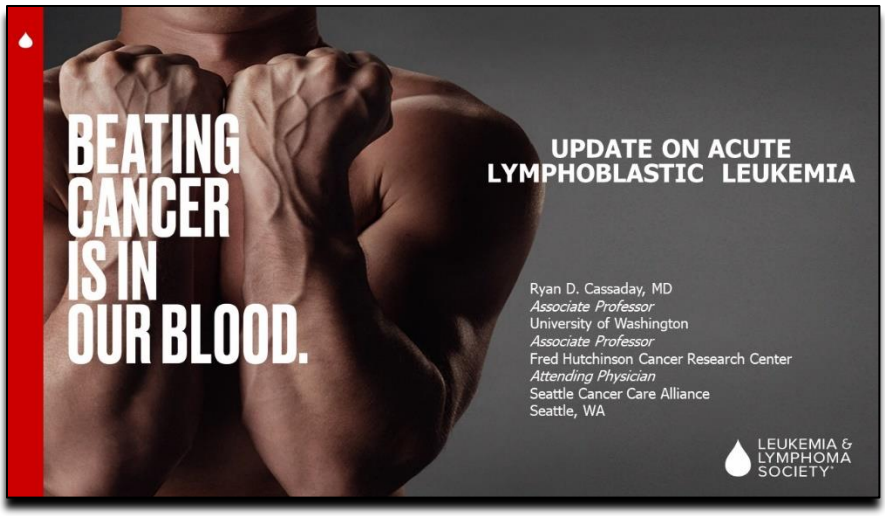


Update on Acute Lymphoblastic Leukemia

Operator
Greetings and welcome to Update on Acute Lymphoblastic Leukemia, a live telephone and web education program. It is now my pleasure to introduce your moderator, Lizette Figueroa-Rivera. Thank you. You may begin.

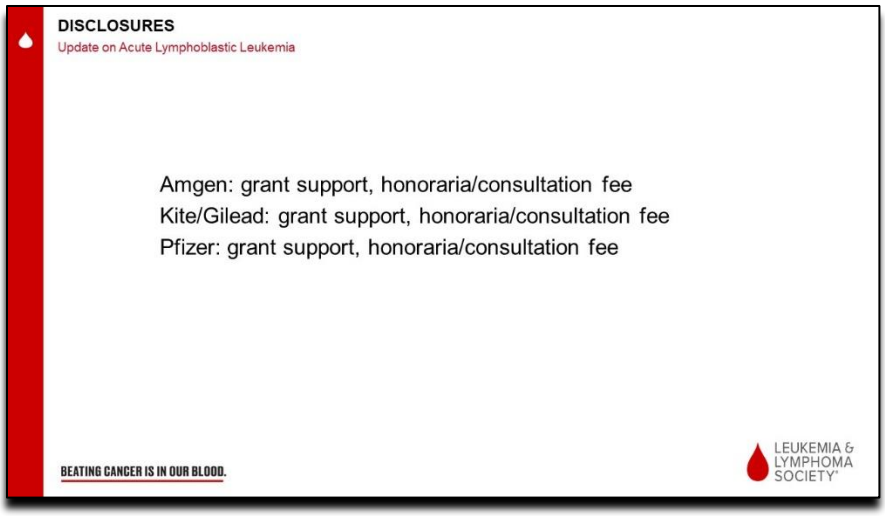
Welcoming Remarks

Lizette Figueroa-Rivera
Hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. LLS is at the forefront of the fight to cure cancer. We have invested nearly $1.3 billion in research. We're leaders and advancing breakthroughs in immunotherapy, genomics, and personalized medicine. This research saves lives.

As the leading source of free blood cancer information, education, and support for patients, survivors, families, and healthcare professionals, LLS helps you navigate you or your loved one's cancer to ensure you have access to quality, affordable, and coordinated care. Research will help us achieve an end to cancer. In the meantime, you need help before, during, and after your treatment and diagnosis. And LLS is the leading nonprofit to do just that.

And for this program we would like to acknowledge and thank Kite, a Gilead Company, and Takeda Oncology for their support.

I am now pleased to introduce Dr. Ryan D. Cassaday, MD, Associate Professor at the University of Washington and Fred Hutchinson Cancer Research Center and Attending Physician at Seattle Cancer Care Alliance in Seattle, Washington. On behalf of The Leukemia & Lymphoma Society. Thank you so much for volunteering your time and expertise. Dr. Cassaday, I am now privileged to turn the program over to you.



Disclosures

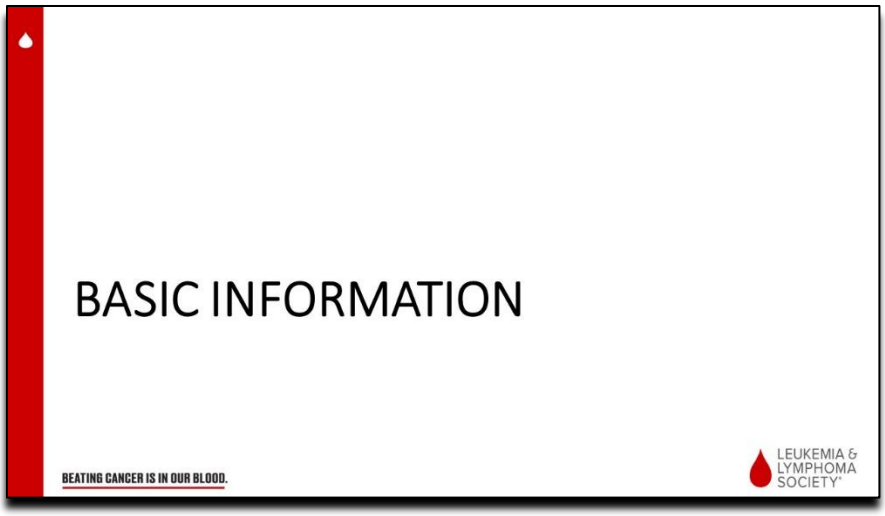
Ryan D. Cassaday
Thank you very much, Lizette. And thank you all for attending. It's really a pleasure to speak to you all today. The LLS is a great organization. I'm honored to have been invited to do this.

Topics

So, understanding that the audience is both geographically and also perhaps, from a knowledge perspective, pretty diverse, I wanted to try to make sure that I can speak to all of you, regardless of where you or your loved one is that in their path with this diagnosis. So, for some of you that are more familiar with some of the basic information, you may find this a little bit pedestrian or a review. But again, my hope is that you'll still be able to get some useful information out of this discussion.

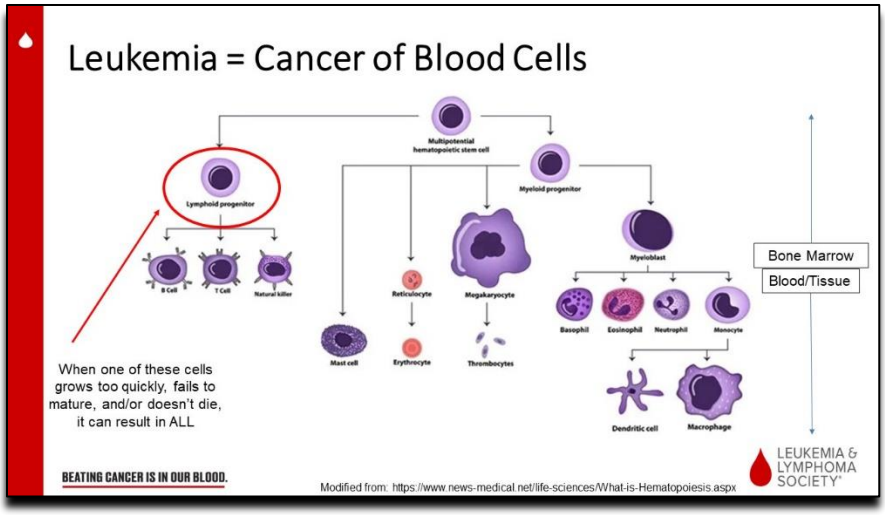
So, the topics I plan to include or cover include, again, some basic information about ALL touch on some high-risk features. So, things when we identify as doctors who treat this disease, we maybe

worry a little bit more about how things are going to go, including a very important topic: measurable residual disease, abbreviated “MRD.” And then we'll take some time getting through into some of the different treatment approaches that are available, including the different modalities we use: chemotherapy, immunotherapy, and blood and marrow transplantation.



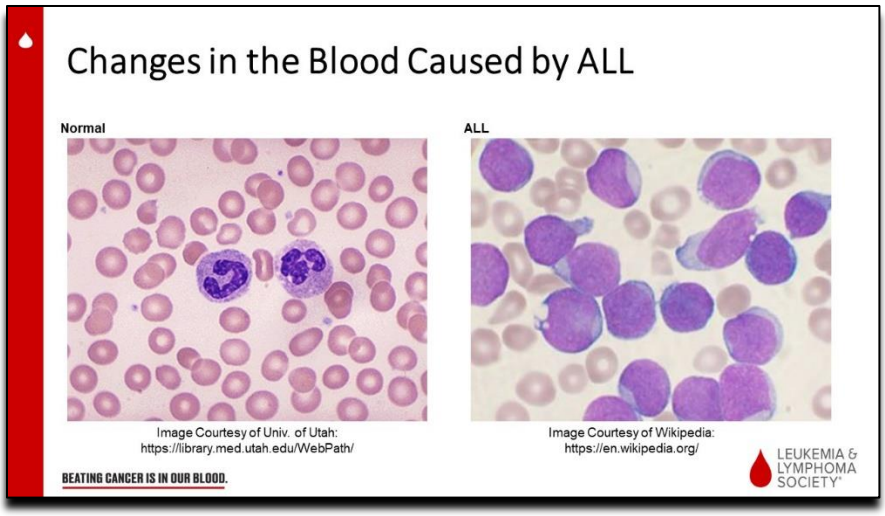
Basic Information

So, to start with some basic information. So, leukemia is a cancer of blood cells.



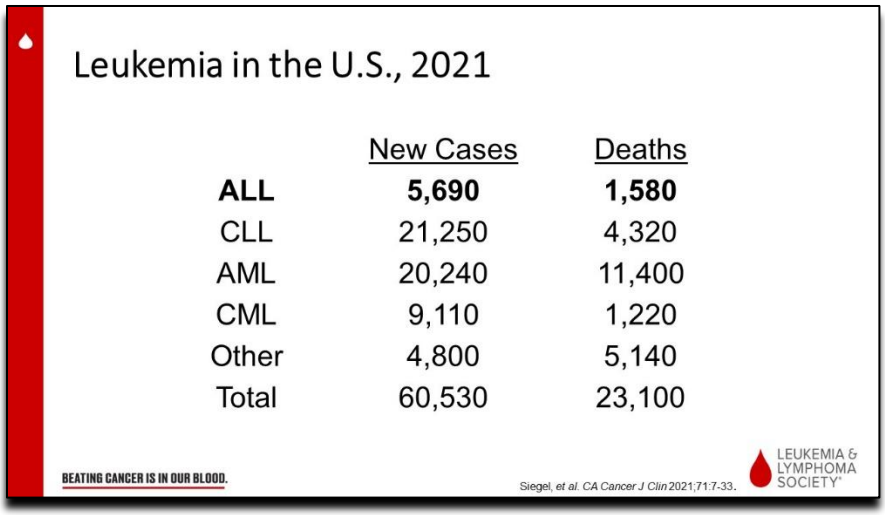
Leukemia = Cancer of Blood Cells

So, this cartoon picture here is meant to depict how our blood cells are made. And you can see at the top of this slide are immature cells. And as these cells grow and divide and become more specialized, they leave the bone marrow and go out and circulate in our peripheral blood and go into our tissues and do a variety of different jobs that are really important for normal physiologic states. When one of these cells highlighted in red—these so-called lymphoid progenitors—when one of these cells begin to grow too quickly, failed to mature through the usual steps that they should take, and then importantly, also doesn't die the way it's supposed to, this is what can turn into ALL. And if that happens, the cells start to grow and divide and expand in the bone marrow, and can prevent the bone marrow from functioning properly, thus leading to a variety of other sort of downstream complications.



