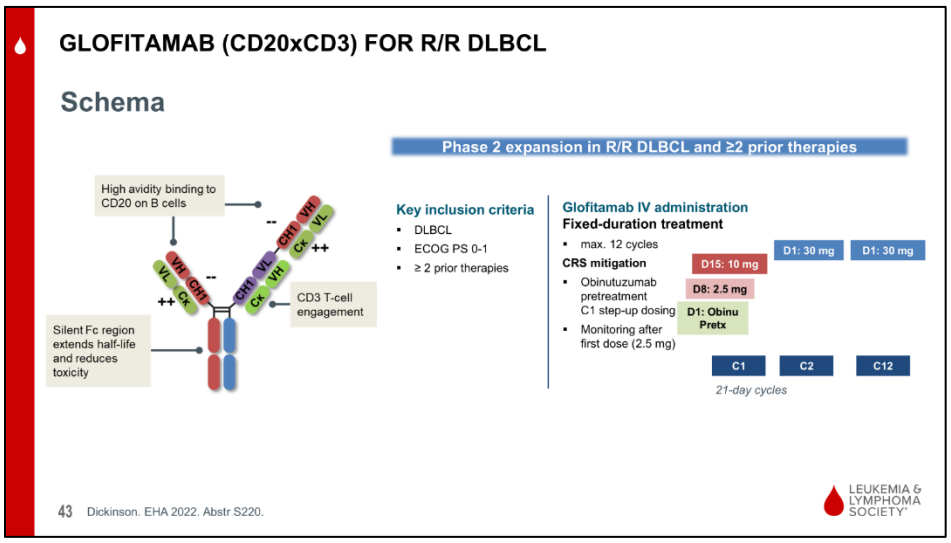
I'm going to quickly talk a little bit about the numerous things we have that are third-line therapies. This is remarkable because we did not have any of these things 10 years ago, and most of them we didn't have 4 years ago. This is really rapid progress. The progress in lymphoma has been more rapid than in any other cancer in the world and breast cancer is kind of the second most rapid development of new therapies.

So I'll just mention a bit about each of these, but not too much about them in detail. And then these are FDA-approved, but I have to at least mention that we have some recent great clinical trial results. I'm just alluding to them, but these combinations, so these are medicines you've already heard of. You see lenalidomide [Revlimid®] also shows up here as an approved therapy, but these are novel combinations of them, using them in combination with chemotherapy or in combination with other antibody drug conjugates. So even though these are not FDA approved, all the components, the ingredients are FDA approved maybe in some other context. So we might be using these, we say off-label because these randomized trials were quite recent. This one was just published earlier this week in *The Lancet*. And so we can be thinking about these even though they're not quite FDA approved yet because the components are FDA approved.

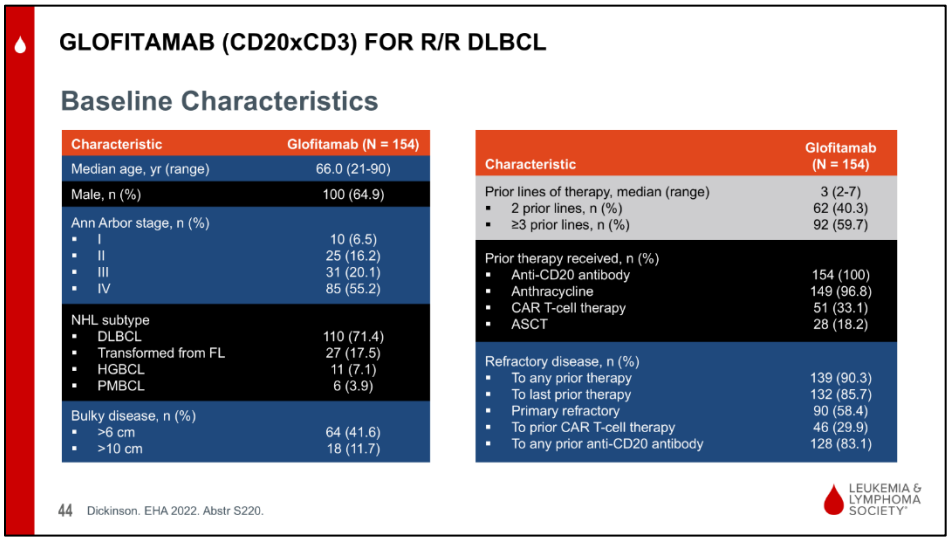


This awesome new class of medicines we call bispecific antibodies. Two examples I'll mention in a moment. The concept is very elegant. We have old antibodies like rituximab, which grab a lymphoma cell and then kind of softly bring a type of immune cell called an NK (natural killer) cell over to kill that lymphoma cell. And that's pretty good. But we found out later that in fact if we can bring a T cell, this potent immune cell that's very good at killing other cells if guided to, if we can bring that T cell over to the lymphoma cell, the killing is much more potent. And so we've accomplished that by these, we say bispecific antibodies. Bispecific because they're specific for a lymphoma cell and specific for a T cell, they bring the T cell over to the lymphoma cell and sort of make these two cells kiss. And in this case, we call that the kiss of death because the T cells kill these lymphoma cells.

