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- This is the Immunotherapy Options for Leukemia Patients webinar, part of the Leukemia Research Foundation Spring Series. And we're very glad to be joined today by Doctors Gregory Behbehani from Ohio State University and Dr. Adam Kittai from NYU Grossman, Long Island School of Medicine, Perlmutter Cancer Center, I believe, and I will be introducing them in just a moment. But before I do, I have a few housekeeping items to take care of.

So first, I would like to thank the supporters of this program. We have Johnson & Johnson, which is a supporter of this Spring Series, and additionally, our sustaining supporters, AstraZeneca, Jazz Pharmaceuticals, Merck and Syndax. And finally, the supporter of this immunotherapy session is Autolus.

The Leukemia Research Foundation's mission is to cure leukemia through innovative research funding and to support patients and families. The Foundation has raised over \$95 million in support of our mission since our founding in 1946 and has funded research grants to over 750 investigators worldwide. Our support programs for leukemia patients and their loved ones include information and resources on our website, education programs and financial assistance and lots more.

For today's program, all participants will be muted, but we welcome your questions in the Q & A box at the bottom of the zoom screen. Please note that you should check the box where it says anonymous if you don't want your name to appear with your question. Otherwise your name is going to show with the question. If you already submitted a question at registration, please know that we have your questions and we will do our best to cover as many as possible. After today's program, you will be sent a brief evaluation or a request for evaluation through email. Please take a moment to complete the evaluation so that we can improve future programs. Also, this webinar will be recorded and a link to it will be sent to all registrants for anyone who needs to leave earlier, would like to watch the replay with captioning and a transcript in their own time. Please note that AI scribes and automated note taking tools may be removed from the session.

We are grateful to have Dr. Gregory Behbehani and Dr. Adam Kittai with us today to cover this exciting avenue of potential treatment for acute and chronic leukemia patients. Dr. Behbehani is a hematologist oncologist who provides clinical care of patients with acute myeloid leukemia and acute lymphocytic leukemia. He also serves as assistant professor of internal medicine at the Ohio State University. Dr. Behbehani received his medical training at University of Cincinnati where he also earned a PhD in molecular genetics. He completed a fellowship in hematology oncology at Stanford and later completed a postdoctoral fellowship in the laboratory of Gary Nolan focusing on applying mass cytometry to the characterization of clinical samples from patients with hematologic malignancies. He joined the Leukemia and Hematologic Malignancies Program at OSU, The James in 2015.

Dr. Kittai is an Associate Professor at NYU Grossman, Long Island School of Medicine and Director CLL Program at Perlmutter Cancer Center having recently moved there from the Icahn School of

Medicine at Mount Sinai in New York. Dr. Kittai has a strong background in clinical trials and population based studies and has authored numerous publications in high impact journals. His research and clinical focus is on CLL, Richters Transformation and Related Disorders. He is the primary investigator of multiple investigator initiated trials exploring the use of small molecule inhibitors with novel designs and deploying cellular therapies for CLL and Richter transformation. Dr. Kittai is also interested in redefining prognostic features for patients with CLL in the era of targeted therapies as well as defining and mitigating racial disparities that exist in CLL. He has been the recipient of multiple teaching awards and is an active member of the American Society of Hematology Committee on Training. Thank you both so much for joining us today. Dr. Behbehani will get things started with an overview of immunotherapy and current options both approved and in trial for acute leukemias. I'm gonna stop sharing. Thank you both

- All right. Thanks so much. Appreciate the great introduction. Lindsey, can you see my screen? Okay. All right. As Lindsey said I'm Greg Behbehani, I'm an Assistant Professor at Ohio State University and one of the leukemia faculty treating leukemia patients and helping run leukemia trials as well as basic science work here at Ohio State. I do not have any disclosures. So today I wanted to talk a bit about what is immunotherapy. I had a chance to review some of the questions. So I wanted to start a little bit basic about what exactly do we mean when we talk about immunotherapy and how would that apply to leukemias. So I'll talk a little bit about the major types of immunotherapy, antibodies, antibody drug conjugates, bispecifics, CAR T cells. I do wanna mention though I'm not gonna talk about it 'cause it's really more of a separate talk about bone marrow transplant, which is really the original immunotherapy, which is giving someone an entirely new immune system so that that immune system will kill your cancer. But that is kind of beyond the scope of what we're doing today. I'll talk a bit about how leukemia is formed very briefly and how this leads to how we can target them with immunotherapy. And then I'll go into some of the specific immunotherapies currently available for AML. Unfortunately, we still only have one really approved immunotherapy, gemtuzumab ozogamicin, but it has a role in which it can be very effective. And then I'll talk a lot more about ALL immunotherapies which have really revolutionized the treatment of acute lymphoblastic leukemia, specifically inotuzumab ozogamicin, blinatumomab and CAR T-cell treatments. And then I'll talk just a little bit about some future treatments and an overview of the kinds of things that are in trial right now.

So what is immunotherapy? Basically immunotherapy refers to using a treatment that harnesses the body's immune system to actually kill cancer cells. This has been done for quite a while actually. Bone marrow transplants for 50 years. High doses of immune stimulating cytokines have been used for a while though their role is quite limited. IL-2 in renal cancer for instance. But more recently antibodies and antibody products have become the mainstay of immunotherapy and this allows very specific targeting of the cells of interest and allows us to target even other cells. Lastly, there's tumor infiltrating lymphocytes which are becoming very important for solid tumors but don't really have a role in leukemia.