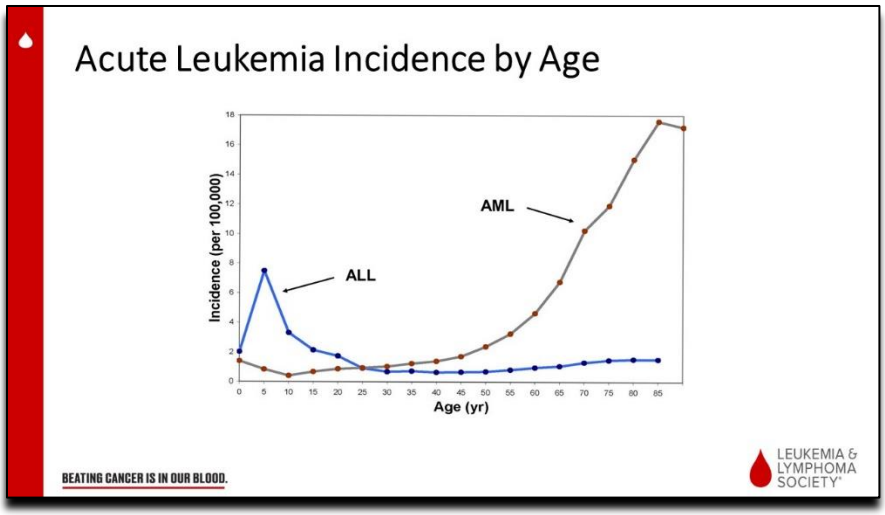
Changes in the Blood Caused by ALL

So, this slide shows a couple different pictures of microscopic views of our blood. So, this is blood drawn from a person, undergone some chemical stains, and then put under a microscope. And the picture on the left is what a normal blood smear looks like. These are normal neutrophils, normal white blood cells, floating around amongst a collection of red blood cells—the more sort of salmony-colored cells. Now contrast that with a picture on your right: That is from a patient with ALL. And you can see these larger, blue-colored cells that are sort of taking over the blood stream. And that is what can happen sometimes in people with ALL. And it can lead to a number of different sort of consequences or complications. So, that's the kind of thing that we can see in people when they're first diagnosed.



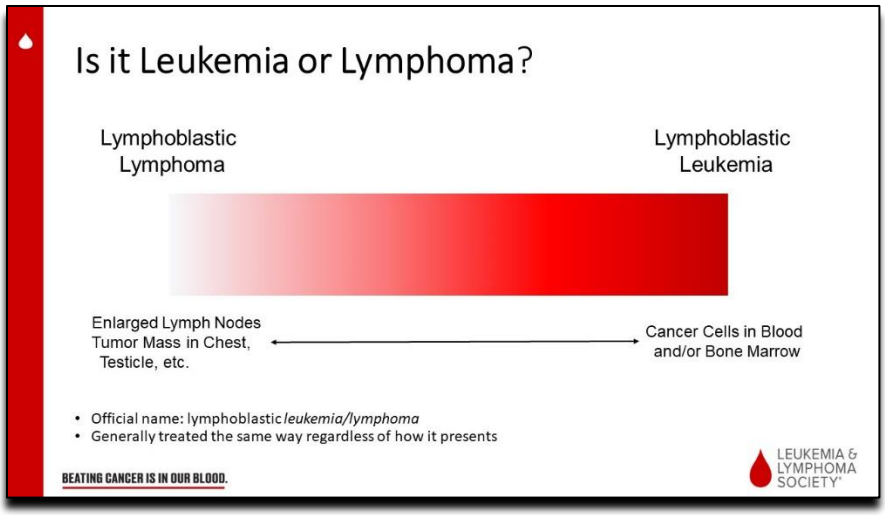
Leukemia in the U.S., 2021

Now for some statistics. So, these are numbers taken from the United States—ALL across the age spectrum. About 6,000 or so people are diagnosed with ALL every year in the entire United States. So, it's a pretty rare disease. And unfortunately, about 1,600 people with ALL will die every year. And if you compare that to other leukemias, it's actually the rarest form of leukemia that is encountered, again, across all age spectrums.



Acute Leukemia Incidence by Age

And if we look at it broken down a bit more by age, you can see that unlike AML, which is the gray line with the red circles, that basically as we get older, AML is more and more common. ALL has a rather interesting, I guess, age distribution, and that it's most common in young people. So, ALL is the most common type of any cancer in children with a peak incidence here around the age of, you know, 5 to 10. And then it tails off quite a bit. So, that by the time you get to about the age of 30 or so there's this very low-level background incidence—perhaps a bit of an uptick—as folks start to get more into the 60s and 70s age range. But really, the majority of cases of ALL are occurring in younger people. That's not--but of course, that's not to say it doesn't happen in adults. It's just a lot less common.

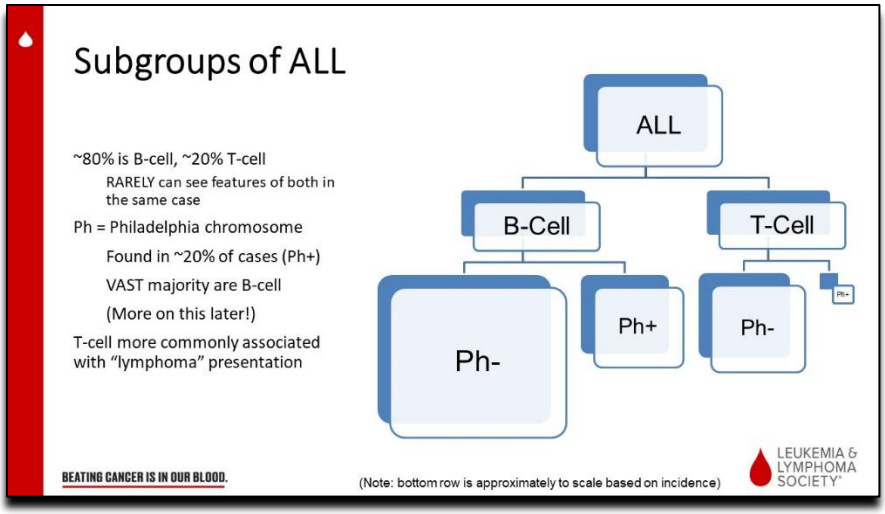


Is it Leukemia or Lymphoma?

A common thing that will come up when I, you know, talking to patients or speaking to people about their diagnosis: Well, is it leukemia or is it lymphoma? And a somewhat unique feature of this disease is it can have sort of almost a spectrum of presentation. So, on the left, some people when they're first diagnosed will have large lymph nodes often in the chest may have other organs involved; men that can involve a testicle, for example. When we see that without really any cancer cells in the blood or bone marrow, we tend to call it more of a lymphoblastic lymphoma. Whereas on the other end of the spectrum, we can see people that have none of those features in terms of enlarged lymph nodes or those sorts of things, but clearly a lot of these cancer cells floating around in their blood or in their bone marrow, then it becomes more of a lymphoblastic leukemia. And in fact, when our pathologists

make this diagnosis, the technical term they typically use is lymphoblastic leukemia/lymphoma, to sort of speak to the fact that it can present across this general spectrum or of sites.

But despite that sort of heterogeneity, really, we tend to treat these two different sort of presentations similarly in terms of the chemotherapies and things of this nature. We don't know why this happens. There's probably some underlying biologic reason why. And some people that cancer cells tend to stick together and grow on tumors whereas in others they grow primarily in the blood or bone marrow. But to my knowledge, no one has really been able to figure out why.



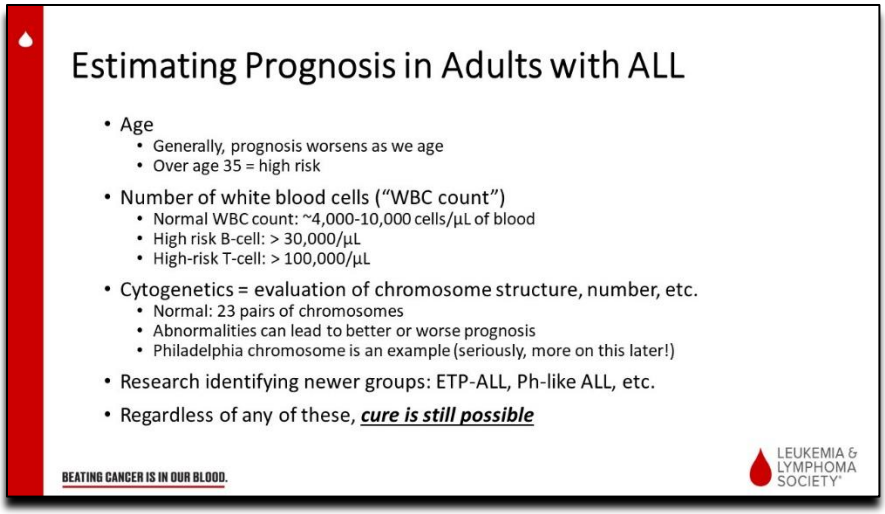
Subgroups of ALL

Further subgrouping ALL. So, there's a few different categories that are sort of thought of when we talk about ALL. The figure on the right is my attempt to sort of break them down in a somewhat organized manner. But about 80% of cases of ALL will be of the B-cell type, whereas the remainder are typically of the T-cell type. There are very rare cases of patients that will actually have features of both. But these are two different parts of our immune system: B cells and T cells. And depending on which of the precursor cells ultimately turns into the leukemia, that's what we ultimately refer to it as.

The other important way that we discriminate ALL is the presence or absence of something called the Philadelphia chromosome. So, this is an abnormal genetic sequence that is found in some people with ALL. About 20% of cases, the vast majority are B cell. But there are rare cases of T-cell ALL that has this Philadelphia chromosome. We'll talk a little bit more about that in a later slide. And importantly, to point out the T-cell type is the one that typically is more commonly associated with the lymphoma presentation. So, if you were to think of a typical patient with lymphoblastic lymphoma, that patient probably has the T-cell type. Though there are some cases of B cell that present in that fashion.

High-Risk Features

So, now to transition. So, after making the diagnosis and starting to think about sort of, you know, treatment and so forth, there are some risk features that we look at: things that have been identified over years that we know if they're present or absent can potentially portend to a harder course with treatment.



Estimating Prognosis in Adults with ALL

So, there's a number of ways that we can estimate prognosis. So, age is one. So generally, prognosis worsens as we age. Historically, this has been defined at a relatively young age of age 35. So classically, people over the age of 35 are thought to have higher-risk disease. And again, that speaks to the fact that this is a disease primarily of younger people.

