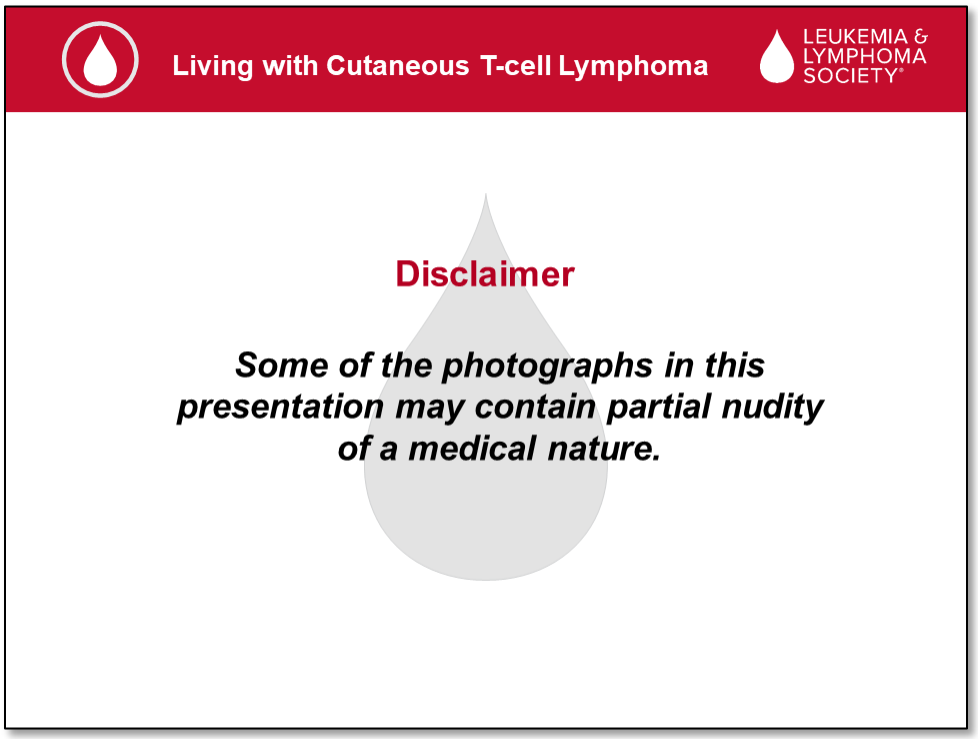
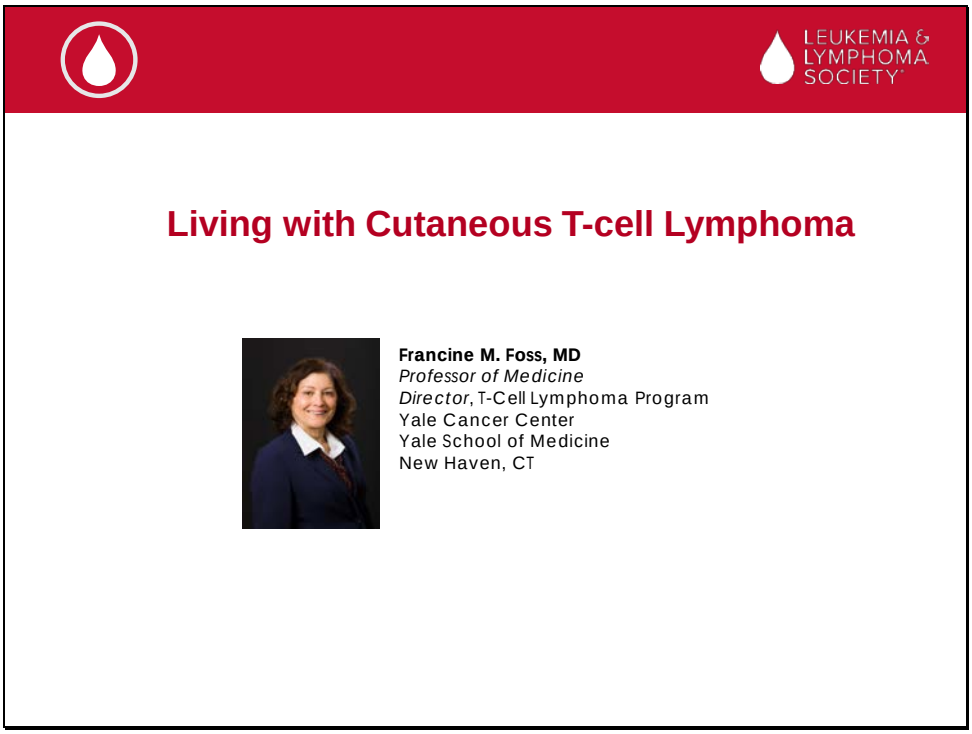
Slide 1 – Living with Cutaneous T-cell Lymphoma



Slide 2 – Disclaimer



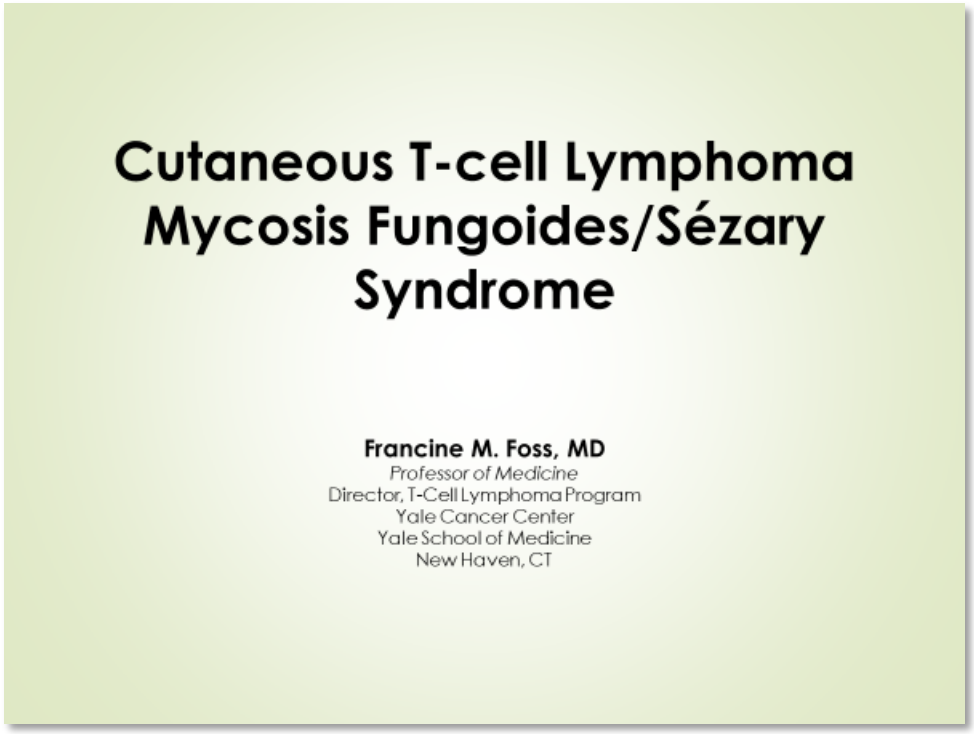
Slide 3 – Living with Cutaneous T-cell Lymphoma

Lizette Figueroa-Rivera:
Greetings and welcome to The Leukemia & Lymphoma Society's Living with Cutaneous T-cell Lymphoma Education Program. I'm Lizette Figueroa-Rivera, Director of Education and Support, and on behalf of The Leukemia & Lymphoma Society, I would like to welcome you.

We're fortunate to have as our presenter Dr. Francine Foss, one of the nation's leading experts in cutaneous T-cell lymphoma. We appreciate her dedication to supporting our mission and her commitment to caring for patients living with blood cancers. We would like to thank Seattle Genetics for support of this program.

Dr. Francine Foss, Professor of Medicine in the section of medical oncology at the Yale Cancer Center, is an internationally recognized clinician and clinical researcher with expertise in adult lymphomas and in stem cell allotransplantation. She is the Founder of the United States Cutaneous Lymphoma Consortium and the Peripheral T-cell Consortium. We thank Dr. Foss for volunteering her time and sharing her knowledge with us.

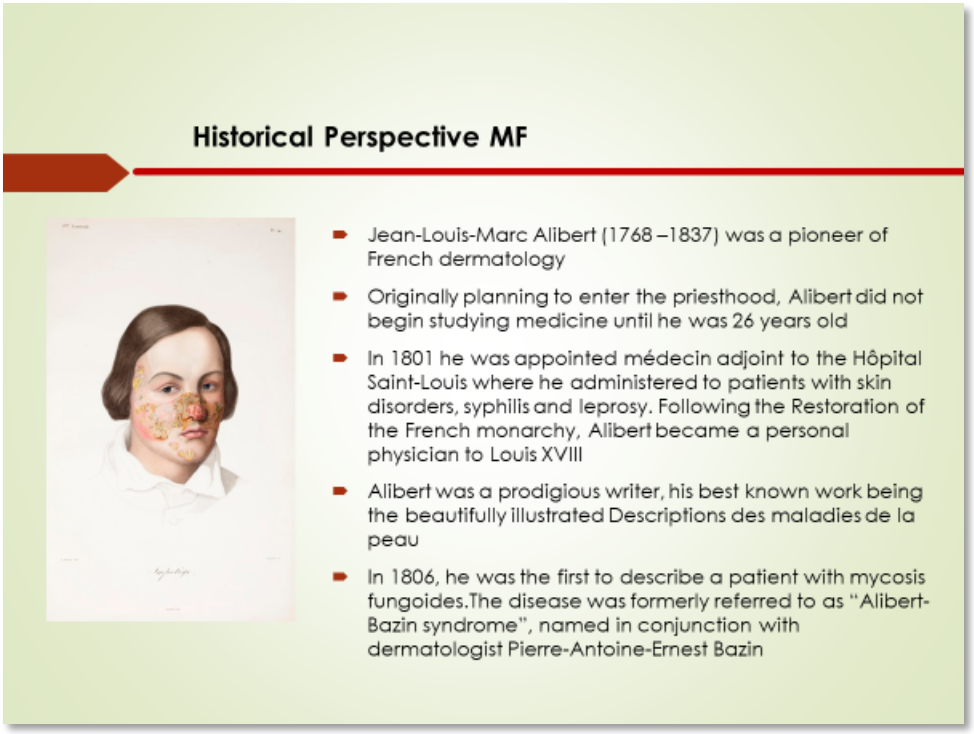
Dr. Foss, I'm now privileged to turn the program over to you.



Slide 4 – Cutaneous T-cell Lymphoma Mycosis Fungoides/Sézary Syndrome

Francine Foss:
Thank you very much, Lizette.

I'm speaking today about cutaneous T-cell lymphoma. That includes mycosis fungoides and the Sézary syndrome.

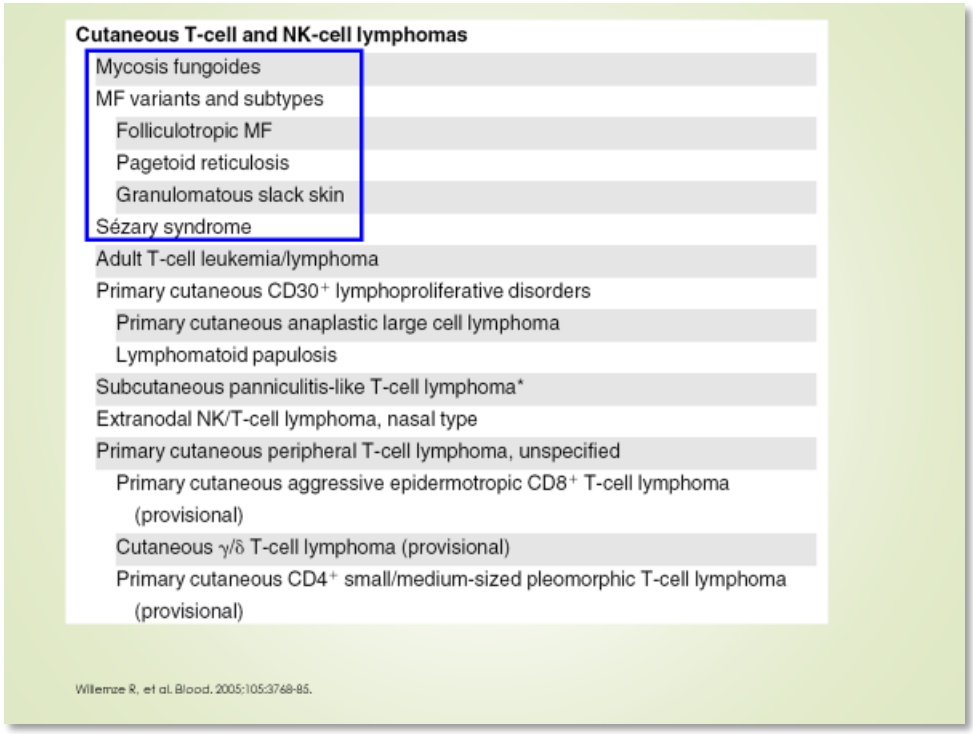


Slide 5 – Historical Perspective MF

I'd like to put a little historical perspective before we start our discussion. So, mycosis fungoides was actually named as a disease back in the 1700s. Jean-Louis-Marc Alibert was a pioneer of French dermatology. He originally had planned to enter the priesthood, but then he decided to study medicine when he was 26 years old.

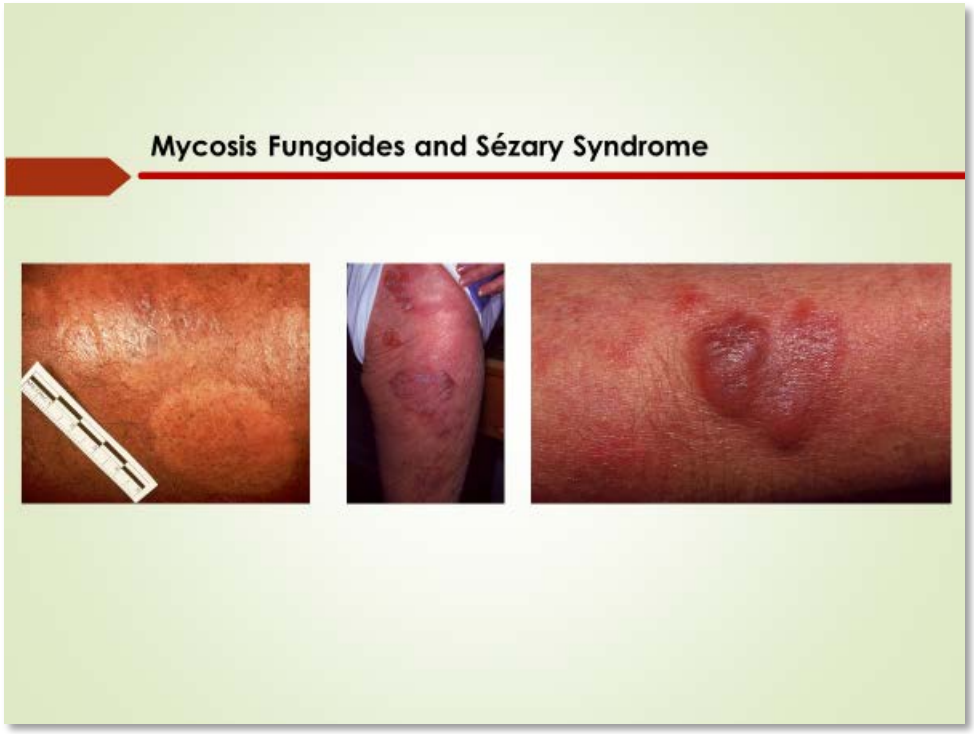
So, he was appointed to a hospital in Paris where he saw patients with skin disorders. He actually became a personal physician to Louis the XVIII. So, he was a prodigious writer and also an illustrator, and he did multiple illustrations of various patients who had skin disorders. And you can see one of those here. This is a patient who later went on to have the disease called mycosis fungoides.

So, in 1806, he was the first to describe a patient with mycosis fungoides. The disease was formerly referred to as Alibert-Bazin syndrome, named in conjunction with another dermatologist, Dr. Bazin, who also was working with Dr. Alibert at the time that this disease was first identified.



