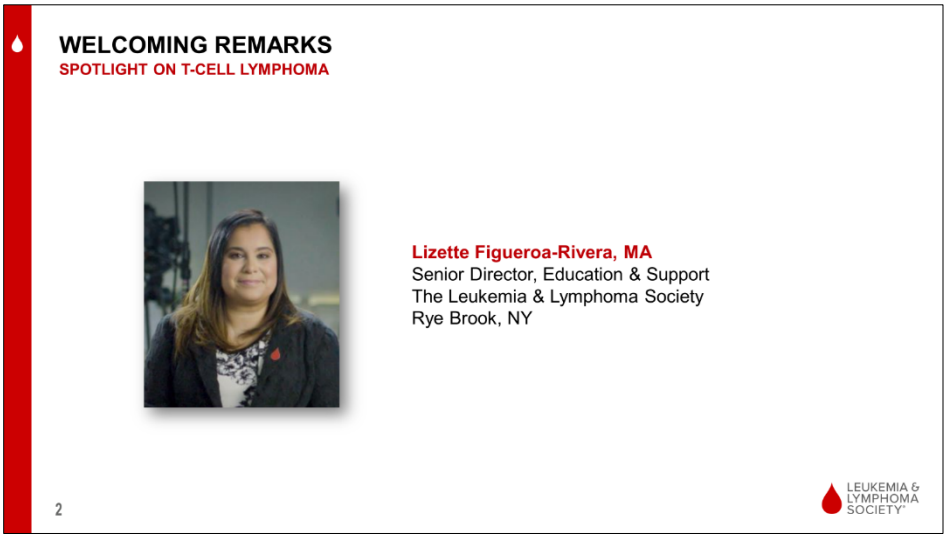
WELCOME AND INTRODUCTION



Lizette Figueroa-Rivera, MA
Hello everyone. On behalf of The Leukemia & Lymphoma Society (LLS), a warm welcome to all of you. Special thanks to Dr. Neha Mehta-Shah for volunteering her time and expertise with us today.

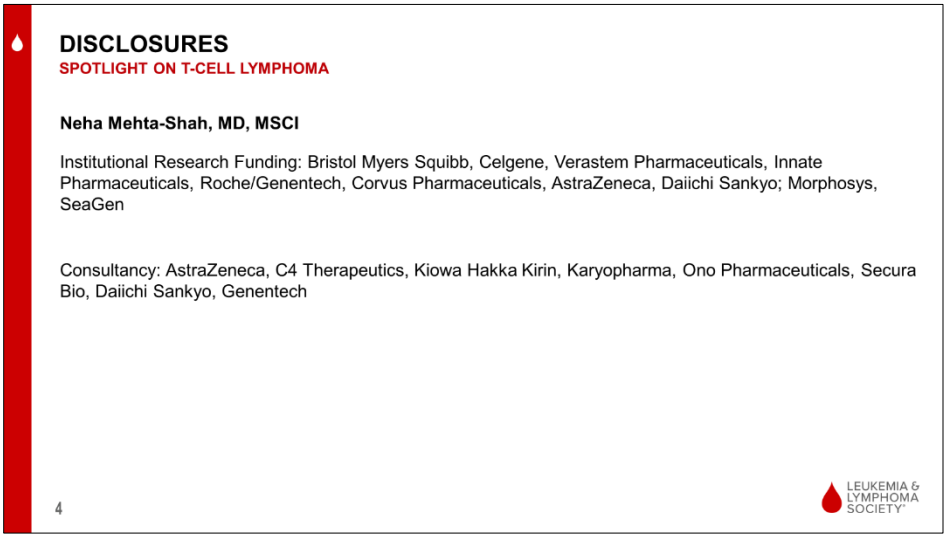
The Leukemia & Lymphoma Society funds leading-edge research for every type of blood cancer. When it comes to cancer, information is power. For many patients and families, coping with a blood cancer diagnosis can be complicated, stressful, and overwhelming. With so much information available online from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

PRESENTATION

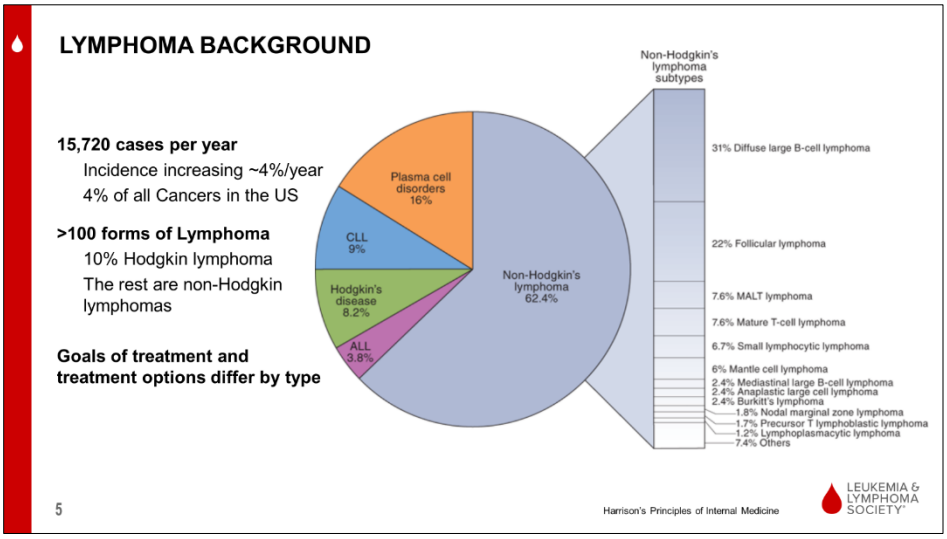
Lizette Figueroa-Rivera, MA
I am now pleased to introduce Dr. Neha Mehta-Shah, an Associate Program Director of the Hematology-Oncology Fellowship and an Associate Professor of Medicine at the Siteman Cancer Center at Washington University School of Medicine in St. Louis.

Dr. Mehta-Shah, I am now privileged to turn the program over to you.

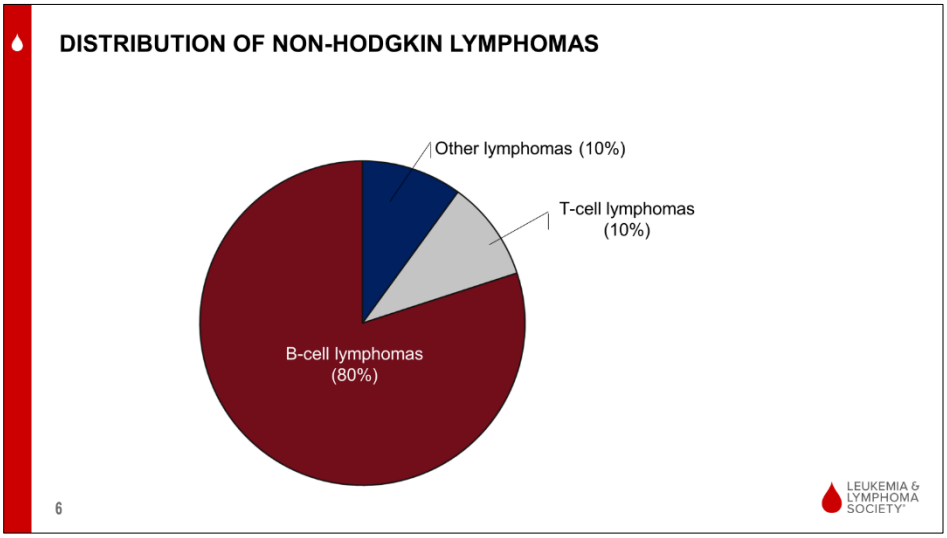
Neha Mehta-Shah, MD, MSCI
Hi everybody, it's my pleasure to speak to you today about one of my favorite topics, which is T-cell lymphomas.



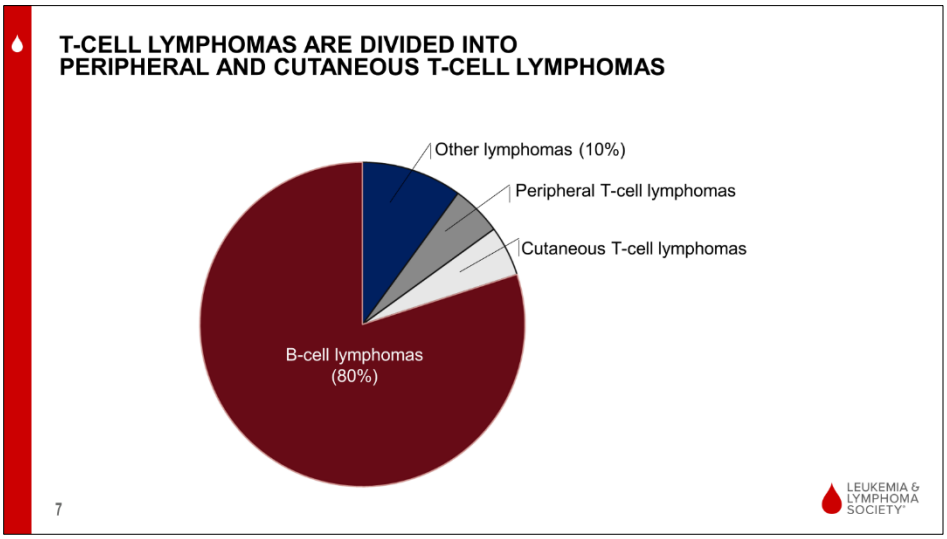
These are my disclosures.



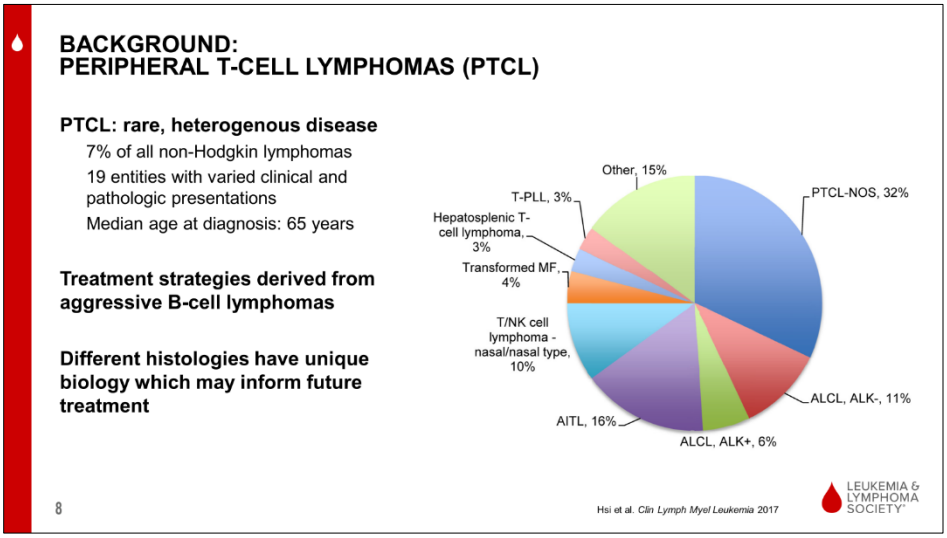
So, you know, T-cell lymphomas represent a subset of non-Hodgkin lymphomas. As you may know, there are many types of non-Hodgkin lymphomas. The incidence of non-Hodgkin lymphomas has been increasing each year, but there are approximately 16,000 patients diagnosed per year with non-Hodgkin lymphomas. And this term represents over 100 different types of lymphoma. About 10% of these are Hodgkin lymphoma. The rest of them are essentially non-Hodgkin lymphoma leaving many, many types of non-Hodgkin lymphoma. And the treatment for each and the prognosis and management is different based on each subtype.



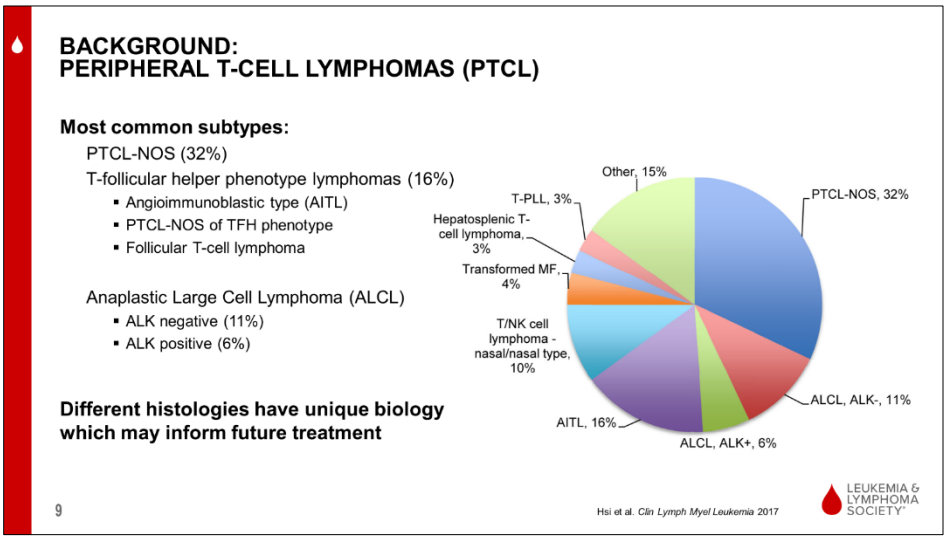
In general, about 80% of non-Hodgkin lymphomas come from B cells, but about 10% come from T cells, and we're really going to be focusing on that rare group of T-cell lymphomas today.



Of the T-cell lymphomas, these are roughly divided in half by what we call peripheral or in the body or systemic T-cell lymphomas and about half have what we call cutaneous or in the skin T-cell lymphomas – lymphomas that originate in the skin and then can go into the bloodstream or the lymph nodes or other parts of the body.

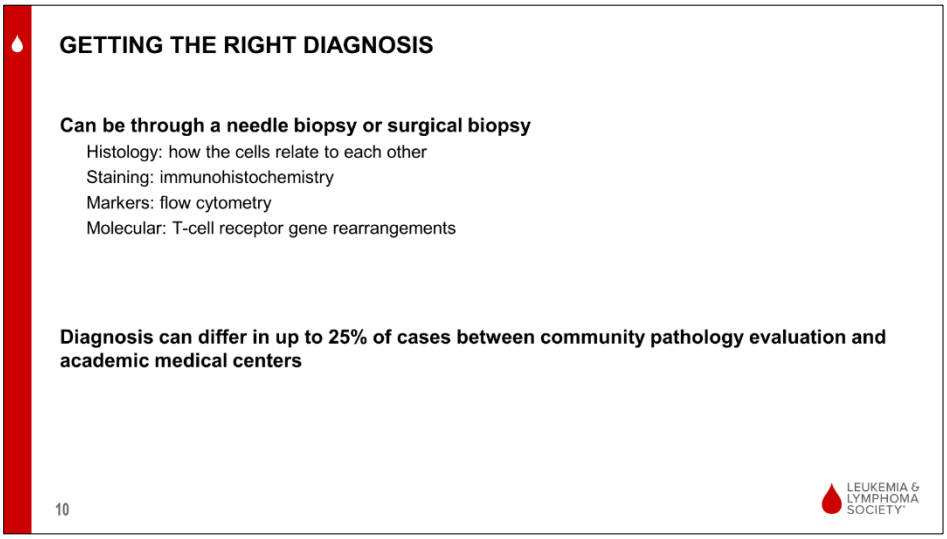


We're going to start by talking predominantly about peripheral T-cell lymphomas or systemic T-cell lymphomas. These are a rare heterogenous group of T-cell lymphomas making up about 7% of non-Hodgkin lymphomas. The term peripheral T-cell lymphoma really refers to 19 different diagnoses. Most patients at the age of diagnosis are in their mid-60s, though certainly we see patients a lot younger than that as well as considerably older than that. And until recently, we have been really using our knowledge of B-cell lymphomas to treat T-cell lymphomas, meaning the treatments that were developed or derived were really derived from treatments that were commonly used for fast-growing B-cell lymphomas and then extrapolated to T-cell lymphomas. But over time, we've learned that different histologies have unique biology that certainly can inform future treatment and that's starting to change the paradigm for how we treat these diseases.