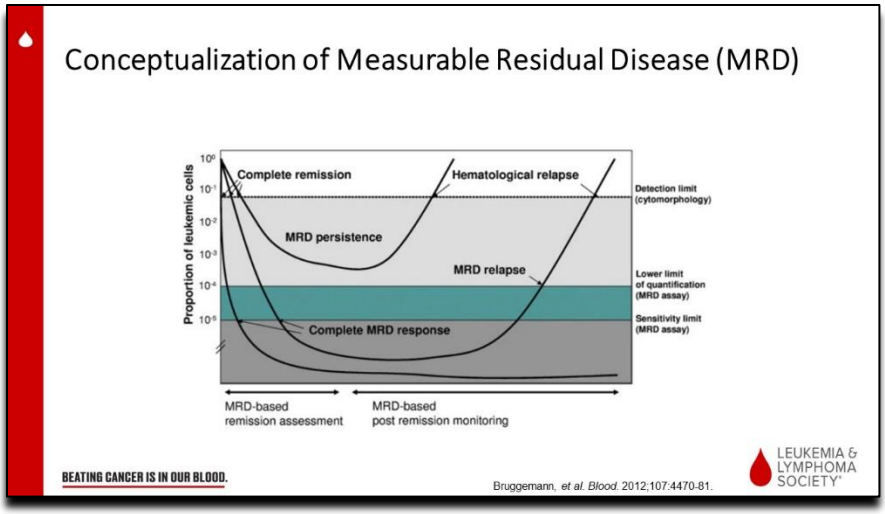
The number of white blood cells in your blood—or the white blood cell count—when you're first diagnosed is also thought to have prognostic significance. So normally, people have about 4,000 to 10,000 white blood cells in a microliter of blood. Just think about that for a minute. We're talking 1,000th of 1 milliliter of blood has several 1,000 white blood cells. And that's just one type of cell in your blood. Now, a person that has a lot of these leukemia cells floating around in their blood over 30,000, for the B-cell type, and over 100,000, for the T-cell type—that's considered high risk as well.

Cytogenetics are a test that we do on the cancer cells themselves to look at our chromosomes in those cancer cells. They can count the number of chromosomes present. There's normally 23 pairs of

chromosomes. You can look at the numbers, other abnormalities. There are certain sort of classically redundant abnormalities that we can find in the cytogenetic testing that can be associated with the worst prognosis. The Philadelphia chromosome to which I alluded earlier is an example of this. Again, I'll talk about this more later. But this is one area where this can come into play.

There are lots of ongoing research studies to try to understand other risk groups. For example, there's a certain subtype of T-cell ALL that we refer to as ETP-ALL that we know historically, based on fairly large studies, does not unfortunately do as well as other types of T-cell ALL. There's this so-called Philadelphia chromosome–like ALL. So, that there's a whole host of others that are being explored that are still kind of working their way into routine clinical practice.

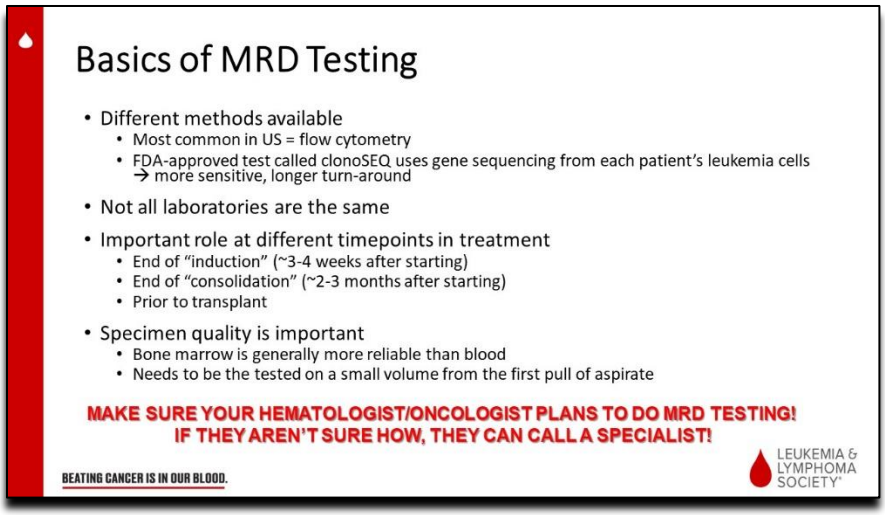
Regardless of any of these things, though, cure is still possible. So, even if a person is diagnosed with ALL and it has several high-risk features, with rare exception, generally speaking, the goal of the treatment that we give is to still cure them.



Conceptualization of Measurable Residual Disease (MRD)

Now, I mentioned this earlier, but MRD (measurable residual disease) is a really important tool and an important factor in assessing how well a patient is doing with treatments. So, this is something that the step after treatment begins. And essentially what it's telling us is: How many cancer cells did we get rid of? How many are left and behind that we can see? And this graph here that I've shown that came from a technical medical journal—so it's a little bit on the higher end in terms of complexity, excuse me. But essentially, what these lines show are the courses of three hypothetical patients, where one line shows a patient who had when they were first diagnosed had a very rapid reduction. The why the left side here, the y-axis is essentially, like, how many leukemia cells are still present—if you want to think about it that way. This patient had a drastic reduction in the amount of leukemia to the point that even with fancy tests we can't see it anymore. That patient's more likely to do well long term.

There are also patients that you can have an initial response that maybe isn't as fast, but it is below that level of detection. But unfortunately, it can still come back despite our inability to detect it for a while. And then there's this third patient here that even though they got treatment and their blood counts got better and maybe symptoms improved, we can still detect small amounts of leukemia with the test we have. And unfortunately when that happens, there's a really high chance that we don't do something else, the disease is going to come back. So, this idea of MRD is a really, really important concept and one that is a routine part of clinical management and treatment decisions, really, for adults and children with ALL.



Basics of MRD Testing

So, some basics of MRD testing. There are different methods available, the most common used in the United States is a technique called flow cytometry that looks for unique protein signatures on the surface of the leukemia cell as sort of a marker for them, and then can quantify how many are detected. There's also an FDA-approved test called clonoSEQ that goes even deeper, more sensitive. It can actually do specific genetic sequencing of the leukemia cell and then look for cells in later samples that have that same sequence. So, very sophisticated testing; does take a little bit longer to come back because of some of the complexity involved, but it's increasingly used now.

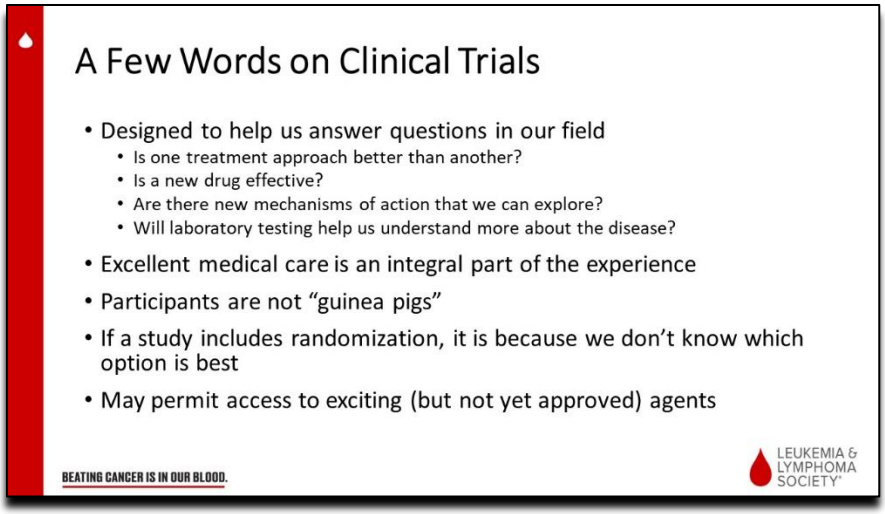
It's important to know that not all laboratories are the same. So, some laboratories will say they do full cytometry, that maybe they don't do a very good job at it, frankly. There are different time points that this can be assessed, and they have certain prognostic significance. So, the end of induction or the first sort of few weeks of treatment, that is an important time frame. Then usually 2 or so months later—so, about 3 months into treatment or at the end of consolidation. If patients are undergoing stem cell transplantation, before that it can be very important. So, it's often assessed at multiple times during treatment.

Specimen quality is really important. Generally, at this point bone marrow is still the preferred method to assess for this. Again, the cancer cells we think originate in the bone marrow. So, we kind of have to go there to find them, even when they're at low levels. It needs to be tested on a small volume of the first pull of the aspirate. For those of you out there that has seen or undergone a bone marrow exam, you're familiar with this. There's often, during the procedure, they often have to take several different pulls. So, that first pull we think is sort of the best one to do MRD testing on.

So, make sure that your hematologist oncologist plans to do MRD testing and during the course of treatment. And if they aren't sure how to do that, they can call a specialist—somebody like me or somebody at a closer facility or medical center to try to help do that. It's really important. And I think a lot of oncologists out there, not that they don't want to do this, it's just ALL is pretty uncommon. And testing like this is still sort of a research tool for a lot of other cancers. It's not the case with ALL. It is a standard part of treatment that really needs to be done. And sometimes doctors in the community just may not be familiar with these nuances.

Treatment Approaches

So, I'm gonna talk a little bit about treatment approaches, now sort of broken down into different categories. So, just to start with some general principles about newly diagnosed patients. But before I do that, I want to spend a few words talking about clinical trials.



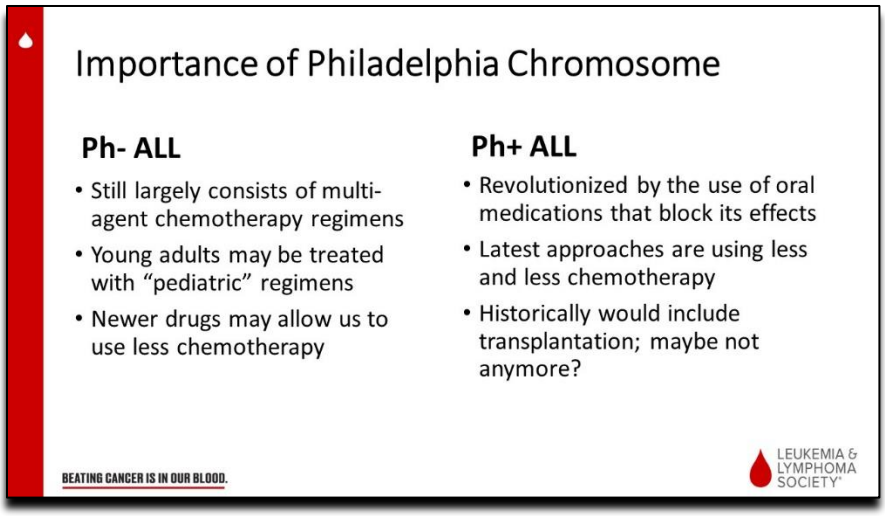
A Few Words on Clinical Trials

So, clinical trials are designed to help us answer questions in our field. And then depending on the circumstances, the questions can be very different. So, it might be trying to answer if one treatment is better than another. We might be trying to understand if a new treatment is effective. It might be looking at new treatments altogether that look at new ways of trying to kill cancer cells. Or it may have to do with laboratory testing where it isn't necessarily a new treatment, but new techniques or technologies to try to understand more about the disease itself.

Excellent medical care is an integral part of the experience. So, people that go on clinical trials will still get excellent medical care that is meant to give them good safe outcome, period. Participants are not guinea pigs. So, people often say this sort of in a colloquial sense, "I don't want to be a guinea pig." And that's, you know, there's certainly validity to that. But unlike guinea pigs, people that participate in clinical trials have autonomy. It's voluntary. If they start, they can take themselves off the study. That is not the way guinea pigs do things when they're involved in studies, at least not to my

knowledge. If a study includes randomization, the reason it's randomized is people—experts in the field—we honestly don't know which of these two options is better. Where if truly if we had both options available, flipping a coin would be just as likely to find the right answer. So, randomization is meant to try to speak to that fact: that we don't really know what is better. It can be unnerving or unsettling to think, “well, my doctor isn't involved in the choice” or “I'm not involved in the choice.” Well, it’s because we don't know which one’s better.