Slide 6 – Cutaneous T-cell and NK-cell lymphomas

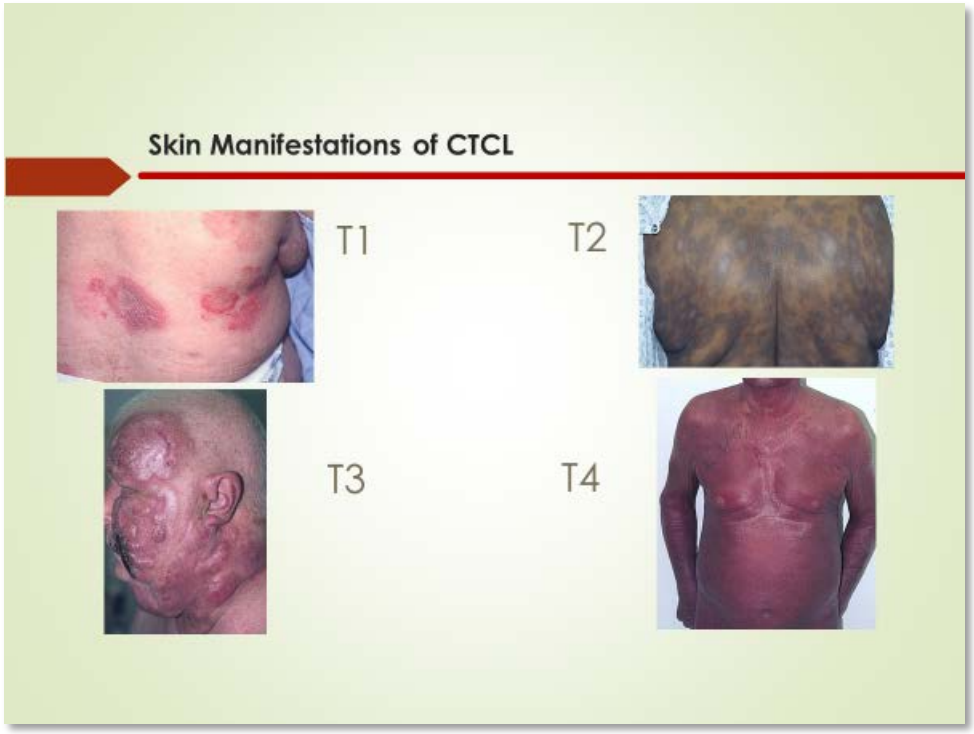
So, if one now looks at the modern era, with the most recent classification of cutaneous lymphomas by the WHO (World Health Organization), mycosis fungoides and the Sézary syndrome are only two of a number of T-cell lymphomas that occur in the skin. But, today, our discussion is going to be limited only to these two.



Slide 7 – Mycosis Fungoides and Sézary Syndrome

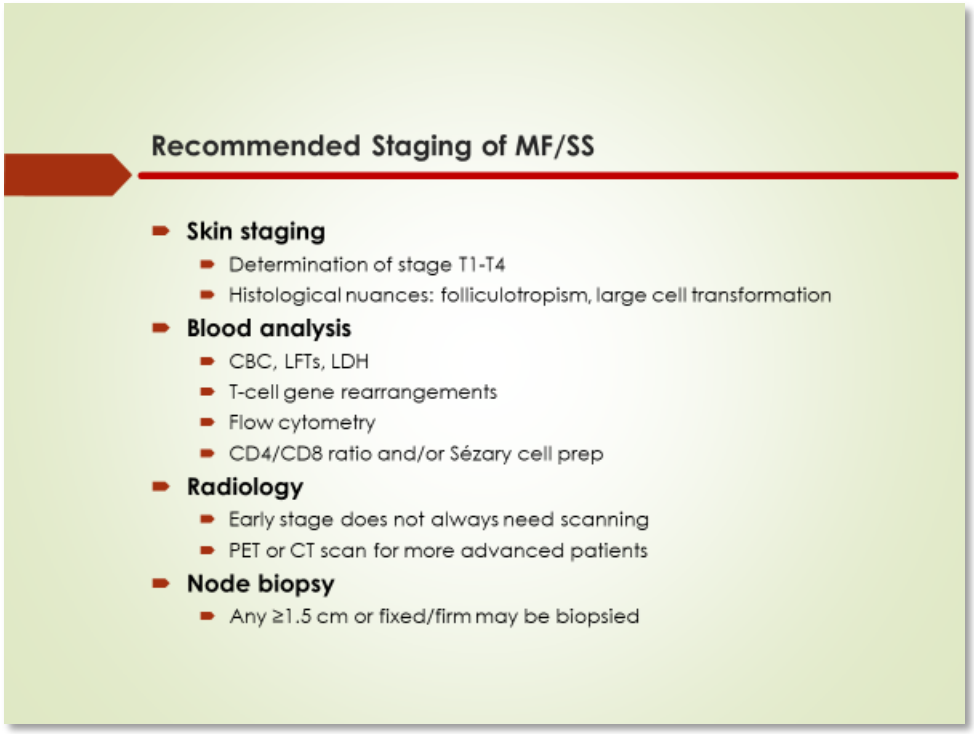
The next slide shows how patients with mycosis fungoides and Sézary syndrome can present. So, you can see that the clinical manifestations are very heterogeneous. And this could look like anything, like psoriasis, eczema, a skin reaction to something topical, or a diffuse drug reaction with diffuse redness of the skin.

So, early on in the course of the disease, patients can have a number of different clinical manifestations, and again, it usually takes a number of clinic visits, maybe even a number of biopsies, before a patient is really diagnosed accurately with this disease.



Slide 8 – Skin Manifestations of CTCL

The disease is classified based on the type and extent of skin manifestations. So, some patients could present with very localized disease with patches and plaques that involve their skin. T1 disease is patches and plaques involving 10% or less of the body surface area. T2 disease involves greater than 10% with patches and plaques. T3 is a patient with cutaneous tumors. And T4 is a patient who has diffuse redness of the skin or diffuse erythroderma.

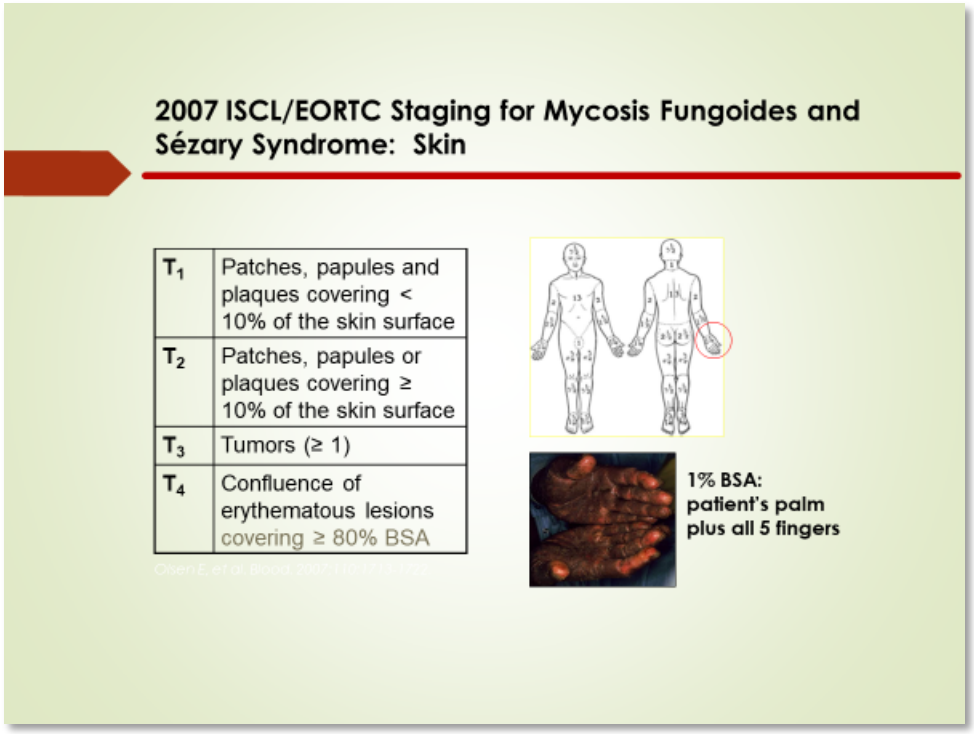


Slide 9 – Recommended Staging of MF/SS

The staging system for mycosis fungoides and Sézary syndrome relies on a number of different clinical manifestations of the disease and laboratory tests. I talked a little bit about that skin staging T1 through T4, but in addition, we look at other factors in the biopsy such as the presence of follicular tropism or large cell transformation. In the peripheral blood, we look at the CBC or the blood count as well as other things like the LDH, which can be a prognostic marker for this disease. We also do molecular tests to look for rearrangements of the T-cell gene receptor. We do flow cytometry to look at the circulating cells or the Sézary cells that may be present, and we also do what we call a CD4/CD8 ratio, which is another way of looking at whether or not there are malignant Sézary cells circulating in the blood.

We try to do scanning in our patients, particularly those with more advanced disease. CAT scan or PET scan both are appropriate for patients. The patients with very early stage disease may not need a scan. Oftentimes, I will get one for patients who have more extensive patch or plague stage disease as part of my initial staging.

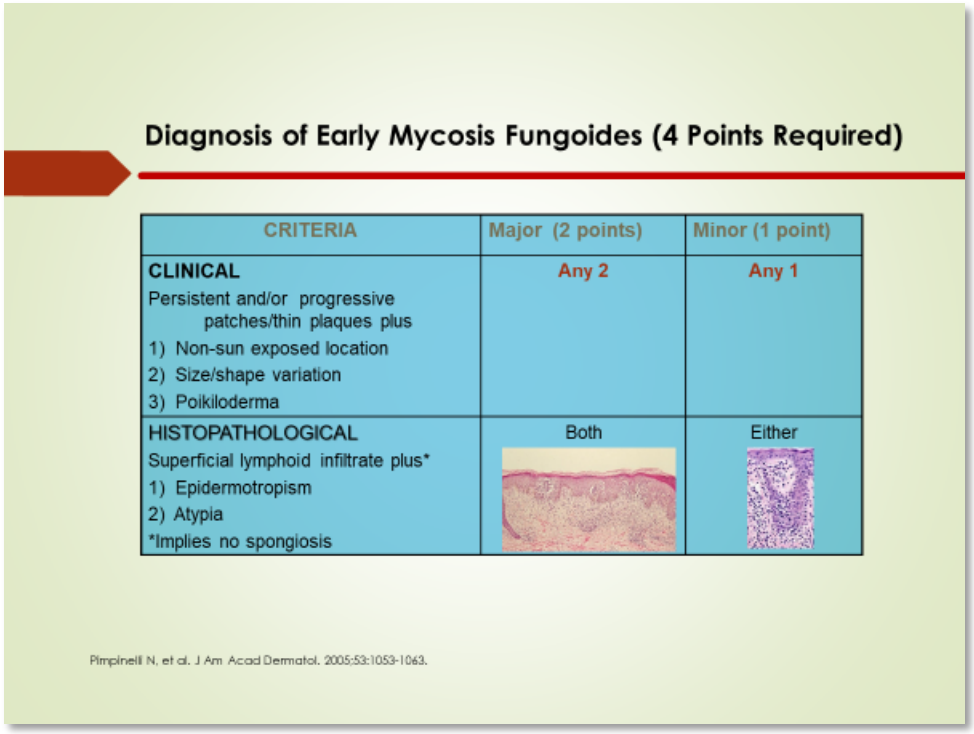
And then, finally, there's a question of a lymph node biopsy. So, it's difficult to know on scans when an enlarged lymph node could potentially be involved with mycosis fungoides. So, we've set aside a cut-off for ourselves, as far as what we consider to be an enlarged node or a node that we would be worried about, and that's a node that's greater than 1.5 centimeters. We can oftentimes biopsy these nodes with a core needle biopsy, but sometimes we actually need to go in and excise the lymph node. So, obviously, it's easy to excise a lymph node under the arm or in your groin, which is easily accessible. But, if the only lymph node is deep down in your pelvis or in your abdomen, we may opt to go for a core needle biopsy.



Slide 10 – 2007 ISCL/EORTC Staging for Mycosis Fungoides and Sézary Syndrome: Skin

So, again, I just want to talk about the skin staging, because patients in the audience who are listening to this may have been patients in clinical trials with one of our new drugs, and they may have seen the skin staging sheets appear in the clinic. So, we look at the skin staging based on the degree and extent of involvement. And I mentioned patches, plaques, tumors, and erythroderma. But then we have these little, doughboys that are shown here that show the different, parts of the body and how much of a percentage of the body each of these represents.

And so, we use these to try to estimate or quantitate the amount of skin involvement in our patients. And this is very helpful to follow patients, both in routine clinical care and certainly on clinical trials. And I just show you a picture here of involvement of the hands. So, oftentimes, patients will have cracking or thickening of the skin on their hands and feet. And of course, this can be a significant issue with respect to pain as well as, uh, the ability to use your hands.

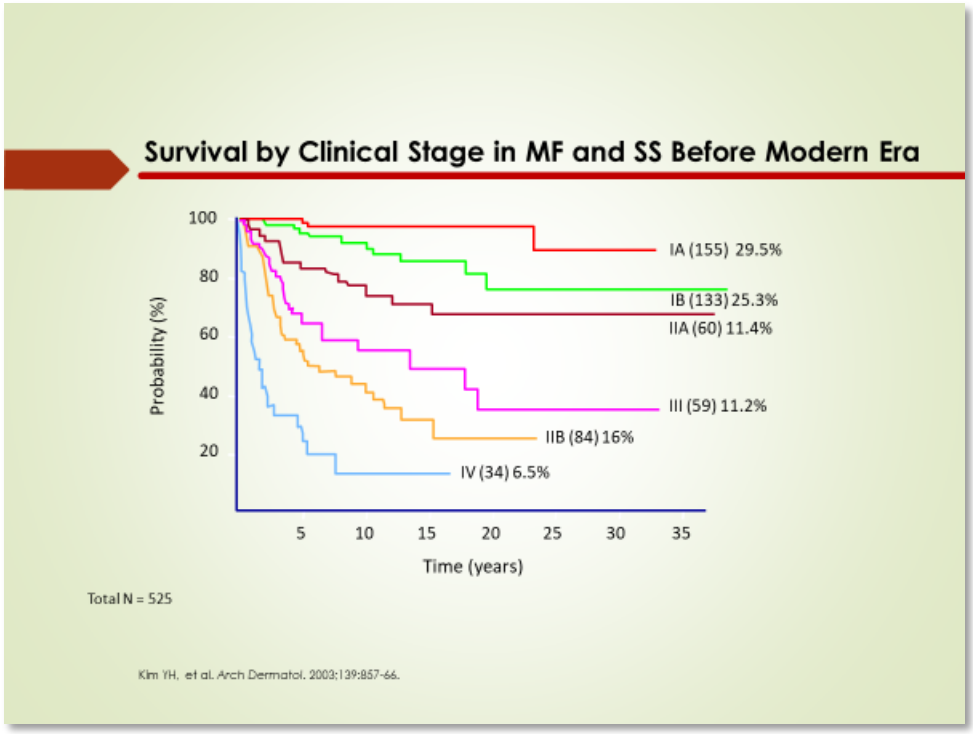


Slide 11 – Diagnosis of Early Mycosis Fungoides (4 Points Required)

So, early stage mycosis fungoides can be mistaken for a number of different diseases, particularly, things like psoriasis or eczema or other types of dermatitis. And so, it can take a little while before this is diagnosed.

We have established some criteria to help us to diagnose mycosis fungoides from other benign skin entities, and this just shows you what some of those criteria are. So, on the bottom, you can see the skin biopsy, which shows the top layer of the skin, and then immediately under that top layer, we have these infiltrates with these malignant T-cells that look like little round balls. And you can see in the close-up, that little clearing area, is the area where these malignant T-cells are actually penetrating into the skin.

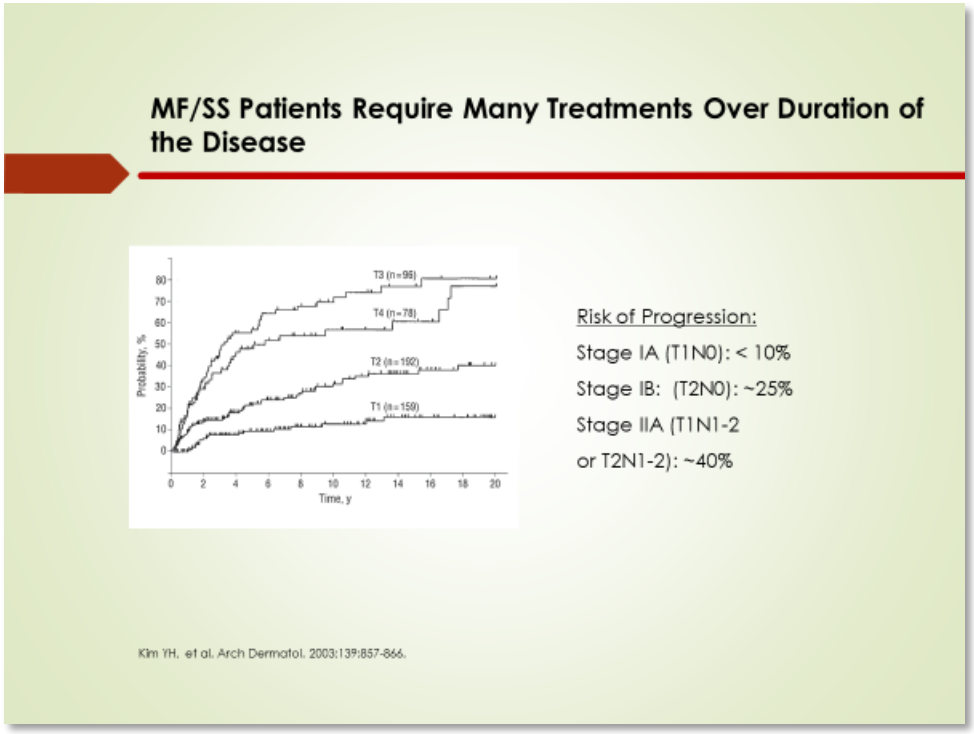
So, we certainly look for those kinds of findings, and we also look at where the disease occurs on the skin. One of the things, with mycosis fungoides is that it typically occurs in non-sun exposed areas such as areas of the trunk or the buttocks. And there are certain features, shown on the slide that we look at, and we assign a point system to try to identify which patients actually have this disease versus some of the benign diseases that I mentioned.



Slide 12 – Survival by Clinical Stage in MF and SS Before Modern Era

So, the skin staging is really important to understand how patients are going to do. And this just shows you some typical outcomes for patients. I want to tell everyone in the audience to look at this slide from the perspective that this is data that was published in 2003, and it goes back 25 or 30 years. That's not really the modern era, and it's certainly not the era that our patients are living in. And I'd like to say that many of these curves are changing as we are introducing new drugs for the therapy.