The most common types of T-cell lymphoma are peripheral T-cell lymphoma-not otherwise specified, also written as PTCL-NOS; those that are derived from the follicular helper cells. These are most commonly something called angioimmunoblastic T-cell lymphoma or angioimmunoblastic type, peripheral T-cell lymphoma of T-follicular helper phenotype, or follicular T-cell lymphoma; and

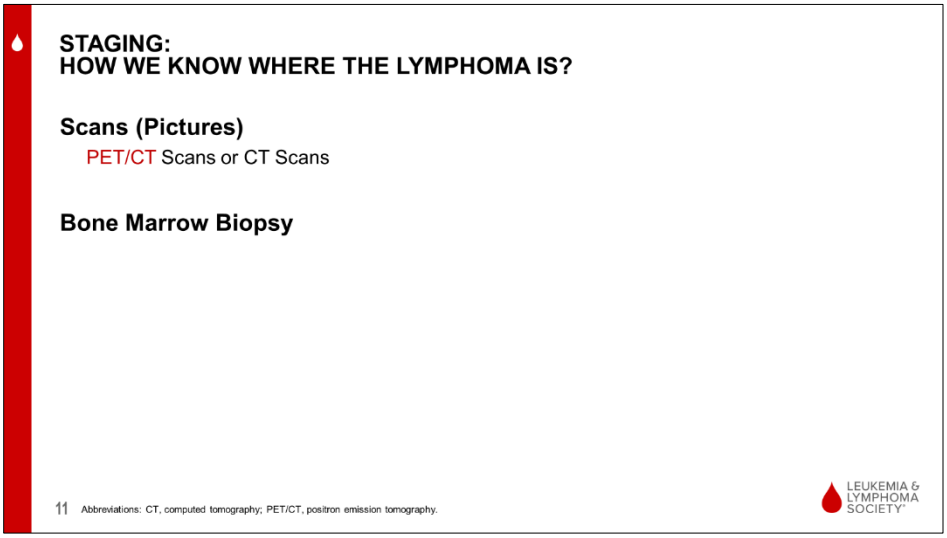
different classification systems name these slightly differently. The third most common group is the anaplastic large cell lymphoma group, and these are then subdivided further by whether they express this protein called ALK (anaplastic lymphoma kinase) or they don't express this protein. And we're learning that each of these really is probably a distinct group of different diseases driven by different biology.



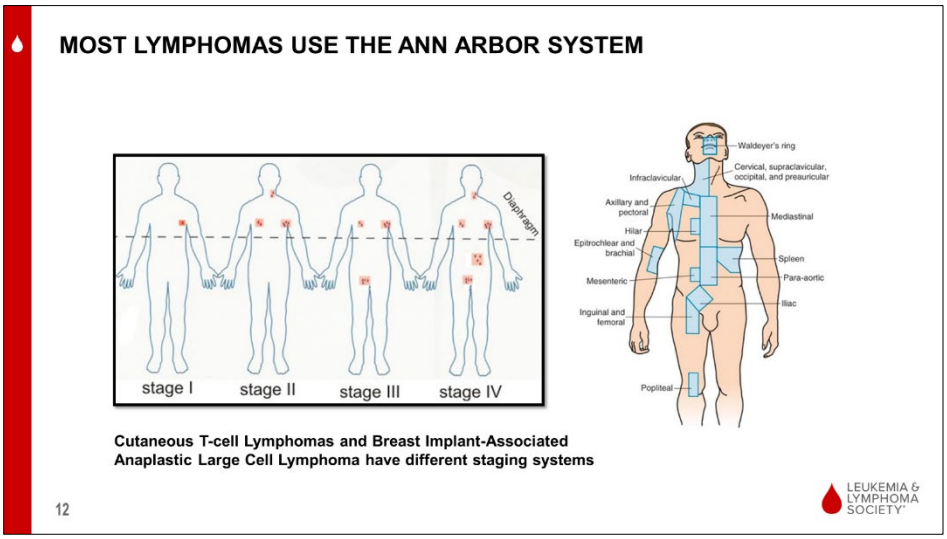
But before some people come into us with a suspicion for something like a T-cell lymphoma, how do we figure out whether they even have a lymphoma? This can be done through a needle biopsy or a surgical biopsy. And what we'll do is we look at those cells and the tissue under the microscope to see which cells are overrepresented. Do they look normal or abnormal in appearance? Are they growing in an abnormal way, growing into other structures that they shouldn't be? How [do] those cells relate to each other, and which other cells are they surrounded by? And then, ultimately, we do tests called staining to look at which proteins are on the cell surface and flow cytometry also to look at what proteins are on the cell surface to tell if all these cells came from the same cell, like in a cancer way, or did they come from different cells and they're working just as a normal part of the immune system to help to fight off an infection or in the setting of a surgery or trauma.

Sometimes this is still hard to discern if there's truly a lymphoma and sometimes we do a test called a T-cell gene rearrangement to look at the barcode of a protein called a T-cell receptor. And because each T-cell should have a unique barcode, barcodes that come from the same cell should have the same T-cell barcode and we can use the sequencing of that T-cell gene receptor to determine if these cells came from one cell in a cancer way or from different cells more in what we call reactive ways.

Just to know, because T-cell lymphomas are rare and sometimes very difficult to diagnose, patients can go through more than one biopsy to arrive at the diagnosis and sometimes between a community pathology evaluation and a pathology evaluation at an academic center, 25% of the time the specific diagnosis may differ. So getting your pathology reviewed at a site that tends to see these diseases a little bit more may be a good idea.

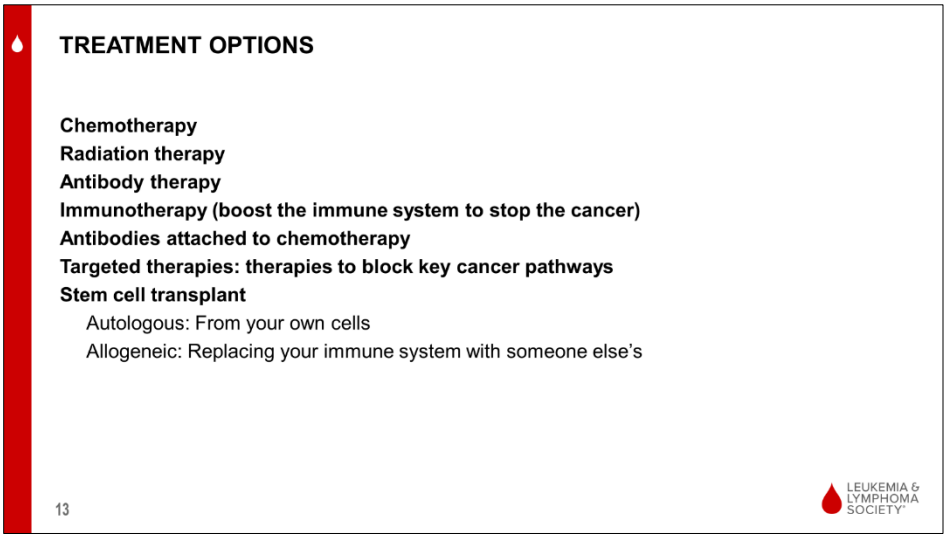


Once we know someone has lymphoma, how do we know where that lymphoma is? We do something called staging. Predominantly we do this through PET (positron emission tomography) scans or CAT (computed axial tomography) scans. We prefer PET scans in T-cell lymphoma mainly because these are better at looking for areas outside of lymph nodes, and we think that's particularly important in T-cell lymphoma. And then in T-cell lymphoma, we do think there's a role for getting a bone marrow biopsy to evaluate whether there's lymphoma in the bone marrow itself. So that's commonly done as part of our staging for peripheral T-cell lymphomas.



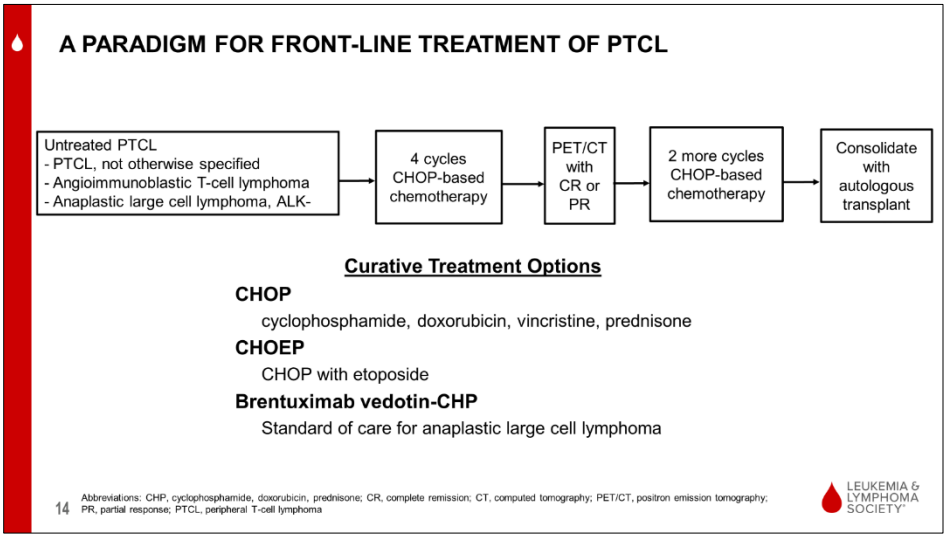
And just like other forms of lymphomas, we use an Ann Arbor staging system. This is essentially looking at where the abnormal tumors or lymph nodes are. If you have one area of enlarged lymph nodes in just one region, that's considered to be Stage I. If you have more than one region on the same side of the breathing muscle called the diaphragm, we call that Stage II. If it's above and below the diaphragm, we call that Stage III. And if it's in areas outside of the lymph nodes, we call that Stage IV. And these stages were originally derived from fields that were used to determine

[prognostic factors] and give radiation for Hodgkin lymphoma and then have been used in both B-cell and T-cell lymphomas.



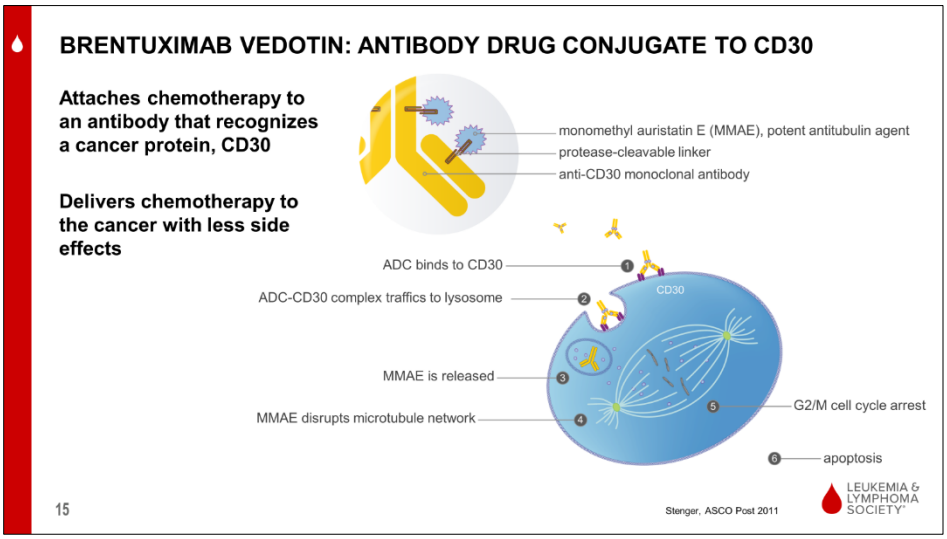
What are the treatment options for patients who have peripheral T-cell lymphomas? Certainly, one of the mainstay options includes giving chemotherapy medicines. Another option includes giving radiation therapy. Sometimes we use antibody therapies or antibodies tagged to chemotherapy. Sometimes in some lymphomas, we use immunotherapy that's used less commonly in T-cell lymphomas. And then we'll talk about the role of stem cell transplants in T-cell lymphomas briefly. But there are two basic types of stem cell transplants. There are the autologous transplants (that is, from your own cells) versus allogeneic transplants, which is from someone else's cells.

These are fundamentally different processes. So when you do an autologous transplant, you're getting high-dose chemotherapy in the hospital for a few days, and you get your own stem cells infused back to you through a catheter. And those stem cells help to repopulate or regenerate your normal bone marrow. So essentially, you're getting high-dose chemotherapy and getting your own stem cells back as a rescue or like fertilizer to help the bone marrow grow. Whereas an allogeneic transplant is replacing your immune system with someone else's immune system, basically giving you chemo[therapy] and radiation to make your immune system very weak and then giving someone else's stem cells to you, usually also through a catheter, and using those new stem cells from someone else to help find the cancer and detect the cancer as foreign. And that's a form of immunotherapy essentially.



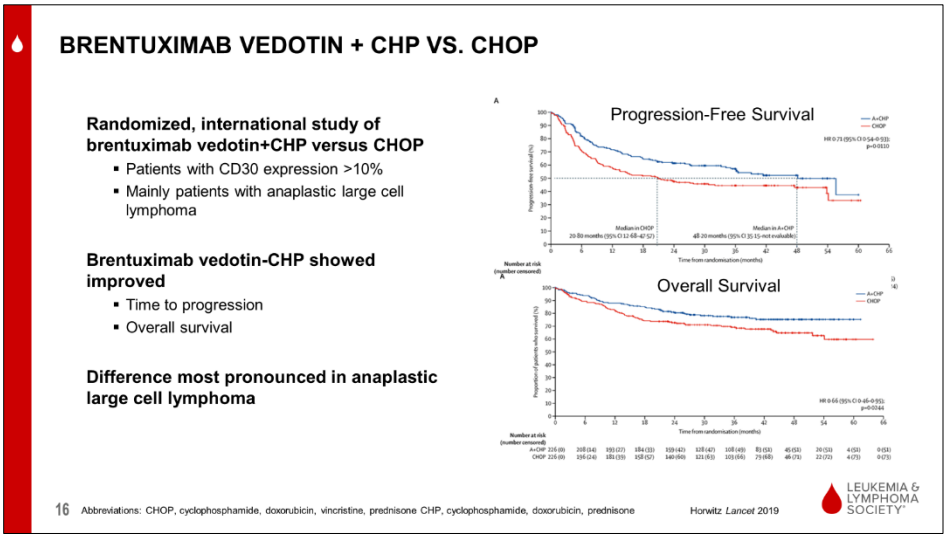
So when I see patients with peripheral T-cell lymphomas who have not been previously treated for the most common subtypes, we consider doing chemotherapy using a combination that's based on something called CHOP. CHOP is a three-chemo medicine: cyclophosphamide (Cytoxan®)-doxorubicin (Adriamycin®)-vincristine (Oncovin®) with prednisone, the steroid. And there are variations on this theme, adding either another chemo[therapy] called etoposide (Etopophos®) (that is, CHOEP [cyclophosphamide-doxorubicin-etoposide-vincristine-prednisone]) or adding a medicine called brentuximab [vedotin] (Adcetris®) that we'll talk about a little bit as well.

I usually do four cycles of chemotherapy. We do a scan in between to see if patients are responding. And for patients who are achieving complete remission, there are data to support doing a stem cell transplant from your own cells or an autologous stem cell transplant to see if this could increase the chance that the lymphoma will stay away for a long time.

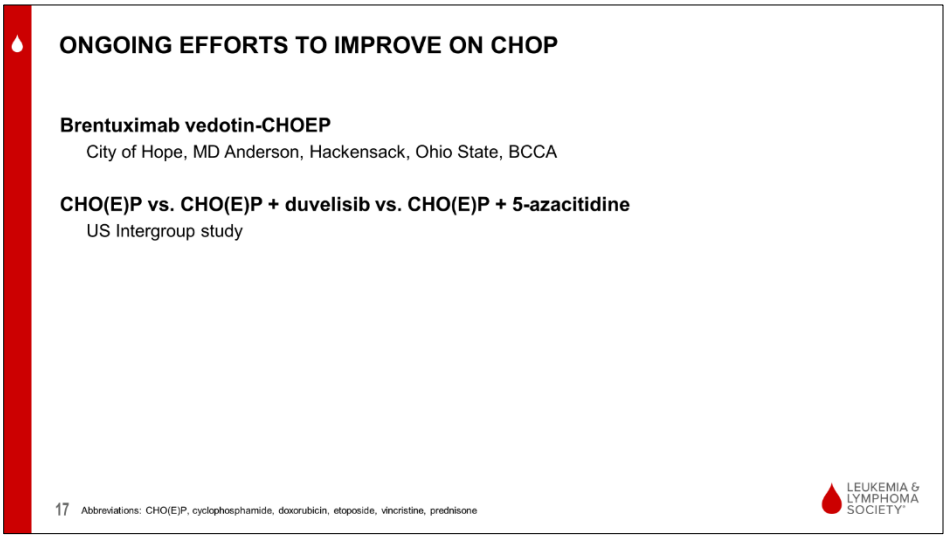


Brentuximab vedotin is an antibody tagged to chemotherapy. It's an antibody against a protein called CD30. The antibody finds the cancer cells and because it's tagged to chemotherapy [it] helps to

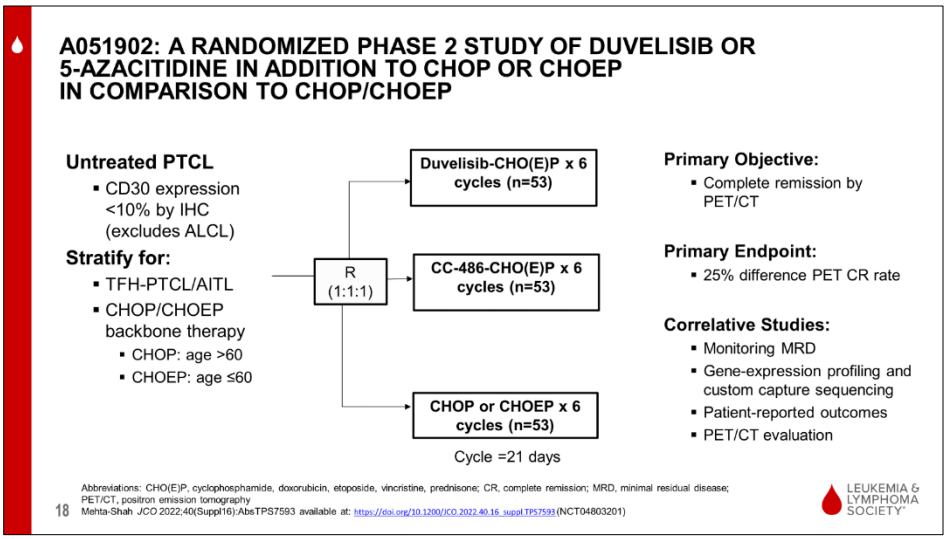
deliver chemotherapy to the cancer cells directly and tries to deliver chemotherapy to cancer cells ideally with less side effects.