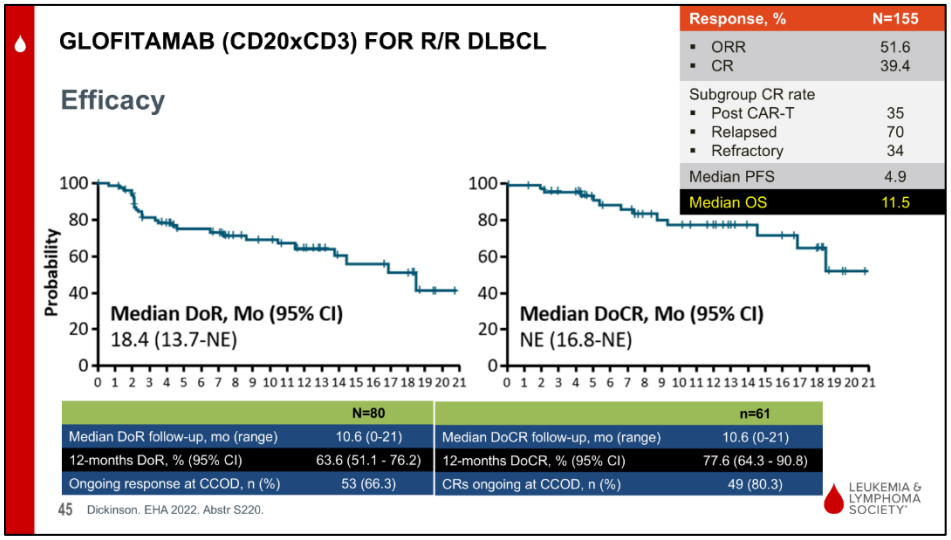
Ultimately, it's not that different than CAR T cells, but whereas the CAR T cell is made in a factory, this one is literally being made in your body after we give this bispecific antibody. So we call it an off-the-shelf therapy. It doesn't have to be made for each person.



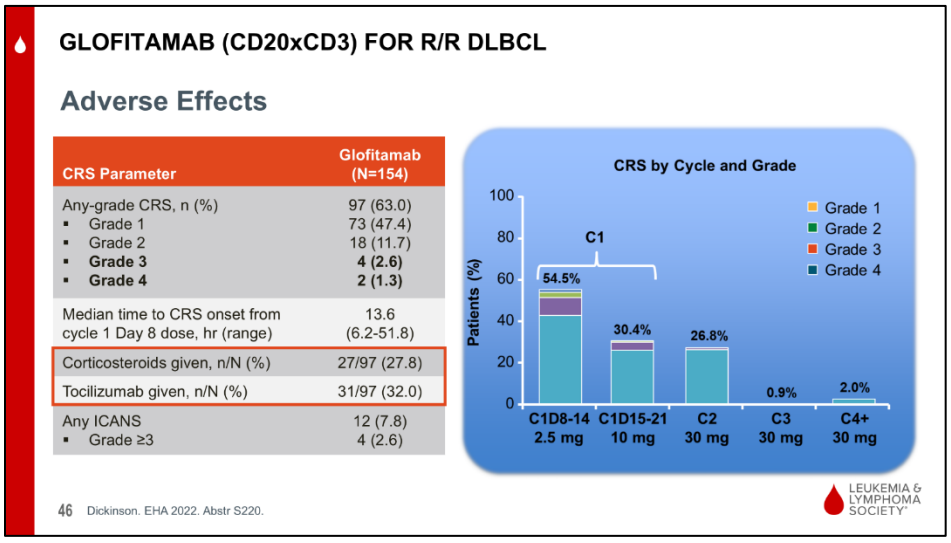
Two examples of bispecific antibodies. The first one, glofitamab [Columvi™]. I'm just showing you that its molecular structure is a little bit different than others. I'm not going to talk about the details. And a unique feature of these bispecifics that we have to not give the full dose on day one. We have to give people, we call step-up dosing, a baby dose, two-and-a-half milligrams, a toddler dose, 10 milligrams, and then the full grownup dose. And I'll mention why in a moment.



Glofitamab, the first trial of this bispecific antibody, I won't speak too much about the patients, but they all had DLBCL here and all had had prior therapies like chemo and many of them CAR T cells that had failed and despite that, the results were pretty good.