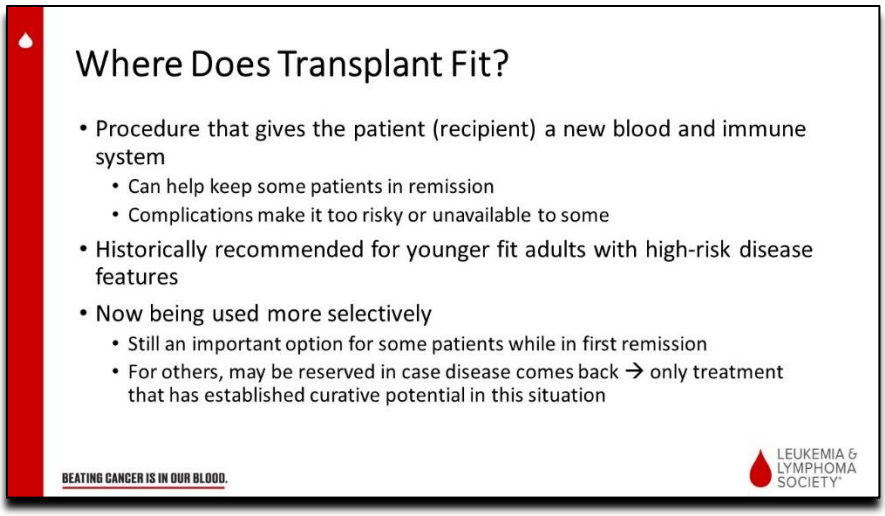
And another thing about clinical trials, and this shouldn't necessarily be thought of as like a selling point, but often it can permit access to exciting but not yet approved agents. So, maybe there's been some early studies to suggest that a particular treatment approach is really been promising or really exciting, but there's a study going on to hopefully prove that it's better than a standard. That may be the only way to get access to that new drug.



Importance of Philadelphia Chromosome

So, stepping away then from clinical trials and thinking more about treatment approaches, more broadly. Again, this is where the Philadelphia chromosome becomes important. So, I’ve broken this into two columns, because really when we think about treatment approaches the distinction is really critical. So, for those that do not have the Philadelphia chromosome or Ph-negative ALL, this treatment still largely consists of multiagent chemotherapy regimens. Young adults may be treated with so-called pediatric regimens. And young adult is typically defined, you know, anywhere between less than 30, less than 40. There are newer drugs that may allow us to use less chemotherapy, though those studies are still sort of ongoing. On the other hand, for Ph-positive ALL, the treatment of this disease has been revolutionized by the use of oral medication that can block the specific biological effects of that genetic sequence and the product of it.

The latest approaches are using even less and less chemotherapy. And historically, because the outcome for these patients was so poor, we would recommend that everyone undergo a transplant if they got into remission. That is changing now as we've gotten better therapies.

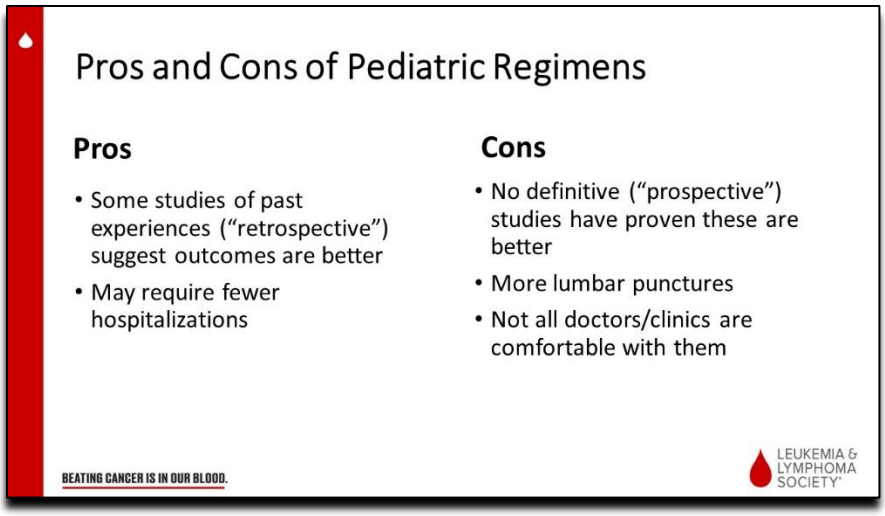


Where Does Transplant Fit?

So where does transplant fit? So, a stem cell transplant is a procedure that gives a patient, the recipient of the transplant, a new blood and immune system. And this can be a really important tool to help some patients stay in remission. It is not a primary treatment. A transplant is really only something for someone who's gotten into remission. However, the complications of this procedure can make it too risky or just frankly unavailable for some folks. It's historically recommended for younger fit adults with high-risk disease features—again, people that we think could tolerate this complex treatment and are thought to be at fairly high risk of having their leukemia come back. However, it's gotten a little bit more complicated now, where I think we're using it now a little bit more selectively and hopefully better. It's still an important option for some patients who are in first remission. But for others, we may decide, you know, I think that there's a good chance your leukemia's going to stay away and not 100%, but a good chance. And I don't want to subject you to those risks. And if the leukemia at those come back, we might be able to then use a transplant then, when we know historically that's about the only thing that can really work long term, at least based on the tools we have right now.

Treatment Approaches

So, to dig a little deeper then into different treatment approaches. So, these are for newly diagnosed patients with Philadelphia chromosome–negative ALL, talk a little bit about the so-called pediatric regimens.



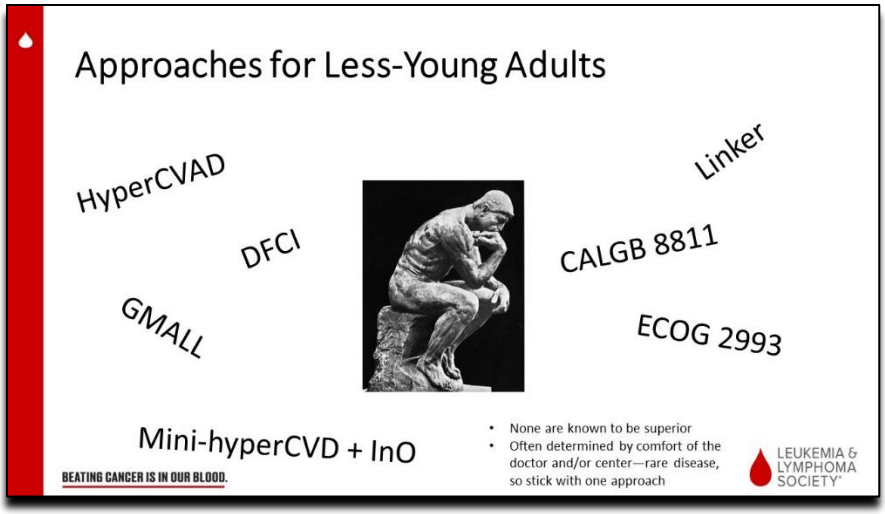
Pros and Cons of Pediatric Regimens

So, the pros of these. So, some studies that have been done suggest that the outcomes are better when we take an approach like this. However, they are not perfect clinical trials. They're mostly what are so-called retrospective studies: so, looking in the past and comparing it to prior experiences. And you know, things go well, a lot of folks don't have to spend much time in the hospital. Some patients only need to be in the hospital for a few days. The remainder of the treatment is all ambulatory as an outpatient. The cons of this approach is sort of, speaking to my first point before on a pro, the flip side. There are no definitive studies or prospective studies that are proven to show that this is better. There may be more procedures, like the lumbar punctures, which no one likes having to go through. So, there may be more of those. And probably most importantly, from a practical perspective, not all doctors or clinics are comfortable with these treatment approaches.

Example of a Pediatric Regimen for ALL: VERY Complex

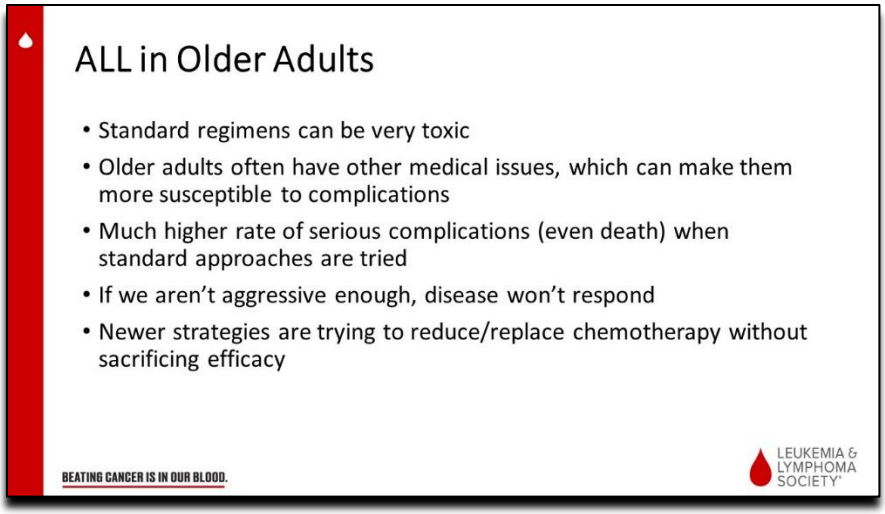
So, this is, again, this is a picture, a figure or excuse me, a table technically taken from a technical medical journal showing the details of a so-called pediatric regimen that we would use for a young adult with primarily Philadelphia chromosome–negative ALL. I'm not going to go through all the details of this. I'm sort of breaking 15 unwritten rules about effective PowerPoint presentation by including it. But it helps underscore even for those of you that aren't oncologists out there that a lot of details in here, right, a lot of different, you know, acronyms and numbers and stuff, this is very, very complicated. I think it's the most complicated type of treatment in all of oncology, not just leukemia, but truly all of

the different types of cancers we treat. And if you only see a couple patients with this diagnosis a year, trying to learn how to do this is really challenging.



Approaches for Less-Young Adults

So, for less young adults, of which I am technically one, it's complicated. Not so much in the details of the treatment, but how to choose. There's lots of different options out there, sort of an alphabet soup of different regimens and complications. None of them are known to be better than any other. So, there hasn't ever been a head-to-head study to show that one approach is better. And again, for a lot of folks in the community that treat this disease, you might only see it once or twice. So, doctors will often just sort of learn one approach, get comfortable with it, know that it's effective, know that it's safe, and that's what they will use. Again, speaking to the fact that we really don't know which of these is better.



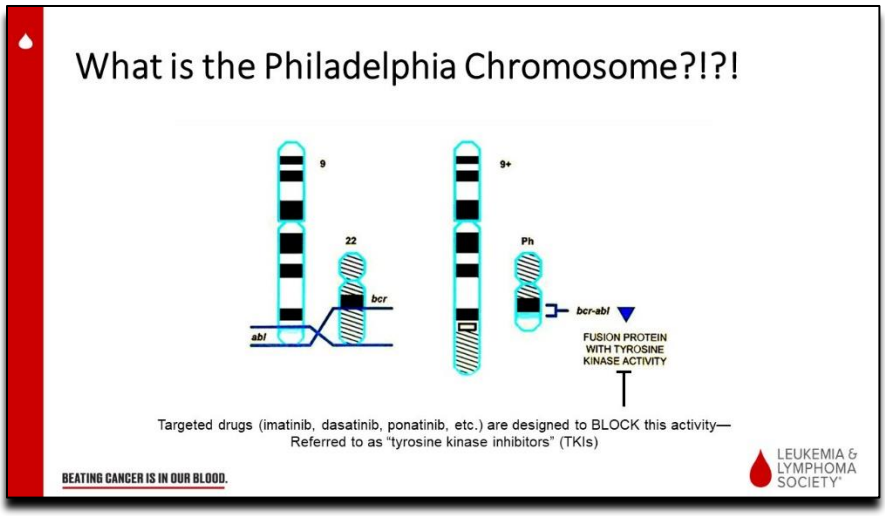
ALL in Older Adults

Now, if we look specifically at ALL when it happens in older adults, and that is historically defined. Usually, as over the age of 60 or so, these standard regimens to which I've alluded to before they can be very toxic—prohibitive even, in some cases. Older adults often have other medical issues which can make them more susceptible to complications. So, heart disease, diabetes, kidney disease—things like this. There's a much higher rate of serious complications, even death when standard approaches are tried. However, if we aren't aggressive enough with treating underlying leukemia, the disease is not

going to respond, and people can ultimately die from the disease itself. So, newer strategies out there are trying to reduce or replace chemotherapy, without sacrificing how effective it is, or perhaps introducing new drugs to see if we can again take out some of the more toxic parts. But a lot of those studies are still ongoing.