So, brentuximab was approved for people whose lymphomas had come back and then was subsequently studied as part of people's initial treatment for T-cell lymphoma. So in this international study called ECHELON-2, half of the patients got CHOP chemotherapy and then half of the patients got brentuximab with a variant of CHOP called CHP, which was CHOP chemotherapy without the vincristine chemotherapy, so cyclophosphamide-doxorubicin-prednisone. And this was for patients who had CD30-expressing T-cell lymphomas. They required that more than 10% of the cells had CD30 expression, and most of the patients on this study had a disease called anaplastic large cell lymphoma which always expresses CD30. What was found was that giving brentuximab in combination with chemotherapy not only prolonged how long people remained disease-free but also improved overall survival, making this the standard for patients who have anaplastic large cell lymphoma (ALCL) and certainly an option for other patients who have CD30-expressing peripheral T-cell lymphomas.

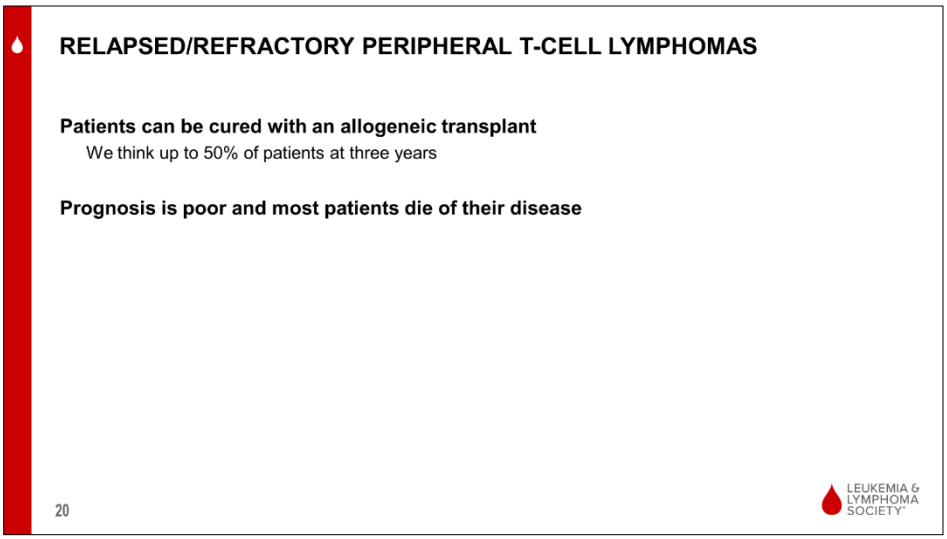


There are current efforts to improve on this further. There's a study that's run through City of Hope giving brentuximab vedotin with a regimen adding etoposide, so cyclophosphamide-doxorubicin not actually giving vincristine-etoposide-prednisone (CHEP-BV). And so that study the initial results have been presented and subsequent studies are likely going to be underway. And then there's a U.S. intergroup study that I'll highlight in just a second for patients who have T-cell lymphomas that have less than 10% CD30 expression.

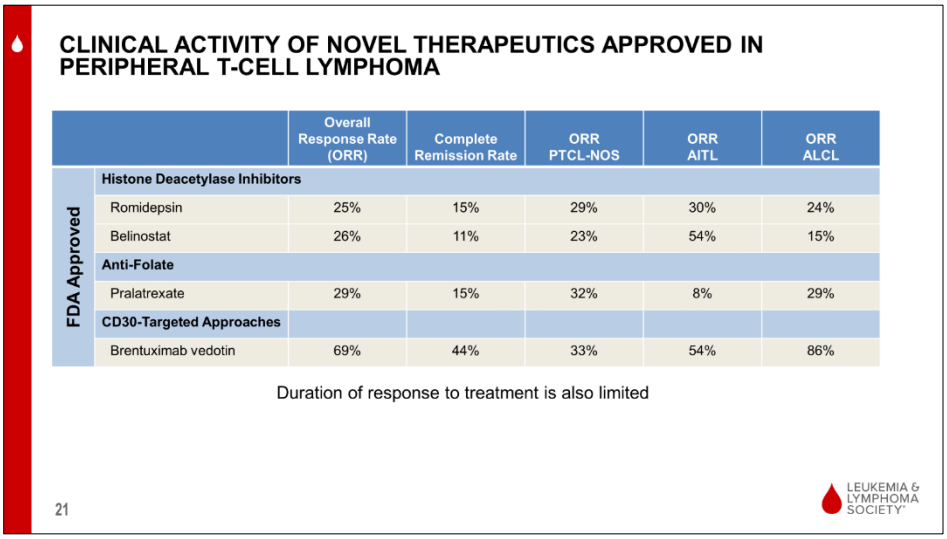


This study is called A051902. It's open nationally. It can be open at community centers as well as academic centers where patients are receiving either CHOP or CHOEP chemotherapy. Based on how old [they are], they receive either CHOP or CHOEP; and then one in three patients gets an additional pill medicine called oral azacitidine (Vidaza®) with the chemotherapy and another one-third gets a pill called duvelisib (Copiktra®), which we'll talk about later as well, in combination with the chemotherapy hoping to improve upon CHOP or CHOEP. So if you're newly diagnosed, be mindful that this study is out there and may be available in your neighborhood.

So what happens if my cancer comes back after CHOP chemotherapy?



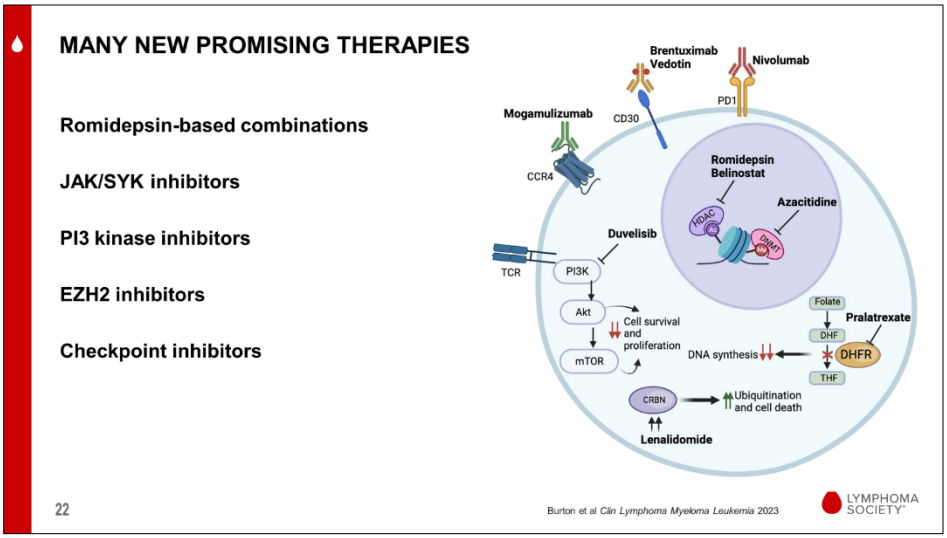
Unfortunately, we think that for many people who have peripheral T-cell lymphoma that does come back, many people do die of this disease leaving a lot of room for improvement, but there are more and more therapies out there and more and more in development. For those who can achieve a remission and are candidates for things like a donor stem cell transplant, a donor stem cell transplant can be curative in almost 50% of patients. And so, if you are eligible [and] if you're healthy otherwise, it's worth talking to your doctor about whether you're a candidate for a stem cell transplant from another person or an allogeneic transplant.



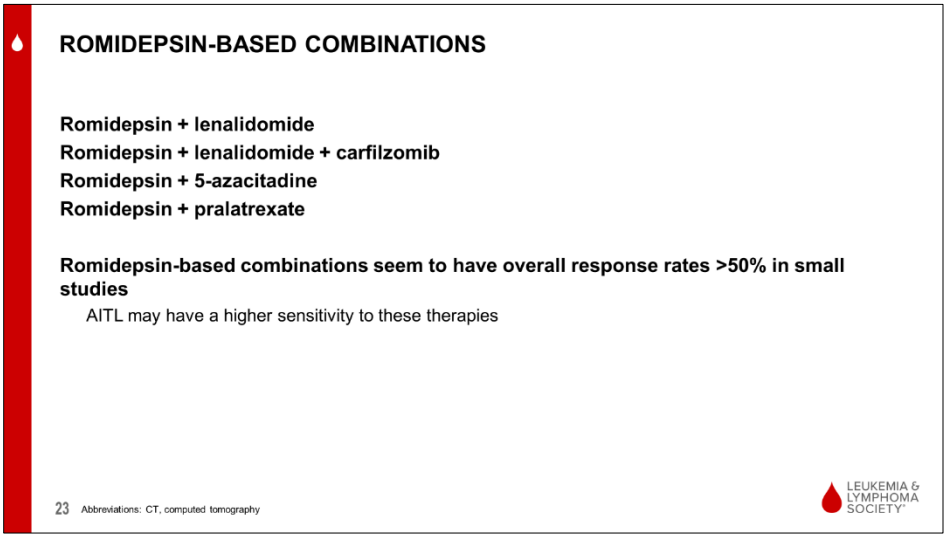
Because T-cell lymphomas are relatively rare, there's been until recently relatively limited research for drugs that are specifically for T-cell lymphomas. There were four drugs that were approved for T-cell lymphomas. These include a medicine called romidepsin (Istodax®) and belinostat (Beleodaq®). These are what we call histone deacetylase inhibitors – medicines that change the way the genes are expressed in the cancer cells. And these work for about one in four patients who have peripheral

TRANSCRIPT

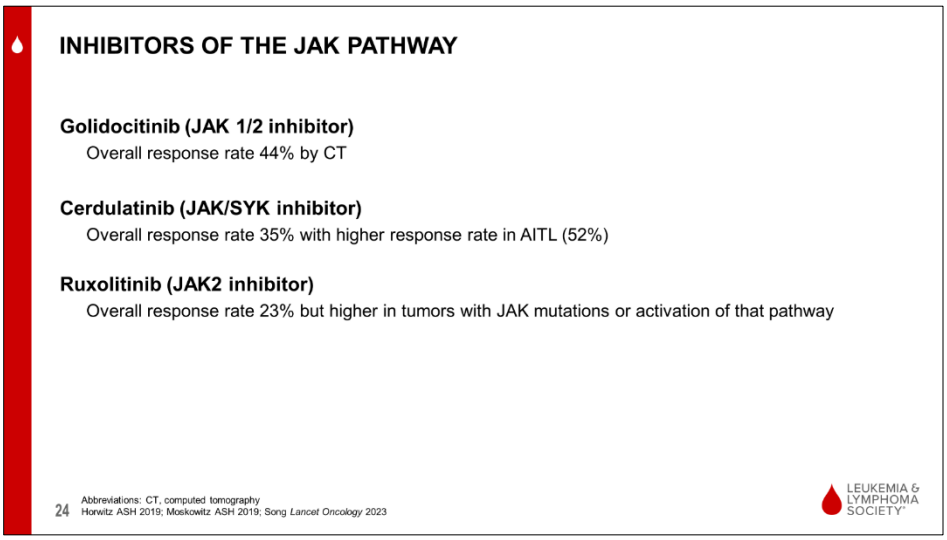
T-cell lymphoma, putting about 15% of patients in complete remission. Pralatrexate (Folotyn®) is an antifolate analog that's like a different type of chemotherapy family. Pralatrexate also works in about one in four, one in three people who have peripheral T-cell lymphomas. And then brentuximab is also used for patients whose lymphomas come back and in anaplastic large cell lymphoma where all the lymphoma cells express CD30. It works in the vast majority of people, and it can work but a little less reliably in other forms of T-cell lymphoma.



With that, I wanted to highlight that there's a lot of hope on the horizon for patients with peripheral T-cell lymphomas. There are many new combination strategies, new classes of therapy, and these include medicines that are combinations of histone deacetylase inhibitors like romidepsin, JAK (Janus tyrosine kinase) inhibitors, PI (phosphatidylinositol or phosphoinositide) 3 kinase inhibitors, EZH (enhancer of zeste homolog) 2 inhibitors, and we'll talk a little bit about medicines to boost the immune system to fight the cancer like checkpoint inhibitors.

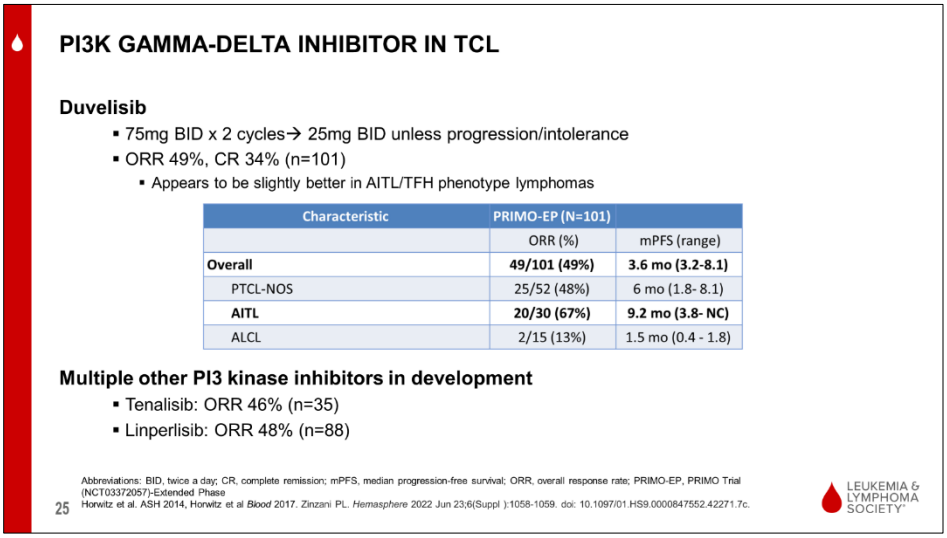


So with regards to romidepsin-based combinations – as I mentioned, romidepsin is a histone deacetylase inhibitor [that] changes the way the genes are expressed in cancer cells, has been approved for T-cell lymphomas for more than a decade, and has been studied now serially in combination with multiple other drugs. One oral drug called lenalidomide (Revlimid®), which is also an immunomodulatory drug approved for other lymphomas and multiple myeloma, studied with 5-azacitadine initially studied in the injection formulation of that drug and studied in combination with pralatrexate. And it looks like thematically that the patients who get romidepsin-based combinations do have a higher response rate than with romidepsin alone, but it seems like those patients who have T-follicular helper phenotype lymphomas are particularly more prone to respond to romidepsin and romidepsin-based combinations.



With regards to JAK inhibitors – JAK inhibitors are an important part of what we call the transductional pathway and there are multiple JAK inhibitors that have been studied in peripheral T-cell lymphomas. The newest one on the block is a drug called golidocitinib, which was recently presented at both the ASCO (American Society of Clinical Oncology) and the ASH (American Society of Hematology) [2023] annual meetings and recently published showing that it works in almost 44% of patients using CT scan parameters, probably slightly higher using PET scan parameters and seems to be a drug that people can tolerate for a long time. On the study for patients who were responding, they remained on the drug for almost 20 months. So that drug is not currently available, and my guess will be will likely go through additional studies before it gains [U.S.] FDA (Food and Drug Administration) approval but is something that's, hopefully, on the horizon.