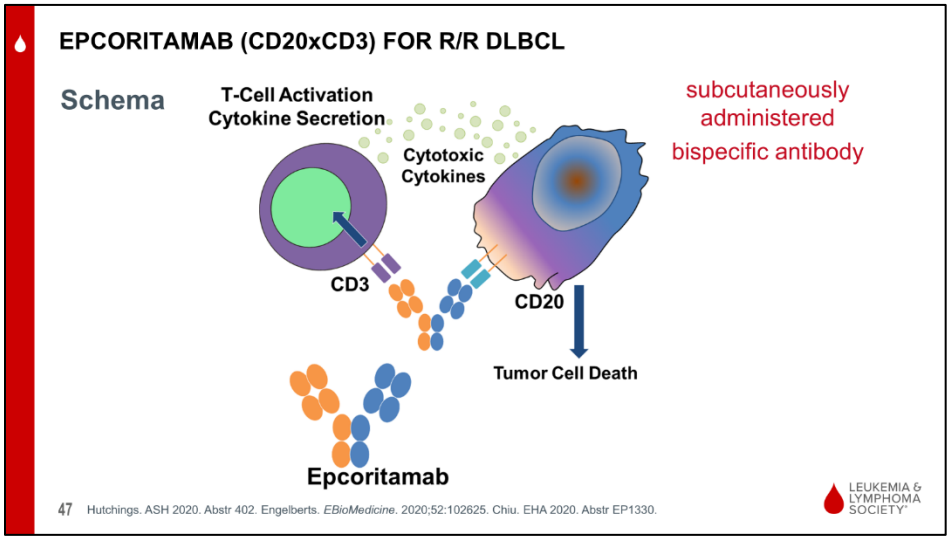


We had many patients who had remission. The remission rate here, as you can see on the top right, the remission rate was 50%, but the complete remission rate was almost 40%. That's actually a lot better than other things in this setting when other therapies have failed and the patients that got a remission were likely to stay in remission for more than a year and many of them staying in remission for more than two years. Could any of them have been cured? Probably. We don't know yet. Ask us again in a couple more years and we'll give you a clearer answer because we won't know. The only test is not a PET scan, but the test is the test of time and so we need a little more time to say maybe what fraction of these patients may have been cured. But I certainly have patients who got this medicine who are in remission for four years, it's a real chance they were cured.

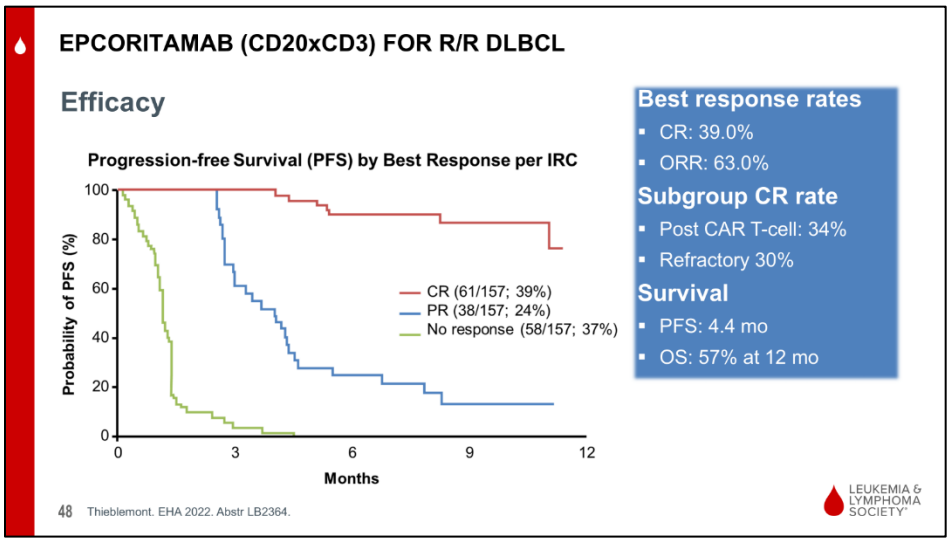


And glofitamab, as I mentioned, we give it in the step-up dosing. And the reason is because it has this one similar side effect to CAR T cells called CRS (cytokine release syndrome). And a few of the patients have high-grade versions of that. But I want to just give the punchline here, this cytokine release syndrome, which again can cause a fever,

could possibly land people in the intensive care unit if they have a high-grade (grade 3/4) event; those high-grade events were pretty rare, less than 5% of people. So overall, not too bad. And they only really happened on this one dose of the therapy, or much more likely to happen on this first dose of the therapy. So, we have to watch patients very closely. And we do put the people in the hospital, our patients, for usually one day while they're getting this first dose of the therapy and hopefully most patients go home the next day.

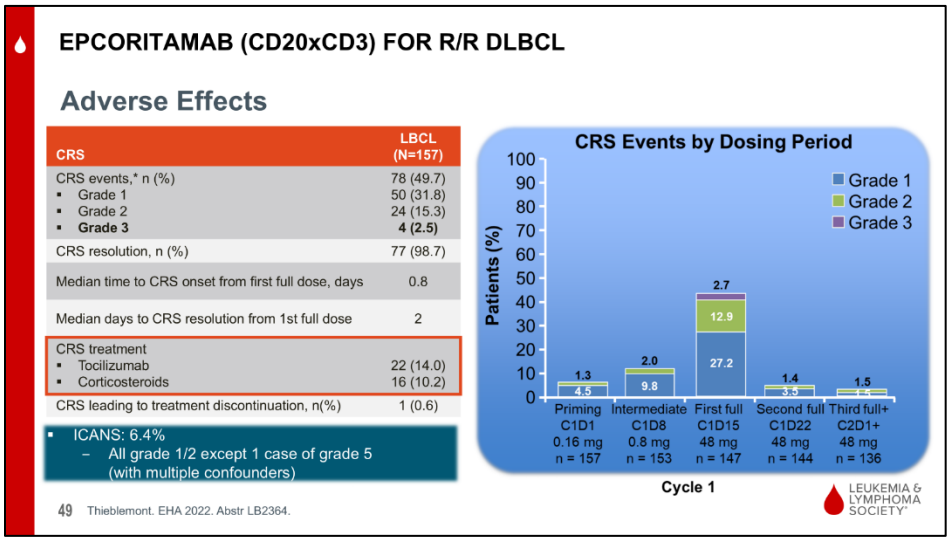


Epcoritamab [Epkinly®], another example of a bispecific antibody. Similar concept, bringing the immune cell, the T cell over to the lymphoma cell.