But, if you look at what we were faced with say 15 or 20 years ago, you can see that patients who had the Sézary syndrome stage III and patients with more advanced disease such as tumor stage disease did not do as well as those patients on the top who had patch or plaque stage disease.

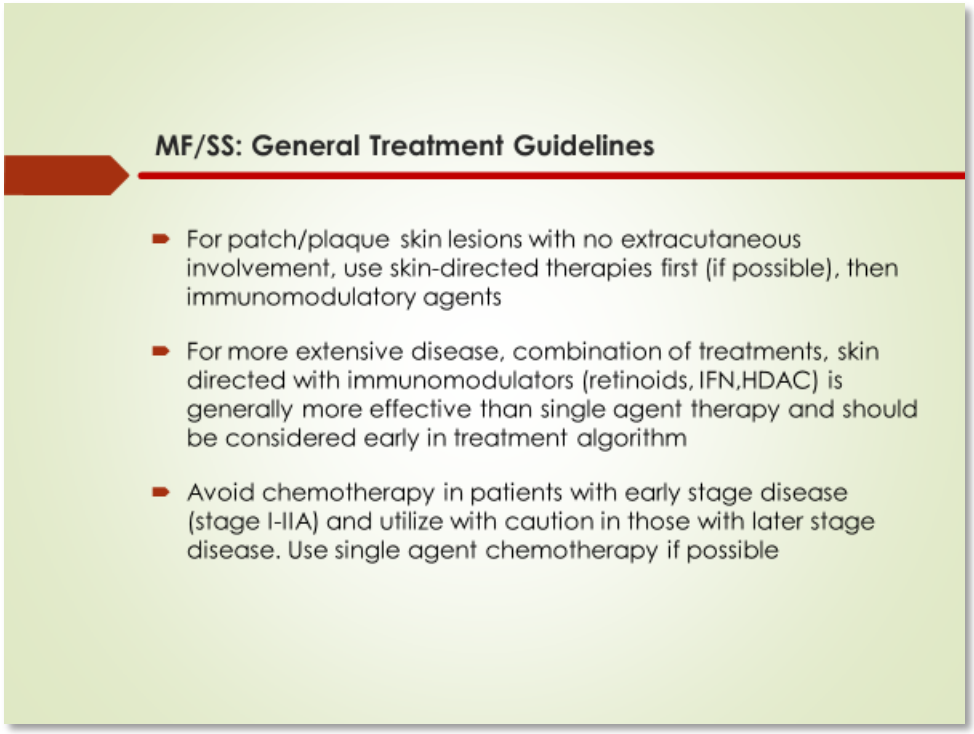


Slide 13 – MF/SS Patients Require Many Treatments Over Duration of the Disease

One of the things about mycosis fungoides is that our patients are oftentimes on treatment for a very long time, so they start with one treatment, and then they continue on treatments for a very long period, oftentimes 15 or 20 years or more. So, patients are always asking the question, well, what is the risk that I'm going to progress from an early stage to a more advanced stage of disease? And again, this is very old data from 2003, again, before the modern era of the types of therapies that you're receiving now. But, you can see that the risk of progression was highest for the patients who had more advanced disease to begin with. So, patients in the audience who have patches and plaques, the T1 and T2 patients, you can see that they can go for a very long time, and only about 40%of them will ever progress.

Again, this is important information when you're thinking about yourself as a patient and you've just had this diagnosis and you really are projecting into your future.

Now, as we have these new therapies, that we've been fortunate enough to be using in the last 10 or 15 years, I'm hoping that as we produce these curves that we'll see that fewer of our patients are progressing.

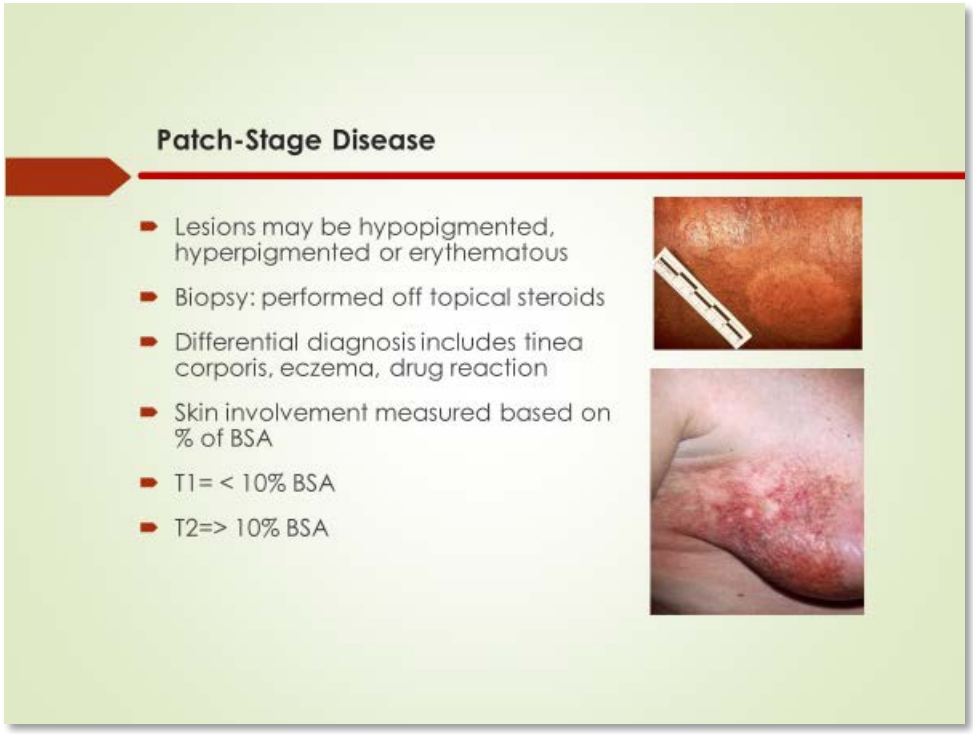


Slide 14 – MF/SS: General Treatment Guidelines

Well, what are the general treatment guidelines for mycosis fungoides? Again, it really depends on the clinical features and what kind of skin disease is present in the patient. So, those patients with a patch plaque stage disease with very favorable disease can actually use skin-directed therapies. In addition, then if they need other treatments, we oftentimes opt for oral or immunomodulatory types of therapies.

Patients with more advanced disease oftentimes require a combination of skin-directed therapy and immunomodulatory therapies and oftentimes then may move on to have some single agent chemotherapies as well.

One of the rules that we all try to play by when we treat mycosis fungoides is to avoid aggressive chemotherapy, particularly in the early stages of the disease, where we know that patients can do very well with these immunomodulatory and topical therapies. And likewise, with more advanced stage disease, we try to avoid very aggressive multi-agent chemotherapy that can make patients more susceptible to developing infections.

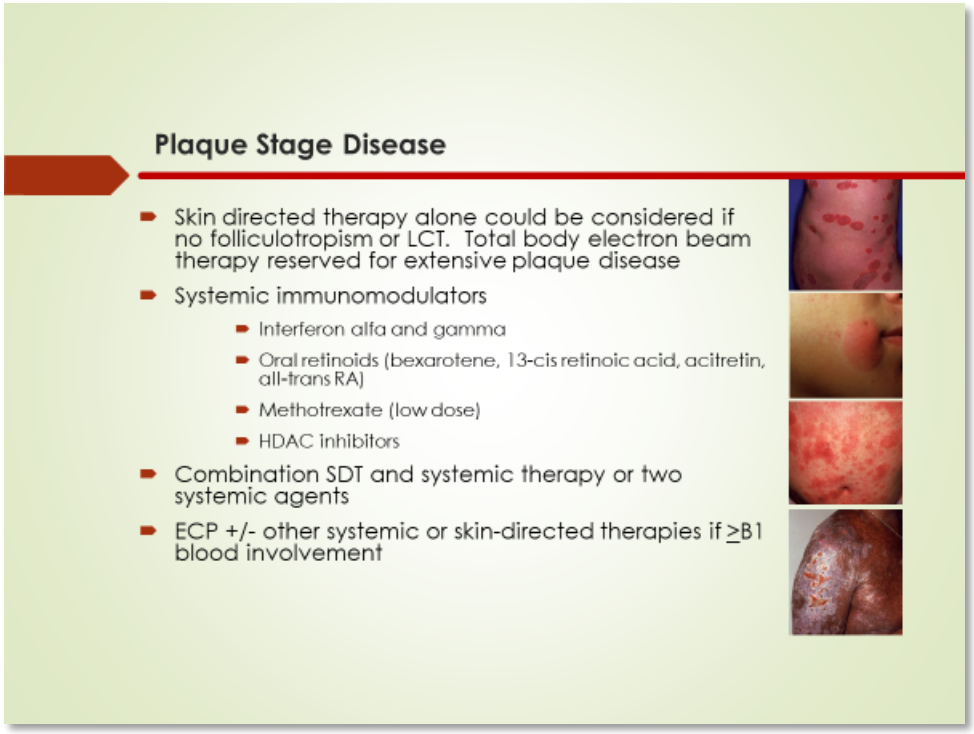


Slide 15 – Patch-Stage Disease

I'm going to talk a little bit about the different stages of disease and how we approach them clinically.

This is a patient with patch stage disease, and you can see what I mentioned about the truncal distribution on the buttocks, on the breast area, and in areas that don't get a lot of sun exposure. These lesions can be hyperpigmented or hypopigmented, and they can have a number of different clinical features, as you can see here. What we try to do is to do a biopsy, but hopefully, the patient has not been using topical steroids because that can affect the biopsy. So, usually we'll take a patient off steroids for a couple of weeks if we want to make a biopsy or repeat a biopsy.

The differential diagnosis for these early stage patients includes various things like fungal skin infections, eczema, and other things. And I mentioned how we actually look at the degree of skin involvement - 10% or less being T1, and 10% or greater being T2.



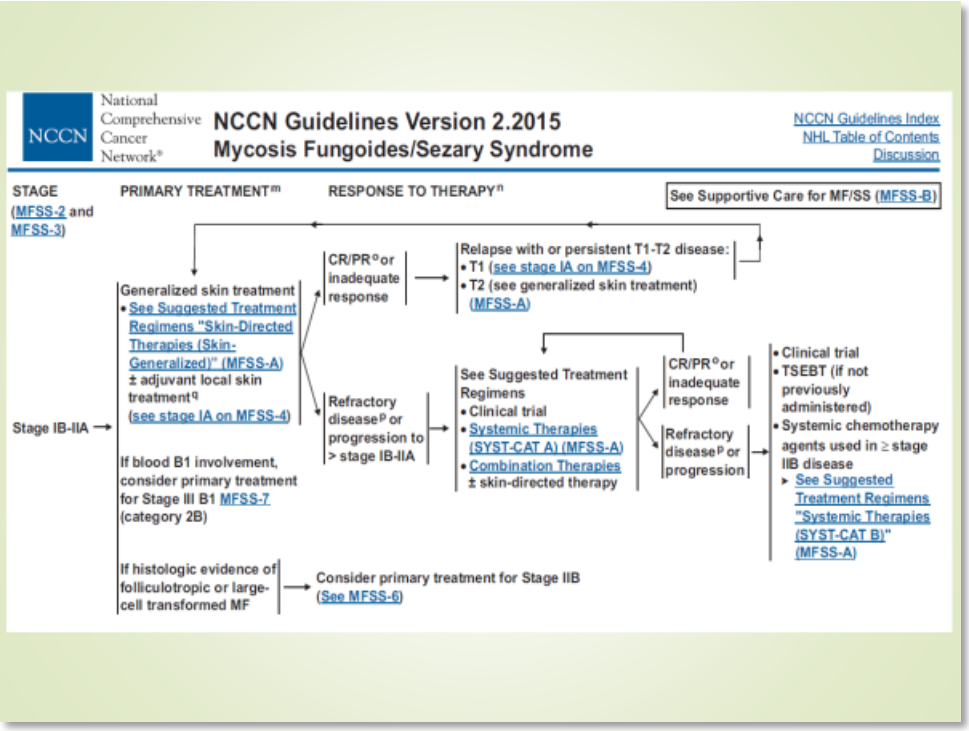
Slide 16 – Plaque Stage Disease

So, what about the kinds of treatments for patch and plague stage disease? I mentioned that skin-directed therapy is oftentimes the first thing that we do, and there are a couple of things, again, in a biopsy that would suggest that we might need to do something more than that, and that would be the presence of large cell transformation or this folliculotropic feature of mycosis fungoides.

We do use radiation therapy in this disease, and the radiation therapy oftentimes involves just a few spots that are radiated. But we can do what we call total skin electron beam radiotherapy, and that's generally reserved for patients that have more extensive involvement of their skin.

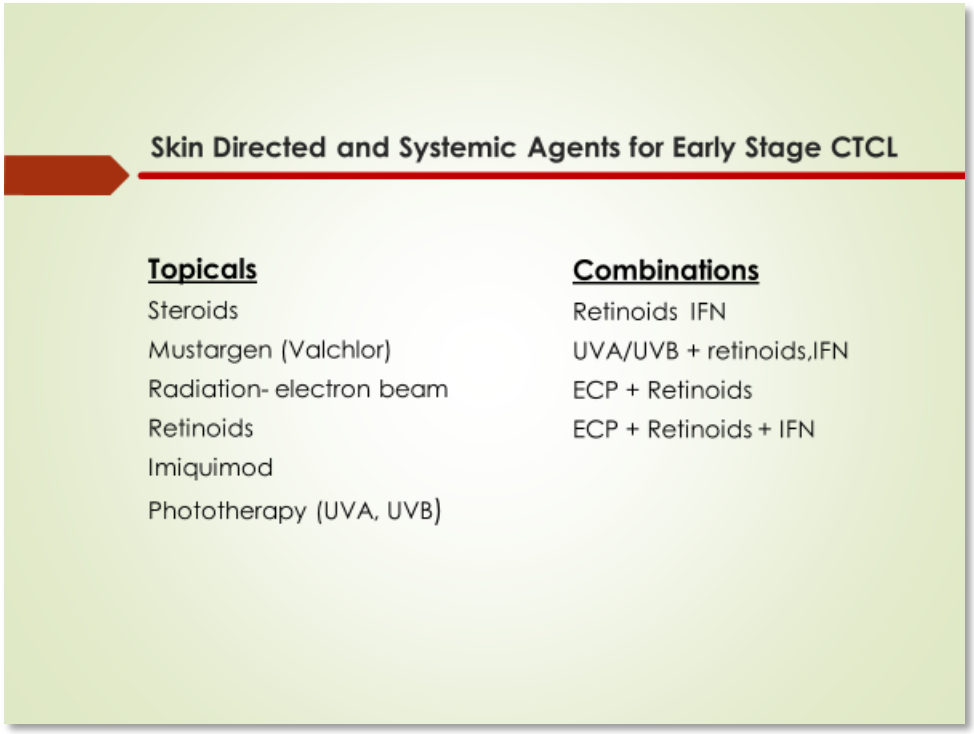
The kinds of systemic immunomodulatory therapies that I alluded to include a number of different things. There are different types of interferons, interferon alpha and gamma. There are oral retinoids such as bexarotene, cis-retinoic acid, acitretin and all-trans retinoic acid. There's low dose methotrexate, and there are drugs called HDAC inhibitors, and we'll talk a little bit more about each one of these.

In addition, we have the combination of the skin-directed therapies with systemic therapies, oftentimes a good approach. And then another treatment that we have is called ECP or photopheresis, and this is a treatment where we take blood out, it passes through a machine where it's exposed to ultraviolet light and a chemical, and then it goes back into the body. And this is used either by itself or in combination with other therapies, in particular for patients who have evidence of blood involvement.



Slide 17 – NCCN Guidelines Version 2.2015 – Mycosis Fungoides/Sézary Syndrome

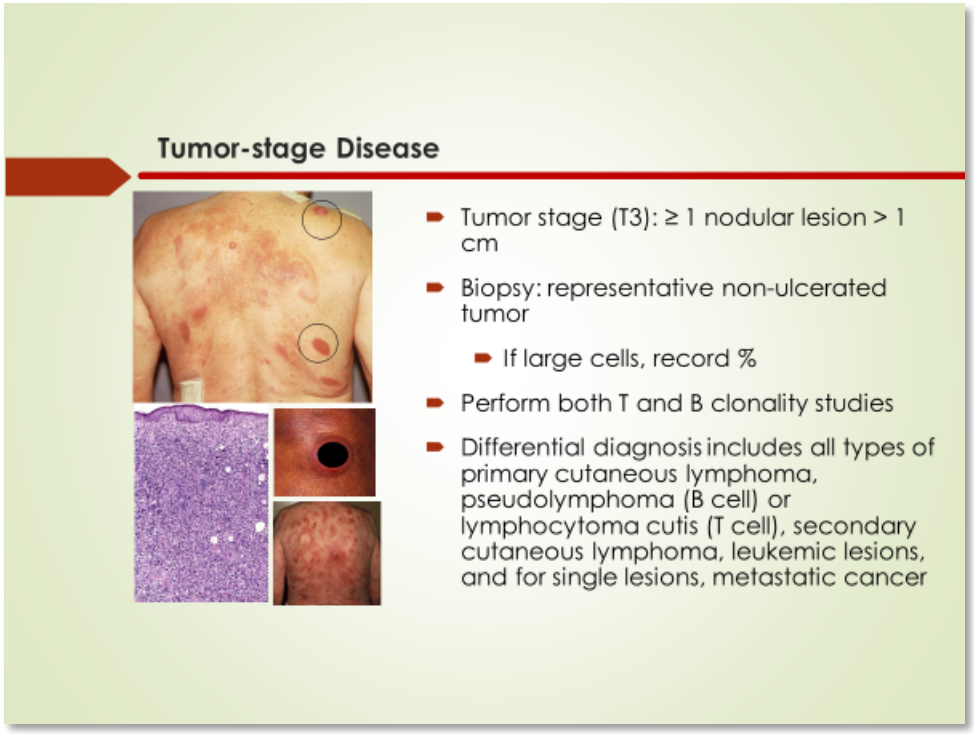
The next slide just shows you that we do have, what we call NCCN guidelines, which are National Cancer therapy related guidelines that really look at clinical approaches to patients with cancer and base the treatment recommendations on clinical evidence from clinical trials. And you can see this is a typical algorithm, which shows you that there are different things that you might do, whether or not a patient has blood involvement. And then after they respond or have refractory disease, the algorithm would lead you in a different direction. So, again, these are available to clinicians. Oftentimes, we look at these, but the truth is that our treatment for most patients is based on the individual patient and a lot of patient-specific factors.