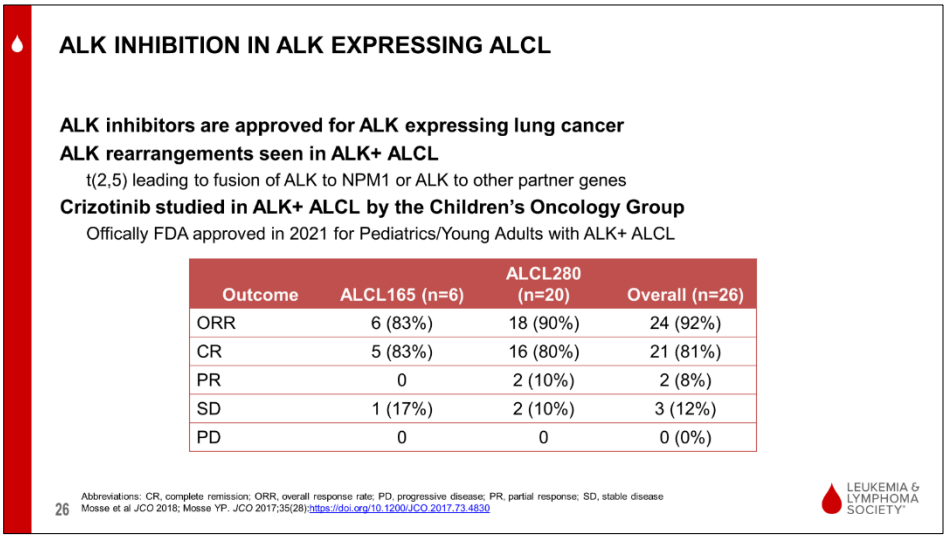
Other JAK inhibitors, like cerdulatinib, have been studied also showing activity in T-cell lymphomas with some higher response rate, again, in T-follicular helper phenotype lymphomas and ruxolitinib (Jakafi®), which is a drug that is approved for other diseases like myeloproliferative neoplasms, and looks like it works in about one in four patients who have peripheral T-cell lymphomas or T-cell lymphomas as well, leaving that as an option for some patients.



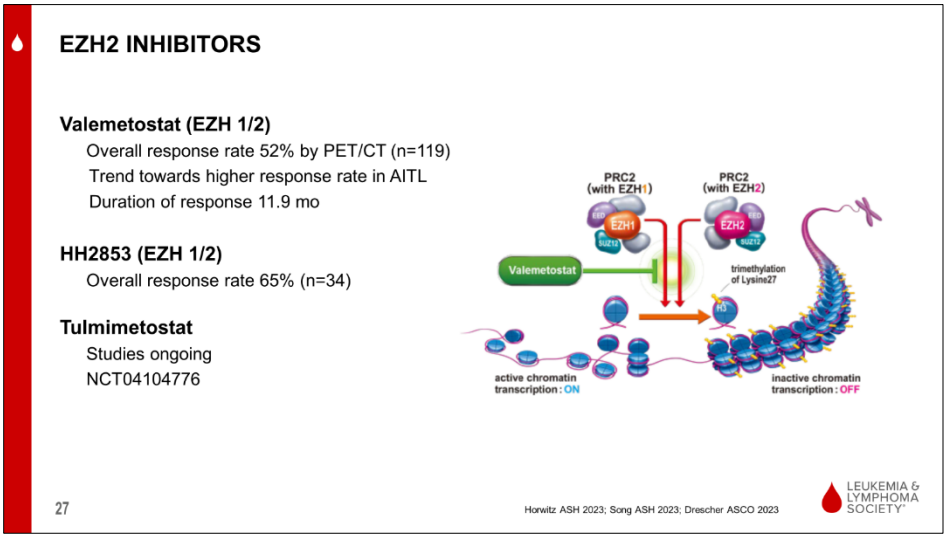
PI3 (phosphatidylinositol 3) kinase inhibitors are a group of oral treatments that inhibit a protein that is also involved in cell signaling. And there's been multiple PI3 kinase inhibitors that have been studied and these seem to work particularly well for T-cell lymphomas compared to other lymphomas. And in the T-cell lymphomas now routinely it looks like they work in about 50% of patients with about one-third of patients going into complete remission.

The drug that's been studied most extensively is a drug called duvelisib. It was studied in a study of 100 patients internationally called PRIMO where it looks like for all patients it works in almost 50% of patients but in angioimmunoblastic T-cell lymphoma it probably works a little bit better, although the studies weren't designed to look for differences based on what subtype of T-cell lymphoma you have but that seems to be a little bit of a trend.

Other PI3 kinase inhibitors are in development or in studies with combinations; these include tenalisib and linperlisib. And so be on the lookout for options for PI3 kinase inhibitors as part of your care as well.



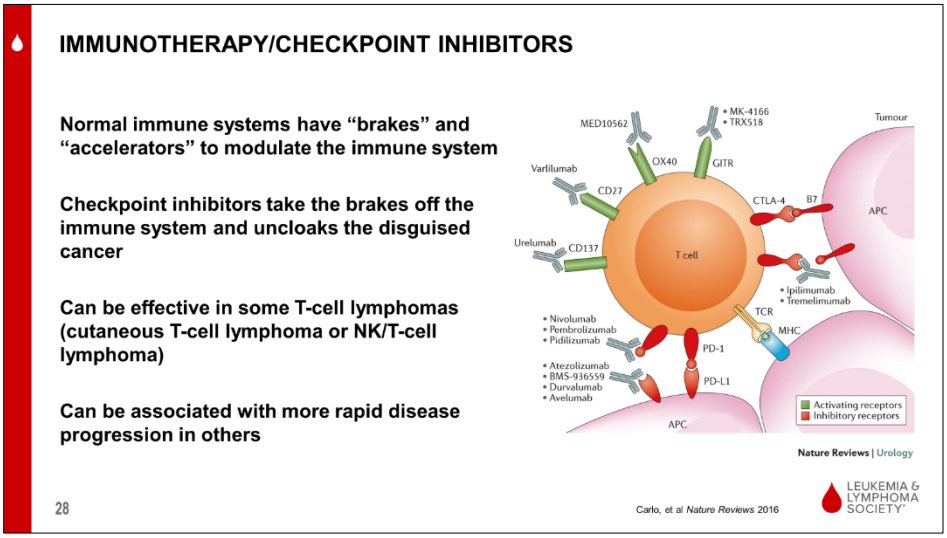
For those who have anaplastic large cell lymphoma that does express that ALK protein, ALK-expressing anaplastic large cell lymphoma tends to occur in younger people overall. There was a study done looking at using an ALK inhibitor in patients who had anaplastic large cell lymphoma expressing the ALK protein. Because ALK inhibitors have been developed for lung cancer extensively already, they were able to do a study in 26 children who had ALK-positive anaplastic large cell lymphoma and showed that it worked to reduce the lymphoma in 90% of patients. So, this is certainly an option if you have relapsed ALK-positive anaplastic large cell lymphoma as well and is currently approved.



Another class of medicines that we think is important and on the horizon for T-cell lymphomas is a class called EZH2 inhibitors. EZH2 inhibitors have already been developed and approved for diseases like follicular lymphoma and now are on the horizon for T-cell lymphomas. These are, again, medicines that change the way that the histone proteins bind to DNA (deoxyribonucleic acid). Also, we think [they] are changing the way that the genes are expressed by cancer cells, although we're figuring out exactly how they work in T-cell lymphomas. There have now been multiple EZH2 inhibitor studies in T-cell lymphoma, some of which were highlighted at our recent American Society for Hematology [annual] meeting in December [2023] showing that these work in probably 15 plus percent of patients as well.

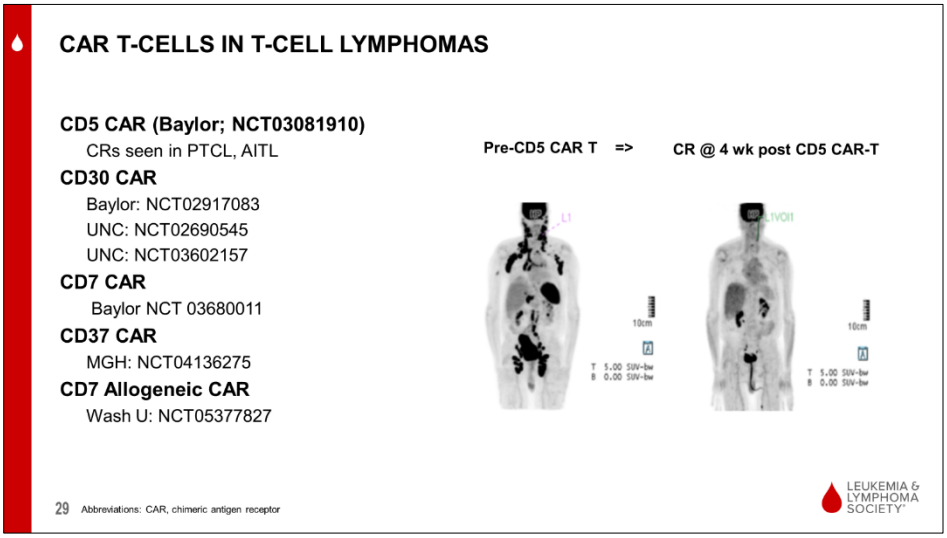
A study of valemetostat (Ezharmia®) called VALENTINE was an international study of almost 120 patients. It looks like by PET and CT (computed tomography) [scans], the drug works in about 52% of patients. And for those for whom it was working, it's continued to work for an average of about a year.

So at the same meeting, they highlighted that there were other EZH2 inhibitors. A drug called HH2853 (tazemetostat), in a smaller study of only 34 patients, looks like it's quite active in T-cell lymphomas as well, and studies of tulmimetostat are currently ongoing as well with also very, very small numbers but positive response rates. So, look out for these drugs in the list of clinical trial options that you might have. Again, those drugs are not currently available commercially.

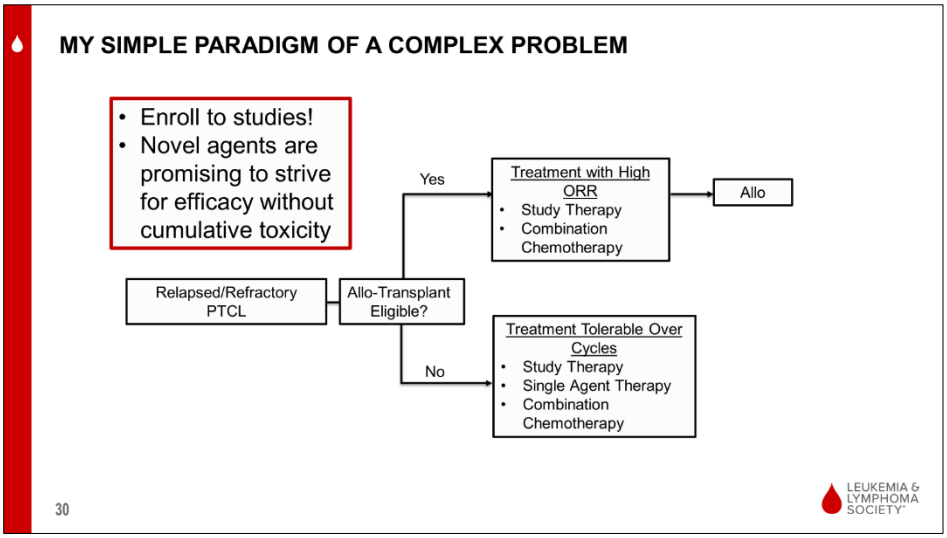


So no talk right now about cancer care can be complete without talking about checkpoint inhibitors or immunotherapy. As you may know or have heard, the normal immune system has accelerators and brakes to help detect foreign things as being foreign and help accelerate the immune system to help detect these foreign things and kill them off like bacteria, but also mechanisms to put on the brakes to prevent your own body from rejecting itself. And so these checkpoint inhibitors are molecules that get in the way of that mechanism. And what cancer cells are able to do is they're partly your own cells but they're partly foreign, but they've developed a mechanism from hiding from the immune system. And what the checkpoint inhibitors do is they uncloak the cancer cell from the normal immune system and help the normal immune system find the cancer cells.

And for certain types of T-cell lymphomas this can be quite effective. For example, for NK (natural killer) T-cell lymphomas, we think that this is a rare type of T-cell lymphoma driven by the mono virus or the EBV (Epstein-Barr) virus. And we think that they can be particularly active. And certainly checkpoint inhibitors have activity in skin lymphomas that we'll talk about a little bit later. But for other types of T-cell lymphomas, they've been associated with making the cancer actually grow faster because it activates not only the normal immune T cells but could activate the cancer T cells too. So there are certainly probably ways for us to learn how to better harness the checkpoint inhibitors in T-cell lymphomas and much of that work is currently ongoing.

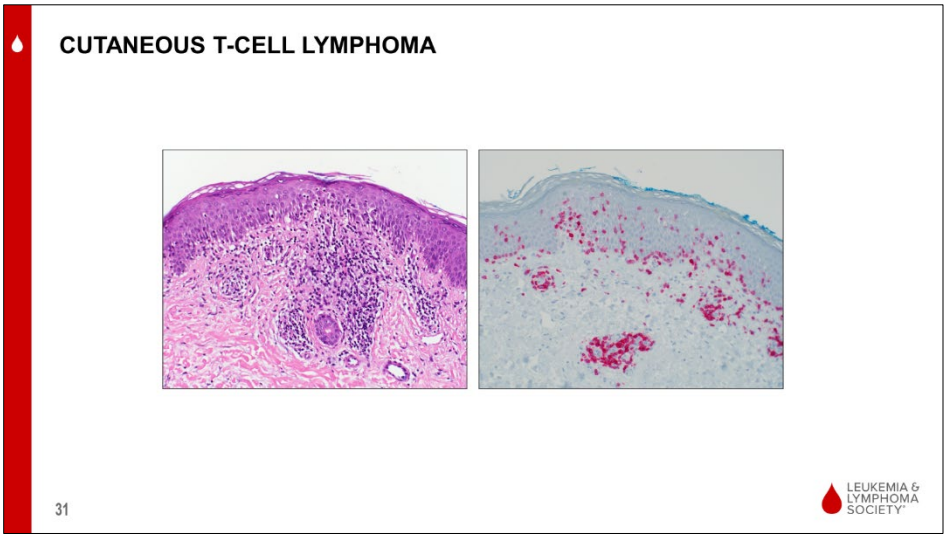


CAR (chimeric antigen receptor) T cells, which are genetically engineered immune cells that are programmed to fight the cancer, are approved for B-cell lymphomas. Their development in T-cell lymphomas has been a little bit farther behind because it's been more challenging to develop these in this arena. But there have been a number that are currently in clinical trials. These are against different targets against the T cells, including CD5, CD30, CD7, some using donor cells or allogeneic cells and some from your own cells. So more to come on these, I think, in the upcoming year or so.

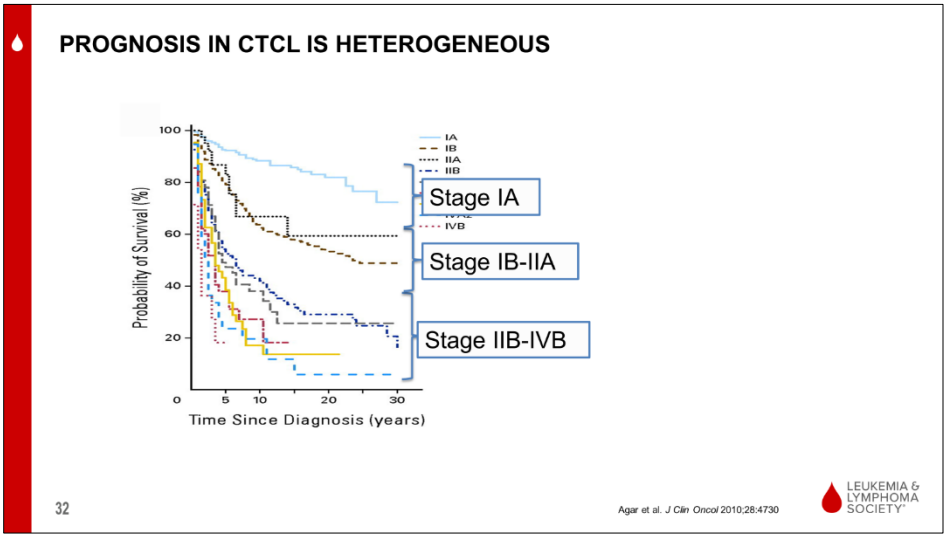


So for patients who have peripheral T-cell lymphoma whose lymphoma has, unfortunately, come back, we consider doing a stem cell transplant from donor stem cells if you're eligible for that, meaning you're in good health, you're of an age where we think that could be a safe thing to do, and you have a donor. And if you're not, we consider combination or single-agent therapy using either chemotherapy or some of these more novel therapies to keep you well and keep the lymphoma at bay. And if you're eligible for a transplant, the goal is to get you into remission as soon as possible to get you there. But as you can see, the response rate to some of these novel therapies in clinical trials is very, very promising relative to some of the other options that patients have. And so, to really

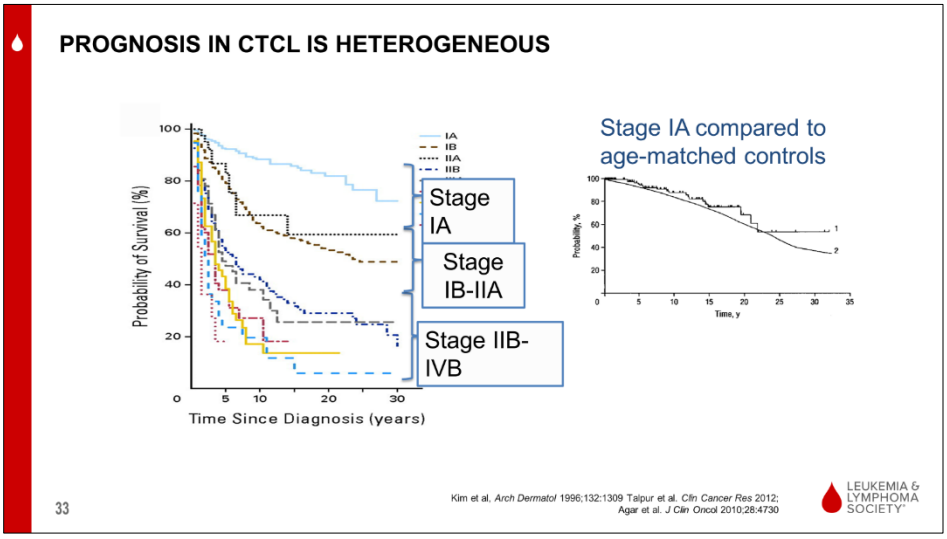
consider clinical trials very carefully in your portfolio for future options when you have T-cell lymphoma I think is particularly important.