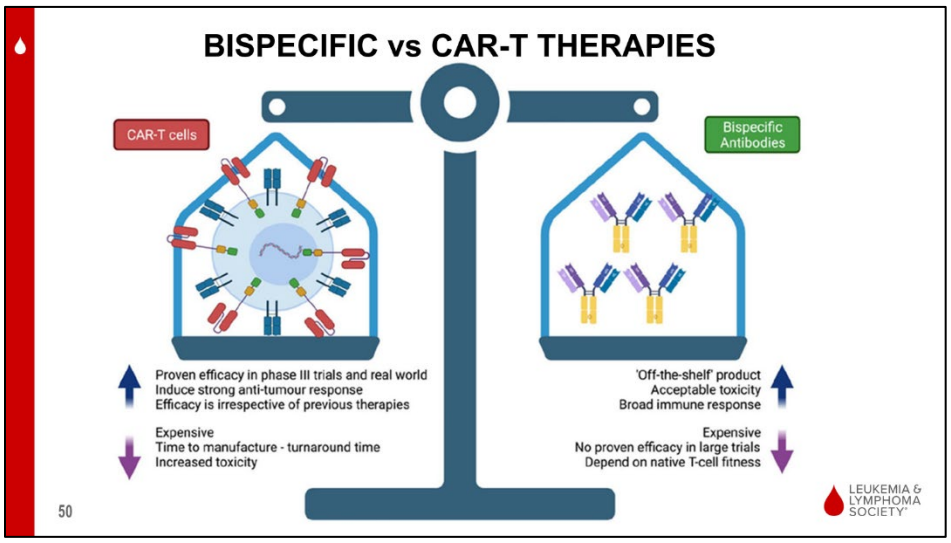
And again, this first trial, we had patients with complete remissions, almost the identical number to that last one I showed you, 39% complete remission. And the folks who had a complete remission have, this is earlier data, only showing you about one year's worth of data, the folks that had a complete remission were very likely to stay in remission for at

least a year. And we have even a bit more follow-up nowadays. I won't go more detail there.

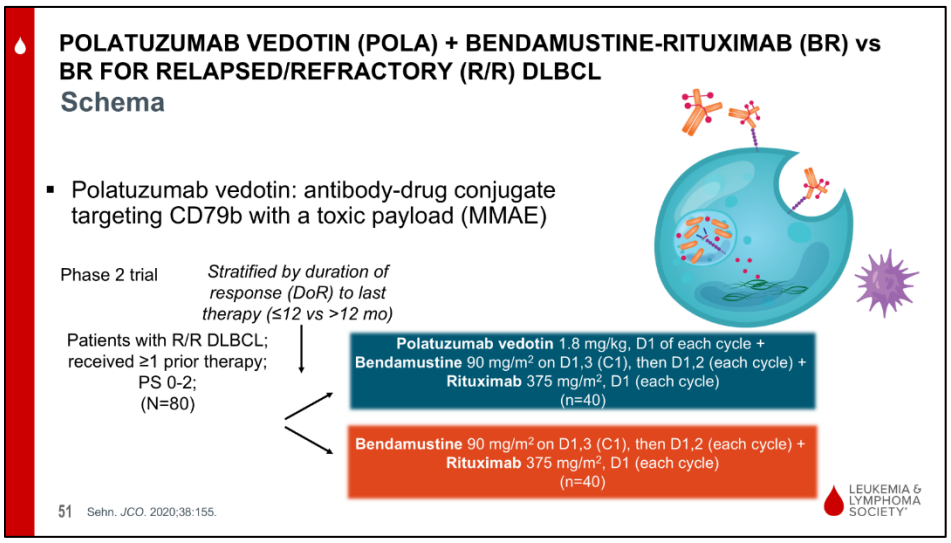


Same concept as the other bispecific and therefore a similar side effect. That cytokine release syndrome again can occur.

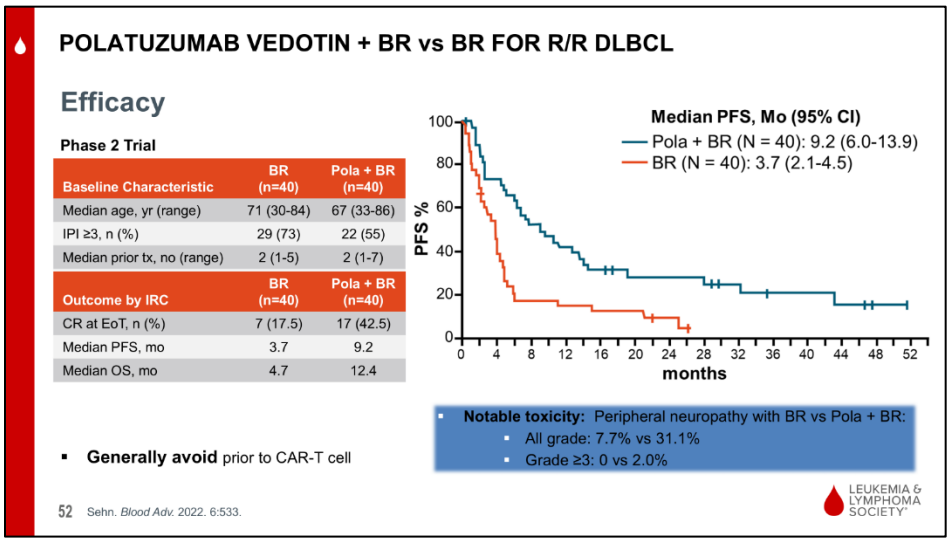
Again, we give a baby dose the first day, a toddler dose the second week, and then a grown-up dose the third week. And when they get that first grown-up dose, we again admit patients to the hospital for one day because the chance of getting this side effect, CRS (cytokine release syndrome) is considerable. But thankfully only a tiny fraction of people, about 3% here, have high-grade cytokine release syndrome. So for that 3%, very significant, they're going to be in the hospital for a few days at least, but for everyone else (that is, the 97% of people), hopefully they can go home the next day.