So I'm gonna talk about the four that are primarily used for leukemia treatment - antibodies, antibody drug conjugates, bispecific antibodies and CAR T cells. These are generally more specific than traditional cytotoxic chemotherapy, which is generally targeting cells that are growing fast or are more sensitive to damage. And again, one of the first and most effective immunotherapies is an allogeneic stem cell transplant, in essence replacing the immune system. But this has a lot of logistical complexity and the risk of that new immune system attacking the host.

So what types of immunotherapy do we use in leukemia? So antibodies, just plain regular antibodies that can be made in humans or mice. These basically function the way antibodies function in your immune system to give you immunity, they bind specifically to their target and this are the ends of the antibody that will bind to the target and that target can be any protein really some and sometimes even carbohydrates and other things. And then the tail has some signaling activities that can gently stimulate the immune system.

Rituximab is one of the first antibodies that were used therapeutically and still important for CLL as Dr. Kittai will talk about. But these can also be used to block the target that you're trying to block and this is the most common way they're used in solid tumors. So in solid tumors they bind this into the antibody to immune inhibitory molecule. Usually CTLA4 or PD1 is the most common and that turns off the immune system. But these can also be used to bind to things to stimulate the immune system.

Next we have antibody drug conjugates. These are sometimes immunotherapies and sometimes just very specific targeted chemotherapies. In this case we take an antibody that has a specificity to bind into something we're interested in and then we attach something to it. This is often a chemotherapy so that the chemotherapy just goes to the cells that we're trying to target. But it can also be other things, a toxin or something that stimulates the immune system. Bispecific antibodies are one of the newer agents and have really begun this revolution. These act as a set of handcuffs essentially where one end attaches to the target that you're interested in the cancer cell typically and the other to T cells. And basically I tell patients it's like handcuffing a wolf to a sheep. Fortunately in this instance the sheep is the cancer cells and the wolf is your immune system. And handcuffing the two together stimulates the immune system to kill the cancer cells.

And CAR T takes that concept a step further where we put the antibody fused to an activating receptor inside the cells so that now the cells become the drug. And the advantage here is that the cells can replicate, they can copy themselves, they can divide, they can proliferate, and they can persist for years, sometimes even decades.

So how do we figure out what we're going to target? So I think this requires a quick step back to where do acute leukemias come from? And this here is a graph of hematopoiesis that I won't go into too much detail, but just as human beings start as a single fertilized egg cell and then those cells divide and turn into more specialized cells, the same thing happens on a daily basis in our blood forming system. There's a long-term hematopoietic stem cell that can give rise to every kind of blood cell and one of the first things it does is decide if it's gonna be a myeloid cell or a lymphoid cell. And from the myeloid cells you get all the normal white cells that you most commonly think of, granulocytes, monocytes, et cetera. You also get blood forming cells and platelet forming cells and then you also get B and T cells. The T cells don't really stay in the marrow very long and aren't represented here.

So what happens to turn this into a cancer is that mutations are picked up usually in AML and the common myeloid progenitors or the committed granulocyte monocyte progenitor cells. And that leads these cells to grow in an unregulated way and they continue to differentiate somewhat and some of the more differentiated versions of them grow even more. And this eventually takes over the bone marrow. Similar thing happens in ALL. Most commonly mutations occur in these Pro-B

cells. These immature B cells though they can also rarely happen in common lymphoid progenitor cells or in more mature cells as Dr. Kittai will talk about in CLL. And again, once those mutations occur, these cells proliferate, they still can differentiate into slightly more mature cells that also proliferate and take over the bone marrow.

So what does this have to do with immunotherapy? Well these particular cell types each have particular patterns of proteins on their surface and these patterns of proteins occur for a good reason. These are usually receptors of growth signaling molecules or they can be receptors that allow cells to stick in the parts of the body that they're supposed to stick. In AML the most common ones utilized right now for immunotherapy are CD123 and CD33 that can be present on both common myeloid progenitors, granulocyte monocyte progenitors and more mature monoblasts. From there the surface markers change and become more specific, but targeting CD 33 in particular targets almost all AML cells.

The problem however with this is that these cells give rise to almost all the blood cells. So the monocytes, the granulocytes, the blood forming cells, the platelets, and so perpetually eliminating these CD 33 positive or 123 positive cells comes with a lot of toxicity. You won't have any of these cells and that can be difficult to tolerate but it can be done in a transient way and that can be effective in certain cancers. In ALL the situation's a little bit better. CD19 and CD22 are highly expressed particularly on Pro-B cells and later lineages. But more variably on more the less commonly transformed common lymphoid progenitor cells. We can, this can allow targeting of otherwise chemo resistant leukemia cells and fortunately people can live quite reasonably well for a long times, even decades without any B cells, which is something that's quite surprising. But we've known for quite a while since the days of Rituxan. But occasionally we'll see transformation in cells that are more immature than this and don't really have 19 and 22. And obviously those two protein targets cannot be used for patients that don't have them on their leukemia cells.