So now we're going to switch gears to talk about cutaneous or in the skin lymphomas. These are fundamentally treated with a different paradigm, so we'll talk about that. These are lymphomas that start off in the skin and may always stay in the skin. And they have these abnormal cells that infiltrate the top layer of your skin called the epidermis between the lower layer of your skin called the dermis. And you can see those cells, I kind of highlighted it in pink, tagging that border in this picture.

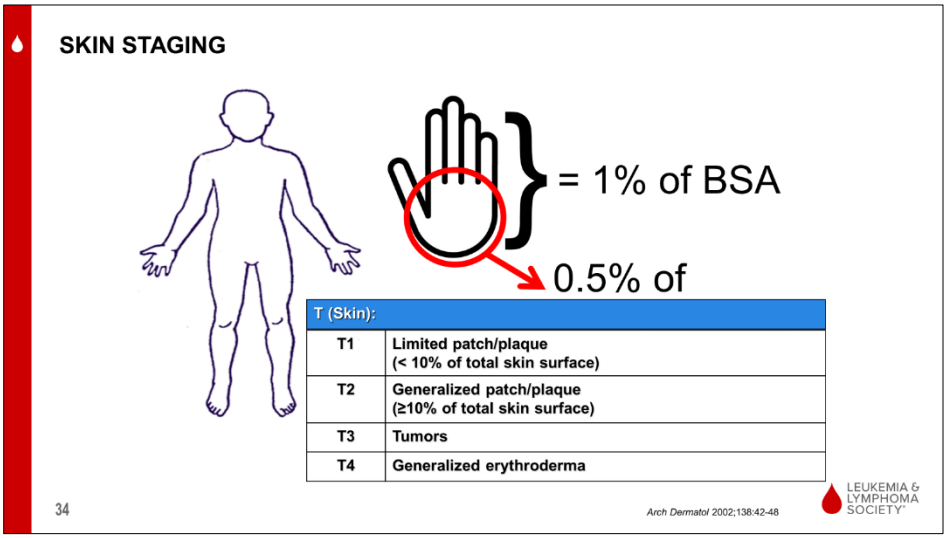


The prognosis for patients who have cutaneous T-cell lymphomas is very variable. There are some patients who have early-stage disease which looks like just a patch of eczema or psoriasis on their skin that they treat with topical steroids that live a totally normal life expectancy and have less burden from their disease or their skin and it doesn't affect their quality or quantity of life tremendously. Whereas patients who have this disease in the form of more extensive disease throughout the body or tumors or lymph nodes that are involved can certainly have a worse prognosis.

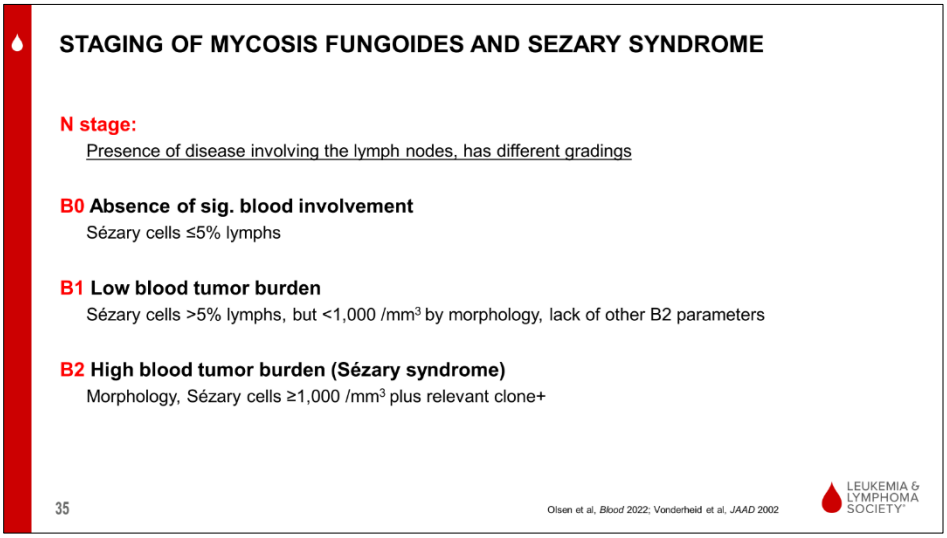


Those who have early-stage disease who predominantly see dermatologists have similar life expectancy to anybody they went to high school with. So, if you are carrying early-stage mycosis fungoides or cutaneous T-cell lymphoma just to know that out of reassurance.

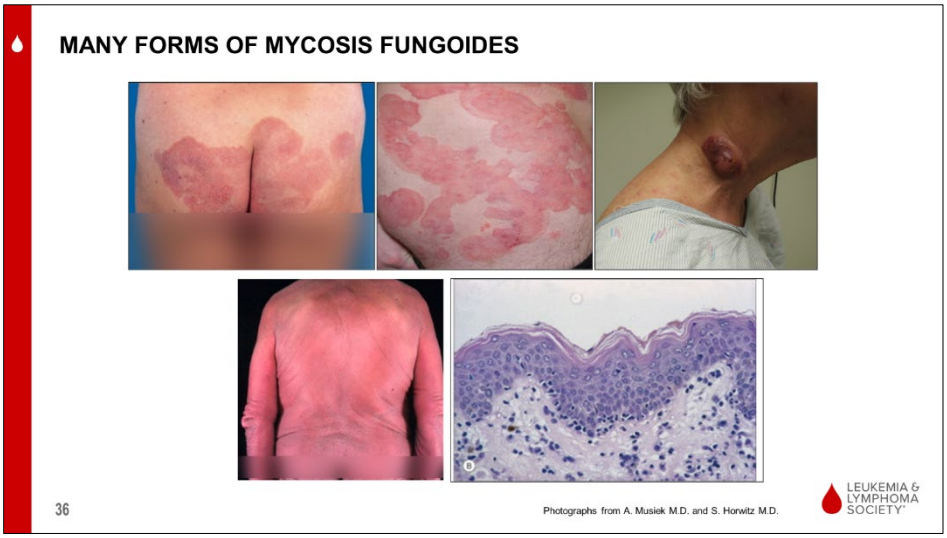
The term cutaneous T-cell lymphoma, I should mention, refers to many different types of lymphomas that occur in the skin. But the most common are mycosis fungoides or Sézary syndrome which is a variant of that disease when it occurs in the bloodstream. And we'll get to that in a second of how do we figure that out. When patients are diagnosed with cutaneous T-cell lymphomas, we also stage them. And to do their staging, we look at their skin exam, we look at their blood, and then we often will do an evaluation to see if they have any lymph nodes or any more in the body involved.



To evaluate the skin, we really do a very careful skin exam measuring how much lymphoma, how much of the skin, total body surface area of the skin is involved with lymphoma and how much of that is in flat patches, thicker areas called plaques, or areas that are raised like tumors, or are they kind of red all over and we call that erythroderma.

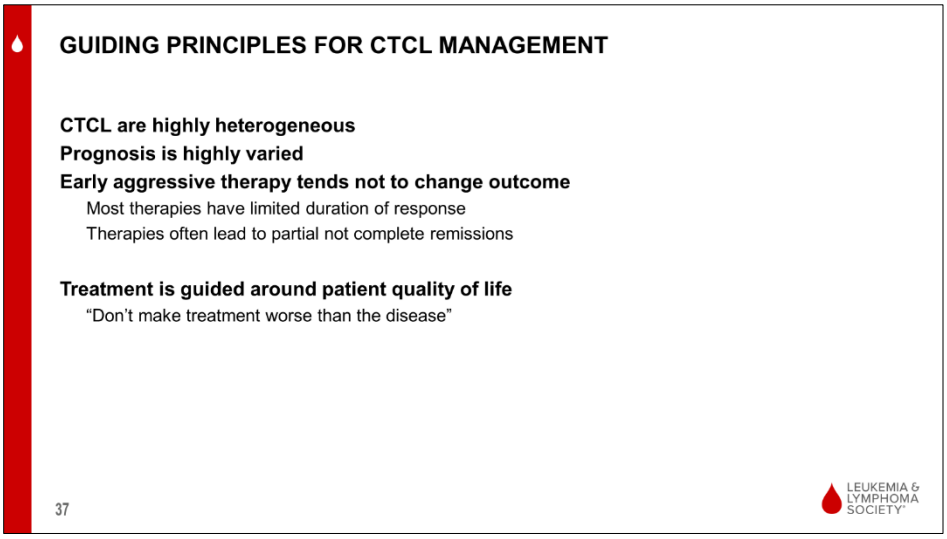


To determine whether patients have blood disease, we do tests of the blood, often flow cytometry, to look for the number of cancer cells relative to normal immune cells. And when patients have a higher degree of burden of lymphoma in the bloodstream, we call that Sézary syndrome. So that's essentially just a variant of cutaneous T-cell lymphoma but closely related to mycosis fungoides or part of the continuum of the same disease. We also look at the lymph nodes. We call that the end staging and that's based on the presence, or the absence of lymph nodes involved with the cancer.

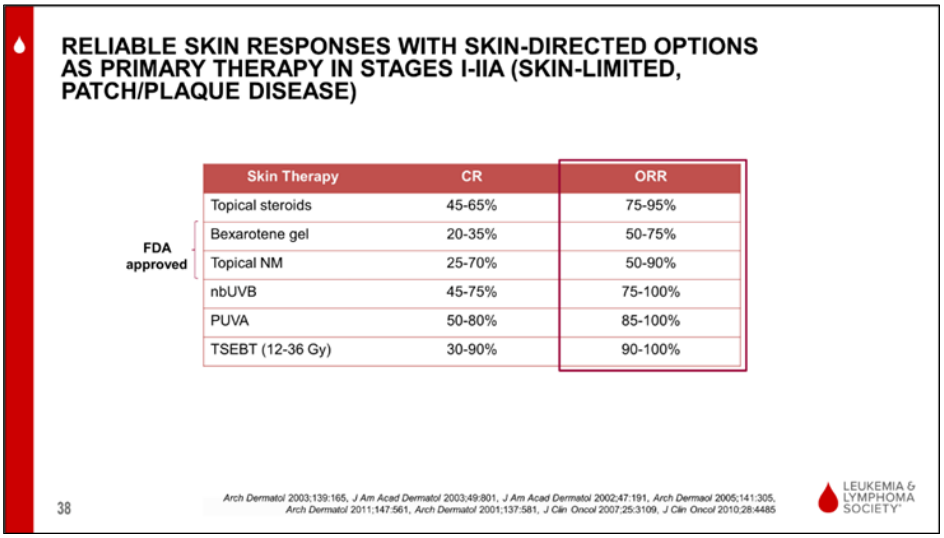


So as you can see, there are many forms of mycosis fungoides. Patients can have patches. This disease tends to live in areas where the sun doesn't see and so oftentimes the areas that we see patients have the disease is on their buttocks or upper thighs or under their arms. So it's important if you have spots there to feel comfortable showing your doctor those areas as well. If you have thicker spots of disease that you can kind of feel as raised, we call those plaques. You can see that in the second picture. The third picture reflects someone who might have a tumor of mycosis fungoides. And then the fourth picture shows erythroderma or someone who's red all over. And what's common

amongst these is that they have that typical abnormal cell lining, that border between the dermis and the epidermis, that defines this disease.

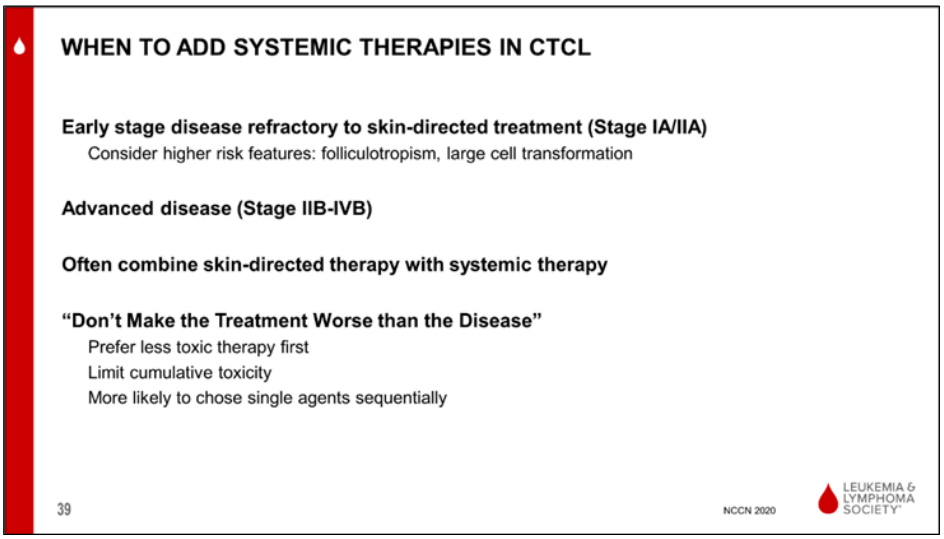


As I mentioned, how people look and feel with this disease can be highly variable. The prognosis can be highly variable. And we know that unlike in the systemic T-cell lymphoma, the early aggressive treatment doesn't necessarily change the outcome. And so we tend to give tolerable single-agent treatments or things that people can continue on for a long time with the goal of improving their quality of life. And so we always tell our patients in our clinic that the goal is to make life on treatment better than life with the disease. So we don't want the treatment to be so burdensome that it affects their quality of life more than the disease ever would have.

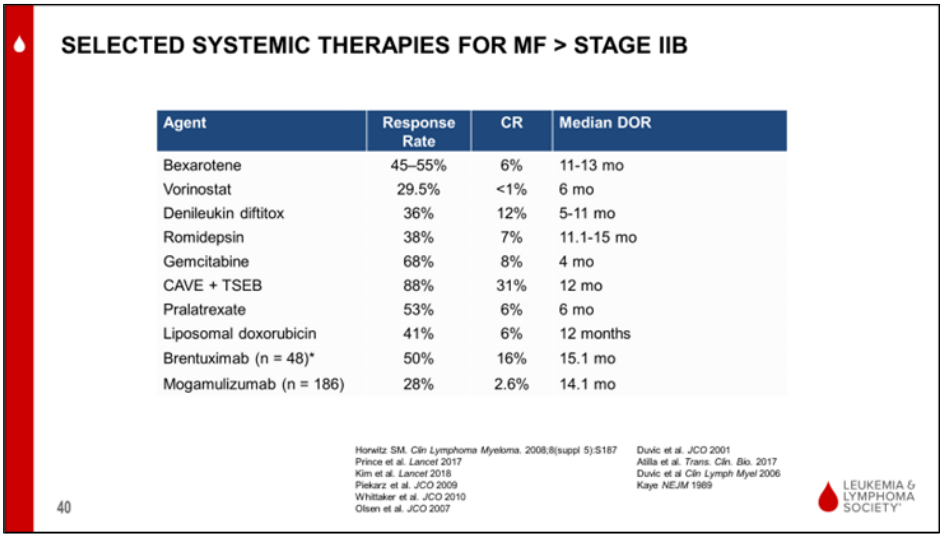


So for patients who have only disease in the skin, we often consider giving treatment just to the skin that doesn't have other side effects throughout the body. This could be with things as simple as giving topical steroid creams or could involve other medications like topical chemotherapy like nitrogen mustard or topical retinoids like bexarotene.