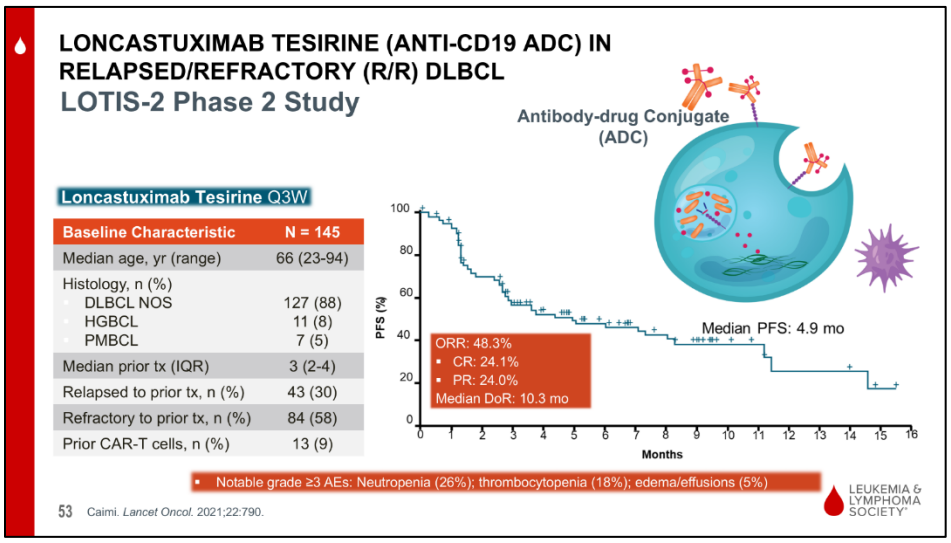
And then people frequently say, "What's better, CAR Ts or bispecifics?" There's no simple answer one's better than another. CAR T cells have a better precedent of curing more patients because, for one thing, we don't have enough time on these bispecific trials to know how many people were cured, and they might be a little bit more potent, but they certainly have some more toxicity compared to the bispecifics. Hard to get into the details, but some more toxicity. And the most important part is they take time to make, they're made for each patient. It takes weeks to make CAR T cells for a given patient and sometimes even a few weeks to get it all set up. So bispecifics are off-the-shelf and that way it may be a little bit easier to use, certainly easier to combine with other therapies. So to answer, I think, Charlie's question from many minutes ago, we are now bringing bispecific antibodies not just into third-line therapy but trying to do trials in frontline therapy in combination with chemotherapy to make those cure rates hopefully significantly higher. And we're super optimistic about those and those trials are almost nearing completion already, so we'll get answers from them soon.



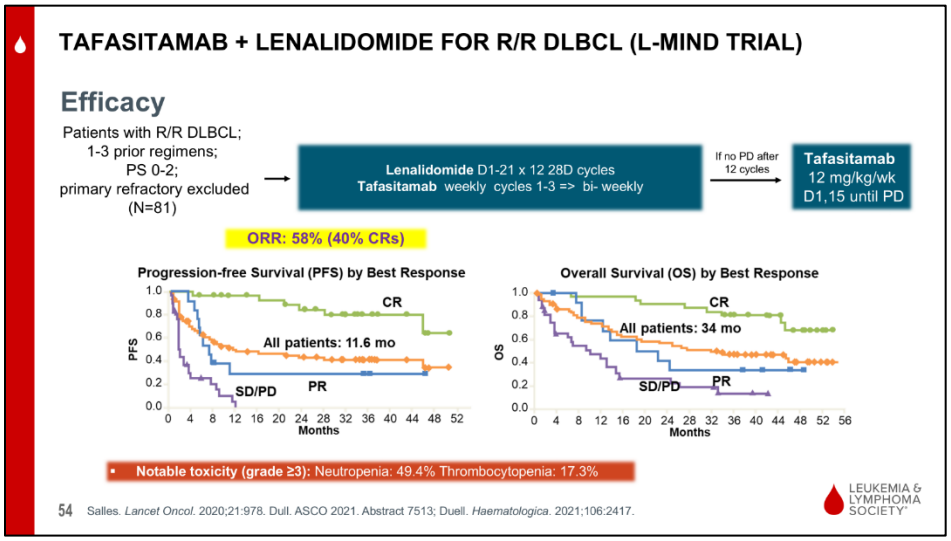
And I'll just mention a few other third-line therapies. I already mentioned polatuzumab that is now part of frontline therapy for some people, but we also use it as a third-line therapy combined with this other chemo called bendamustine (Bendeka®, Treanda®).



And we do that based on this trial. I won't go into the details, but you see here, folks that got bendamustine as a third-line therapy had rapid relapse, whereas those that got pola plus benda stayed in remission for longer. So that was what made this become an FDA-approved therapy.