So that brings us to the actual drugs. The first one is gemtuzumab ozogamicin or Myelotarg and this is an antibody against CD33 shown here linked to a relatively large but very potent toxin called calicheamicin. This will bind to the CD33 positive myeloid cells and progenitor cells, get internalized and then this toxin will bind to the DNA and again it is very potent even for cells that aren't growing and is very effective at killing those cells. This was approved for relapse disease but primarily these days is used in combination for chemotherapy for patients with good risk disease to increase cure rates. And this is a meta-analysis of the use of gemtuzumab that shows for these good risk patients it can very significantly increase the chance that chemotherapy alone can cure their leukemia whereas it has less effective for the intermediate risk and higher risk patients. Of note gemtuzumab has some fairly significant toxicity to the liver, which is usually fine in an initial treatment but can manifest after a transplant. And it's another reason why patients with higher risk disease that are gonna need a transplant are less likely to get it.

Very closely related is inotuzumab ozogamicin which is used in ALL very similar except now the antibody is targeted CD22 but the same toxin again very effective but has toxicity to that toxin that can damage the liver. It can be used as a single agent that's actually quite well-tolerated in patients with relapse disease with reasonable results. These don't look great with you know, 20 to 30% of patients surviving at two years. But that's actually good unfortunately for patients with relapsed ALL and it can be combined with chemotherapy. But just like with gemtuzumab it's now seeing a lot

more use being combined upfront for patients initially diagnosed to create more tolerable therapies.

And this is a recent study published just last year from the Alliance Oncology Group that shows the combination of inotuzumab with blinatumumab which we're gonna talk about next and no real chemotherapy giving pretty good response rates and survival rates to older patients who do not have very effective treatment options and treated in this case without any true traditional chemotherapy.

The most important agent in this group right now in ALL is blinatumomab. So again this is a bispecific- one end of it binds to CD3 the immune system cell and the other end binds to CD19. This basically attaches T cells which are capable of killing tumor cells to the tumor B cells and really all B cells and this then stimulates the T-cell to kill the tumor cell. You can develop resistance to this due to loss of CD19 and occasionally due to suppression of the activity of the T cells. But it is uncommon but it does create some toxicities because the activity of this T-cell really revs up the immune system and that can lead to toxicities like cytokine release syndrome and neurotoxicity that Dr. Kittai will be talking about next.

Interestingly, when we started using bispecific T engagers like blinatumomab, we recognized that these seem to work best for patients that don't have a lot of disease. So we can use it in patients who are relapsed and still get pretty good results with you know, 30-ish percent of patients in remission out to two years if they've fully relapsed. But we get much better results if we use it before someone's relapsed and particularly when they have very little residual disease. So even patients with a 10th of percent of leukemia cells have a very poor outcome if we don't do something else. But giving these patients blinatumomab makes a huge difference leading to much improved event-free survival and overall survival and that's where blinatumomab is being used most these days.

And this is most prominently shown in a study recently published the E 1910 study which was originally planned to use blinatumomab for patients who had residual disease. But during the trial it was recognized that this was really useful for those patients. So then the trial shifted to only studying patients that had no measurable disease at all, even at a low 10th of a percent level. And even still those patients had a huge benefit from getting blinatumomab to eliminate those tiny bits of disease that we otherwise can't see. And since this study it is now fairly common that basically every patient with acute lymphoblastic leukemia will get blinatumomab to catch residual amounts of disease that we can't readily see and prevent relapse.

Lastly, that brings us to chimeric antigen T-cell receptors CAR T. Currently there's three approved products. Most commonly brexucel which is an abbreviation for brexucabtagene autoleucel and obecel, which is an abbreviation for obecabtagene autoleucel. There is also a third tisagenlecleucel but is only available for pediatric patients for the most part though up to age 25. So in this treatment we take cells out of the patient's body and we convert them into the drug by adding in a construct. The currently available receptors look like this where we take the antibody binding in to CD19 from an antibody here, the SCFV and we attach it to the internal part of a T-cell receptor along with Frankenstein together piece of a co-receptor that is also needed for T-cell activity and put this into the cell. And once that's into the cell they become programmed killers to attack whatever this antibody binds, which in this case for ALL is CD19. And the advantage of this is not only that they are effective at attacking the cells but they can also persist.

So these cells can still divide and make copies of themselves that still express this receptor and this can continue and sometimes for decades but on average about one to two years the cells will be around but unfortunately sometimes they can be suppressed by the tumor or the cells around the tumor. And this is called exhaustion and is one of the mechanisms of failure along with of course losing the antigen that they target.

Here's the process by which they're made, patient comes in, gets blood collected, we insert genes permanently into those cells that then code for the receptor. This is often done with a virus but can also be done by other genetic means. Then we expand those cells until we have millions and millions put them into a bag and then infuse them back into the patient who first needs to get some chemotherapy to sort of make room for these lymphocytes and then the cells patrol their body killing off the cancer cells but with potential for side effects of that intense immune activation that can occur.

Here's a meta-analysis of multiple trials of CAR T, which initially started in pediatric patients, hence this large group of less than 20 year olds. And we can see this is relapsed patients which is really where this is used for the most part only in patients with at least some measurable disease but primarily relapse disease. And we can still see very good results for this patient population. With 64% of patients alive here at 24 years across multiple studies and a long tail of patients that that are seemingly cured in adults we don't have quite as good a results with 19 targeted CAR Ts, which is this next line but still 40% response rates and there's some things we can do to make that even better with pre-treatment. And again a large group of patients that are seemingly cured with this therapy.

And then targeting CD22 can also be done by CAR Ts though no commercially available products right now in adults and it's not quite as good but all of these treatments are way better than the expected survival of patients with relapse disease getting chemotherapy, which I've sort of indicated over here. So really only about 30 or 40% of patients will be in remission and around in the zero to six month range. And when you go out to two years we're really down to 10% with traditional chemo. So a huge improvement over where we were for relapse patients.