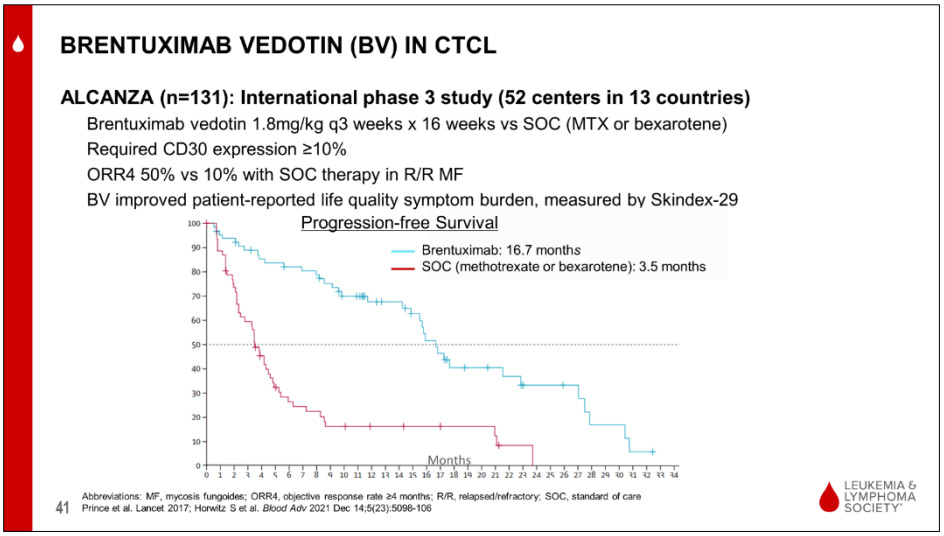
Other options for treatment include giving light therapy. UV (ultraviolet) light can actually kill the cancer cells and UV light penetrates deep enough to get the cancer cells but not necessarily to injure other parts of the body. And so we often use medicated UV light therapy to reduce the likelihood of developing skin cancers from the light therapy as well. But that can be very effective and in some patients we do low-dose radiation to treat the areas and sometimes low-dose radiation throughout the body.



So when do we consider moving from skin-directed therapy to other therapy for this disease? Well certainly if you're on skin-directed therapy and it's not working for you, then we have to consider something else. Certainly patients who have disease in lymph nodes or other part of the body or the bloodstream we may have to consider other treatments. For some patients who have higher risk features, we may consider other sorts of treatment. These include people who have something called large cell transformation or follicular tropism. But the principle is still the same, you don't want to make life on treatment worse than life with the disease. So choose single agents sequentially and limit the cumulative toxicity. Pick the things that are easiest for patients first; and if those work, that's terrific. Then you found something that works for patients but also doesn't lead to long-term quality-of-life issues.

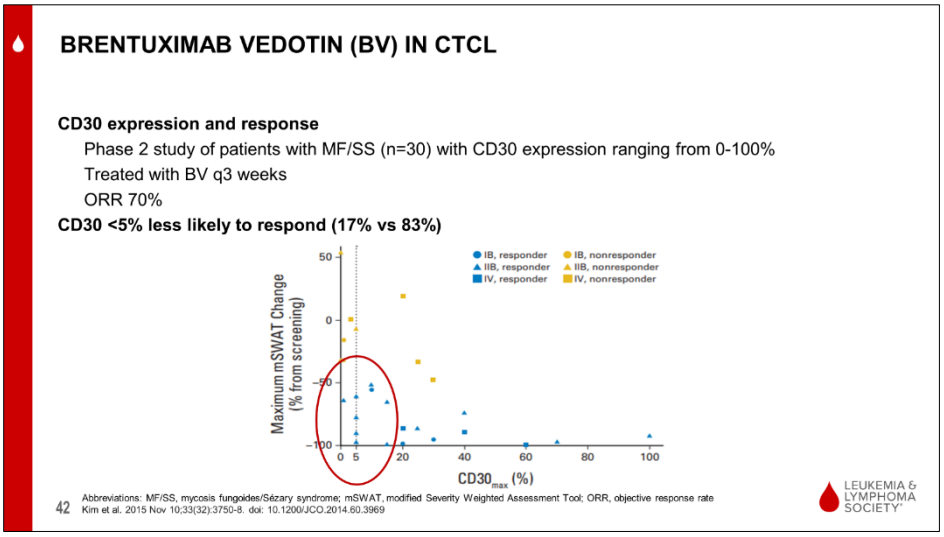


This is just a sampling of medicines that we sometimes use for patients who have cutaneous T-cell lymphomas systemically. We're going to highlight a couple of the ones that were recently approved based on large international studies, but these include oral pills like a retinoid called bexarotene (Targretin®); histone deacetylase inhibitors like romidepsin or vorinostat (Zolinza®); chemotherapy options as single agents and then we'll talk a bit more about the use of brentuximab and mogamulizumab (Poteligeo®) in just the next slides.

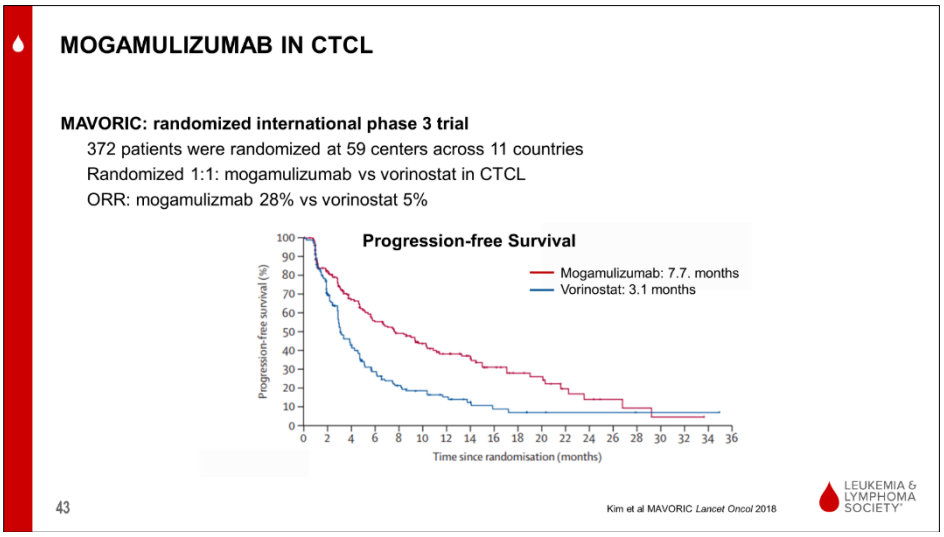


Brentuximab is that same antibody against CD30 tagged to chemotherapy. This was studied in cutaneous T-cell lymphomas (CTCL) as well for patients who did have over 10% of the cancer cells express that CD30 protein, and patients received this as an infusion every three weeks on the study. And the other patients on the study by a flip of a coin got standard-of-care medicine which could have been pill chemotherapy like methotrexate or bexarotene which is an oral retinoid. And what they found was that in patients who got the brentuximab about half the patients responded versus about 10% for patients who got their standard-of-care therapy but also giving brentuximab improved quality

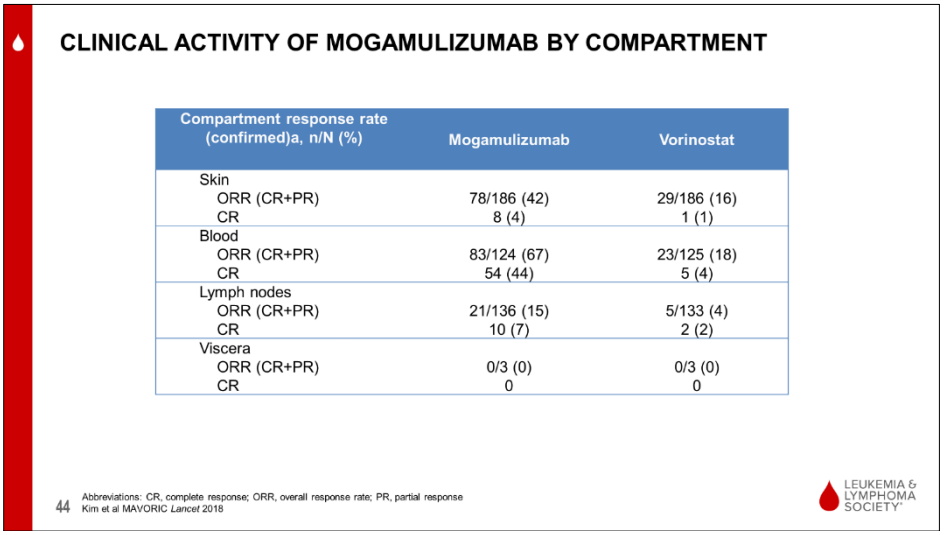
of life as well as progression-free survival. And this led to the approval of brentuximab in cutaneous T-cell lymphomas.



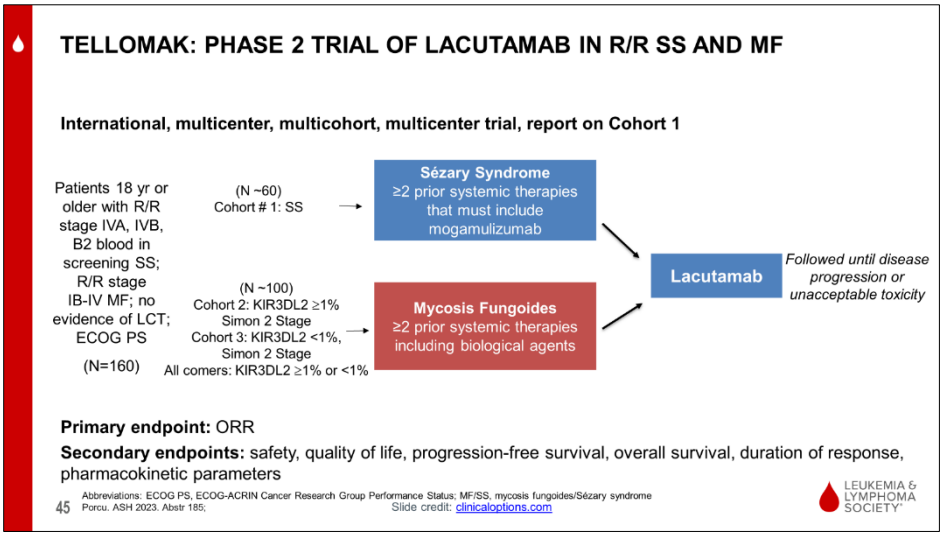
To be honest, many patients with cutaneous T-cell lymphomas don't have a high expression of that CD30 protein, but we've learned that it can work even when the expression of CD30 is very low, although when patients have much lower expression of CD30, the likelihood of responding is also lower. It's not zero so it's on the list of things that we consider for our patients.



Mogamulizumab is an antibody against CCR (CC chemokine receptor) 4. It's not tagged to chemotherapy. It essentially flags the cancer cells and then allows your immune system to gobble them up. This was studied in an international randomized study against vorinostat, which is an oral histone deacetylase inhibitor. It was found in this international study that patients who got mogamulizumab not only had a higher response rate but also had a longer time to their next treatment, and a longer what we call progression-free survival, meaning they remained well without progressing for longer when they got mogamulizumab.

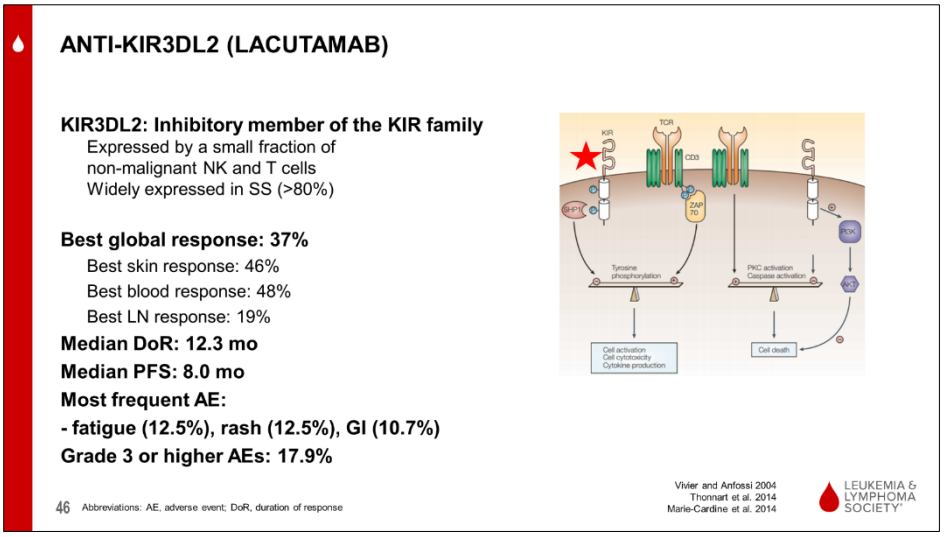


The other thing that we noticed when patients got mogamulizumab is that it was particularly good at treating the lymphoma burden in the bloodstream. So, for those who had a high bloodstream amount of lymphoma like people with Sézary syndrome, for example, mogamulizumab worked to reduce the lymphoma in the bloodstream in two-thirds of patients. So, this is very commonly used for Sézary syndrome now because it seems to have a proportionately higher activity in the bloodstream and in the skin.

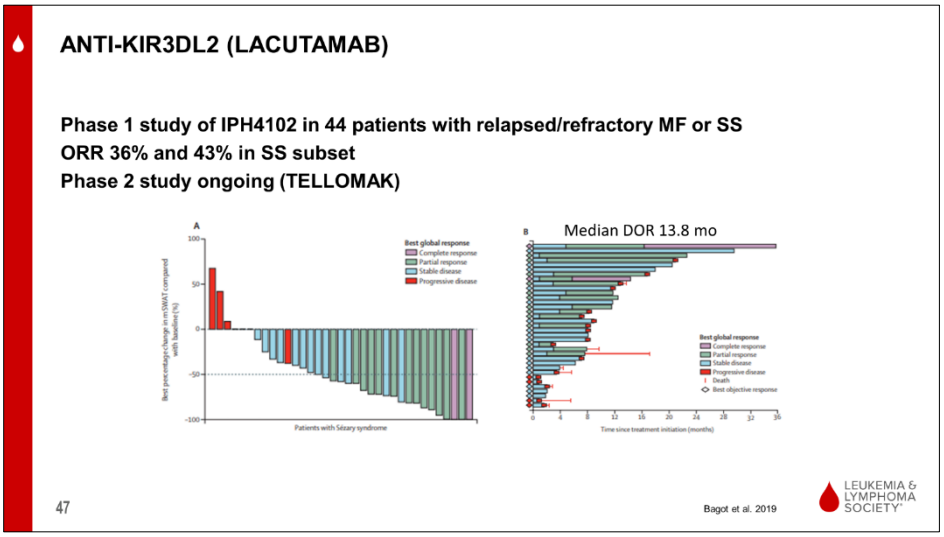


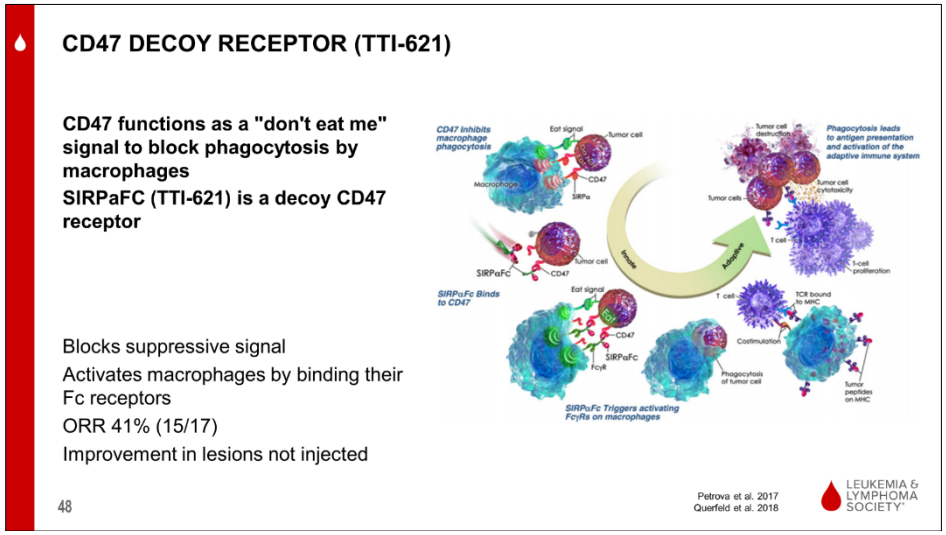
Building on this was the TELLOMAK (T-cell Lymphoma Anti-KIR3DL2 Therapy) study. So lacutamab is another type of antibody, again, a blind antibody, no chemotherapy, against a protein called KIR (killer cell immunoglobulin-like receptor) DL (three Ig domains and long cytoplasmic tail) 2. And most patients, almost all patients with Sézary syndrome cells will express that KIR3DL2, making it an attractive target for Sézary syndrome. And then patients with mycosis fungoides could also have expression of KIR3DL2. So this international study of lacutamab included patients with Sézary syndrome; they all had to have mogamulizumab in the past to go on this study. This was only patients who progressed after they received mogamulizumab and they went on to get this drug lacutamab.