Slide 18 – Skin Directed and Systemic Agents for Early Stage CTCL

So, the kinds of early stage treatments that we use topically include topical steroids, topical nitrogen mustard, which is also called Valchlor®. I mentioned the radiation therapy, the topical retinoids, another drug called imiquimod, which is a drug that's used less often but oftentimes very effective. And then we also use phototherapy, so UVA and UVB. So, phototherapy is also used extensively in patients who have psoriasis.

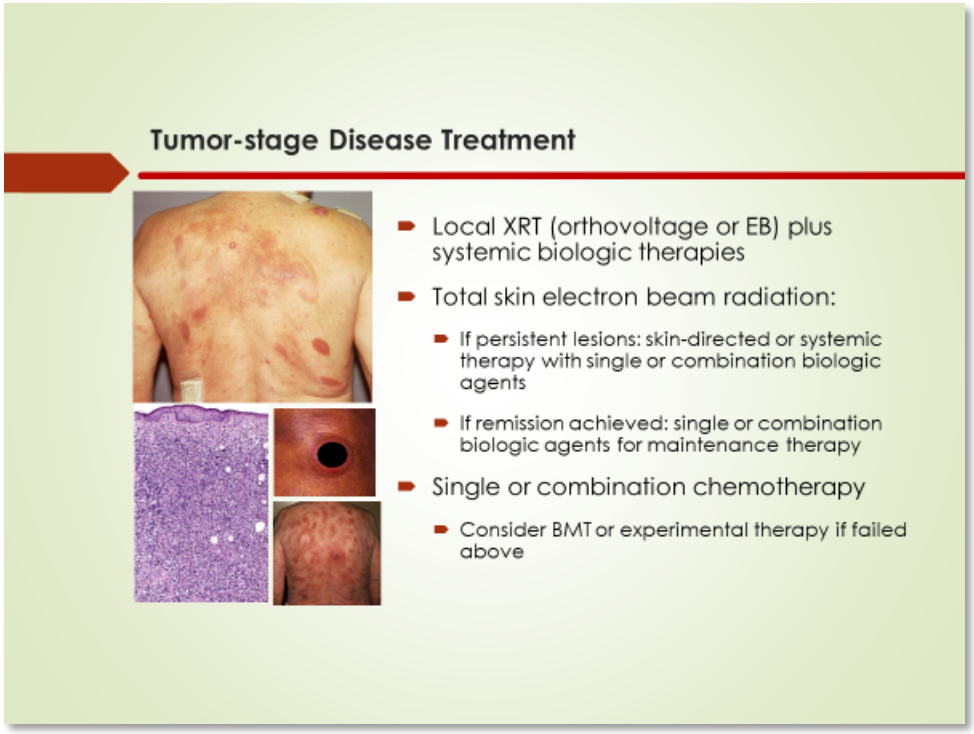
And then the combinations are those types of topical therapies with other therapies, such as ultraviolet light with the retinoids, ultraviolet light with interferon, the photopheresis treatment with either retinoids or interferon, or possibly all three. And so oftentimes, these are the kinds of strategies that we use in early stage patients trying to exploit these immunotherapies to the greatest degree possible before exposing patients to other more toxic therapy.



Slide 19 – Tumor-stage Disease

Well, tumor stage disease, again, is more aggressive than patch plaque stage disease, but tumor stage disease really is a number of different things. So, you can see, the patient I'm showing here has underlying patch plaque disease, but then he's developed some tumors. So, we can see this or we can see a patient who comes in only with tumors who had not had preceding patch plaque stage disease.

So, we need to obviously biopsy these tumors, and we tried to look to see whether or not they have large cells or have large cell transformation. And we record the number of large cells. So, we might say like 25%, of the cells are large or 50% of the cells are large. We also look at clonality for the, T-cell receptor, and then we look at other things that could be in the differential diagnosis. And there are things like pseudo lymphoma or leukemia cutis if a patient has underlying leukemia, for instance, that could look like this. And you can see the picture showing different types of tumors. They can be very small or they can be large. And you can see the skin biopsy here, which is very blue with a lot of blue dots, showing that there's a very extensive involvement of these tumor cells in the skin of these patients with tumor stage disease.



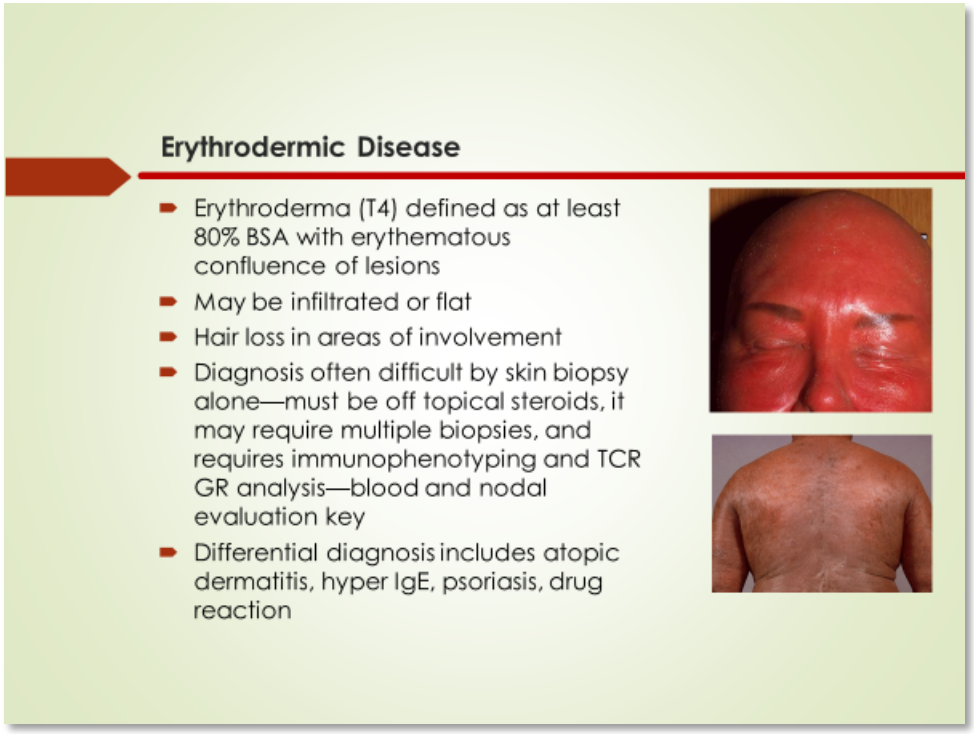
Slide 20 – Tumor-stage Disease Treatment

Well, tumor stage disease can be treated a number of different ways, and again, it really depends on the whole picture for the patient. So, if a patient presents like this gentleman you see on the top with patch plaque disease and now he's got a couple of tumors, we could just locally radiate these tumors, so just put a very small radiation field on and take care of those tumors, and they would shrink down, and then we could continue to treat with whatever treatment we were giving for the patch plaque disease.

If there are a lot of tumors, then we might opt to treat the whole skin with total skin radiation therapy. Oftentimes, though, tumors can come back after we radiate them, so we generally will follow on after the radiation with additional systemic therapies. Those could be biologic therapies, or those could be other types of chemotherapy.

So, patients could have tumor that come and go, and they can persist with their very long clinical course with this disease, but there are some patients with tumor stage disease who have a much more aggressive presentation with multiple tumors, not easy to get those tumors to go into remission. And those are the patients for whom we consider doing something more aggressive, particularly either entering them on a clinical trial if we have one or considering an allogeneic bone marrow transplant as a potential way to cure that patient.

So, these tumor stage patients, as you'll see later on in the talk, are those patients that are among those that we would consider going to transplant.



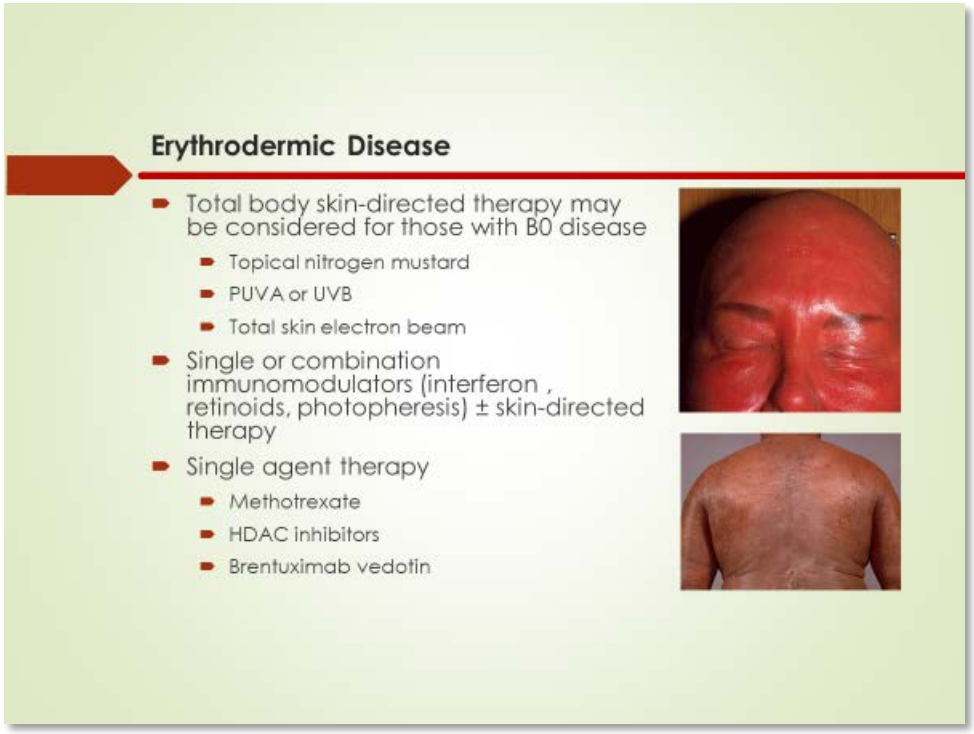
Slide 21 – Erythrodermic Disease

Now I want to turn to erythrodermic disease. So, erythroderma is basically redness of the skin, and you can see a couple of patients here with varying degrees of erythroderma. Erythroderma is defined as this diffuse redness of the skin. In most patients, 80% or more of their body surface area is involved. Now, this can be very flat or it actually can be infiltrated and feel very rough to the touch.

One of the classic things about erythroderma is that there's hair loss, and oftentimes patients will lose not only the hair on their head but their eyebrows, and the hair on their chest and their legs as well.

Erythroderma is also very itchy, so these patients oftentimes will present with very extensive itching. And again, we need to do a biopsy to confirm the diagnosis. And again, topical steroids can interfere with the biopsy, so we want to make sure that patients are off the steroids. And again, we want to document the presence of the malignant cells in the skin, but also, we look in the blood, and in the patients with erythroderma, they have a higher chance of having involvement of the lymph nodes. And so these are patients in whom we would do the scans, and we would try to get a core needle biopsy if we thought we could do that safely.

Again, the differential diagnosis is very broad and includes things like atopic dermatitis, psoriasis, or drug reactions.

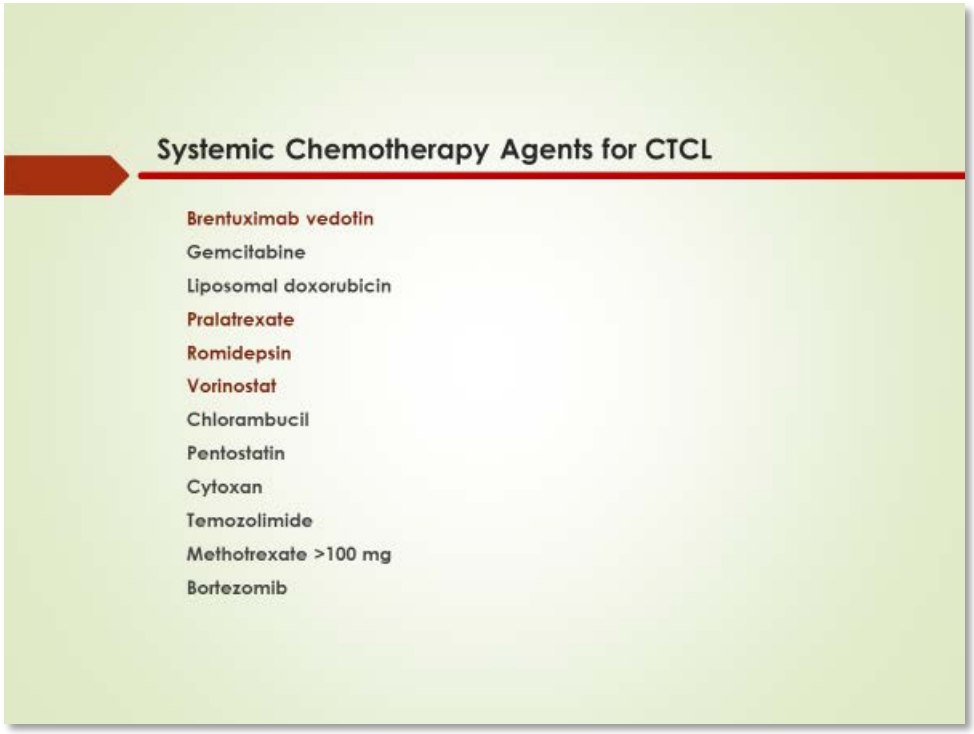


Slide 22 – Erythrodermic Disease

So, the treatment for erythrodermic disease is a little bit different than the approach for patients with patch plaque disease. These patients are patients who may classically be treated with photopheresis. In addition, these patients may be treated with various kinds of topical therapies. They may be treated with ultraviolet light as well.

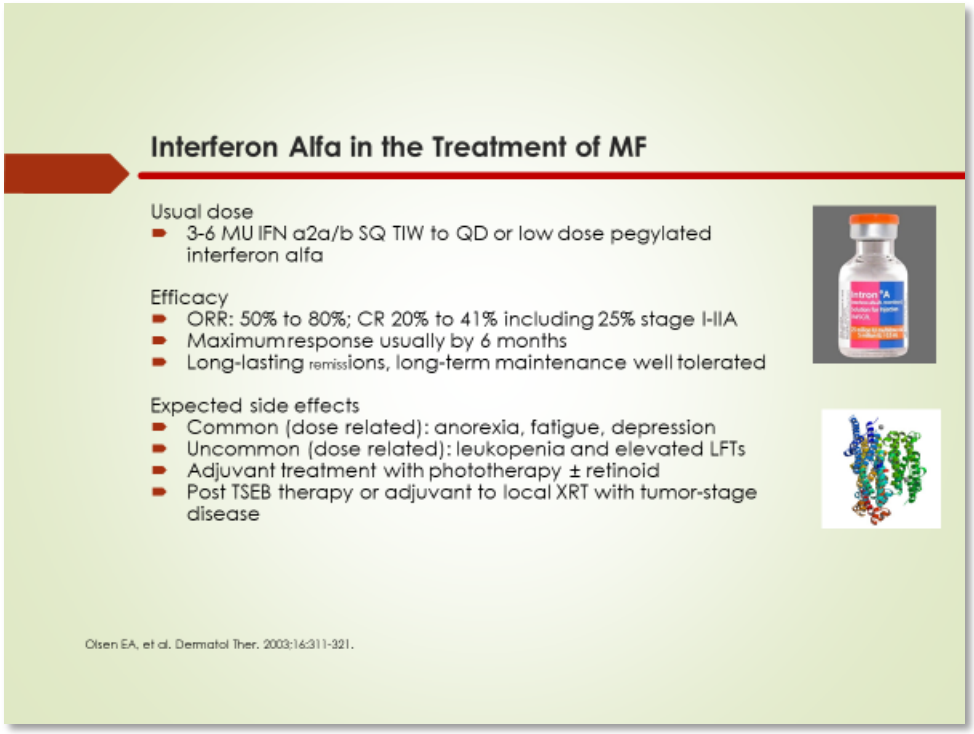
These patients tend to respond very well to the immunomodulatory types of therapies, so photopheresis by itself, the addition of retinoids or interferon to photopheresis, or the addition of retinoids or interferon to the ultraviolet light therapy oftentimes can help these patients tremendously. But many of these patients will need more systemic therapy, and so we try to use single agent systemic therapies such as methotrexate, the histone deacetylase inhibitors, which I'll talk more about, and now we have a new drug brentuximab vedotin that was FDA approved, as well.