And that brings me to kind of some things that are going on in the future. So there's several new types of immunotherapies and development, new whole classes. So in addition to regular T cells, gamma-delta T cells are a subset of lymphocyte that's rare but does not have a T-cell receptor, so cannot cause graft versus host disease and can be very effective at killing cancer cells or other targets. You can also modify these with CARs as well, but they can work by themselves, Expanded NK cells can also kill cancer cells and they can also be modified into CAR cells. These CAR cells can have those, you saw those other different kinds of constructs, these can make them more resistant to suppression and these are known as "Armored" CARs. There are also things called "Universal" CARs, which are CAR T cells that no longer have a T-cell receptor so they can not cause attacks on patients and so you can use cells from other people off the shelf and these can also be made where the construct that the antibody that binds can be attached separately and so you can change their specificity.

There's also TriSpecific antibodies where in addition to binding cancer cell to an immune cell, they can also have an additional marker that either binds a different part of the cancer cell or binds two parts of the immune cell or adds in an immune signaling molecule to enhance the killing.

And then some of the things that I've already talked about are being improved. So there's new bispecific CAR T cells where in addition to binding the 19 antigen they can sometimes bind CD22 at the same time or CD20, which really gets around the chance of any one marker being lost by the cancer. There are better BITEs -two molecules, one that has some data presented at EHA called surovatamig that uses slightly different binding domain for CD3 that doesn't bind quite as tightly and a higher affinity binding site for CD19. And this seems to create a little bit better efficacy and less toxicity. And then a very interesting construct called VNX-101. So this isn't really an antibody, this is actually a virus that is a gene therapy. So, and this gene therapy produces what is essentially blinatumomab. So inside an adenovirus a section of the adenovirus' DNA was removed and in its place, DNA coding for blinatumomab was inserted and then this can then be injected. These trials have just started in humans but the data that's published is in mice from Tim Cripe's lab here in Columbus at Nationwide Children's Hospital. And this is just an experiment you can't really see is very well in the bottom, but the mice were injected with leukemia cells, then they're injected with the virus. The virus then goes into the mouse and in various tissues primarily the liver starts making blinatumomab. That blinatumomab then kills off most of the leukemia and even with re-challenge the mice that were treated with the virus that makes the blinatumomab analog for the most part all survive and all these blank spaces are where the mice have died off and can no longer be imaged. So preliminarily there's been some evidence of response in the patients and this trial is open at multiple sites for patients with refractory disease. And with that I'll stop. I apologize I didn't have a timer. So how are we doing on time, Lindsey?

- Sorry, I think we're gonna do fine but we'll, we'll just, we'll do the best we can with the Q & A and Dr. Kittai, if you wanna take over.

- All right, great.

- We can, we can maybe go back to the conclusions or kind of summarize everything later.

- Okay. Yeah. - All right. Do you guys see my shared screen?

- Yes.

- Alright, so I'll go ahead and take over. Thanks for the great introduction Greg. And talk about ALL and AML. I'm gonna reinforce some things such as the bispecific antibodies and the CAR T and I'll talk about a little bit about toxicity as well.

So we'll talk about immunotherapy treatment for leukemia, focusing on chronic lymphocytic leukemia today. Here are my disclosures. So there are a few different immunotherapy options for patients with CLL. There's the classic anti- CD20 monoclonal antibodies and for those folks who might have CLL out there, there's a high chance they may have gotten in one of these during their treatment course. We also have CAR T which is relatively new for CLL and we'll go over what is it, when to use it, how well does it work and what are the toxicities and long-term efficacy outcomes. And we'll also talk briefly about bispecific antibodies which are currently not approved for CLL. And

again through go through what is it, when to use it, how well does it work and what are the toxicities and long-term efficacy.

So to start out we'll talk about anti-CD20 monoclonal antibodies and Dr. Behbehani made a point to discuss how basically what these are are engineered antibodies that are given to patients with various malignancies that target certain proteins that are on the outside or surface of the cell. And so what the anti-CD20 antibodies are in the name they target CD20 and all B cells express CD20 including patients who have CLL express CD20 and CD20 is actually one of the pan-B cell markers. So they actually occur on the outside of all B cells and all lymphomas. So the agents that are currently approved, and I apologize for the spelling mistake, are obinutuzumab and rituximab and obinutuzumab is the favored anti-CD20 antibody for patients with CLL 'cause there's been a couple of clinical trials that have shown that the efficacy of obinutuzumab combined with other agents typically fare better than patients treated with rituximab. And usually when we're using these anti-CD20 antibodies they're used in combination. So they're used in combination with venetoclax or acalabrutinib and they're given as an infusion and they're usually given weekly for the first cycle and then once a month after that. And these antibodies have really revolutionized the way that we treat lymphoma, specifically diffuse large B-cell lymphoma but certainly have had a role for patients with chronic lymphocytic leukemia as well.

To get onto some of the new stuff, let's focus on CAR T and bispecific antibodies. So Greg went over this briefly but I think this is important to mention is that CAR T cells are engineered T cells that are derived from your own body. So how this works, and this was a image that was taken from cancer.gov from the NIH's website. How this works is that you get hooked into a machine and what the machine does is it filters out all of your T cells. They then take these T cells that they filter out and they bring them to the lab and the T cells have a gene inserted into them that allows these T cells to target the CD20 or CD19 depending on the CAR T that you're looking at. And then the CAR T cells can express this antibody on the outside of its cells and then you're given back your own cells that now are engineered to target the cancer. And so as you receive these CAR T cells, the T cells can then have a honing beacon that can then attack the CAR T cells. And so that's how this works. It basically is a way to re-engineer your own immune cells to attack the cancer.