And thus far, only the Sézary syndrome results have been publicly presented, and we expect the mycosis fungoides results to be presented sometime this year as well.

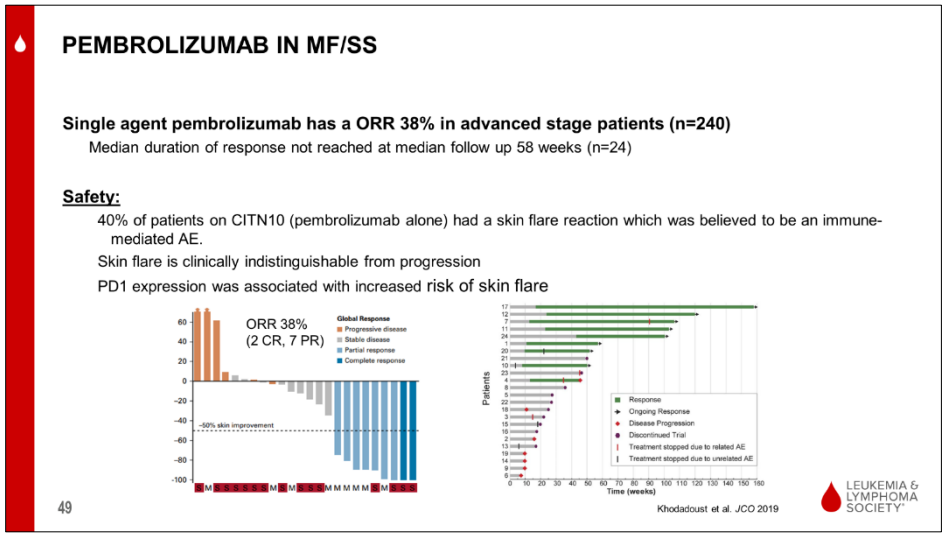


But what we found so far was that in the blood, it looks like for people who have Sézary syndrome, it works for almost 40% of people and almost half of those patients had improvement in their blood with the lacutamab drug. And for patients for whom it was working, the average person could be on for about a year or so. And it was very well tolerated with minimal side effects. So this was a phase 2 study with the hope for allowing for registration or FDA approval based on this study and I think more to come about whether we'll achieve that approval in the upcoming months.



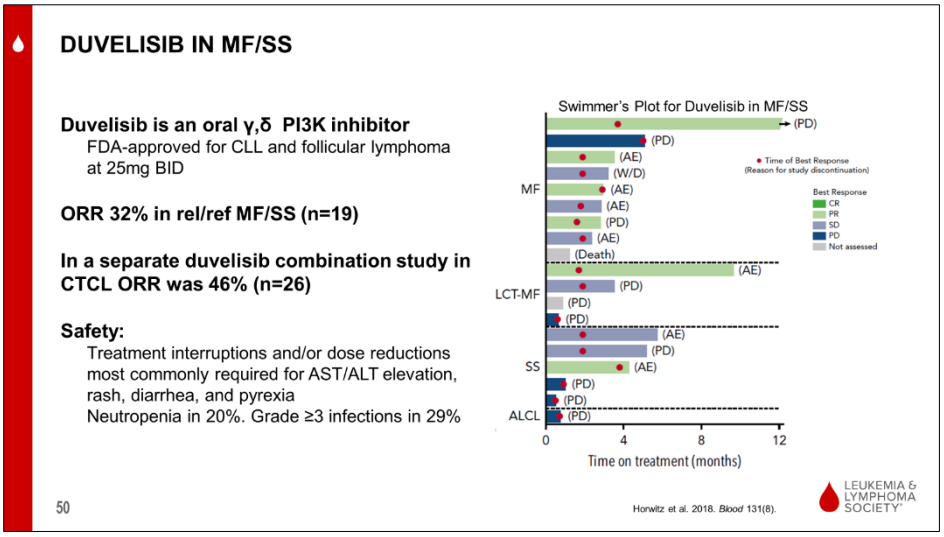


The next group of drugs I just wanted to point out as on the horizon for cutaneous T-cell lymphomas are in this family called CD47 receptor. So CD47 is on the cancer cells and tells these other cells, called macrophages who are like the garbage-eating cells, to say, “Do not eat me.” So it prevents the macrophages from coming and gobbling up the cancer cells. And what the CD47 antibodies or decoys do is they block that CD47 receptor allowing for the macrophage cells to come and eat up and gobble up the cancer cells. And in some of the studies using CD47 antibodies or CD47-related drugs, it looks like they work in almost 40% of patients, although these studies have all been less than 20 patients. There are currently further national studies using drugs for CD47 in combination with drugs like mogamulizumab that you consider looking out for as well.

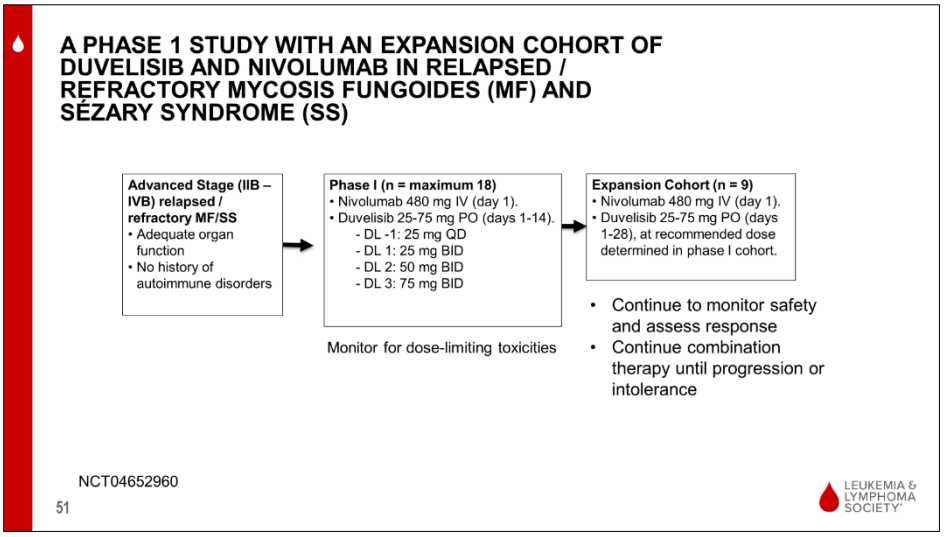


Additionally, as I mentioned, checkpoint inhibitors, or medicines to boost the immune system to fight the cancer, have been studied in cutaneous T-cell lymphomas. A study of pembrolizumab (Keytruda®) shows that it works in almost 40% of patients. And for patients who it does work for, it can work for a long time. One of the notable things that we have noticed is that patients who get checkpoint inhibitors for cutaneous T-cell lymphomas can develop a skin flare or rash that improves

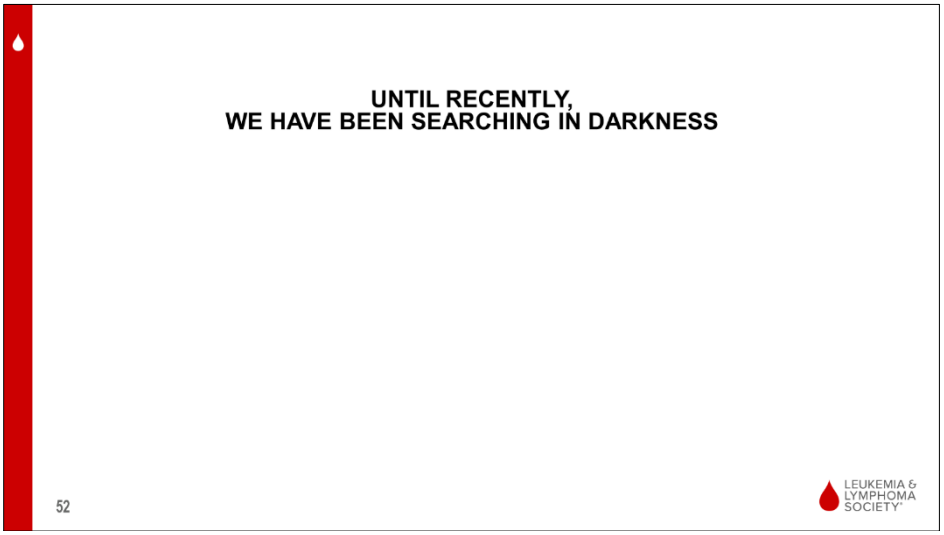
with management like topical steroids or holding the medicine, and that's pretty typical for patients but may be just a sign that the immune system is working to kill the cancer cells.



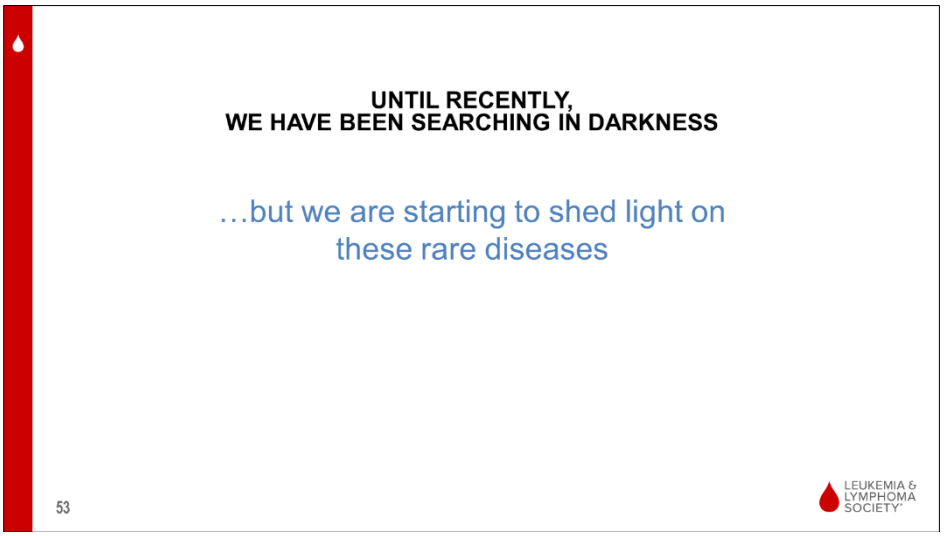
Drugs like duvelisib, the PI3 kinase inhibitor, have also been studied a bit in TCL (T-cell lymphomas) much less in CTCL (cutaneous T-cell lymphomas) than in peripheral T-cell lymphomas and it looks like in CTCL it probably works for 30 to 40% of patients.



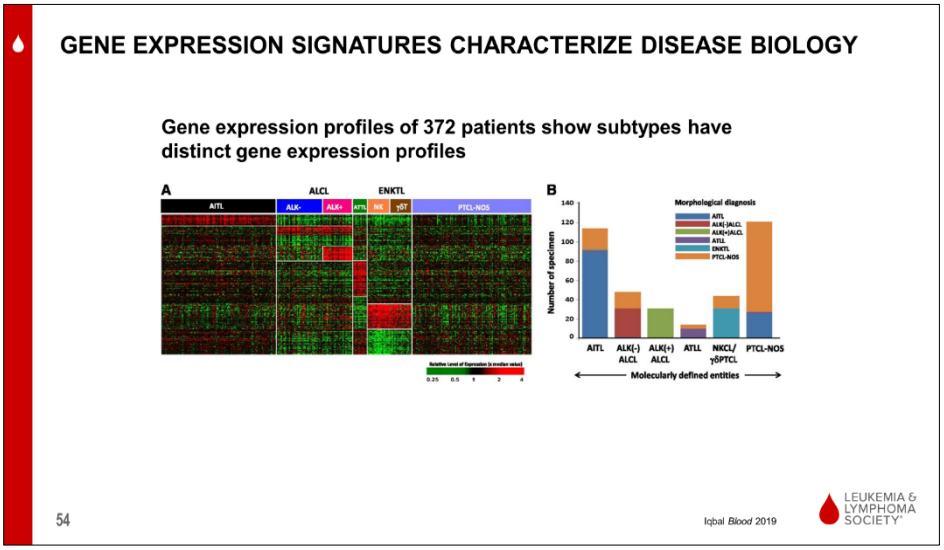
And there are currently studies ongoing to combine drugs to boost the immune system to fight the cancer with drugs like duvelisib that are also currently ongoing throughout the country. So to look out for trials in cutaneous T-cell lymphoma when you're considering what options you have pending you have access to some of those studies.



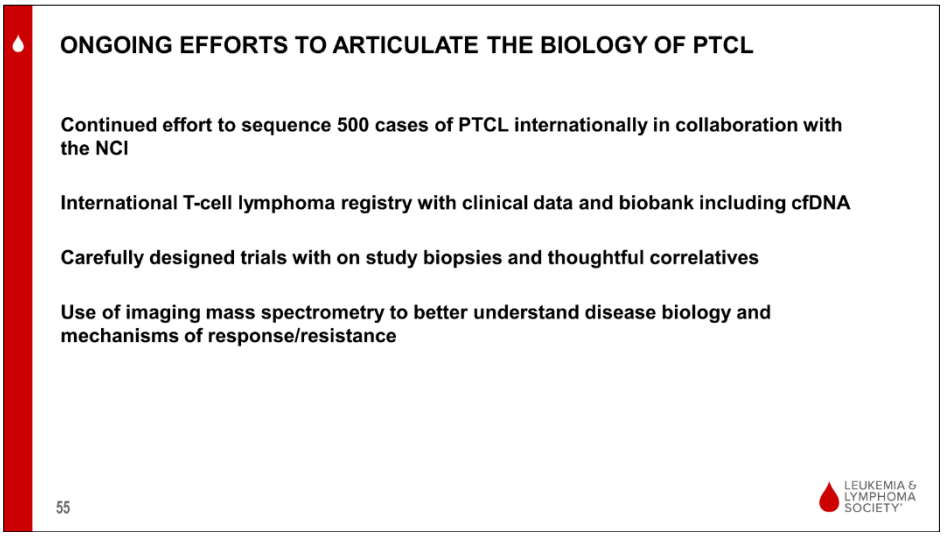
So with the next few slides I'd just like to share, until very recently in T-cell lymphomas, we have been kind of searching in the dark just borrowing what we knew about B-cell lymphomas and then transcribing that information to T-cell lymphomas without really making therapy specific for T-cell lymphomas or understanding even how these T-cell lymphomas functioned on a biologic basis. We were grouping all the T-cell lymphomas together instead of starting to think about which subtype did better or worse with certain therapies and how these subtypes were different from each other, which they clearly are different.



But we're starting to shed light on these rare diseases and a lot of that work has been through participation in clinical research, some of which has been supported by the LLS.

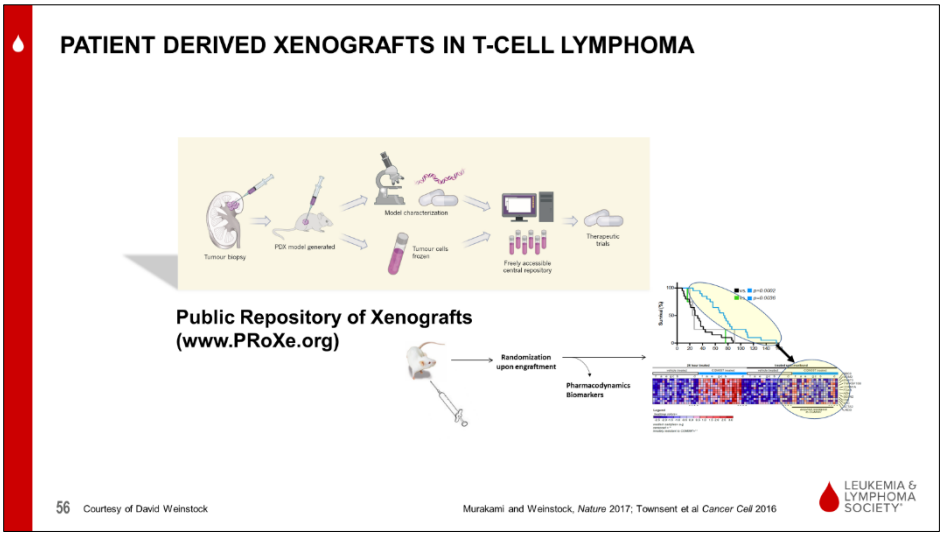


There have been attempts to look at what genes are expressed by the cancer cells and which mutations are in the cancer cells. Some of this has been done by Javeed Iqbal, PhD, at University of Nebraska to show that when you look at the genes expressed in the cancer cells, you can probably also use that information to better understand the biology of the cells.