The patient with erythrodermic disease, with the Sézary syndrome, oftentimes have circulating malignant cells and these patients oftentimes also are more prone to develop infections because their immune system is not normal. And so, oftentimes, we may have these patients on prophylactic antibiotics if we're treating them with aggressive therapy. In addition, we like to avoid putting central lines or portacaths in these patients because they tend to get infected.



Slide 23 – Systemic Chemotherapy Agents for CTCL

Once we get to the point where we're thinking about more aggressive systemic chemotherapy for patients, there are a number of different, drugs that we can use. And on this slide, I put in red the drugs that are FDA approved for patients with cutaneous T-cell lymphoma, and those include brentuximab vedotin, which is the newest drug to be approved, romidepsin, and vorinostat, and pralatrexate. But, there are lots of other drugs that we use that are also effective, and that includes gemcitabine, liposomal doxorubicin or Doxil®, pentostatin, Cytoxan®, methotrexate I mentioned, and then other drugs, as well.



Slide 24 – Interferon Alfa in the Treatment of MF

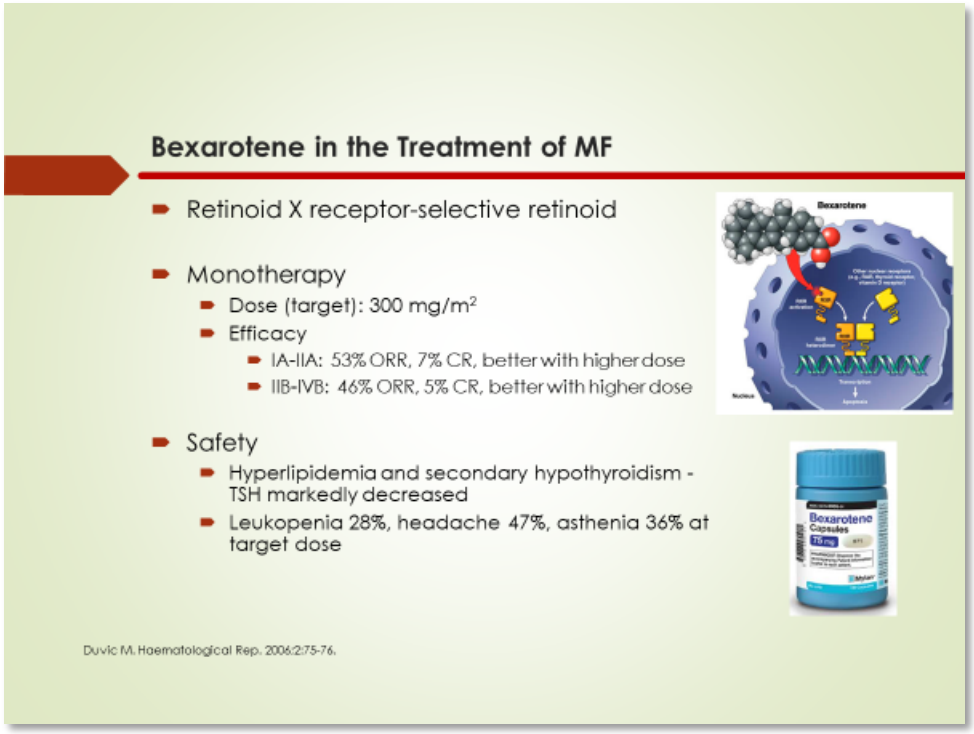
So, let's talk a little bit about some of these commonly used therapies. Interferon alpha is probably one of the oldest drugs used for patients with mycosis fungoides. We've been using it now for about 30 or 40 years. So, interferon is given subcutaneously under the skin, and there are a number of different schedules and a number of different doses that are used. So, oftentimes, the patient will get the drug three times a week, but in some cases, we may actually give it every day.

If you look at long-term data following patients for a long time on interferon, the overall response rate could be ranging from 50 to 80%, and about 20% of patients can have a complete clinical response. Many of these patients are those patients with the early stage disease.

Usually, it takes about six months to actually get your best response. And then once a patient has a good response, we put them on maintenance therapy, which would be spacing the treatment out perhaps, you know, once a week, then every other week, and then every couple of weeks.

Now, interferons are associated with lots of side effects that include fevers and chills, weight loss, fatigue, and depression. Usually, when a patient is on interferon, after a couple of months, these side effects tend to go away.

In addition, the interferons can cause lowering of the blood counts. There are some issues with the thyroid as well as with sexual functioning that we need to pay attention to, in patients who are on long-term interferon. In addition, we use interferon with many other therapies such as phototherapies. We can use it with retinoids. We can use it after the total skin radiotherapy. So interferons actually were used very, very, very, very often, until some of the newer drugs became available. And in fact, there are still many patients that have been maintained on interferon now for the last 15, 20 years or so.



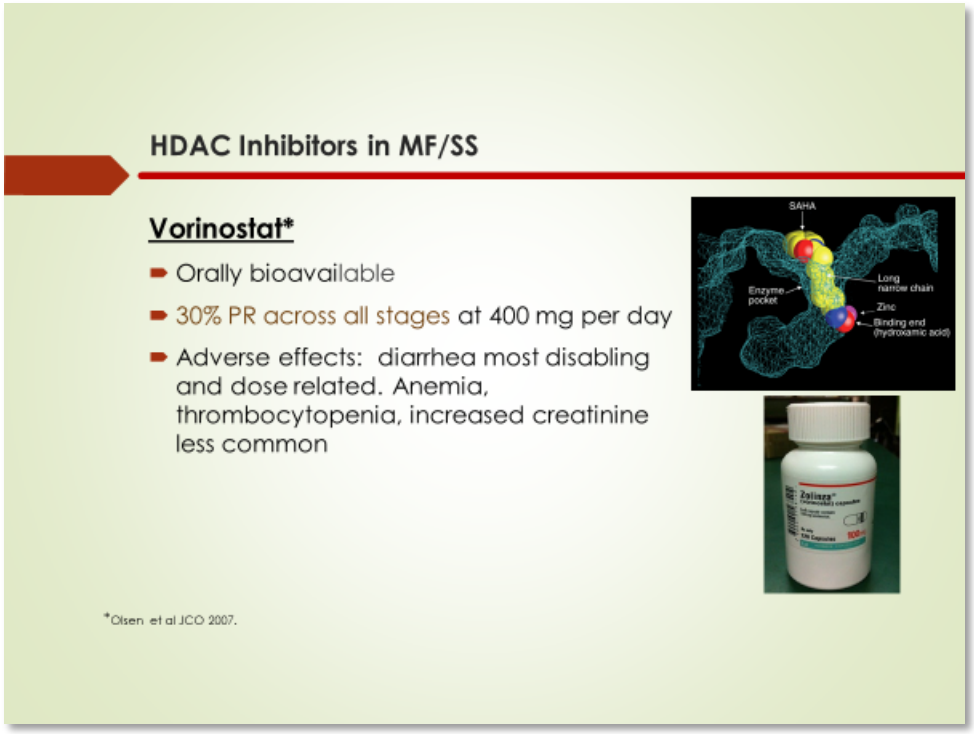
Slide 25 – Bexarotene in the Treatment of MF

One of the other most commonly used drugs is bexarotene, which is a retinoid. So, it's a different class of retinoid than the acitretin and the type of retinoids that we use for acne. The bexarotene is available both as a pill as well as a gel that you can apply directly to the skin. So, the pills, the bexarotene pills were FDA approved for patients with either early or advanced stage mycosis fungoides, and you can see on the slide that they were very effective with response rates ranging from 46 to 53%. And there tended to be a better response with a higher dose.

You can see in this little cartoon that the way these retinoids work is that they actually get into the cell, and they actually modify the transcription of various genes that are important in the disease itself.

Now, other things that the retinoids can do is that they can cause elevation of your cholesterol and the lipid levels in your blood, and they can lower your thyroid function. So, patients on bexarotene need to have frequent blood work, and we need to actually replace the thyroid hormone with Synthroid, and we need to actually give some medications to lower the lipids and the cholesterol. And these are reversible once we stop the bexarotene.

In addition, some patients can have lowering of their blood counts, and they can feel fatigued with the bexarotene. But, generally speaking, we're able to administer this drug to most of our patients, and it's oftentimes the first systemic type of therapy that patients will have. In many cases, we're lowering the dose, and we're following the levels of the lipids and the cholesterol, and we're modifying treatment, based on how the patient actually does with the therapy.



Slide 26 – HDAC Inhibitors in MF/SS

The other oral drug that's used very frequently is vorinostat, and vorinostat is an HDAC or histone deacetylase inhibitor. The histone deacetylase inhibitors also work by effectively binding to the genes and affecting the transcription of the genes and the proteins that are made in the tumor cells. And this just shows you in this cartoon how this molecule SAHA, which is vorinostat, kind of fits into this particular pocket of this enzyme and affects the way that the genes are being transcribed in the cell.

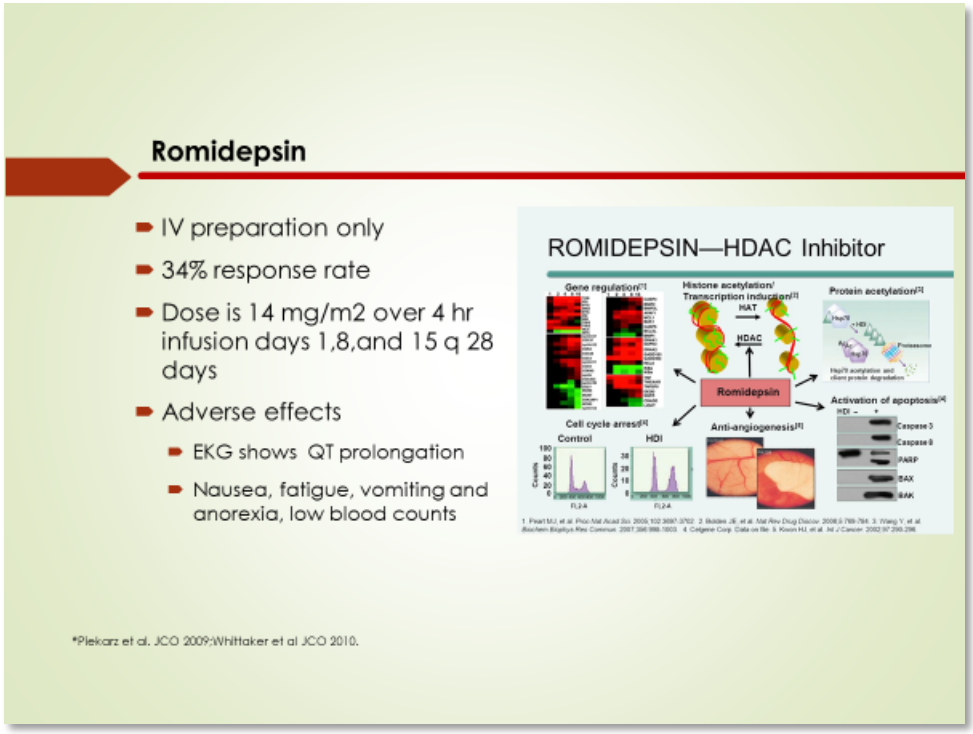
So, the activity of vorinostat in a clinical trial in patients with mycosis fungoides was about 30%. So, one in three patients had a good response to this drug and the drug was given at the dose of 400 milligrams per day.

Now, like other drugs that we use, we oftentimes modify the dose, and many of my patients actually are taking a 200 milligram dose and are having a very good clinical effect with that. The side effects of vorinostat include diarrhea, which can be disabling in some patients, as well as the lowering of the platelet count, which actually isn't a really big clinical problem for us. And some patients can have a slight increase in their creatinine level, or their kidney function.

Now, all of these effects are very quickly reversible when you stop the vorinostat. And again, both bexarotene and vorinostat are drugs that need to be taken every day, seven days a week.

Slide 27 – Vorinostat – Visible Improvements in Skin Lesions

This slide just gives you an example of how these drugs are doing in patients with the disease. So, this is a patient who has tumor stage disease, and you can see the tumor here. And you can see as the patient progresses on, with the vorinostat, you can see that the tumor pretty much goes away. And that's a typical thing that will happen in our patients on vorinostat.



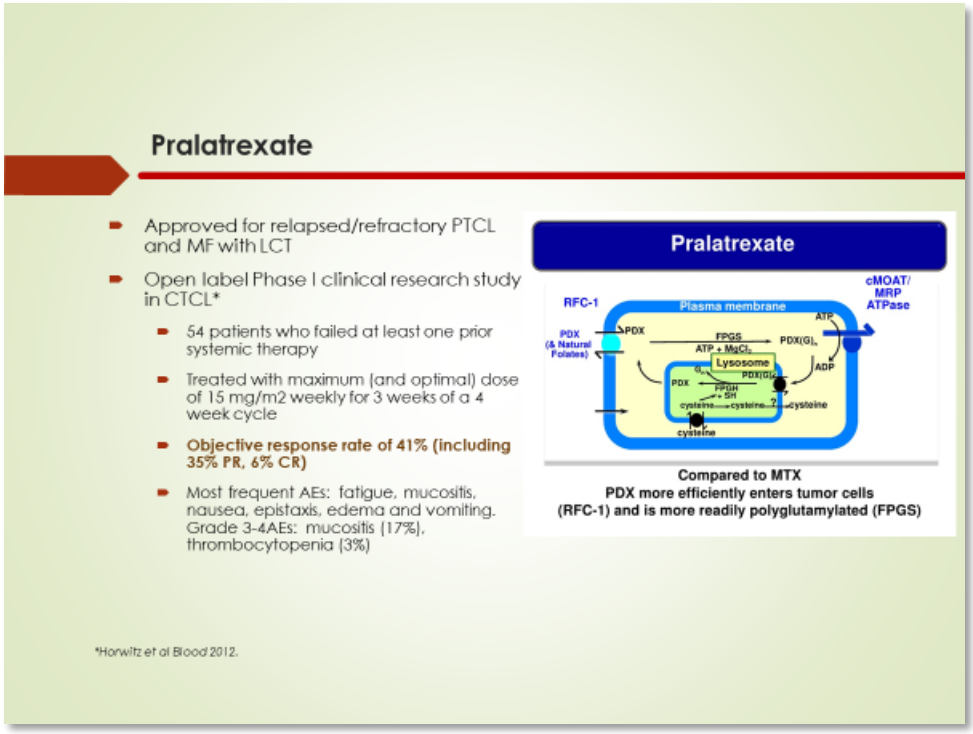
Slide 28 – Romidepsin-HDAC Inhibitor

So, we also now have an intravenous histone deacetylase inhibitor, and that drug is called romidepsin. And again, this is FDA approved for patients with cutaneous T-cell lymphoma as well as patients with aggressive T-cell lymphoma. So, the romidepsin has a number of different effects, and I show you this picture just to show you how complicated the mechanism of some of these drugs is, that they affect the expression of different genes, but they also affect proteins, as well. And they affect, as you can see, a number of different pathways in the cell that lead eventually to cell death.

So, the romidepsin is given intravenously. It takes four hours to get the infusion, and it's given on days one, eight, and fifteen every 28 days, so three weeks on and then one week off. And the response rate is very similar to vorinostat, which is about 34%, in the case of romidepsin. And the side effects are also somewhat similar. Patients can have fatigue, they can have nausea, low appetite. And also, there can be some changes in the EKG that we see, but that doesn't really have a clinical effect on the patient.

So, when I give romidepsin to my patients, one of the major things that happens is patients come in and say they're fatigued, and they have a change in their taste, and perhaps their appetite is off a little bit. So, as they're on the drug for longer, those effects can be better or worse. In the case where they get worse, I generally try to lower the dose, and in some cases, I actually give the drug every other week, which can be just as effective for some patients.

Romidepsin, and vorinostat are drugs, like the bexarotene, that can be given for a very long period of time. And oftentimes, once a patient has a good response, we'll keep them on the drug, in a maintenance setting. And so, we have patients that have been taking these drugs now for two, three, four years.



Slide 29 – Pralatrexate

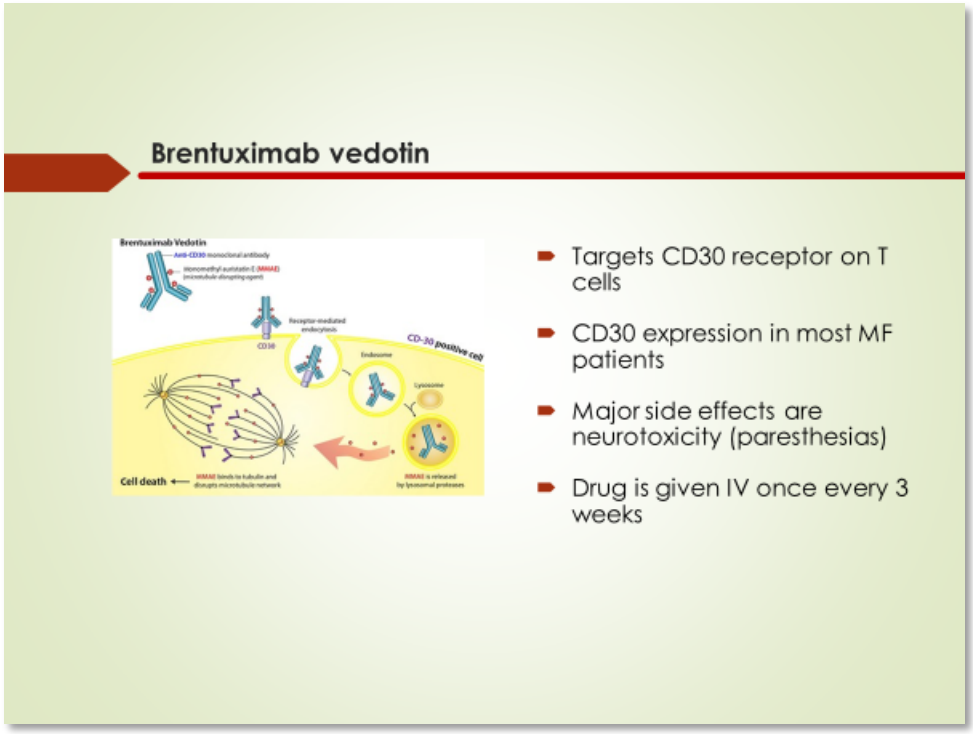
The other drug that's new and has activity is pralatrexate. Pralatrexate was approved by the FDA for patients with aggressive T-cell lymphoma, but we included patients with mycosis fungoides and large cell transformation on that clinical trial that led to the approval of the drug.