And so to focus on guidelines, so these are the NCCN guideline recommendations and this is pretty much the bible for all oncologists and it gives you an idea of where this particular agent is placed in the sequence of treatments for patients with CLL. So I just wanna highlight here that the only anti-CD19 CAR T that's currently approved is lisocabtagene maraleucel or lisocel. And you can use the lisocel along with the BTK inhibitor called ibrutinib. And particularly I like to use lisocel plus any BTK inhibitor. I don't necessarily use ibrutinib alone but that's getting into the nitty gritty of things. And I wanna highlight that this particular CAR T cell, per our guidelines, is that it's recommended after we use our classic medications for CLL which are BTK inhibitors and BCL2 inhibitors, BTK inhibitors being ibrutinib, acalabrutinib and zanubrutinib and BCL2 inhibitors being venetoclax. So the point I'm trying to make here is that you have to get through a lot of therapy before anyone's really gonna recommend a CAR T-cell therapy for you for CLL.

And so this schema highlights that as well. If you look all the way to the right, I highlighted lisocabtagene maraleucel and so to the left is active surveillance, first treatment, second treatment, and then third line treatments. So once again, I'm trying to highlight here through a consensus guideline that patients really need to get through a lot of therapy before we get to CAR T-

cell therapy. And the reason that is, is that CAR T-cell therapy comes with significant cost and toxicity which I'll discuss. Whereas our general first and second line therapies for patients with CLL tend to be very well tolerated. So in order for CAR T or anything else to surpass a threshold to be used in a earlier line of therapy, it really needs to be as safe as possible and work really well.

So once again, you know, before I even consider anybody for CAR T cell therapy, they must have received a venetoclax-based regimen. They must have received a classic covalent BTK inhibitor. Nowadays they must also receive a non-covalent BTK inhibitor and also they should have received an anti CD20 antibody as we had talked about, including obinutuzumab, which as we said is a type of immunotherapy. So once again this is a journey for patients with CLL, they're gonna get treated with a lot of things over their lifetime and CAR T is really the last point. It's something that we really save before until people are exposed to multiple different agents until they get to that.

So how do we learn, how do we get to an approval for lisocel for CAR T? So this is the Transcend CLL004 study. And so how this worked is that patients were allowed to enroll onto the study if they've received a prior covalent BTK inhibitor and they had to have high risk features, meaning had to have over two lines of therapy or over three lines of therapy. And what works with CAR T, something to think about, is that from the time that the blood is taken from the patient's body to the manufacturing of the actual drug itself takes about three weeks. So let me go back to that schema, I just wanna show you this again. So to get from step one all the way to step four that takes about three weeks. And so typically what happens, patients get leukapheresis and so that's when they take the blood out of patients and they then get chemoimmunotherapy and then they get the lisocel. And so this entire process from the blue to the red, that's the three week process and the chemotherapy is there to prime the patient to accept the lisocel, to accept the CAR T and not reject it. And so after they get the lisocel, it's just a one-time dose, they then follow those patients forward and that's how this clinical trial was designed.

And the original results of the lisocel for relapse refractory CLL study was actually a little bit disappointing where there were 49 patients treated but only 21 patients actually responded to the medication. And so what we call this is a Kaplan-Meier curve. How you interpret this is that going from left to right is time and flat curves are better. So the green curve on top, the green gray curve, those are patients who had a complete response. So patients who did responded super well to the CAR T and we couldn't detect their CLL. The red line is patients who had a partial response, the blue is all comers and the purple are people who did not have a response. So the idea here being that if you had a complete response in the gray, you can see this line is the highest and goes out the longest, that means those patients lived the longest. But when I'm looking for a therapy, having only 21 patients respond out of 49 is not good enough for us to really adopt this particular therapy for patients with CLL.

But interestingly enough there was an update of this study where they combined the lisocel with ibrutinib and based on this study is the reason why I had said earlier that I always combine CAR T with a BTK inhibitor. And so in this study patients 100% had to receive a prior covalent BTK inhibitor. About 75% had received venetoclax and about 75% had received both. So this was really a modern cohort of patients who received all of our classic therapies for CLL prior to enrolling onto the study which makes the results of this study even more impressive. So when the ibrutinib was combined with the lisocel, you can see here that 44 out of 51 patients responded right? So that's very different than 21 out of 49. So the majority, the vast majority of patients responded to the therapy and you

can see that these curves go on much longer across time and that even the patients who had a partial response did pretty well where they hadn't progressed really by the last time this study was presented. And so to compare these numbers back-to-back to each other, you can see that the lisoel alone was far inferior to lisoel plus ibrutinib. And this is the reason why we recommend using BTK inhibitors with CAR T-cell therapy to boost the effect and allow patients to have a really good response, especially for these patients who really had nothing else to go for them by the time they got to the CAR T.