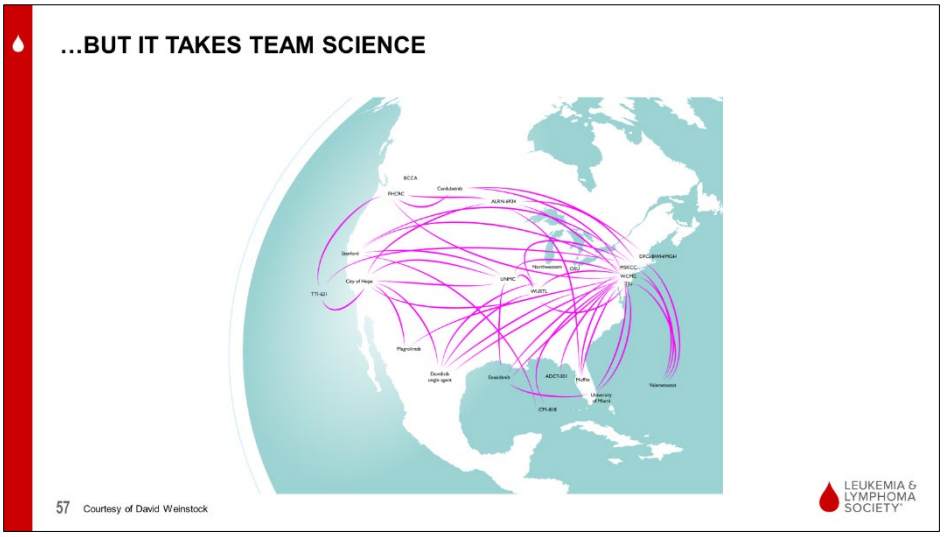


And there are ongoing efforts through the National Cancer Institute (NCI) to do genetic sequencing on a large battery of T-cell lymphoma cases internationally to better understand the genetics of the subtypes of peripheral T-cell lymphoma to develop better targeted therapies. Much of what we've learned about T-cell lymphoma so far has been done through clinical trials and careful analysis of the biopsies on the clinical trials to better understand which patients respond the best to a specific therapy and then going back to figure out why does that happen. And that's led to considerable achievements in the field. And with newer and newer technology, we're better able to do this both based on looking at RNA (ribonucleic acid) sequencing, DNA sequencing, how these cancer cells relate to each other under the microscope using things like imaging mass spectrometry. And I'm very

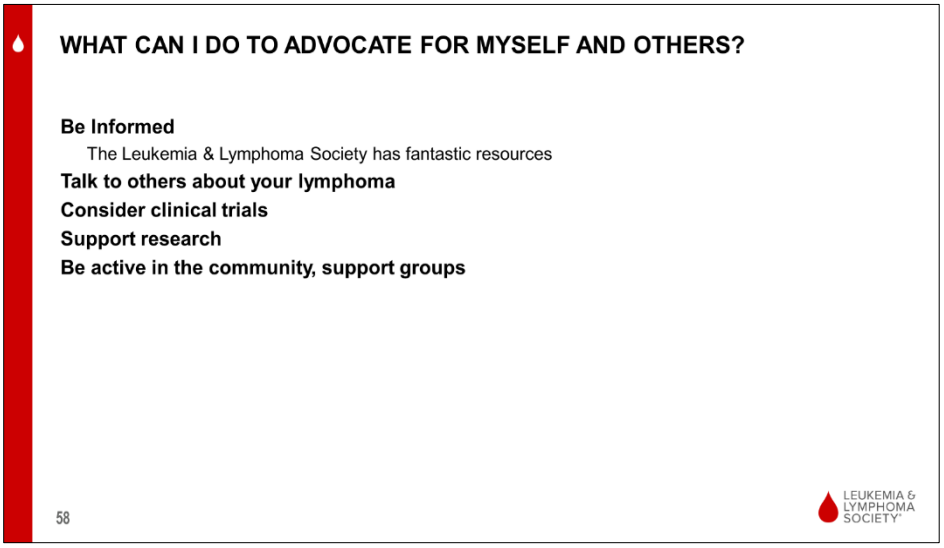
hopeful that the field is only going to continue to grow and, hopefully, result in improvement for care for our patients.



One of the ways that we have been doing this is by developing mouse models of T-cell lymphoma. Specifically, some of this work has been pioneered by David Weinstock to develop a public repository of mouse models for T-cell lymphoma to be used for early drug development.



But in rare diseases, it certainly takes what we call team science. One center or one place in the country really cannot do this work alone. Because these diseases are uncommon, we know that it takes a whole team of us to work together to figure out how to make the future for patients better. And we're really lucky to be working in a community of very invested, engaged, passionate T-cell lymphoma researchers who are really willing to work together, to answer questions and to develop better treatments for patients.



So what can you do if you or a loved one is suffering from lymphoma, specifically T-cell lymphomas? I think being informed is critical. I think by listening to a podcast like this, you're already doing some of your due diligence to understand what might be available. The Leukemia & Lymphoma Society has fantastic resources and ways of helping you navigate how to find clinical trials or clinical trial opportunities in your area.

Be comfortable. When you have a rare disease, it can be very isolating and if you feel comfortable talking to other people about your lymphoma and your lymphoma journey, you may realize that other people may have gone through something similar and may have some pearls to share with you about their experiences.

For certain, consider clinical trials as part of your armamentarium of options. Certainly, they're not the only option, but I think as you've seen today, some of the clinical trial options are really directed towards your specific type of lymphoma and might be a particularly attractive option to consider as part of your treatment.

Supporting research and advocating for research in whatever manner that you choose to is also incredibly important and become active in your community and your support groups specifically around blood cancer research.

And with that, I wanted to thank you and leave you some time for questions.

QUESTION-AND-ANSWER SESSION

Lizette Figueroa-Rivera, MA
Thank you so much, Dr. Mehta-Shah, for volunteering your time with us today to discuss T-cell lymphomas and current and emerging therapies. As you mentioned, it is now time for our question-and-answer portion of our program. For everyone's benefit, please keep your questions general without many personal details so Dr. Mehta-Shah can provide answers general in nature.

Doctor, the first question comes from Michael and Aaron. They're asking about the status and likelihood of CAR T-cell therapy in T-cell lymphomas.

Neha Mehta-Shah, MD, MSCI
I think it seems like there are a number of questions about CAR T-cell therapy in T-cell lymphomas. The CAR T cells are genetically engineered T immune cells, T lymph cells that are either added or

subtracted or modified in a way to identify the cancer cells. And what they do is they add a specific protein or subtract other proteins off of those other T cells to help them find the cancer cell. And so, as you can imagine, in B-cell lymphomas, using this completely different group of cells has led to huge improvement in the care for patients with B-cell lymphomas.

In T-cell lymphomas it was a little harder because figuring out how to develop CAR T cells that killed the lymphoma cells but didn't kill the other immune T cells or the CAR T cell construct itself, like causing them to kill each other – we call that fratricide – was more difficult. So, there have been a number that have been in development. All of these studies have been relatively small but some of these, including a CAR T-cell against CD70, a CAR T-cell against CD5, have been a little bit further along in development. There have been some CD30 CAR T-cell constructs that have been around for a while and studied both in Hodgkin lymphoma and T-cell lymphomas. And there are some allogeneic CARs, like ones that you don't have to manufacture from your own cells, which might have certain advantages in some T-cell lymphomas that are currently being studied including here at Wash U [Washington University].

So, I think [there's] a lot on the horizon. I imagine it will be a few years before these things are mainstream, but we anticipate that there are going to be more clinical trial options for CAR T cells and T-cell lymphomas, but those may be only available at certain centers across the country.

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

Ann from Connecticut
Yes. Hello, doctor. I'm having a hard time reconciling the treatment I had five years ago. I was diagnosed with AITL (angioimmunoblastic T-cell lymphoma). Now I never had the type of symptoms they talk about. How should I reconcile myself with the diagnosis?

Neha Mehta-Shah, MD, MSCI
Sorry to hear that, Ann. It sounds like you said you were diagnosed five years ago, and my guess would be [you] already went through treatment. I think if you had a question about whether you had the diagnosis, then I would probably talk to your doctors about it. And if you wanted to get a second opinion at an academic site to review the pathology, you certainly could. But there are patients who don't have other symptoms of lymphoma, like fevers and night sweats and weight loss, who do truly have lymphoma. And, in fact, some of the studies suggest that the less symptoms going into it, those patients do a little bit better [with] better long-term prognosis just based on registry data. So, I hope you're doing well, and I hope that answered your question.

Lizette Figueroa-Rivera, MA
Thank you for the question, Ann. And the next question, doctor, comes from Laura. Laura's asking, "Has there been any research on the effects of a pregnancy on someone diagnosed with CTCL?"

Neha Mehta-Shah, MD, MSCI
Hey Laura, that's a great question. There's not any specific research on pregnancy although in one of the cutaneous lymphoma nonprofit organizations called the Cutaneous Lymphoma Foundation there is a specific section in the patient education materials on effects of certain drugs on breastfeeding,

pregnancy, and pregnancy consideration. So, some medicines are safe to take in pregnancy and other medicines for treatment for cutaneous T-cell lymphoma are not safe to take in pregnancy. And so for our young patients, whether they're pregnant or thinking about becoming pregnant or thinking that there's a possibility in the future they might be thinking about expanding their family, we have that discussion with them upfront about which medicines we think are safe to start and which ones are not and which ones we would have to hold. But we don't have any reason to believe that becoming pregnant makes your cancer worse, so we just don't want the lymphoma to become overly burdensome during the course of a pregnancy. But a lot of skin-directed treatments are completely fine during pregnancy and even some oral medicine treatments.

Lizette Figueroa-Rivera, MA
Thank you, doctor. And the next question is coming from Stephanie. She's asking, "Is there any overlap between adult and pediatric T-cell lymphoma, specifically T-cell acute lymphoblastic lymphoma?"

Neha Mehta-Shah, MD, MSCI
Yes. That's a great question. T-cell acute lymphoblastic leukemia [lymphoma] is actually a different disease that we didn't really talk about. It's treated more like a leukemia more often and so it's treated more like a disease called ALL (acute lymphoblastic leukemia) and so that most often falls in the hands of the leukemia doctors. And we do know that treating even young adults or youngish adults with the chemo[therapy] type of regimens that we use in the pediatric-age group is thought to be potentially beneficial for patients. And so many of the adult oncologists are starting to take on this young adolescent combination strategy approaches for that disease. But I have to admit that's not a disease that I treat every day. We have some experts here who assist in the majority of those patients.

Lizette Figueroa-Rivera, MA
Thank you. Harjit is asking about subcutaneous panniculitis T-cell lymphoma with HLH (hemophagocytic lymphohistiocytosis). "Is there a standard treatment? Already have an allogeneic transplant but really where to find more information about these rare types of diagnoses of T-cell lymphomas."

Neha Mehta-Shah, MD, MSCI
That's a great question. The disease is called subcutaneous panniculitis-like T-cell lymphoma. As I mentioned, for cutaneous T-cell lymphomas, mycosis fungoides and Sézary syndrome are by far the most common, but there is very many rarer types of cutaneous T-cell lymphoma of which subcutaneous panniculitis-like T-cell lymphoma is one of them. And that disease originally, about like seven or 10 years ago, we used to call all of those lymphomas that occur underneath the surface of the skin around the fat lobule subcutaneous panniculitis-like T-cell lymphoma. And it turns out we now think there're two groups of those. Ones we still call subcutaneous panniculitis-like T-cell lymphoma which tend to have a less aggressive course and a group of them we now call cutaneous gamma-delta T-cell lymphomas that tend to have a faster growing or more aggressive course.

With the cutaneous gamma-delta T-cell lymphomas, these patients tend to have a higher rate of developing HLH or hemophagocytosis with their lymphoma, which is like a hyperinflammation disorder that can happen as a complication of lymphoma, though there is a subset of patients with

subcutaneous panniculitis-like T-cell lymphoma, don't have cutaneous gamma-delta who also have HLH. There is no consensus about how to best manage those patients. I think different teams across the country have a slightly different approach in their management. Some choose to manage them very aggressively with chemotherapy and a bone marrow transplant. Some have chosen a milder option, and I don't think, unfortunately, there's no right or a wrong answer and the decision to pursue one avenue versus another is very patient-and-provider-specific as a shared decision-making because they're often complicated decisions.

The best places to learn more about those, I would say, again, can include places like the Cutaneous Lymphoma Foundation because they're only devoted to cutaneous lymphomas and so they can connect you with other patients or providers who have an expertise in that disease.

Lizette Figueroa-Rivera, MA
Thank you. Leslie is asking, "How do I go about asking my doctor if they have typed my PTCL-NOS?"

Neha Mehta-Shah, MD, MSCI
Leslie, I think that's a great question. I think what you can ask is, you can say, "Well I was just trying to read more about my disease, and do you think that I have a specific subtype of cutaneous T-cell lymphomas? I heard that there are ways of better classifying these now." And then they should be able to let you know. I think specifically the question to ask is whether you have that T-follicular helper phenotype because we think the biology of that is a little bit different than the other forms of peripheral T-cell lymphomas. And the ways your doctor can do that is either by sending the pathology out to an academic medical center where they would routinely check for those things, and then sometimes they send it for mutational testing to look for cancer mutations in the cancer cells and that can be done through one of many commercial and readily available platforms.

Lizette Figueroa-Rivera, MA
Thank you. Joan is asking about photopheresis therapy for CTCL. Is that a good treatment?

Neha Mehta-Shah, MD, MSCI
Yes. So that's a great treatment. I'm glad people are asking all these questions of things that we didn't get a chance to talk about. So photopheresis is like giving light therapy to your blood. So once a month or so people get two IVs placed or a catheter. They have their blood go through a machine that actually gives the light therapy to your blood and then returns your blood back to you. And that is a very old therapy for cutaneous T-cell lymphoma that we know is very safe to do. It works the best in patients who have a small amount of disease in the bloodstream. But I would say if there's a treatment that works for you that's controlling the lymphoma and controlling your symptoms and is not causing other side effects, then that's a good treatment for you.

And so we've had some patients on photopheresis do really, really well for many, many years. Other patients it really doesn't work that well to control their symptoms. But if it's working for you and it's not too cumbersome and it's practical, then we think that's a great option if it controls your disease burden.

Lizette Figueroa-Rivera, MA
Thank you. And our last question today is from Edith. Edith is asking, "If remission is achieved for T-cell lymphoma, how long can one generally expect to remain in remission posttreatment?"

Neha Mehta-Shah, MD, MSCI
Yes, that's a great question to end with. Like the goal if you're in remission at the end of your treatment is that your remission lasts forever. The goal of your initial treatment for systemic T-cell lymphomas is curative, meaning you finish your treatment, and you live your whole life and the lymphoma never comes back. And so that would be our goal.

Lizette Figueroa-Rivera, MA
Well, thank you so much, Dr. Mehta-Shah, for your continued dedication to patients and for being able to present this webcast for us today.

CLOSING REMARKS

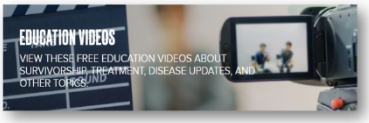
Lizette Figueroa-Rivera, MA
And if you weren't able to get your question answered, you can contact us at The Leukemia & Lymphoma Society and speak to an Information Specialist at 1-800-955-4572 and Information Specialists are available to speak with you from 9 AM to 9 PM Eastern Time or you can reach us by emailing us at LLS.org/ContactUs.

I do want to let you know that patients, as well as caregivers, can also schedule a free personalized nutrition consultation with our dietitians at LLS.org/Consult. Again, that's LLS.org/Consult.

LLS EDUCATION & SUPPORT RESOURCES

Online Chats

Online Chats are free, live sessions, moderated by oncology social workers. To register for one of the chats below, or for more information, please visit www.LLS.org/Chat.



Education Videos

View our free education videos on disease, treatment, and survivorship. To view all patient videos, please visit www.LLS.org/EducationVideos.

Patient Podcast

The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit www.TheBloodline.org.

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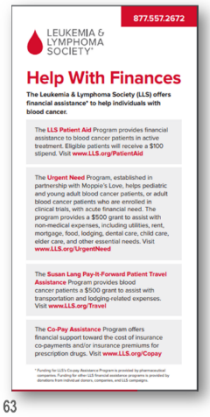

The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancers: www.LLS.org/Finances

To order free materials: www.LLS.org/Booklets

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Again, thank you, Dr. Mehta-Shah, for sharing your knowledge with us. And to all of the patients, caregivers, and professionals participating in today's program, on behalf of The Leukemia & Lymphoma Society, thank you for sharing your time with us. Goodbye and we wish you well.

Neha Mehta-Shah, MD, MSCI
Thank you to LLS for having me and for all the excellent work that you do for leukemia and lymphoma research and supporting patients and families. We're all very grateful to you. And thank you all for your participation.

Lizette Figueroa-Rivera, MA
Thank you, doctor.