Treatment Approaches

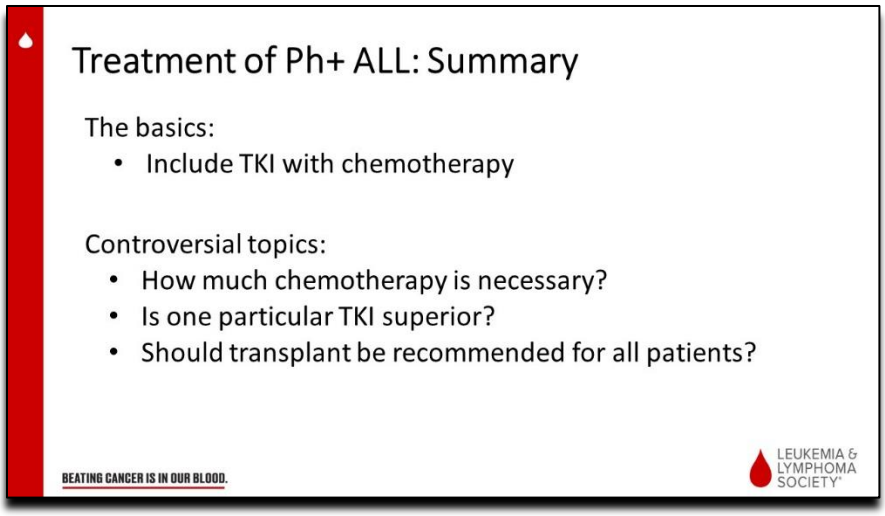
Now for newly diagnosed Philadelphia chromosome positive ALL, it's a different story. Or it's a more rapidly evolving story, I guess I would say.



What is the Philadelphia Chromosome?!?!

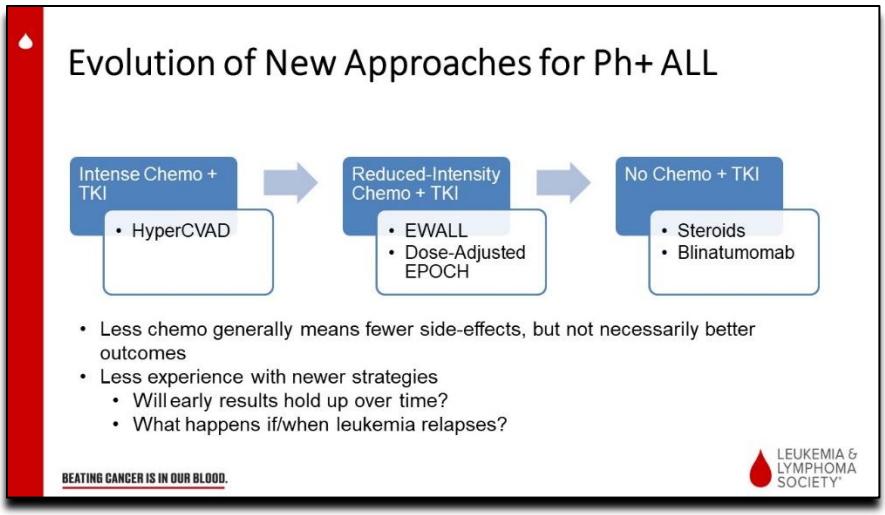
So, having alluded to it now 15 times or so over the course of this talk, this is actually what the Philadelphia chromosome is. So, on the left, you can see a normal sort of a cartoon depiction of two normal chromosomes. So, this is how our DNA is sort of wound up into ourselves and packaged. And we have 23 pairs of these chromosomes. And on the ninth chromosome and on the 22nd chromosome, there are two genes that are normally not near each other. And in someone that has the Philadelphia chromosome, that genetic material gets swapped, ultimately bringing these two genes together, which creates a brand-new sequence of DNA. Which is essentially a whole new genetic code that tells these cells to make this protein that essentially acts like putting a brick on the gas pedal, and the cells just start to grow and divide like crazy.

However, or fortunately, there are these targeted drugs now of which there are several: imatinib, dasatinib, ponatinib. There's a couple others that are designed to block essentially like a key in a lock to shut off that activity. These drugs are referred to as tyrosine kinase inhibitors, or TKIs. These have become really, really important tools in the treatment of this particular type of leukemia.



Treatment of Ph+ ALL: Summary

So, the basics of treating Ph-positive ALL. We take a TKI, we add it to chemotherapy, period. However, when you start to get into more of the weeds of this, there are a lots of open questions. So, how much chemotherapy is necessary? Is one particular TKI of these different drugs is one better than another? Should transplants still be recommended for all patients? So, there's still a lot of complexity to this.



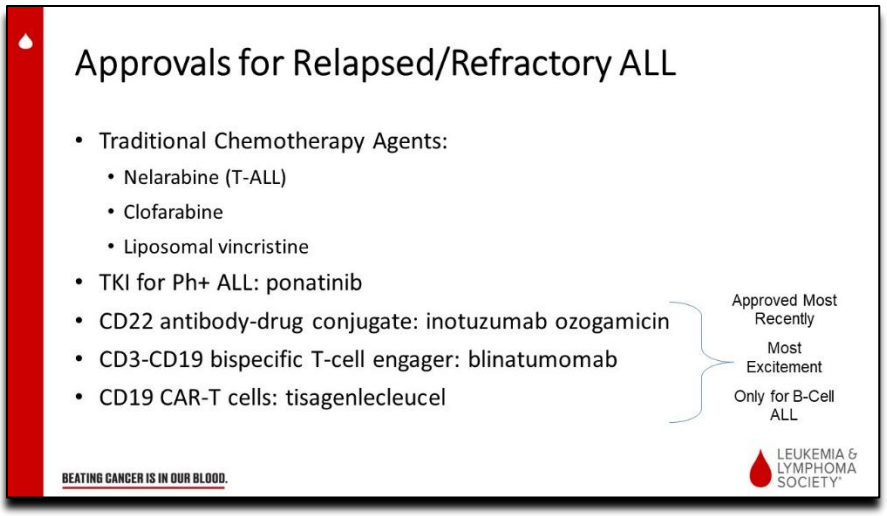
Evolution of New Approaches for Ph+ ALL

There has been a steady evolution of treatment approaches for adults with newly diagnosed Philadelphia chromosome–positive ALL. So, what started out is typically these intense chemotherapy regimens and then this TKI was added. So, hyper-CVAD. It was a common chemotherapy regimen some of you may be familiar with, some of you may be receiving, or have received. With time, there have been numerous strategies where, again, trying to take away some of the chemotherapy that causes toxicity—hopefully not sacrificing the effectiveness. But understanding that TKI by itself can provide a lot of effective treatments. So, there are some newer regimens that are out there that are mentioned on the slide here.

And then we've even gotten to the point where we're not including any chemotherapy at all, where we're adding steroids or an immunotherapy drug called blinatumomab, which we'll talk about a little bit later. By this movement away from chemo, we generally get fewer side effects. But, unfortunately, we don't know for sure that the better outcomes in these newer strategies, we just don't have as much follow-up or as much experience. So, there's been some really nice early results, but will they hold up over time? This is a disease we're hoping to cure. Will we still be seeing people get cured at a higher rate with these newer approaches? And for those who don't have that kind of outcome who do have a recurrence, is it going to be just as easy or just as hard or harder to treat them if it comes back? So, there's a lot of still questions that we have to answer as the field has sort of evolved away from using so much chemotherapy upfront.

Treatment Approaches

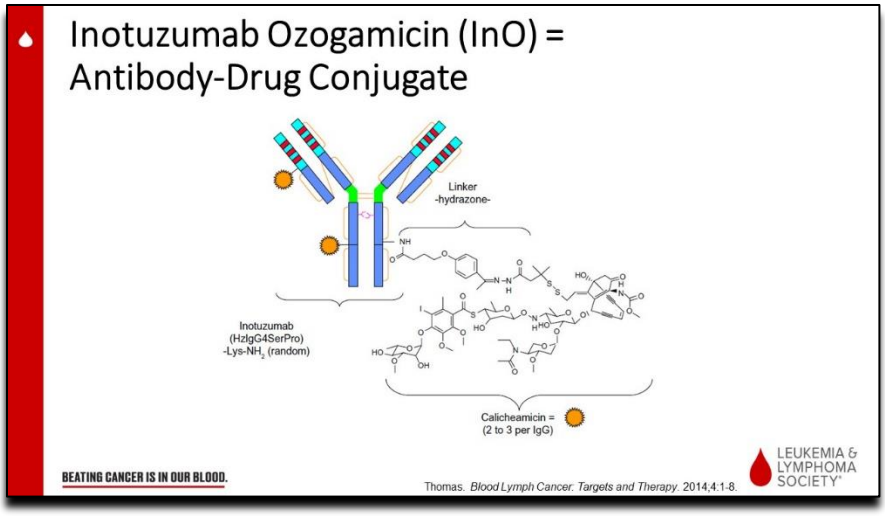
So now, what if that initial treatment doesn't work? So, this is, we are often referred to as relapsed/refractory ALL.



Approvals for Relapsed/Refractory ALL

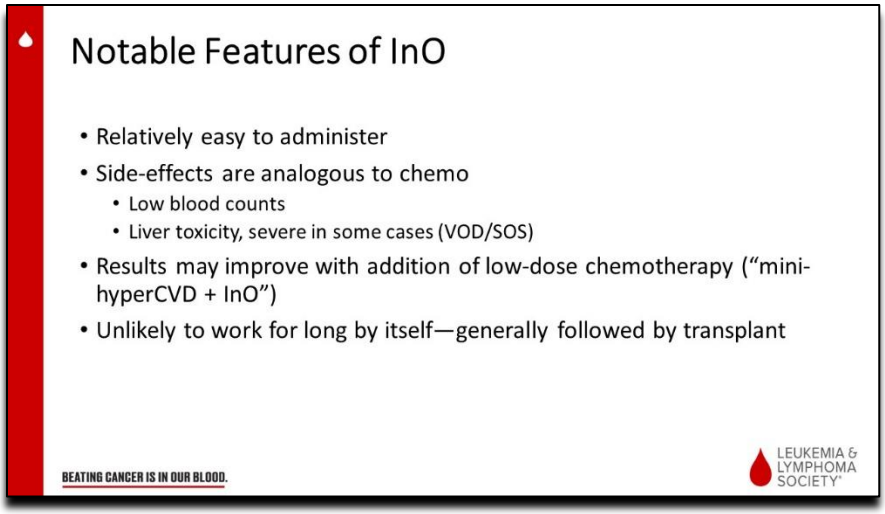
So, there's been a handful of medications or treatments that are approved by the FDA specifically for relapsed/refractory ALL. The slide's going to go through them. There are some traditional chemotherapy agents. So, nelarabine is a chemotherapy drug that is uniquely approved for relapsed/refractory T-cell ALL. There's a couple other drugs: clofarabine, liposomal vincristine. For Philadelphia chromosome–positive ALL, there's the ponatinib is a TKI that is specifically approved for

relapsed/refractory disease. And then some newer kids on the block. So, CD22 is a target that we can exploit using an antibody drug conjugate, which I'll talk about more in a minute. This the generic name for this drug is a mouthful: inotuzumab ozogamicin. There's a CD3-CD19 by specific T-cell engager called blinatumomab. And then there are CD19-targeted CAR T cells. The one that is currently approved for ALL is called tisagenlecleucel. I'm going to highlight these three at the bottom, because they're the most recently approved. They have the most the most excitement behind them. But unfortunately, they are only for B-cell ALL. So unfortunately, while there's a lot of effort to try to use some of these same approaches, but for T-cell ALL these drugs are unfortunately not available for those folks.