So to focus a little bit on the toxicity after talking about the great efficacy that we see with CAR T when paired with BTK inhibitors, there are two main side effects we think about. The first one is called cytokine release syndrome and the second one is called neurotoxicity or ICANS. And how I like to think about these two toxicities is that the drug works so well that it causes the T cells to activate and cause the T cells to look like you're having an infection. So whenever you have an infection, your immune system attacks that infection and the reason why you get a fever or don't feel well is because your immune system is activated. It's not necessarily because you have the infection itself. So basically what's happening here is that the immune system is getting activated against the cancer causing these unwanted side effects. And so cytokine release syndrome is associated with high fevers, low blood pressure, it's caused by T-cell activation and usually occurs about three days after the lisoel is given. For neurotoxicity it's basically confusion that worsens over time and this happens about five days after the lisoel. So the good thing is, although these are scary things, is that we know how to treat them. And now that we have experienced treating cytokine release syndrome and neurotoxicity, especially since CAR T has been available now for over seven years, we know that these things are fixed with drugs called tocilizumab and steroids.

And so when they looked at the rates of these drugs and when we think about rates of adverse events with drugs, we get scared when it's grade three or higher, you can see that the grade three rates of the neurotoxicity and the cytokine release syndrome was, was less than 18% in both. So actually less than 10% for the cytokine release syndrome and less than 18% for the neurotoxicity. So very manageable. Something that we're used to now, something that we can give medications and FYI the grade five is, is death. And so as you can see, no one died from these toxicities while on this study, which is a great thing to see.

So the pros and cons of CAR T-cell therapy. So pros, it can lead to durable responses, it works in patients with high risk CLL and it's a one-time therapy. However, there's significant cost. Toxicity. The manufacturing time takes about three weeks and we need to work on making sure that everybody responds so that way we can accept the safety profile that I had shown you. In addition, typically the CAR T is given inpatient, however that's changing in real time where a lot of CAR T's given outpatient these days.

And just to speed through the bispecific antibodies, because I know that Dr. Behbehani had shared this a little bit is there are bispecific antibodies which work similar to the CAR T but it's a little bit different. So instead of having to manufacture the CAR T from your blood, bispecific antibodies are off the shelf, meaning that they're directly available and there's no wait time. And what bispecific antibodies do is that they basically tag onto the T cell and bring it right to the cancer. So it's another way to basically activate a homing device that brings the T cell to your cancer as opposed to the T-cells floating around not knowing where to go.

So the main bispecific antibodies are epcoritamab, glofitamab, and mosunetuzumab and they all target the CD20 just like the rituximab or obinutuzumab does as described earlier.

The epcoritamab is the one that has the most amount of data currently for CLL, this was a smaller study, it had 40 patients, all patients had prior BTK inhibitor, remember this is off the shelf so there was no wait time. And the median progression-free survival meaning how long did it take for patients to progress after receiving the therapy was about a year.

So the pros and cons of bispecific antibodies. So the pros are is that they're off the shelf, meaning there's no wait time, it's a novel mechanism meaning something that we don't have other drugs that do the same thing. It's generally better tolerated than the CAR T and it's also outpatient. However, it's not available yet for CLL. It has to be given often about once per week and long-term data is not available. Last but not least, we still have a lot of work to do. 60% response rate is not good enough but there's more data comparing it and bringing it with the PTK inhibitors that good. So we'll see how it develops over time.

So in conclusions we have CAR T, it's currently available but given toxicity concerns we don't really use it until patients have gotten the standard of care medications. Bispecific antibodies are currently being developed, they're not approved but they do appear to be safer but maybe not as efficacious as CAR T, but more work on that is being done. So I'll end my talk now and I'm looking forward to discussing any questions that you all have.

- Great, thank you both so much. I think that covered a lot of ground and I want to remind the participants that if you have a question and you would like to pose those questions, you can enter them in the little box at the bottom of the zoom screen where it says Q and A. And once again, if you want your question or your identity to be hidden, please make sure that you click the little box that says anonymous. And in the meantime we're gonna start with a couple of questions that were submitted through the registration. I saw in the registration many people who had questions generally about AML and Dr. Behbehani, I know you covered this a little bit, but maybe just if you could in a nutshell, what's the potential for AML in the future from an immunotherapy treatment perspective?

- No problem. Yeah, so the, a couple problems with targeting AML, unlike B-cell diseases, you can't really live without all your myeloid cells. So you'd have no red cells that we can transfuse that, but that's not a decade long prospect and you'd have no platelets and, and transfusing platelets does not work forever. Usually people can only be platelet dependent for a year or two before they platelets stop working so that's one major problem. The solution to that is to try and find proteins that are only on the surface of the cancer cells and not on the surface of normal cells, normal myeloid cells. And the number of antigens like this are limited but there are some that are being studied. CD123 was hoped to be a little more specific and there are some ongoing studies though most of those have not shown as good of results as we would've wanted. And then the newer treatments like gamma delta T cells work in a slightly different way and those can be effective because they're looking at proteins from the inside of the cell that are now displayed on the surface. And that is probably gonna be the more effective way to do immunotherapy in AML. And just like ALL though, it's probably gonna work better if we can mostly get rid of the leukemia first and then use that to get rid of the last little bit. So some of those studies are just now coming online and I

know we have a gamma delta T-cell study for patients going to transplant with AML that is currently enrolling.

- Great. And since we're covering other forms of leukemia, how about CML? Any anything on the horizon for CML patients?