Pralatrexate works like a drug called methotrexate. So, it's a similar, drug to methotrexate where it basically gets into the cell through the reduced folate carrier, which is on the surface of the cell, and then it affects the metabolism of the cancer cell, leading to death of the cell.

Now, there has been a specific trial for pralatrexate in cutaneous T-cell lymphoma where we treated 54 patients, and we did different doses and different schedules. And we saw a 41% response rate. So, that was actually, you know, pretty good, and we were very happy with that when we saw those responses, particularly in the very advanced stage patients.

And the side effects of pralatrexate are mucositis or mouth sores, nausea, and some lowering of the blood counts. But those, again, are related to the dose. And we find now that if we give medications like folic acid and leucovorin to patients getting pralatrexate that we don't get the high incidence of side effects with mucositis.

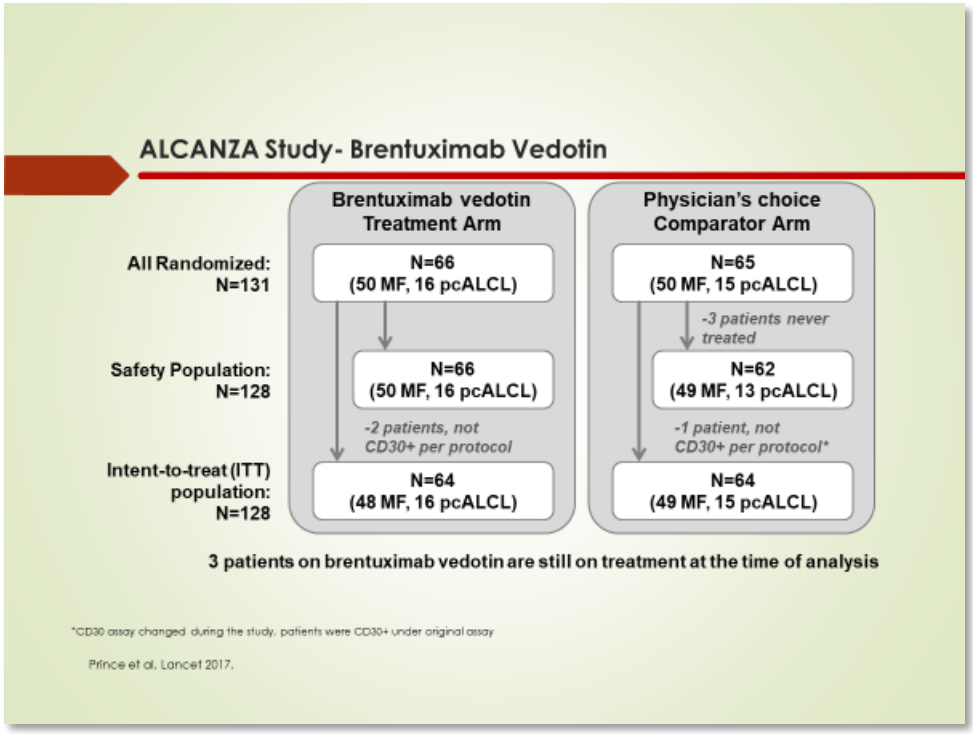
And so pralatrexate is also a very good drug with good activity. The way I give pralatrexate in CTCL is I give a dose weekly for three weeks with one week off, at a dose of 15 milligrams per meter squared. But I have many patients who've actually responded to lower doses, and I have some of my patients coming in every other week or once every three weeks once they have a good response, staying on this drug for maintenance.



Slide 30 – Brentuximab vedotin

While brentuximab vedotin is the newest drug to be FDA approved, brentuximab vedotin is a drug that specifically targets CD30, which is a receptor on the surface of the malignant T-cells. And you can see in the cartoon here where the brentuximab is an antibody that's carrying a charge or a load, and the load that it's carrying is a toxin called MMAE. And so, what happens is this antibody delivers the toxin to the tumor cell by binding to the CD30. It then gets into the tumor cell, as you could see here. Once it's inside the tumor cell, that toxin, that MMAE, comes off, and it goes out, and it actually kills the cell. So, this is really a fancy delivery system to get that toxin into the cell.

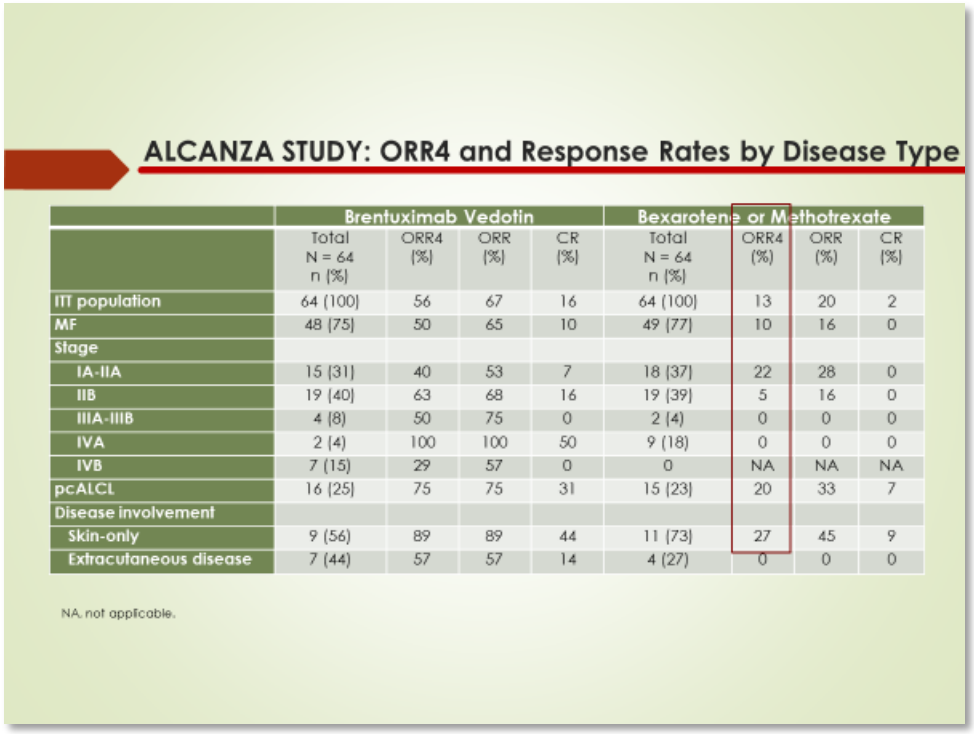
So, it turns out that most of our patients with mycosis fungoides express the CD30 receptor so they respond to this drug. The major side effects of this drug are damage to the nerves, so paresthesias or numbness or tingling, oftentimes in the hands and the feet. And this drug is given once every three weeks by an IV infusion.



Slide 31 – ALCANZA Study – Brentuximab Vedotin

So, this study, as I mentioned, was FDA approved, for patients with mycosis fungoides, and that was based on this study called the ALCANZA Study where they actually randomized patients with mycosis fungoides to either get the drug or to get physicians' choice, which was bexarotene or methotrexate. And you can see, um, that there were about 66 patients entered, uh, on both arms of the study. The patients were randomized, and the overall population was 131 patients who ended up getting treated.

So we were able to compare the response with brentuximab to the response with either the bexarotene or the methotrexate.



ALCANZA STUDY: ORR4 and Response Rates by Disease Type

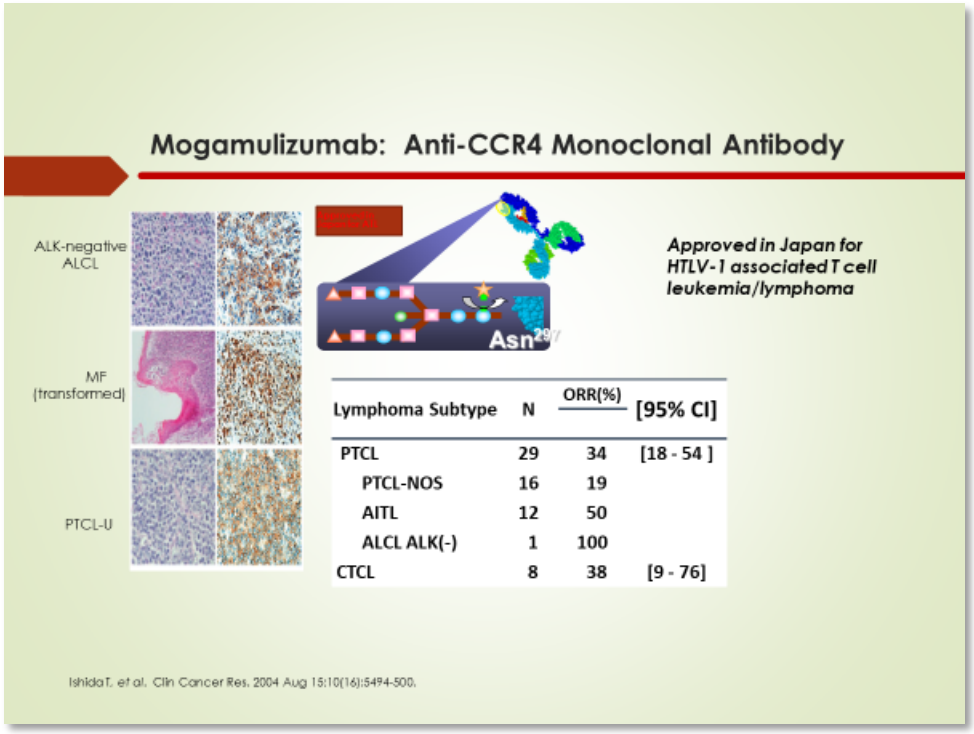
	Brentuximab Vedotin				Bexarotene or Methotrexate			
	Total N = 64 n (%)	ORR4 (%)	ORR (%)	CR (%)	Total N = 64 n (%)	ORR4 (%)	ORR (%)	CR (%)
ITT population	64 (100)	56	67	16	64 (100)	13	20	2
MF	48 (75)	50	65	10	49 (77)	10	16	0
Stage								
IA-IIA	15 (31)	40	53	7	18 (37)	22	28	0
IIB	19 (40)	63	68	16	19 (39)	5	16	0
IIIA-IIIB	4 (8)	50	75	0	2 (4)	0	0	0
IVA	2 (4)	100	100	50	9 (18)	0	0	0
IVB	7 (15)	29	57	0	0	NA	NA	NA
pcALCL	16 (25)	75	75	31	15 (23)	20	33	7
Disease involvement								
Skin-only	9 (56)	89	89	44	11 (73)	27	45	9
Extracutaneous disease	7 (44)	57	57	14	4 (27)	0	0	0

NA, not applicable.

Slide 32 – ALCANZA Study: ORR4 and Response Rates by Disease Type

So, if you look at brentuximab, the overall response rate for patients at four months was, um--you can see here, about 50% of patients with mycosis fungoides, 56% overall if you look at all the different subtypes of cutaneous lymphoma. So, this is a very good response rate for this.

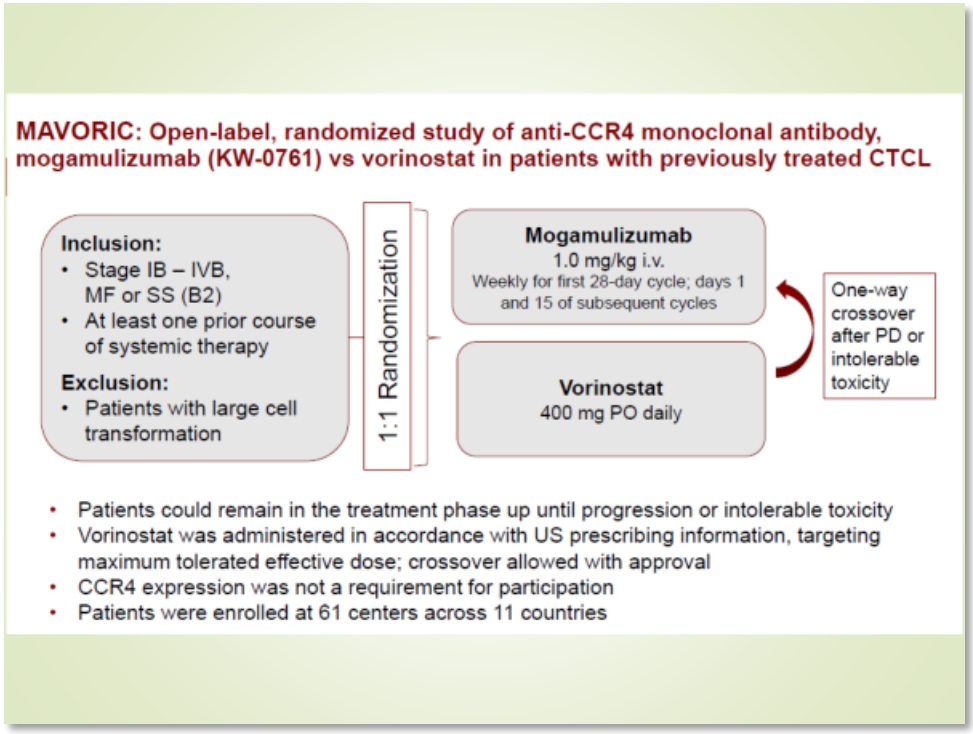
And then if you swing over to the red box and look at the response rate for either the bexarotene or the methotrexate, it really wasn't very good. So, it was about 10 to 13%. So, at least in this clinical trial, they showed that the brentuximab is a very active agent for patients with mycosis fungoides, and you can look at the different stages of disease. So, it seemed to work fairly well for the patches, plaques, tumors, and the erythroderma.



Slide 33 – Mogamulizumab: Anti-CCR4 Monoclonal Antibody

Another drug that I hope is going to be FDA approved, very soon is mogamulizumab. Now, mogamulizumab is a little bit different because, again, it's a monoclonal antibody, against CCR4. But it's doesn't carry any payload or any toxins. So, it's a plain monoclonal antibody.

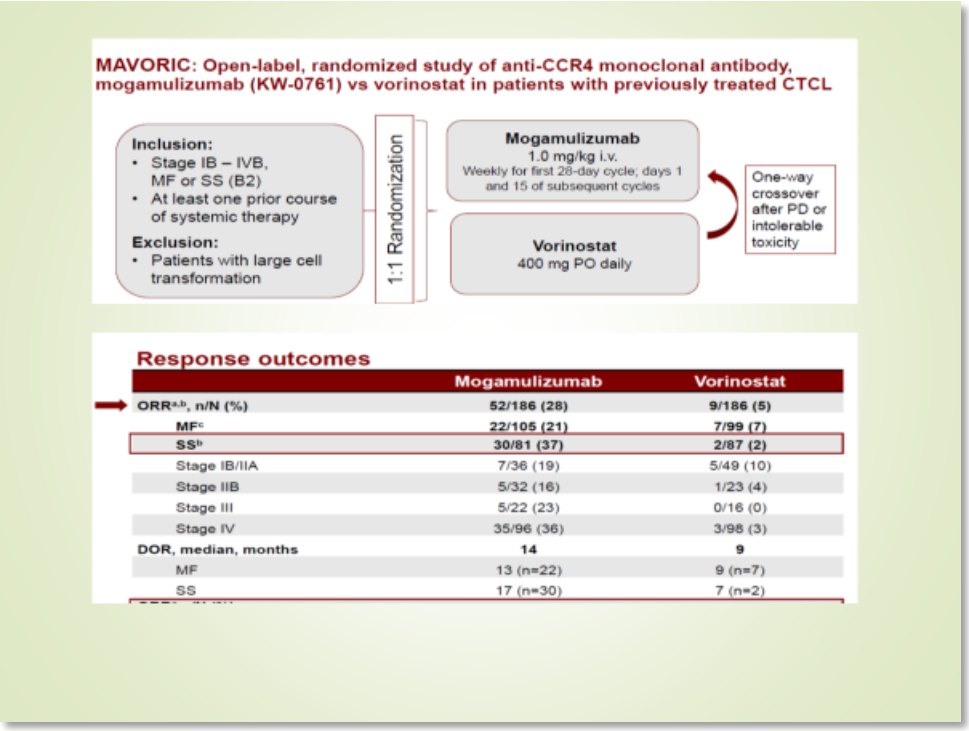
Now, it's targeting CCR4, which is a protein that's expressed on the surface of patients with T-cell lymphoma. And mycosis fungoides is one of those T-cell lymphomas that expresses the CCR4. It has been used in patients with aggressive T-cell lymphoma, as shown on this slide, and it's actually approved, by the equivalent of the FDA in Japan for patients with aggressive T-cell lymphoma and T-cell leukemia.