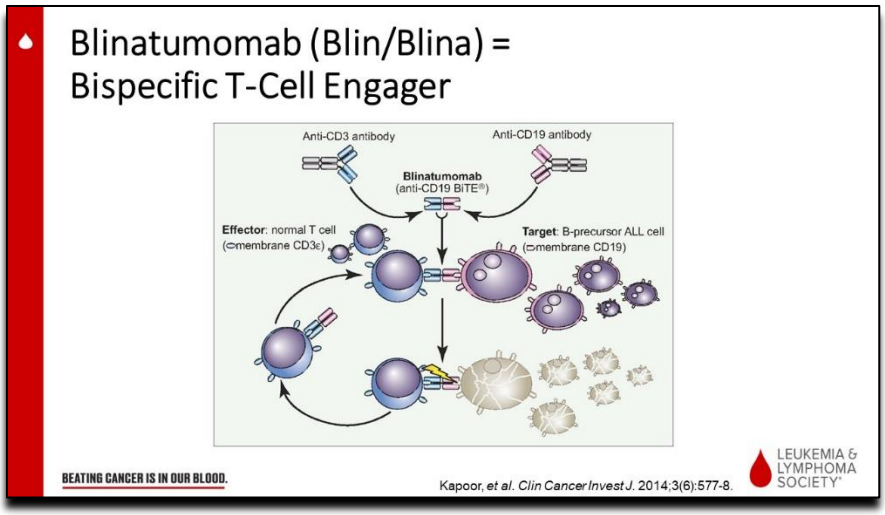
Inotuzumab Ozogamicin (InO) = Antibody-Drug Conjugate

So, inotuzumab ozogamicin. This is an antibody–drug conjugate. So, this is a somewhat technical depiction of what this treatment is. So, the colored portion near the top is an antibody. So, a protein that's designed in a laboratory based on how our immune system works by forming antibodies that are designed specifically to seek out a target. And the target for this antibody is this protein CD22 that's on the vast majority of B-cell ALL cells. But stuck on the end of this antibody is this very toxic, potent chemotherapy drug. So essentially, the way this drug works is it delivers this toxic chemotherapy drug right to the cell that we're trying to kill. The cell will then engulf that whole complex. The chemotherapy gets released inside and then it kills the cell. And it may sound like science fiction, but that is actually how the drug works.



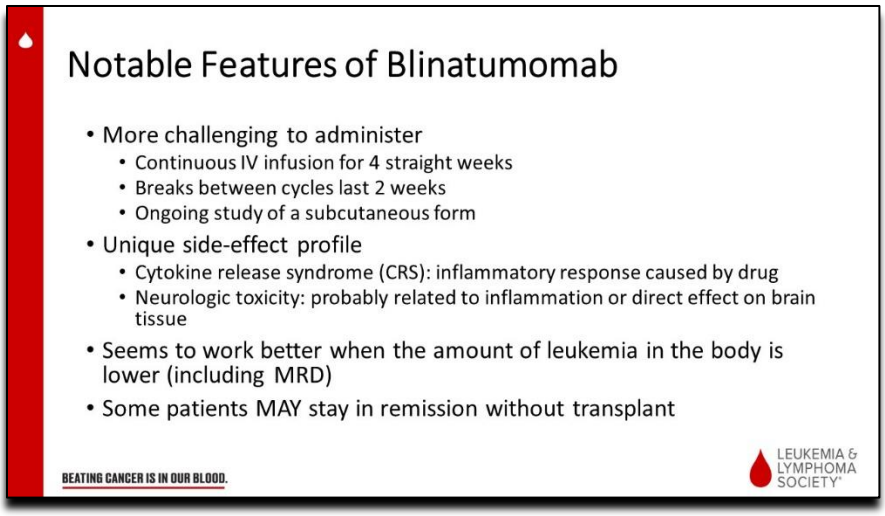
Notable Features of InO

Notable features of this medicine. “InO” is how it's sometimes abbreviated. So, it's relatively easy to administer. It's a weekly infusion that can be done in the clinic. The side effects because it's technically still got chemo as part of it. The side effects are analogous so people can get low blood counts. There's a particular form of liver toxicity that can be concerning. Interestingly, there have been some efforts to take this drug and add it to a sort of a lower-intensity chemotherapy regimen. And that may be better than the traditional sort of standard approach of all this intense chemo. Kind of speaking to what I alluded to before about new approaches for Philadelphia chromosome–negative ALL. When this drug is given by itself, though, it's not likely to work for long. So generally, for people with relapsed/refractory ALL to get this drug, it's typically, we're recommending that they undergo a stem cell transplant afterward.



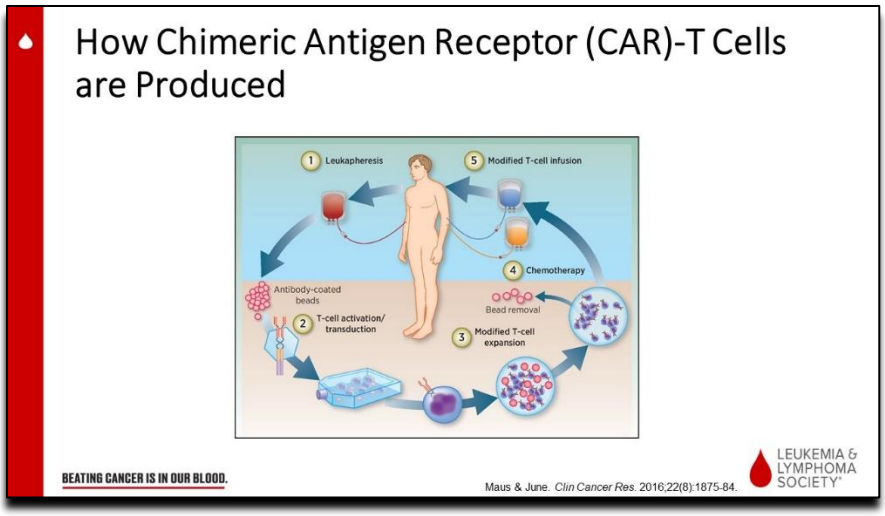
Blinatumomab (Blin/Blina) = Bispecific T-Cell Engager

This is blinatumomab. So, this is again the technical name for this as a bispecific T-cell engagement, also exploits that same sort of concept of antibody technology. But instead, with the way that this drug works is it's the sort of binding part—the business end, so to speak—of two different antibodies, one that binds a protein called CD3 that's present on our immune cells, T cells. And then another part that binds CD19, which is another protein that's on B-cell ALL cells. So, these two fragments of an antibody are stuck together. They're infused into the patient. And they essentially help bring the T cell into proximity with the leukemia cell. And then the immune cell says, “Oh, hey, that's right—we're supposed to kill this.” And it attacks it. Again, sounds like science fiction, but actually how this drug works.



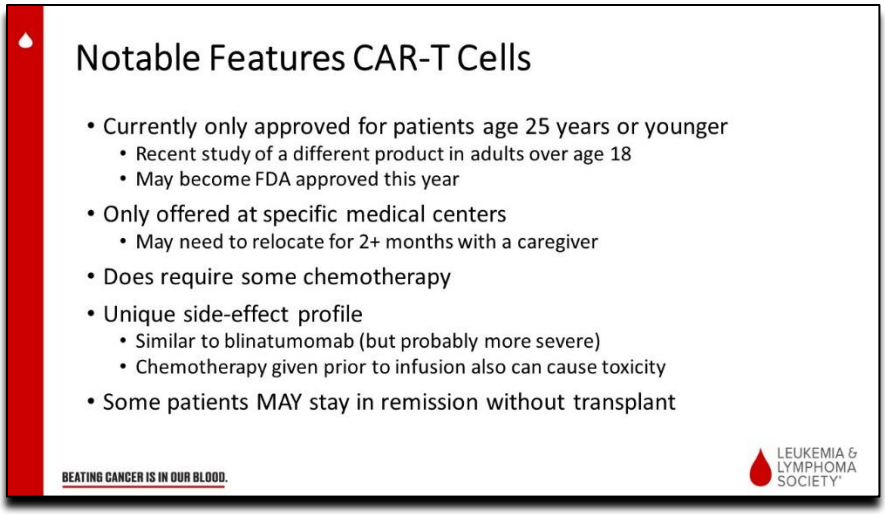
Notable Features of Blinatumomab

Notable features of this medication. It's more challenging to administer. So, it has to be given as a continuous IV infusion for 4 straight weeks—28 days in a row. There are 2-week breaks in between cycles of treatment. There is an ongoing study looking at a subcutaneous form that might be an easier way to administer it, but we'll have to wait and see how that study pans out. It has a unique side-effect profile. So, this is not chemotherapy. But it does cause side effects that are primarily caused by activating the immune system to kill the leukemia cell. And it can look a lot like what happens when our immune system gets revved up to attack infection. So, there's this cytokine release syndrome, which is an inflammatory response caused by the drug. It can be serious—sometimes even fatal in rare cases—but more commonly can be things like fever, body aches, high heart rate, and so forth. Then there's a neurologic syndrome that can develop, probably related to inflammation as well also kind of a spectrum of findings: headaches, fatigue. Some people can get seizures, rarely even more serious problems. It seems to work best when the amount of leukemia in the body is lower. And in fact, what's one thing that's unique about blinatumomab, it's approved to treat that specific scenario of MRD. So, people that have MRD, there have been studies showing that this drug is particularly effective. And that's the only drug out there that I know of that's approved specifically in that situation. And there may be situations where people can get this drug where historically in this situation, we would say, "Oh, a transplant's the only chance of long-term success." There actually may be a subset of people that can get this medicine, if they have a really good response, may not benefit from a transplant. You still don't know who those people are, how best to identify them. So, I would say we generally are still recommending transplant following a response to this. But in time, we may be able to pick out those people where that's not likely going to be helpful.



How Chimeric Antigen Receptor (CAR)-T Cells are Produced

And then lastly, CAR T cells. So, many you on this call are probably familiar with this if you've done any sort of research or investigation into treatment options. This is perhaps the most science fiction of all of these. But essentially, the way this therapy works, for those not familiar, is the patient undergoes a procedure where their T cells or immune cells are removed through a process called leukapheresis. And then those T cells are taken to a lab where they're genetically modified to express a new protein on the surface of them, called the CAR chimeric antigen receptor, that essentially works by helping the cell identify a target—again, CD19 being the most common one currently used. And if the T cell happens to identify a cell out there with that target, it'll get stimulated and activated to kill that cell. So, as these cells are being produced and manufactured, it takes a couple of weeks or so. The cells are then brought back to the patient. Some low-dose chemotherapy is given to kind of make room for the cells in the body. And then we wait and hope that the cell starts to kick in and start being active. So, very complicated and very exciting treatment.