- For the most part we don't need immunotherapy for CML and it probably would not be very effective because CML cells are so very close to normal that it's pretty unlikely that we could find a good antigen. The therapies for CML on the horizon are most likely gonna be things to make TKIs work a little bit better. Venetoclax is being studied in this setting, but other second drugs on top of TKIs are probably going to be the way that that we get rid of that. Though, you know, I still have probably about 20% of my patients that can eventually successfully come off their TKI. So you know, I wouldn't sleep on the drugs that we have and if you have CML and you're not doing well in your current TKI, there's three or four more out there and sometimes I'll put my patients on every single one and then pick whatever worked best.

- Okay, great. And along that same line, there was an individual who in their registration, they are a CLL patient said, what's new? I've had 10 different treatments which have not worked.

- Yeah, so in CLL there's usually always something that's new. So the newest approval is actually pirtobrutinib, which is the non-covalent BTK inhibitor that was specifically designed to work in patients who received prior covalent BTK inhibitor - binds slightly differently - and pirtobrutinib additionally looks like it's very safe compared to the prior BTK inhibitors and is also effective. Other things that are new that are in the pipeline are something called BTK Degraders, which are a little bit different in that they bind to BTK the same target as pirtobrutinib, and acalabrutinib and zanubrutinib, but they only need to bind for a short while and then it degrades the BTK. And so basically it gets rid of the BTK entirely. And so it should work in patients who received prior covalent and non-covalent BTK inhibitors. Additionally, there's a new BCL2 inhibitor that likely will be approved in the next year or two that's called sonotoclax. It's kind of like venetoclax but appears to bind better to BCL2 inhibitor and inhibit even more. So additionally, as I talked about earlier, we're hopeful that there'll be additional advancements for CAR T-cell therapy and as well as bispecific antibodies. So that's generally what's new in CLL.

- Okay. And I just wanna mention for anyone who missed our last series, we had a series in February called New & Emerging Treatments and we had an entire session on CLL. You can find that webinar, the recording of that webinar in our archive also. And the speaker talked quite a bit about those, those different options that Dr. Kittai just mentioned. Okay, so there are a couple of questions in the chat here. One person said I have CLL but more MZL, how would that be treated?

- Yeah, so there's actually a lot of overlap between marginal zone lymphoma treatment and CLL. And so one of the drugs that does have an approval from marginal zone lymphoma that overlaps with CLL is zanubrutinib, it's one of the covalent BTK inhibitors. Additionally, we often use rituximab for patients with marginal zone lymphoma and additionally sometimes we still use chemotherapy for marginal zone lymphoma with bendamustine plus rituximab. So in general there's a lot of overlap between all of the indolent non-Hodgkin lymphomas and in that umbrella includes CLL.

- Okay. Okay. And the first question in the chat, actually, this is a question that sometimes we get, you know the topic of this particular webinar is immunotherapy treatments, but a lot of patients also wanna know how can they boost their immune system generally while they're in some, any kind of treatment for leukemia. So if you can address that, if you have any thoughts on that.

- Sure, I'll take that one. So unfortunately there's not much that has been proven is the answer. So we do know that patients who are fitter, who take good care of themselves typically do better with immunity and immunotherapy and treatment in general, whether or not those patients have better immune systems is something that we are still trying to elucidate. There's some protocols out there that are looking at whether or not exercise can actually improve immunity and improve your immune system with CLL. There's been some data with vitamin D that just shows that patients who take vitamin D have a longer time to first treatment with CLL. But once again it's kind of unclear if those patients take just better care of themselves overall or if it's the actual vitamin D that's doing anything there. More research needs to be done.

Now, truly, and I know this is not exactly what the person's asking, the only way to boost the immune system of somebody with CLL is actually to get treatment. So we know that the worst time for someone's immune system with CLL is when they start treatment. So it's when their disease is at the worst and when they first start treatment. But what happens is, is that over the course of that first six months of treatment, the CLL actually reduces in bulk. So the CLL responds to the therapy and then the immune system can kick back in. And so what we found is that when we looked at patients who received the COVID-19 vaccine and how they did with the COVID responses, we got a good idea of like what was happening with the immune system in those regards. And we saw that basically patients who got the COVID-19 vaccine with high disease burden and had just started therapy, they didn't really respond very well. But those patients who had either not received treatment and had very low level of CLL or had responded treatment with low level of CLL, those patients were more likely to respond.

Additionally, another clue there is what I showed you earlier that with BTK inhibitors, CAR T cells do better. And so what we're seeing is that basically the BTK inhibitors are able to boost the effect of the CAR T cells, which show us that with treatment we actually improve patient's immune system. Because CLL actually is one of the most immunosuppressive cancers out there and it's basically, you know, only surpassed by somebody who's gotten an organ transplant or a stem cell transplant. So patients with CLL have really not great immune systems, especially when there's a lot of it and unfortunately the only real thing that we've found as a tangible solution is with treatment.

- Okay, great. So I am going to take a couple of questions that were asked and incorporate them into something that someone mentioned earlier. So I think it was Dr. Behbehani who referenced the NCCN guidelines. Is that right?

- I think I did.

- Or was it you? Okay, great. So you talked about how NCCN guidelines generally dictate what treatment decisions a doctor will make. And the question that came in in registration was how can patients work with their doctors to ensure that they're making the best possible decisions with immunotherapy. So I know that you know, you talked a little bit and you showed kind of like that rubric of how the decision making tree is followed. Is there some way for patients, if they've, you

know, if they have extenuating circumstances or specific issues that they've been experiencing, maybe some comorbidities, I'm not sure what, how can they best approach their care providers to, to have a productive discussion about their options?