Slide 34 – MAVORIC: Open-label, randomized study of anti-CCR4 monoclonal antibody, mogamulizumab (KW-0761) vs vorinostat in patients with previously treated CTCL

So, in the United States, we just completed this very large study called MAVORIC. Again, this is a randomized trial which enrolled patients with mycosis fungoides or Sézary syndrome who had prior therapies, you can see stages I through IV. And patients were randomized either to receive the mogamulizumab or vorinostat.

Now, if they were on the vorinostat part of the study and they progressed or got worse, they were allowed to get the mogamulizumab. And so, at the end of the day, you can see the results of this study.



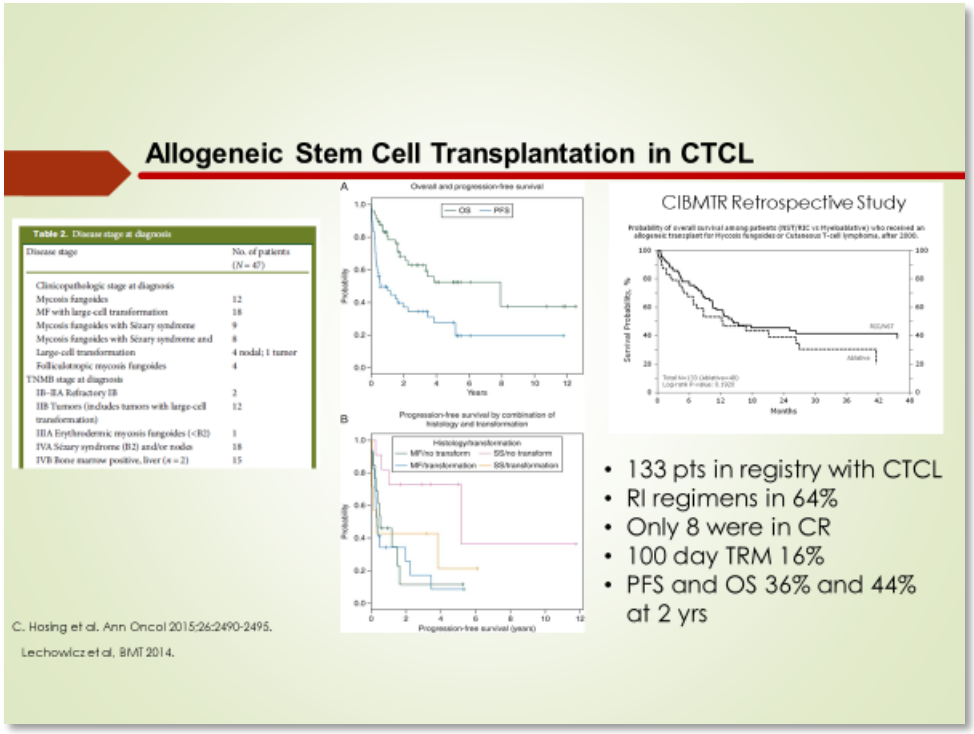
Slide 35 – MAVORIC: Open-label, randomized study of anti-CCR4 monoclonal antibody, mogamulizumab (KW-0761) vs vorinostat in patients with previously treated CTCL

So, this study enrolled a large number of patients with mycosis fungoides and Sézary syndrome. And basically what it showed is that the overall response rate to mogamulizumab was 28%. But, in the Sézary patients, it was 37%. So, it looked like it was maybe working a little bit better in the Sézary patients than in the patients with the patch plaque mycosis fungoides. And you look at the response rates to vorinostat, which were already lower in the study.

So, again, this study is showing that a new drug has very significant activity and a population of patients with relapsed and refractory mycosis fungoides.

So, what are the side effects of mogamulizumab? So, mogamulizumab is a monoclonal antibody. So, it's a protein. And there can be an infusion reaction when you get the drug. So, you might get some chills or a low grade fever. In addition, the drug can deplete some of the normal populations of T cells. So, it's possible that there might be a slightly higher risk of infection. But, our patients who are on this clinical trial all got prophylactic antibiotics just to protect them.

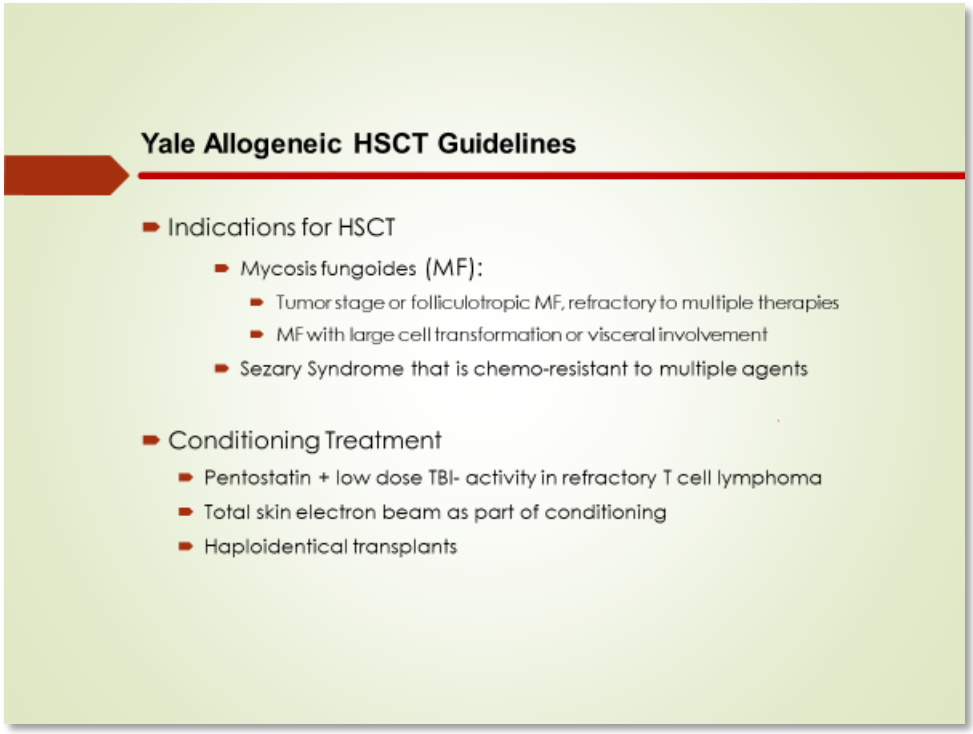
This is a drug that I've used in the clinical trial. It's a drug that, I think, has a lot of activity. I'm very excited about it, particularly for Sézary patients. And I have a number of patients who are kind of waiting in the wings hoping that it's FDA approved soon so that we can use it.



Slide 36 – Allogenic Stem Cell Transplantation in CTCL

So, I mentioned that for some patients, they end up having significant refractory mycosis fungoides and Sézary syndrome, and they need to move on to get an allogeneic bone marrow transplant. So, the good news is that we've shown recently that we're able to successfully transplant patients with cutaneous T-cell lymphoma and also that those patients can do very well.

So, this slide is just some of the early data that's come out of MD Anderson where they've transplanted 47 patients. And they've actually done pretty well with these patients. So, patients are going into remission, and they're staying in remission. Now, on the right-hand side of the slide, this shows you, a review of our Bone Marrow Transplant Registry, which is a very large international registry. And you can see that patients with mycosis fungoides who had transplants--allogenic transplants are shown here. And you can see that, uh, about half of these patients are actually doing very well. Now, interestingly, at the time that we did this review, back in 2014, there were only 133 patients in that registry with cutaneous T-cell lymphoma. I think that, five or six years from now, that number's going to be double, if not triple, because many of us are now doing these transplants in our patients, particularly those with advanced stage disease.



Slide 37 – Yale Allogeneic HSCT Guidelines

Well, what are the indications for doing a bone marrow transplant? And, again, this is an evolution. But, what I'm showing you here are my guidelines for how I decide, at Yale, which patients are candidates for transplant. So, if you look at mycosis fungoides patients, I showed you the survival curves are showing that many, many patients with this disease do very well. They can stay on therapy for a long time and be very stable. But, the patients that may not do so well are those with tumor stage disease. I talked about folliculotropic MF (mycosis fungoides). But, I didn't say a lot about it in the talk. But, folliculotropic can be associated with a more aggressive clinical course, can be harder to treat, and less responsive to therapy. So, again, these patients who have tumor stage or folliculotropic who go from treatment to treatment and don't have a good response to their therapy are certainly patients that should be considered for transplant.

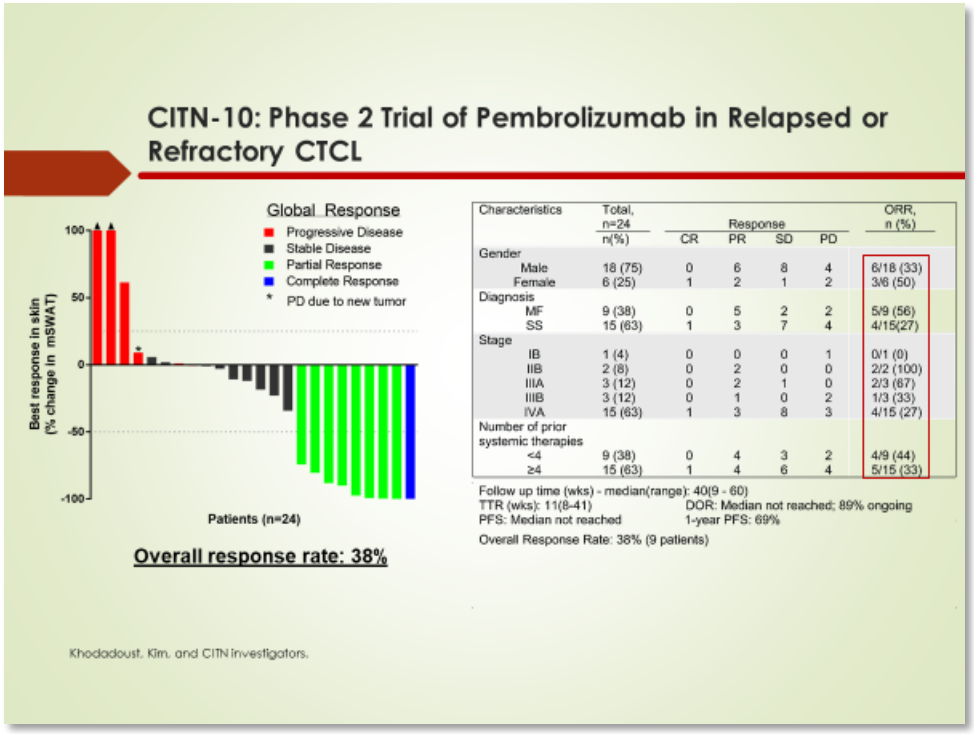
In addition, we've talked about large cell transformation or patients who have a more aggressive clinical course, in particular, patients who develop involvement of their organs, such as their liver, their spleen, their lungs, et cetera. Those are patients with very aggressive disease, and those patients should be considered for a transplant, if they can go into remission with chemotherapy.

And then, there are the patients with the Sézary syndrome. So, again, there are patients with early stage Sézary that can have photopheresis or some of the HDAC inhibitor therapies. And they can do very well, and their disease is very stable. And we get them in remission. And I can say that I've actually had Sézary patients go into complete remission and stay in remission on those kinds of therapies. But, there are also Sézary patients who have more aggressive disease, that go from treatment to treatment, again not that sensitive to the--to the various kinds of therapies, in particular, those that develop big lymph nodes, for instance. And those are patients that should be considered for a stem cell transplant.

So, what we're trying to do in the future is actually--at my institution and others, we're actually trying to identify markers in the malignant cells that would tell us that patients are going to do worse. And those could be some specific gene markers or mutations. So, I'm not going to say anything about that now because that research is in its infancy. But, I'm hoping, over the next two or three years that we'll have some more specific information, pooled information from lots of different centers that are looking at this, to help us to predict which of those patients with Sézary syndrome are going to do poorly and perhaps should be considered for the transplant sooner rather than later.

So, as far as, how we get a patient ready for a stem cell transplant--we have different kinds of conditioning therapies that we use. And, at least at Yale, we use a low dose of total body radiation because we believe that that helps the patient to get rid of any residual disease before the transplant. The other thing that we do, MD Anderson, Memorial Sloan Kettering, and other transplant centers also do, is that we try to do a very short course of total skin electron beam therapy as part of the conditioning just to really clean up the skin to the best degree possible before the patient comes into the transplant.

And then, I--finally, I want to mention haploidentical transplant. So, it used to be that you could only get a stem cell transplant if you had a donor. So, donor would typically be a family member, a brother or a sister with the same parents that might match you. And then, in some cases, we would go to the bone marrow registry and look for unrelated donors that would match you. But, what's happened because of the heterogeneity in our population, smaller family sizes, et cetera, is that there are many patients that don't have a match. So, the haploidentical transplants are done from a brother or a sister that's a half match or a parent that would be a half match. So, this has really opened up stem cell transplant to a larger number of patients. And I've done many of my patients, uh, over the last two years, using a haplo donor. Haplo donors are working very well for patients with mycosis fungoides and Sézary syndrome. And hopefully, more of our patients with be eligible for transplants using this approach.



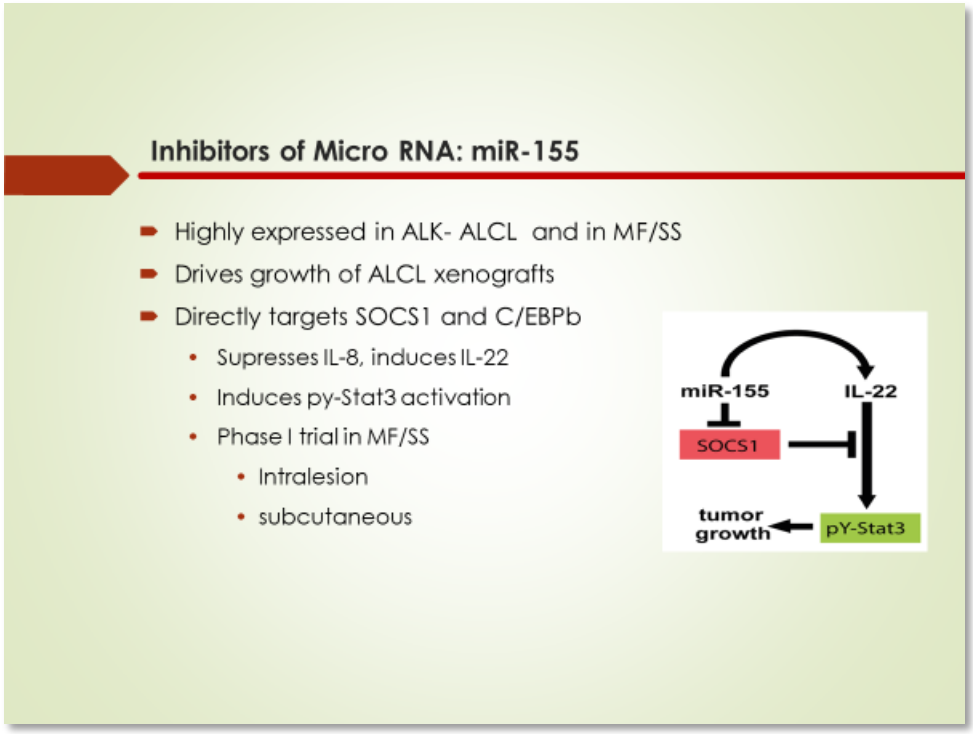
Characteristics	Total, n=24 n(%)	Response CR	PR	SD	PD	ORR, n (%)
Gender						
Male	18 (75)	0	6	8	4	6/18 (33)
Female	6 (25)	1	2	1	2	3/6 (50)
Diagnosis						
MF	9 (38)	0	5	2	2	5/9 (56)
SS	15 (63)	1	3	7	4	4/15(27)
Stage						
IB	1 (4)	0	0	0	1	0/1 (0)
IIB	2 (8)	0	2	0	0	2/2 (100)
IIIA	3 (12)	0	2	1	0	2/3 (67)
IIIB	3 (12)	0	1	0	2	1/3 (33)
IVA	15 (63)	1	3	8	3	4/15 (27)
Number of prior systemic therapies						
<4	9 (38)	0	4	3	2	4/9 (44)
≥4	15 (63)	1	4	6	4	5/15 (33)

Follow up time (wks) - median(range): 40(9 - 60)
TTR (wks): 11(8-41) DOR: Median not reached; 89% ongoing
PFS: Median not reached 1-year PFS: 69%
Overall Response Rate: 38% (9 patients)

Slide 38 – CITN-10: phase 2 trial of pembrolizumab in relapsed or refractory CTCL

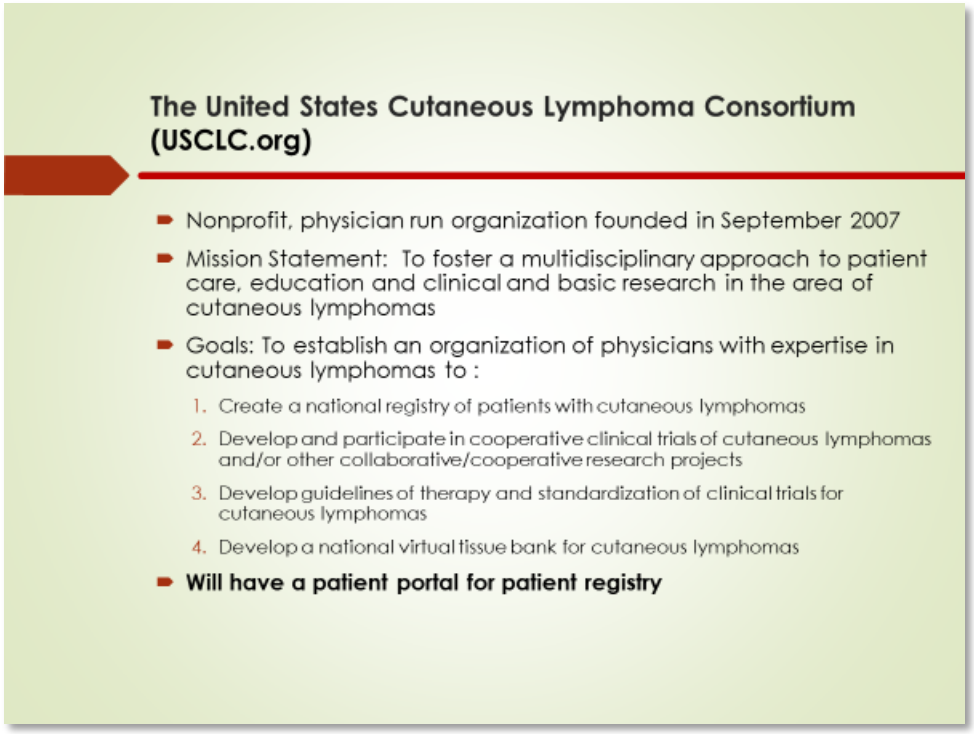
I'm just going to talk about a couple of new things. We've all heard about checkpoint inhibitors. So, drugs like nivolumab and pembrolizumab that have made a big splash in the treatment of Hodgkin's disease and various solid tumors.