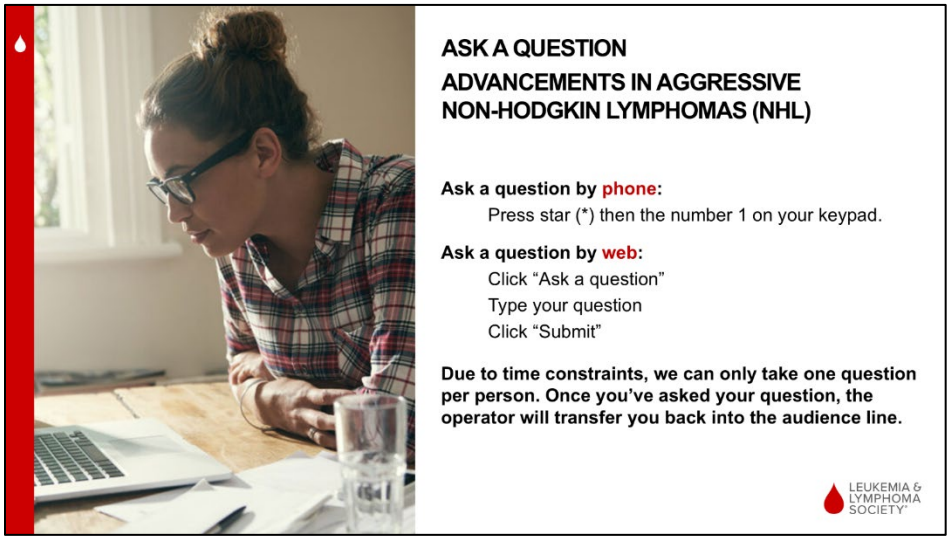


Another antibody drug conjugate called loncastuximab [Zynlonta®], hard to pronounce all these, we just call it lonca. Lonca is a CD19-targeted antibody drug conjugate. [It's the] same concept as what I showed before for the other antibody drug conjugate, [it] brings chemo straight to the lymphoma cell. This is just a single-arm trial of a little more than one hundred patients (that is, 145 patients), and the remission rates were pretty good. Even as third-line therapy, about half of people got a remission and about half of those had a complete remission. So pretty good for a single medicine by itself. I won't say more about it, but I'm happy to field questions.



And then another combination [lenalidomide and tafasitamab (Monjuvi®)]. Lenalidomide is a pill which is been used for multiple myeloma, a different cancer for many, many years and has been used for a few types of lymphomas for the past decade. Tafasitamab is what we call a naked antibody, not an antibody drug conjugate, just an antibody by itself targeting CD19, used in combination with lenalidomide. This is a trial of about one

hundred patients, again, was able to induce remissions in more than half of patients [using] this combination. And the folks that had a complete remission, some of those remissions were very durable. Patients you can see here are going for more than 3 and even 4 years still in remission. So great for some patients. I'm not going to do all the nuance of who is the right patient for which of these therapies, but I'm happy to field questions.



So I think I'm going to pause there. I said a lot, a lot, a lot of stuff. I speak real fast because I'm from New York and I apologize for that, but it's a nice city, so I recommend you come visit. We got a Starbucks recently, so very excited about that. And hopefully, we have 10 minutes for questions, and we may have more than that and we may have to field some of them offline as well.

Lizette Figueroa-Rivera, MA
Well, thank you so much Dr. Brody for volunteering your time with us today to discuss non-Hodgkin lymphoma and the advances in treatment. As you mentioned, it's our question-and-answer portion of our program. And for everyone's benefit, please keep your questions general without many personal details so Dr. Brody can provide answers that are general in nature.

Our first question, Doctor, comes from Edwin, "Regarding the distinction between cure and remission as a person with mantle cell lymphoma, am I correct that the reason mantle cell lymphoma is considered incurable is that the relapse curves never stop going down even after say 8 years in remission?"

Joshua Brody, MD
Edwin, what you say is correct, but I'm going to put a little nuance there. Mantle cell lymphoma is not incurable. It has been called incurable with our historical therapies. In [between] 1980 to 2000, very few patients will be cured with those standard therapies. With 2024 therapy, it might be incurable, or it might be curable, and we honestly don't even know yet because we need to say, look at the people who've been in remission and see how long those remissions last. It's very frustrating because patients have a simple question, "Am I cured, yes or no?" And we don't have a simple answer for them

because the only test is the test of time. So mantle cell lymphoma, instead of calling it incurable, I call it historically incurable. Our therapies are so much better now, between CAR T cells and bispecific antibodies and BTK inhibitors and *BCL2* inhibitors and a few others, that it is possible patients are being cured today.

I definitely have patients who I treated when I used to work at Stanford 12 years ago, and they are still emailing me every year, "Hey, Josh, still alive, still in remission. Year 13 coming up now." Could they be cured? I'm so frustrated to not be able to give you a straight answer, but it's possible. But yes, the curve, instead of plateauing like DLBCL curves, seems historically to keep dribbling down. We have patients still relapsing on year 7, year 8, year 9, so we're a little shy to say that a year-8 person must be cured even if they've been in remission for 8 years because we've had some year-9 people relapse even recently. So, [it is] a little harder to say if someone is cured at what time point. Historically, it looked to be incurable with historical therapies, possibly it could be curable now. So, I don't want to just say MCL is incurable. That is not a true statement. Historically, it was true. It may or may not be true today. But yes, because the shape of the curve.