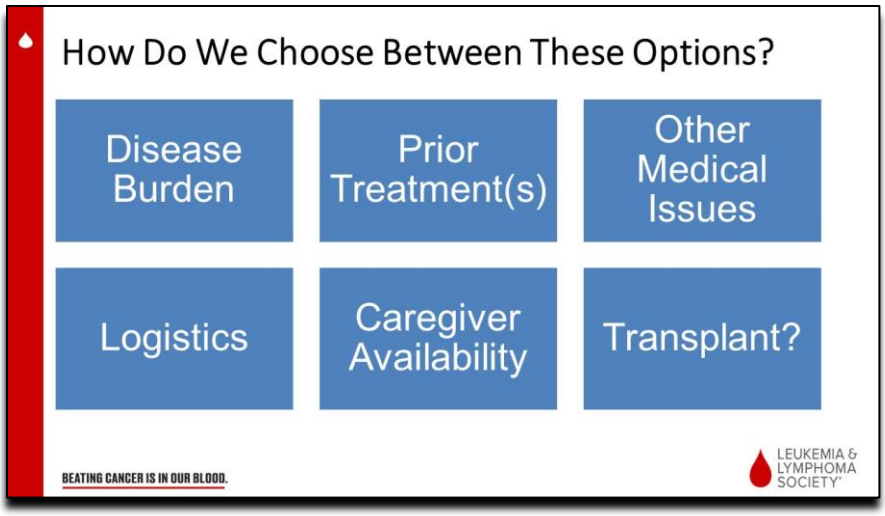


Notable Features CAR-T Cells

So, notable features of this approach, currently only approved for patients aged 25 or younger. There was, however, a recent study that showed very encouraging results using a different CAR T-cell product in adults over the age of 18. And it's currently under review at the FDA. We'll have to wait and see on that decision if it becomes available outside of a clinical trial. This therapy is only offered at specific medical centers. So, depending on where you live or your circumstances, if this is a treatment that's recommended, you may have to relocate for 2 months or more and have a caregiver with you.

So, it's logistically can be very challenging for some folks. It does require some chemotherapy, as I said before. It's relatively low-intensity chemotherapy, but it's chemotherapy nonetheless. It does have a unique side-effect profile. Again, I spoke, that basically the side effects that I talked about with blinatumomab—the same kind of side effects that we can see with this cytokine release syndrome neurologic toxicity—that they're probably more severe overall. And again, there is chemotherapy that's included with this. So, there are side effects of chemotherapy too—low blood counts, nausea, things of this nature—but again, tends to not be too dramatic.

And again, kind of like blinatumomab, there may be patients that can get this treatment and respond, who can stay in remission long term without a transplant. But again, it's a controversial topic. We don't know necessarily how to identify these folks; lots of studies ongoing trying to figure that out.

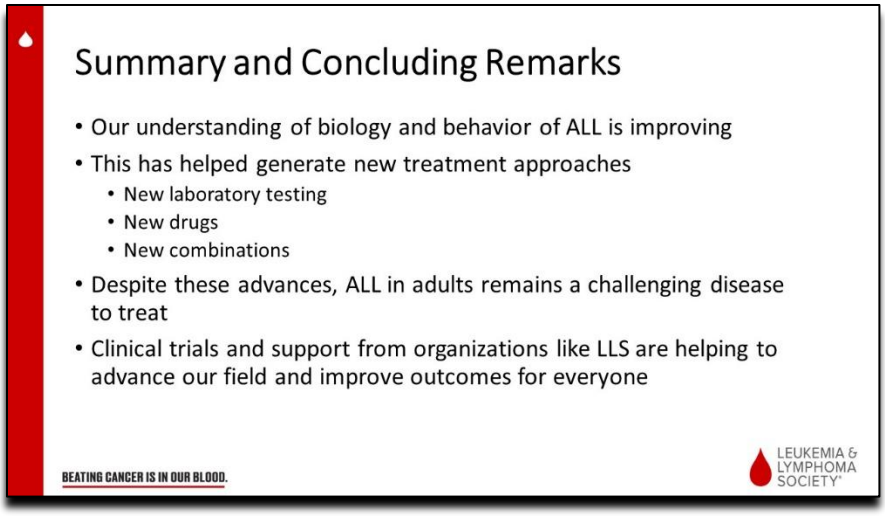


How Do We Choose Between These Options?

So, if you have relapsed/refractory B-cell ALL, there's these different options available. How do we choose from them? Or how do we choose which one is best? Well, the reality is we don't know which one is better, and there's a lot of factors that go into it. So, disease burden may play a role. So, again, blinatumomab maybe works well, in low disease burden. On the other hand, if it takes several weeks for you to get to a place that offers CAR T cells, it might be that you're already too sick. And we're worried that you can't wait that long for some kind of treatment. Specific details of prior treatments may play a role, other medical issues that an individual patient may have. If you already have an underlying neurologic disorder, maybe doing something like CAR T cells is too risky. The logistics that I alluded to before, if you can't get to a place that offers CAR T cells, well, we can't give you CAR T cells. Similarly, if you don't have a caregiver available, some of these therapies require that. And then there's the role of transplant. Did a transplant already happen? Is a transplant part of the plan moving forward? So, all of these things will often play a role in deciding among these different options that are currently available.

Even Though These Are All Good Options...

And even though all of these treatments are good options, particularly for B-cell ALL, clinical trials are still very important to consider. As exciting as these therapies are, there's still room for improvement. That's how we move our field forward. It may provide an opportunity to help us learn about better ways to use these medicines to hopefully help patients in the future.

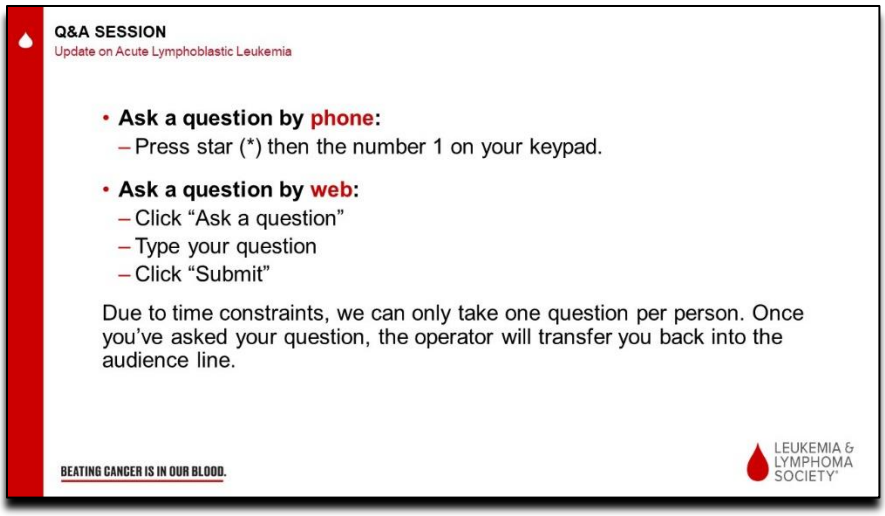


Summary and Concluding Remarks

So, to summarize and conclude, our understanding of the biology and the behavior of ALL is improving. And this has helped us generate new treatment approaches, new laboratory testing, new drugs, and new combinations of those drugs. But despite these advances, ALL in adults remains a very challenging disease to treat. And clinical trials and support from organizations like LLS are helping to advance our field and improve outcomes for everyone.

Thank You

So, with that I'll conclude. And I'm, again, happy to take any questions. And thank you very much for your attention.



Q&A Session

Lizette Figueroa-Rivera
Thank you so much, Dr. Cassaday, for your very informative presentation. It is time for the question-and-answer portion of our program.

I will take the first question from our web audience. Doctor, we've had several MRD questions. First, is it termed "MRD" on lab results? And when should MRD be done? Just at induction or later points during treatment? And someone's asking, "Even after being in remission for 3 years? Should MRD testing still be done?"

Ryan D. Cassaday
Yeah, so I'll try to answer each of those in turn. So, the first one is it reported as MRD? It depends, one of the challenges is different labs will often report things in different ways. So, if the pathologist understands the circumstances and is familiar with this as a concept, they will often state it explicitly somewhere in the report. It may not be in big bold letters, but it may be sort of buried in the details that this level of disease is consistent with MRD. So, it isn't universal. Some labs are better at making it explicit. Others, not so much.

In terms of time, where MRD is important to test, there's actually several in my view. It depends a little bit on those circumstances. Probably the most time-honored and accepted point is at so-called end of induction. So, for most ALL regimens, there's like a 3- or 4-weeks course of treatment, that at the beginning, and there's usually an assessment of response that's done typically with a bone marrow test, at the end of that treatment, again, usually about 3 or 4 weeks after the start. Assessing MRD at that point is typically very, very important. And I can't think of a single clinical trial that's been performed and published where that assessment has not proven to be really important. So, patients that have no MRD at that point historically do quite well. Those that still have MRD, so still have some detectable disease at that point, even though it's only, you know, a few weeks into a treatment course that could spend months or years. Those patients tend to have a higher risk of recurrence or inability to ultimately be cured. It's not--it's depending on the circumstances that may be a fairly drastic difference or may be relatively subtle may not even be enough to change treatment. Other times, I would say, for patients where transplant is part of the plan, certainly assessing before that is important. We know historically if you're MRD negative going into transplant, your chances of success are better.

And for the person who mentioned 3 years out from treatment, there's some controversy in that. I get into some heated debates with some of my colleagues about this. In my view, I don't see that it's very useful for someone that far from treatment. The reality is for people who are in remission, the unfortunate folks who have a recurrence or relapse of disease, those tend to happen in the first year or two. There are definitely relapses that can happen later. So, if you're 3 years, someone is 3 or more years out, the chances of having a recurrence are quite low. So, the likelihood of catching a recurrence at that point with MRD testing is just purport like just based on the mathematics. It's really unlikely. So, I'm not sure it's that useful in that situation. However, there are very thoughtful, very educated physicians who differ with me on that.

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

Operator
Question comes from Madeline calling in from New York. Please go ahead with your question.

Madeline
Yes, I'm just wondering, do you think that the chemotherapy is what causes heart problems? Because I never had heart problems before. But now I do. And I'm just wondering if the chemo is what did that?

Ryan D. Cassaday
Yeah, so there are some chemotherapy agents that can cause heart problems there. Some are better described than others. It depends a little bit on the nature of the heart problem. So, heart disease by itself is an incredibly common healthcare issue in certainly in Americans and around the certainly the developed world. So, whether it was something that was going to happen, regardless of exposure to chemotherapy, or was somehow accelerated or worsened because of chemotherapy can sometimes be hard to tell. But for someone who had no healthcare risk factors for heart disease, good cholesterol, no diabetes, etc., younger age, to all of a sudden get some form of heart disease after starting treatment, that's pretty, particularly they receive certain drugs that we know or associate with heart disease, that's a little bit more compelling.

Lizette Figueroa-Rivera
Thank you. And our next question comes from our web audience. Doug is asking, “Can you please talk about any long-term side effects that we should be on the lookout for now that our daughter has recently wrapped up her treatment?”

Ryan D. Cassaday
Yeah, not because it's the most important, but because we just mentioned in the last question, so there are some relatively uncommon cases long term of heart disease that can occur. I would say the more common ones to be on the lookout for, there are neurologic issues. So, particularly the drug

vincristine, a commonly used medication, and treating ALL can cause sort of a numbness, tingling pain, if it isn't present at the end of treatment it's highly unlikely to develop later. But that is one thing that people can experience for years, sometimes after treatment.

Bone issues are another important one. There are a couple of somewhat unique complications that can occur after treatment of ALL. One of them is sort of an accelerated form of arthritis in our larger joints to the point that some young people need to undergo hip replacement surgery or knee replacement surgery. The technical term for it is avascular necrosis, or AVN. There's probably also a greater risk of thinning of the bones, osteoporosis, diagnosis that we typically only see in older folks, particularly older women. But some of the medicines we use to treat ALL can accelerate that process. So, it's important to be mindful of that as well.

There are probably a whole host of other sort of metabolic issues that might lead to other things: a greater risk of diabetes, greater risk of heart disease as a consequence of that. And another area that I wish we knew more about, but we just don't, is the psychosocial impact of undergoing this treatment. And as those of you in the audience I'm sure are aware, this is a very stressful, to say the least, diagnosis that a person has to go through. And if we're fortunate enough to get them through that it's not uncommon for people to wear some of the scars of that for years, even if they aren't necessarily scars on our skin. So, they're probably greater risk of anxiety disorders and mood disorders and things like that, as a result of that—almost like PTSD, if I can use that term sort of loosely and colloquially. So, those would be the things that I would I generally look out for the folks that have fortunately successfully gotten through that treatment, what to look out for later.