- Yeah, so I actually encourage my patients to be as well informed as possible. And so what I advise my patients to do is go on, like very validated websites like the Leukemia Research Foundation, like the Lymphoma Research Foundation like the CLL Society's websites, these are all nonprofit organizations that's goal is to educate patients and make sure that they're most well-informed. And so leverage those resources. Additionally, the NCCN guidelines does have a patient area. So a look at those as well. I'm actually unfamiliar what they look like to be honest, but I know that there's some patient forward things on there that you can look at to come and be the most well-informed.

The last thing that I'll mention, and I'll throw it back to Dr. Behbehani, and see if he has any advice, is that how I like to say it, is that if you're interested in receiving a second opinion, your physician should be encouraging you to do so. And so talk to them about a second opinion, find out who in the neighborhood might be treating CLL, it might be a, you know, an advanced expert in it, same thing with AML or ALL. And so if you ever feel like you are not getting the information that you want, work with your doctor to find a academic or expert person in the area just to get a second opinion with. And I will say that most physicians should be happy to give you that second opinion because we all want you to get the best care that you can possibly get.

- Great. - Yeah, I would, I would second all of that. I think you do have to be careful online what you look at, but sticking to nonprofit organizations like Leukemia Research Foundation is a great place to start because they're, again, trying to, to provide education. The NCCN guidelines are a bit dense. They can be hard for, for a lay person to read, but there is information for patients there on their website and I agree, if you have a good doctor, your doctor should want you to get a second opinion that is always in everyone's best interests. That's not always practical, but usually someone has a friend or a family member or someone that, you know, some connection to some other place where there are experts in that disease. And I think it always makes sense to talk about that even if you're not gonna be treated there or not gonna do that treatment. But it's a great way to have a good conversation.

And then the last thing is just to have the conversation, like if you're concerned about chemotherapy, try and be very specific about what are the things that you're worried about with chemotherapy, particularly early on. I think a lot of patients, especially with, you know, leukemia therapies, which are generally a lot easier than the kinds of treatments that people get for a breast cancer or colon cancer for instance. People come in with a lot of concerns that are not necessarily founded regarding the kind of chemotherapy that they're gonna get. And, and I'll say the most common thing I hear from patients in the hospital, when I start them on the most intensive leukemia therapy we can give the next morning, they almost always say, well I thought it would be a lot worse than that. So talk about your specific concerns with your doctor, why you might be worried about a particular therapy, why you might want a different one and, a good doctor is gonna take a lot of that into account and I don't mind giving my patient a treatment that's not on the NCCN guidelines as long as we've talked about why are the guidelines the way they are, why do you wanna do something different? Why is that important to you? Why do you feel like that's something that specifically you're gonna do better with? And those are great conversations to have and I definitely encourage my patients to have those kinds of conversations with me.

- Wonderful. Well, we are just about out of time. I'm hoping that this is a really quick question. One person asked if they have taken, this is a very specific situation, if I've taken Keytruda for melanoma in the past, would this make me ineligible for immunotherapy in the future? Are there like specific things that may make someone ineligible?

- No, no, no concerns there. It, you know, if you still need to be on Keytruda right now to control your tumor, that can be a lot more complicated. But if you were successfully treated using a checkpoint inhibitor and you're no longer on it, it really shouldn't have any significant interference with any of the treatments we use for acute leukemia. And I doubt for CLL, either

- There's active clinical trials combining Keytruda with CAR T cells right now in various different circumstances, immunotherapy. So it's not contraindicated in any way in that regard.

- Great. Yeah. Okay. Well I don't see any other questions in the Q and A and we covered a lot of ground. I did wanna point out that I put the link to the [NCCN patient guidelines page](#)\*\* in the chat for anybody who would like it. I'm also going to share my screen again because as a huge fan of the NCCN guidelines I always like to share them with participants. So here we are, right here in this lower right hand corner, you can see that link. Unfortunately it's not clickable here, but it's a pretty straightforward, easy to find website. And as mentioned before, we have a lot of information on our website as well, although nothing like what's on the NCCN guidelines pages. So, but definitely, you know, reach out to us if you have questions.

We're so glad that everyone was able to join us today. I also would like to thank the sponsors once again, Johnson & Johnson and Autolus and thank our speakers. Do you, do either of you have any final words to share or anything that you'd like to say?

- I'll finish up by just saying that, you know, we're developing new medications all the time and, you know, really speak to your doctor, what's new? 'cause they're coming out with, at least in CLL and also in AML and ALL, there's new and safer medications and so there's hope out there. And as we talked about, if ever you are struggling, get a second opinion, look out what's out there, get into support groups and people will help you.

- Yeah, I couldn't agree more. It's an amazing time to be treating hematologic malignancies just from when I trained till now, the number of diseases that we can manage really well that we couldn't has just dramatically increased. And there's so many great trials out there right now and new approaches that, you know, if you are interested in something different or something more, it's out there and you know, either Adam or I would be happy to meet with you and, and talk about options in our diseases.

- Very good. Well thank you so much both for your time. Thank you everyone for your participation and please do keep an eye out for that email inviting you to give us some feedback on today's session and we will be following up in a week or two with the link to the recording and look forward to future programs. So thank you so much everyone. Have a good night.

- Thanks. Thanks a lot.

\*\* <https://www.nccn.org/patientresources/patient-resources/guidelines-for-patients>