Lizette Figueroa-Rivera, MA
Thank you so much. And we'll take the next question from our telephone audience, please.

Marjorie from California
Why does chemo attack lymph nodes, causing lymphedema?

Joshua Brody, MD
Oh, Marjorie, that's a good question, but a tough question. Lymphedema, just for the audience, people have heard the word, “edema.” Edema is any swelling of the legs or any part of the body or sometimes the arms as well. And most edema is just caused by extra salt, extra fluid in the body, sometimes by real problems like bad hearts and so forth, that's edema. But lymphedema is when people are not able to drain their lymph fluid as opposed to regular interstitial fluids. And it can come for lots of reasons, but a common reason is there have been some obstruction of the lymph outflow tract. As opposed to veins bringing back fluids, lymph vessels bring back lymph fluid and lymph vessels can get occluded or clogged or blocked for many reasons.

One reason could be that there's a big lymph node full of lymphoma obstructing the lymph drainage, so a big lymphomatous lymph node can cause lymphedema. Another reason is sometimes people get excisions or big excisional biopsies of many lymph nodes and therefore the lymph drainage is messed up. It's even common in breast cancer. If people get axillary surgery, take out many lymph nodes, sometimes there can be bad lymph drainage after that, and people get swelling of that arm. And then I would not say specifically that chemotherapy causes lymphedema, but chemotherapy could be in the context of one of these other problems, a blockage of lymph nodes from lymphoma. And sometimes even when we fix the lymphoma, the lymph vessel drainage has been so screwed up that it's hard to get good lymph drainage.

For our patients with lymphedema, we send them to a special lymphedema clinic where they do a number of things. It can include lymph massage, it can include just compression stockings, and a few other types of therapies. It can be pretty frustrating. I would say it can occur in the context of chemotherapy, but, for most chemotherapies, we

do not think it is caused by chemotherapy. We give a lot of chemotherapy to people, and we have not seen it directly cause the side effect of lymphedema. That's a good question, Marjorie.

Lizette Figueroa-Rivera, MA
Thank you. And the next question is from Michael. “Is stem cell therapy one of the protocols used in case of relapse or has CAR T replaced that?”

Joshua Brody, MD
So I don't want to give a simple universal answer, but I'll say for most people with early relapse of DLBCL, early means within the first year, for most of those people, I would say that CAR T has replaced stem cell transplant. For people that relapse at year 2 or year 3 or year 4 after their first R-CHOP or whatever it was, it could go either way. Still, for those late relapsers, stem cell transplant is part of the standard recommendation, but that's kind of evolving quickly over time because we still sometimes do use CAR T cells instead of transplant there. So early relapse, almost absolutely CAR T replaced transplant. Late relapse, could go either way.

Lizette Figueroa-Rivera, MA
Another question for you. What is MRD, measurable residual disease?

Joshua Brody, MD
When we use the acronym MRD, we either mean minimal residual disease or molecular residual disease or sometimes measurable residual disease. All the same concept. It is that we can use fancy tests, usually blood tests, and there are a couple of versions of these. The most famous version is called clonoSEQ®, ‘S-E-Q’, C-L-O-N-O-S-E-Q, clonoSEQ, from a company called Adaptive [Biotechnologies]. And it's a blood test that's trying to be an even more sensitive detection of any little bit of residual lymphoma. We use this a lot in CLL [chronic lymphocytic leukemia], sometimes in mantle cell lymphoma as well, where MRD detection has been prognostic. If someone is MRD negative by that clonoSEQ assay, means we cannot even find one tiny bit of their lymphoma in the blood, they do have better outcomes and maybe we can even do something based on that. If they were MRD positive, maybe we should give them more therapy, possibly. That's a tough call.

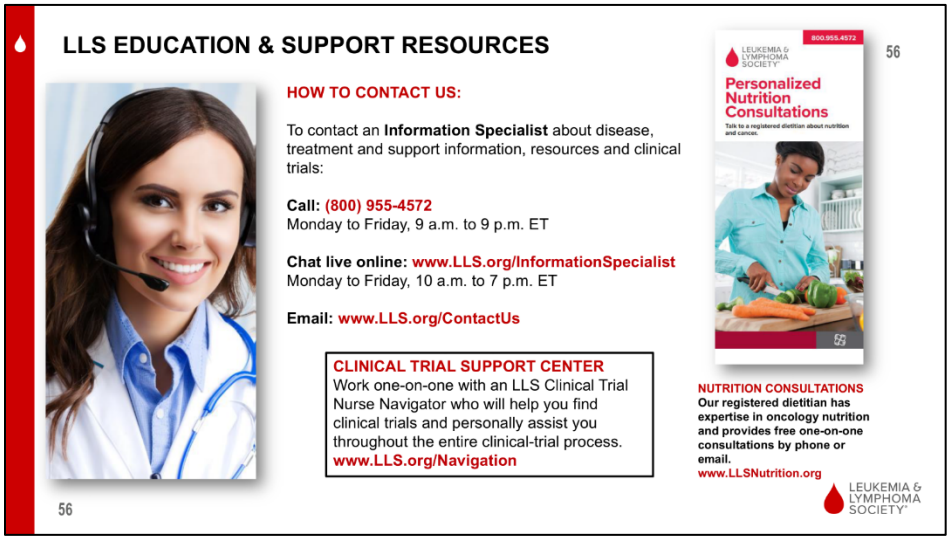
But right now, it's mostly a prognosticator. If someone's MRD negative, they have a somewhat better prognosis with mantle cell lymphoma, probably some types of CLL. In DLBCL and other aggressive lymphomas, we haven't been able to get MRD working very well. It can work for a few patients, but most of the assays are not sensitive enough to define that last little bit of DLBCL. So we're using it mostly in mantle cell, sometimes CLL, sometimes some others. And in mantle cell, maybe that person has mantle cell or knows someone with that because it's the place we've used it the most in aggressive lymphomas. MRD negativity is a good prognosticator. It doesn't mean cure, but it is probably is another step towards cure as well.