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

Operator
Our next question comes from Bonnie calling in from California. Please go ahead with your question. Thank you.

Bonnie
Hi. Yes, I was wondering if you could speak a little bit about GVHD and the leukemia versus, the GVHD versus leukemia effect. Does that apply for ALL?

Ryan D. Cassaday
So, these are issues that are specific to stem cell transplantation. So, by putting that new immune system in the patient, by putting them to a stem cell transplant, that new immune system might identify tissues in the recipient, the patient, as foreign. And that can come in two different ways, as the question alluded to. One, is if that new immune system attacks, healthy tissues in our body, that can cause something called graft-versus-host disease. So, graft, the new immune system attacking the host, the patient, that's arguably the single most common complication of undergoing transplant. It comes in a wide range of forms. It can be minor. It can be fatal. And the treatments for it require suppressing the immune system to try to quiet it down. That, unfortunately, increases the risk of infection. It is a very active area of investigation because we know how important stem cell transplant could be for some people, including some folks with ALL. So, there's lots of efforts to try to reduce the risk of it, come up with better treatments for it. It is a complicated condition that, you know, there are experts out there where all they do is focus on this. So, it is, but it's a really important issue that we have to think about when we talk to patients about going to a transplant. These are the kinds of things that can happen if you go through a transplant that are unique to that procedure.

The graft versus leukemia effect, the sort of the desired outcome in a way of the transplant. So, this is where that new immune system goes in and find something about the leukemia, that it's foreign. So, one of the ways we think people get cancer and leukemia in the first place is our immune system should identify these cancerous cells in their infancy as foreign and attack them. But people that ultimately develop cancer, their immune system failed in some way, it didn't identify them. So, the

hope is by giving them a whole new immune system, that immune system will find those cancer cells and get rid of them. So, that's what the graft versus leukemia effect is. It does happen in ALL. Now, unfortunately, we don't know who's going to get it or how effective it's going to be. And until that time comes that we know, transplant will remain this challenging tool to identify sort of who is sort of best suited to go through it, both in terms of how likely is it going to be to work but also how likely is it the side effects or complications like GVHD could occur?

Lizette Figueroa-Rivera
Thank you. Thank you, Bonnie, for your question. Our next question, doctor, comes from Michael. Michael's asking if a bone marrow biopsy is more or less effective than a PET scan in detecting ALL cells and/or MRD? And can you explain the difference?

Ryan D. Cassaday
Yeah, so a bone marrow biopsy or bone marrow aspirate, bone marrow exam—sort of think of them as all the same. So, this is a more invasive procedure, as many of you are listening in know. So, this is, you know, a needle going directly into the bone marrow, extracting material and sending it to a lab. A PET scan, a positron emission tomography scan, is what PET stands for. It does involve injection of some contrast material. But beyond that is a noninvasive test. It's just a little bit like a CT scan. You'll lay on a table, you go into this doughnut. There's a thing that spins around to take some pictures, and the person undergoing the test then gets up off the table and then leaves. A PET scan can identify groups of cancer cells growing together as a tumor. However, the resolution of a PET scan is nowhere near the sensitivity of some of these more sophisticated tests that we can do on a specimen of blood or in this case, bone marrow. So, when we get a bone marrow sample, we can actually look down, drill down all the way down to individual cells and identify them as cancerous or not. Whereas a PET scan, you need to have probably hundreds of thousands, if not millions, of cells, all grouped together to be large enough for this scan to pick up. So, while a PET scan can be useful in some cases, it unfortunately is not as sensitive at detecting disease, certainly not to an MRD sort of level as a bone marrow aspirate.

Lizette Figueroa-Rivera
Thank you. And Melissa's asking, "Is ALL caused by genetics? Is it hereditary? Or are there any ethnic populations that seem to be at higher risk?"

Ryan D. Cassaday
So, there are rare cases that we can identify are associated with a specific genetic abnormality. There aren't, unlike some diseases like breast cancer, for example, where there are fairly well-established syndromes that we can link to a specific gene that can be passed on from parents to children. It is really rare in ALL to find such an association. There are, that's not to say that it isn't genetic. It's just that so far, our efforts have not been able to clearly identify that in a large group of patients. The fact that this is a disease that happens primarily in children argues that it's probably something they were born with and not so much something in the environment. So, it's not like kids are going around smoking cigarettes and drinking alcohol, where we can describe some of the lifestyle choices to other cancers that can affect older people. In terms of ethnic groups, it's a complicated question. Again, it speaks somewhat to genetics, speaks also to lifestyle factors, environmental factors. There does appear to be for reasons that I don't understand a higher risk of ALL in the Hispanic and Latinx community. Why that is, we don't know. It does not appear to be a drastically higher risk. So, perhaps 50% higher risk compared to sort of Caucasian, European descent individuals. But beyond that, I'm not aware of any specific sort of association with ethnic groups.

Lizette Figueroa-Rivera
Thank you. And Christie is asking, "With the advancements of T-cell treatments, are there studies yet to show the long-term advantages or better prognosis due because of them?"

Ryan D. Cassaday
So, these therapies have really only been around for about 6 or 7 years. So, the very first people to be treated with them have had that amount of follow-up. So, there are certainly anecdotes of people that have survived that long after CAR T cells. But to be able to generalize that to a larger group of people is very challenging. So, I think as some of these studies that are ongoing, as those researchers continue to track the progress of patients who responded to know how long do those responses hold up? If the leukemia comes back, how easy is it to treat them again? What kind of long-term side effects happen? That's when we'll know more. In some ways, the field is already moving so quickly, that we're starting to move these treatments into earlier lines of treatment—particularly in children with ALL there are efforts to use CAR T cells, even as part of the initial treatment, not replacing chemotherapy but sort of building it into a chemotherapy program. So, those are populations of patients that could be cured because of that and then could live decades. But of course, it's going to take decades to get that information. So, at this point, we only have a few years of follow-up to sort of know how successful or how effective these treatments can be. Obviously, with more time we'll get more experience.

Lizette Figueroa-Rivera
Sure. And I think we're really excited that we have so many new things coming up for leukemia patients. And Arnold is asking, “How long does maintenance chemotherapy last?”

Ryan D. Cassaday
Yeah, so maintenance chemotherapy is a standard part of treating most people with ALL, children and adults. If transplant is not part of the part of the initial treatment, there's some exceptions to that. But for people that received chemotherapy, got into remission, the duration of maintenance therapy is usually dictated by the specific regimen that was used to treat them in the first place. Generally speaking, maintenance therapy lasts for about 2 years total. There are examples, though, where it might be 2 years from when the patient was first diagnosed or 2 years from some intervening time in between. So, the short answer is about 2 years.

Lizette Figueroa-Rivera
Thank you. And our last question today is just your thoughts on the COVID vaccine for ALL patients.

Ryan D. Cassaday
Yeah, these are just my thoughts. They are not necessarily backed by any specific studies that have been done because, again, this is a rare situation and an evolving one. I definitely support all individuals that are eligible to get the COVID-19 vaccine. When is the optimal time for somebody with ALL to get the vaccine is debatable. I think at our center for a while, we were hesitant to give the vaccine to people that were actively receiving chemotherapy, because of the concern that their immune system wouldn't be strong enough to even mount a response. And thus, we may have some false sense of security, that they would get protected.

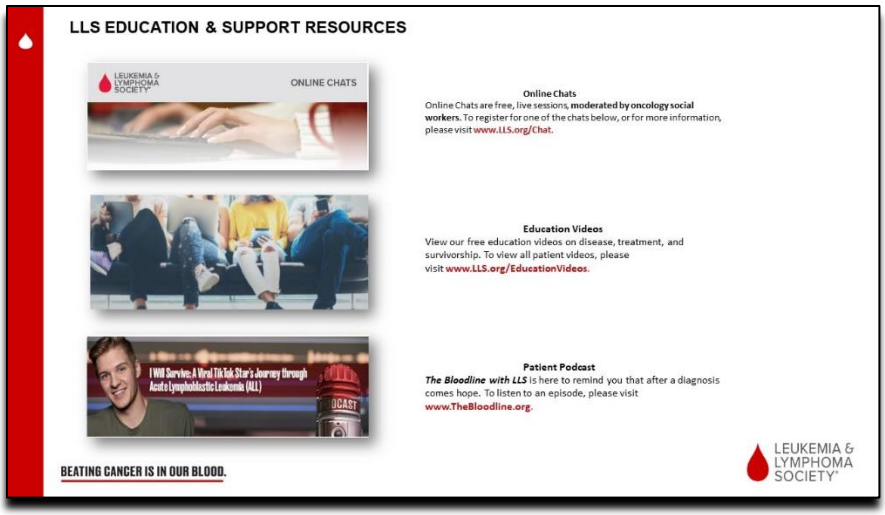
The reality is, if you don't get the vaccine, you have zero protection. And it's hard to know when a person's immune system is going to be strong enough after chemotherapy is done in order to mount that kind of response to the vaccine and thus provide that protection. So, I think definitely talk to your individual doctors about what their individual clinics and hospitals are doing and recommending. I'm starting to think that we might need to not withhold the vaccine but consider doing it. I suspect down the road folks with ALL, if a booster vaccine becomes something that is recommended, could potentially be used after the chemotherapy is done to try to improve it. But the reality is kind of like the flu vaccine in the fall. If you don't get it, you don't get any protection. We still give it to the people on chemotherapy, because at least some protection can be provided. So again, that's just my opinion—not a lot of science behind that. Wish there was more, but perhaps we'll know more in the weeks and months to come.

Lizette Figueroa-Rivera
Well, thank you so much. And special thank you to Dr. Cassaday for sharing your expertise with us and for your dedicated, continued dedication to our blood cancer patients. We can't thank you enough.

Ryan D. Cassaday
Thank you.

LLS Education & Support Resources

Lizette Figueroa-Rivera
And if we were not able to get to your question today, please contact an Information Specialist at The Leukemia & Lymphoma Society at 1-800-955-4572 from 9:00 am to 9:00 pm Eastern Time or go to lls.org/information specialist to chat online or email them. LLS has several financial assistance programs for blood cancer patients.



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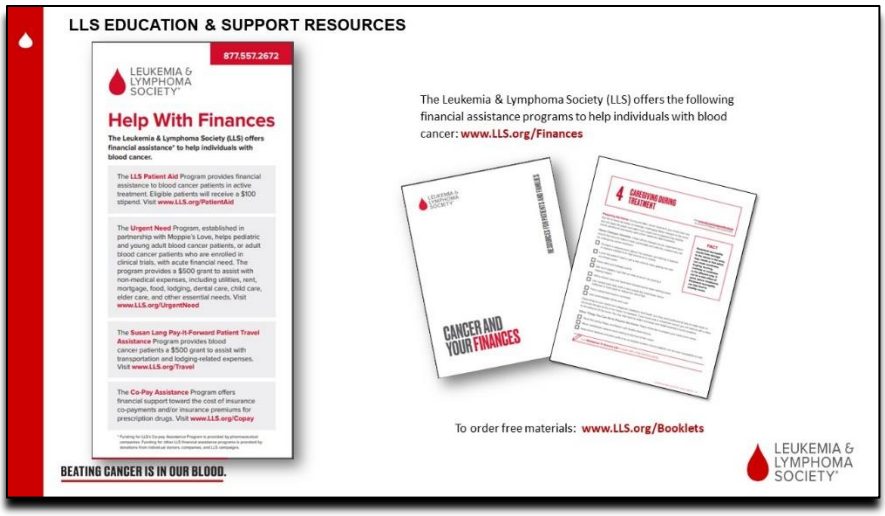

LLS Education & Support Resources

Please visit lls.org/finances for more information regarding our programs or contact an Information Specialist.

Thank You

Again, we'd like to acknowledge and thank Kite, a Gilead Company, and Takeda Oncology for their support of this program.

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