Lizette Figueroa-Rivera, MA
Great, thank you. And our last question today from Stuart. “I've been indolent with MCL for four years. Is it advisable to try to find a clinical trial for indolent MCL or just live with it until it starts to spread?”

Joshua Brody, MD
Oh, that's a great question. So this delightfully good prognosis subset, but a bit rare of mantle cell lymphomas, can have an indolent variant of it. It almost is kind of CLL-like in its presentation, sometimes just in the blood and less than the lymph nodes. And we have patients with indolent mantle cell lymphoma who are going many, many years without therapy. Not all of them. Some of them eventually do need therapy. I have to say, honestly, clinical trials are usually the right answer because a clinical trial is supposed to take the best standard of care and try to add on top of it. There are not many clinical trials for indolent mantle cell lymphoma specifically. And most of the trials for mantle cell lymphoma may or may not include those patients with indolent disease. In the case of mantle cell, a lot of them will.

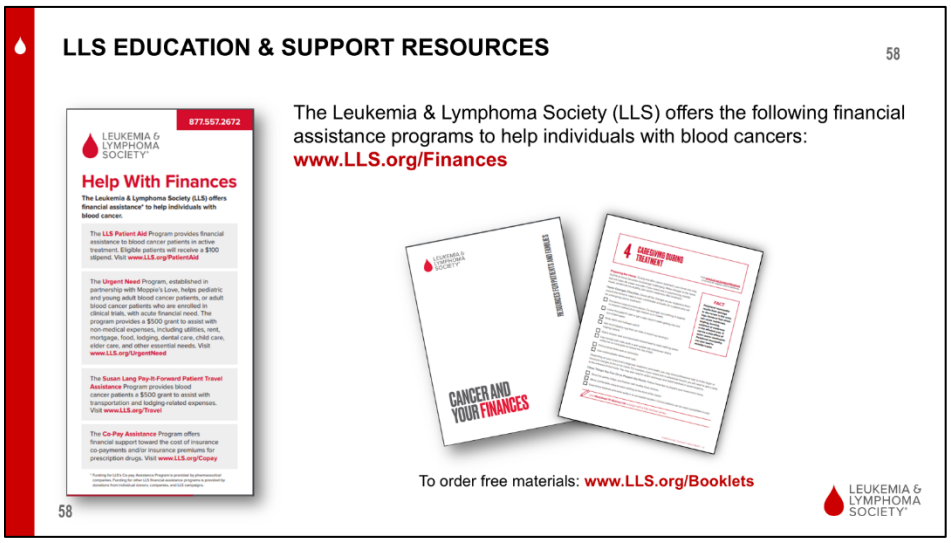
So the question is, “Should I get involved in a mantle cell lymphoma clinical trial in general?” Let me say this, patients with indolent mantle cell lymphoma still are at risk for getting more progressive mantle cell lymphoma over the next few years. So if there's a clinical trial that would get them access to what we think [is a] super-promising medicine, and I'll give an example here, bispecific antibodies. If there was a trial of getting access to a bispecific antibody as part of a frontline therapy for mantle cell lymphoma (and there are very few of those trials), I personally, if it were me or my family member with indolent mantle cell lymphoma, I would really consider that. If it's some other trial of just the same old chemo but with some slight variations, [it] may or may not be much better and there'll be more trial opportunities by the time the person does need therapy.

So if there's some amazingly promising clinical trial, I'm giving that example, maybe seek it out now, because the opportunity may not come around again. Bispecific antibodies seem to be highly effective in mantle cell lymphoma, but unfortunately, I'll be honest, I don't think they'll be FDA approved for mantle cell lymphoma for a number of years, 3, 4, or 5 years from now. Very frustrating how slowly the development has been, but it's because it's a rare cancer, so it gets less rapid attention in drug development. So yeah, for a very promising clinical trial, absolutely. But otherwise, just following closely with your doctor is probably okay.



Lizette Figueroa-Rivera, MA
Well, thank you so much. Thank you all for your questions. And thank you, Dr. Brody, for your continued dedication to patients and for being able to present this webcast for us today. Now, if we were not able to get to your question today, please call a Leukemia & Lymphoma Society Information Specialist at 1-800-955-4572. Information Specialists are available to speak with you from 9:00 AM to 9:00 PM Eastern Time or you can reach out to us by emailing us at LLS.org/ContactUs.

The Leukemia & Lymphoma Society offers financial assistance to help individuals with blood cancer and, for more information, please visit LLS.org/Finances.



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And the full slide set is available on our website, LLS.org/Programs.

To all the patients, caregivers, and professionals participating in today's program, on behalf of The Leukemia & Lymphoma Society, thank you for sharing your time with us. Goodbye and we wish you well.