So, we do have some limited data in patients with mycosis fungoides. And this is a clinical trial that was done at a number of different centers around the United States just showing you that we had a group of patients that we treated, and we had an overall response rate of 38%, which we were really pretty happy with. And we saw responses in patients with different stages of disease. And so, we are now pursuing this with another clinical trial where we combined the pembrolizumab with interferon, and we're also thinking about trials combining it with other things as well. So, I think pembrolizumab or the checkpoint inhibitors definitely play a role in patients with cutaneous T-cell lymphoma. We may not have defined exactly yet how we should give the drug and who we should give it to. But, I think we'll see that in the future.



Slide 39 – Inhibitors of micro RNA: miR-155

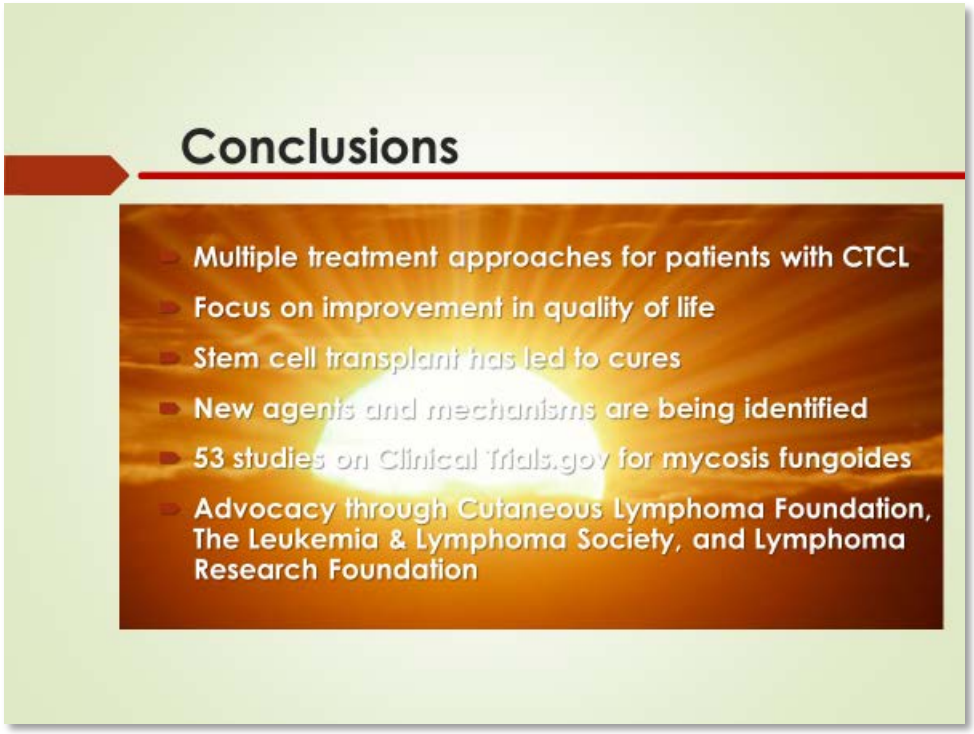
Another new drug that I think is exciting is this drug that's a micro-RNA inhibitor of a specific micro-RNA. It turns out that this micro-RNA is highly expressed in patients with mycosis fungoides. We can show that this micro-RNA suppresses the growth of tumor cells, and, in particular, that's been shown in patients with Sézary syndrome as well. And so, we did a clinical trial where we injected this into the actual tumors or lesions on the skin of patients with mycosis fungoides. And then we injected it under the skin, and I'll say that we're now at the next stage in the clinical trial where we're giving this drug intravenously. And this drug is working very well. But, again, it's in early development of this drug. So, hopefully it will be able to move forward in a larger study.



Slide 40 – The United States Cutaneous Lymphoma Consortium (USCLC.org)

Now, this slide really just provides you with some information about what the community of physicians is doing, to try to advance the state of the art with mycosis fungoides and Sézary syndrome. So, we have developed the United States Cutaneous Lymphoma Consortium. And this is a nonprofit physician run organization that's mission is to foster a multidisciplinary approach to patient care, education, and clinical and basic research in cutaneous lymphomas. So, we are trying to include all physicians who treat these diseases. One of the things that we've done that would be of interest to patients is that we've created a national registry that's going to be used not only by doctors but also by patients. And we're including different types of cutaneous lymphomas, including cutaneous B-cell lymphoma. We're developing a network of centers that can do cooperative clinical trials and cooperative research. We're also trying to develop guidelines for therapy and trying to standardize some of the measures for clinical trials. And, more importantly, we'd like to develop a national virtual tissue bank so that we're collecting tissue for the kinds of genetic studies I talked about that will help us to improve therapies in the future.

And for patients in the audience who are listening, we actually have developed a patient portal so patients can actually get into this registry, and they can record their symptoms, and be part of this effort. And that is being cosponsored by the Cutaneous Lymphoma Foundation as well.

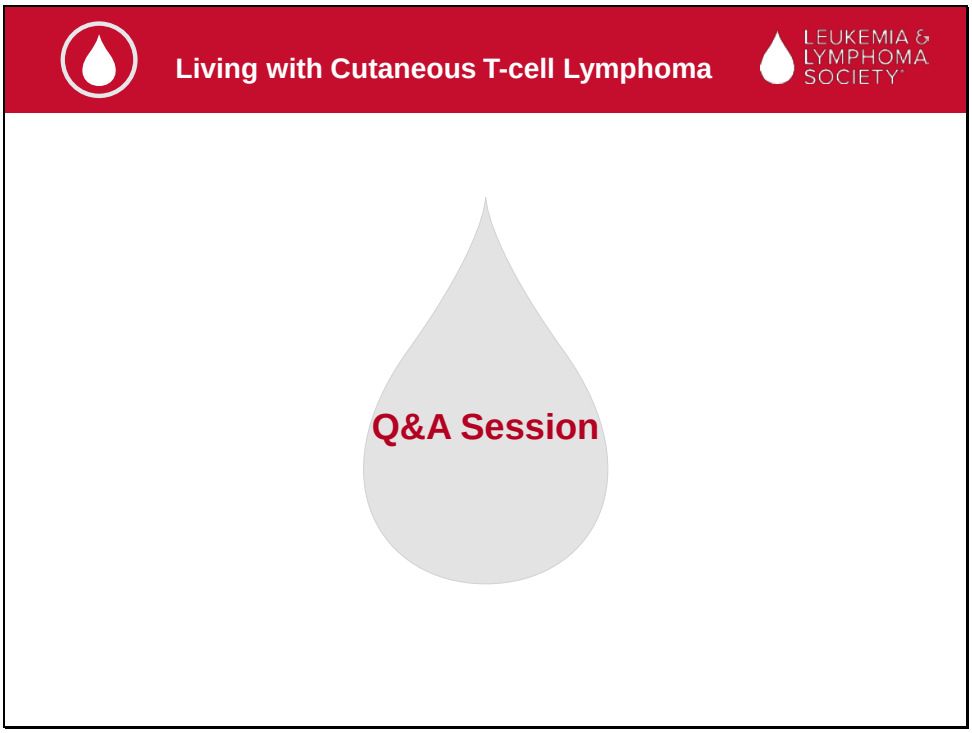


Slide 41 – Conclusions

So, just, in summary, my conclusion slide was carefully selected, showing in the background a sunrise because I think we're just right at a pivotal point with this disease now where a lot of things are happening. There's a lot of excitement, and I think the best is yet to come for patients with cutaneous lymphoma.

So, we have multiple treatment approaches that I've talked about. We also are now focusing on improving quality of life, which is obviously very important for our patients. We're trying to actually move beyond treatment to cure. We're starting to talk about curing this disease, and certainly the stem cell transplant is one way to get to a cure. We also are collecting tissues and studying the biology and learning about new agents and new mechanisms that could be exploited for clinical trials. And when I actually went and looked on ClinicalTrials.gov, which is the national website where we register all of our clinical trials, there are 53 clinical studies now for patients with mycosis fungoides. So, clinical research is really growing in this area.

And then, also advocacy is growing as well. So, in addition to The Leukemia & Lymphoma Society that's sponsoring this webcast, the Lymphoma Research Foundation and the Cutaneous Lymphoma Foundation also are providing both patient advocacy as well as research dollars to help our patients with cutaneous lymphoma. And I just want to say that it's been a pleasure to work with all of these organizations. And they have worked collaboratively, both with us as physicians, as well as with patients who have this disease. Thank you very much for your attention.



Slide 42 - Q & A Session

Lizette Figueroa-Rivera:
Thank you so much, Dr. Foss, for providing us with this very important update. It's now time for our question and answer portion of our program. We have received some pre-submitted questions from patients and caregivers alike that have contacted LLS through our online community or have spoken to one of our Information Specialists.

Doctor, the first question is asking--should patients be seen on a regular basis by both a dermatologist and an oncologist, and who do I contact when I have a side effect?

Dr. Francine Foss:
So, that is an excellent question, and oftentimes, there can be confusion on the part of the patient when they're involved in multimodality care. But, I would say that it really depends on where you are and the proximity of those physicians. So, many of our patients with earlier stage disease are managed primarily by the dermatologist. They may come to see the medical oncologist for a consultation, and they may have some intermittent visits with the medical oncologist. But, for the most part, most of their therapy is directed by the dermatologist. The dermatologist would then make the referral to medical oncology when they feel that the disease is at the next level where the medical oncologist needs to get more involved.

But, there are many areas of the country where, there may not be a dermatologist that has expertise in cutaneous lymphoma. And the medical oncologist may actually be the primary provider. So, I think it's really important to identify who your providers are, in your area and what makes the most sense for you as a patient. And I would say that it could go either way. And, in addition, I also want to mention to patients, that many patients who live in an area of the country where there may not be a disease experts could travel, uh, if they can travel, to one of the disease experts, regionally and, that physician is willing to work with their

community physicians as well, so that they can keep most of their care local and close to home. But, they have the expert advice.

Lizette Figueroa-Rivera:
Thank you, doctor. And the second question--I heard that the average time to diagnosis from the start of a rash is six years. Is that true? And why can't it be detected or diagnosed earlier? I was diagnosed years after. And is this type of cancer better to treat earlier rather than later?

Dr. Francine Foss:
That is a very complicated question. And I think it reflects the frustration on the part of patients who have had these symptoms and these rashes, and they've been going to different providers, and it's been years and years before anybody has made a definitive diagnosis. So, one of the problems with mycosis fungoides is that the--incidence of new cases per year in the United States is probably about 1,500 to 2,000. But, the incidence of all kinds of other skin conditions is much higher than that. And, as I've shown you in the slides, this disease can mimic many of those other skin conditions. So, it can be very difficult at first to really identify this as a malignancy, in its earlier stages. And it may not be incorrect for the local dermatologist or- physicians to treat with topical steroids and see if the rash goes away and then, you know, maybe give some oral steroids and see if it gets better. But, at some point, if- a rash like this is persisting, you know, for months and months, I would at least advise that there should be a skin biopsy.

And that may or may not be helpful early on. So, I showed those criteria to point out the fact that there's still a lot of confusion with the very earliest stages of the disease because it can overlap a little bit with some of those benign skin conditions. So, we don't have a really good answer to that question. But, I would tell patients that, if there's something that you're worried about--and this goes for anything--and you're not getting an answer that you feel satisfied with, then you should probably seek another opinion.

Now, I just want to say too that there are many patients I see with mycosis fungoides that had actually had some form of dermatitis. I also have patients who have psoriasis and mycosis fungoides at the same time. So, again, it's- still very confusing, and it really would just depend on the rash, the patient, how long they've had it, what things they've done for it. But, I would ask patients to please try to seek another opinion if they're not satisfied.

Lizette Figueroa-Rivera:
Thank you. We definitely talk to patients and do advocate the second opinions, especially from key opinion leaders and specialists in the field because we do find that a lot of patients are not really diagnosed early or have said that they have had symptoms for a while. So, thank you for addressing that.

The next question says--infection with the HTLV1 virus has been linked with adult T-cell leukemia and lymphoma, although most people infected with the virus do not develop lymphoma. This infection is prevalent in parts of Japan and the Caribbean. So, does CTCL affect certain ethnicities more so than others?

Dr. Francine Foss:
The answer to that question is that it doesn't really affect ethnicities differently. But, --the incidence in Asian folks is lower than it is in Caucasians. The disease in African Americans tends to be a little bit worse. It's more common in men. It's probably more prevalent in African Americans. Again, these are difficult because we don't always diagnose it correctly early on. There is no known inheritance pattern for mycosis fungoides.

But, I will say that I've had patients who have had other family members with the disease. I've also had identical twins where one has had it and the other has not. So, we don't fully understand why one person gets it and another one doesn't. But, there are some clues with respect to patients who may have had a history of allergies or atopic dermatitis or other kind of immune mediated things in their past that perhaps they might be slightly more likely to develop a disease like this.

Lizette Figueroa-Rivera:
That's interesting. Thank you. The next question, treatment for CTCL also requires frequent visits. In light treatment, for example, is done three times per week. A patient needs to make time to do that, and they need transportation, not to mention CTCL treatment is not offered everywhere. These kinds of things make it difficult for some groups of patients to access regular therapy. Any thoughts on how to ensure patients are more readily able to adhere to treatment?

Dr. Francine Foss:
That's also a very good question, um, and it is very hard for some of our patients who travel a long way to get to a treatment center. So, sometimes our treatment decisions, unfortunately, are made based on what is feasible for a patient. The good news with mycosis fungoides is that there are a number of different options so that it isn't just one thing with no other option. Now, with respect to ultraviolet light, there are ways of getting a lightbox at home, for instance. Radiation, of course, you would need to come. We provide an opportunity to get housing locally in a hotel associated with our hospital, for instance, and I know that organizations like The LLS do provide, some help or can help patients to find help, either financial or logistic types of help, to get to the treatment center.

The other thing that's difficult for patients is paying for some of these, oral therapies out of pocket because many patients don't have good insurance. So, again, there are organizations and networks that are trying to help those patients to get copay assistance. But, it is a major issue for patients, and the frequency of the treatments and the longevity of being on therapy are issues that really affect quality of life, and those things need to be addressed when we start thinking about kind of a long term treatment plan for the patient.

Lizette Figueroa-Rivera:
True. Thank you. And we do provide transportation as well as copay assistance programs through The Leukemia & Lymphoma Society. So, thank you for mentioning that. And I will provide the number for our Information Specialists later in the program.

The next question is about transplant. Is stem cell transplant the only curative treatment option for CTCL?

Dr. Francine Foss:
The answer to that question is no because I have patients who have been cured with other modalities. But, the number of patients that are cured is very small, and we really collectively don't have a handle on how to predict which patient is going to be cured with any particular modality. So, at this point in time, the stem cell transplantation is one way that we can cure a patient. It may be the best way from the point of view of us having the data and the evidence of showing that 50% of patients are cured. But, we just don't have the evidence yet with the use of some of the other therapies. But, again, I think patients should not expect a cure unfortunately because, if you actually look at the data that I've shown you, -it's really only about 10% of patients that have a very good lasting complete remission. So, I think it's that the process of identifying which patients are going to be cured is still in evolution.

Lizette Figueroa-Rivera:
Thank you. And the next question is--can physicians start patients on immunotherapies as first line treatment instead of starting with an older treatment such as chemo or radiation since immunotherapies have less side effects?

Francine Foss:
Absolutely. And, in fact, we're trying to advocate that. So, we're trying to educate physicians who are not as familiar with the disease to think about immunotherapies first. And immunotherapy is a very broad term. It could include anything like interferon. It could include the light treatments with interferon. It could include photopheresis. More recently, we have the checkpoint inhibitors. But, I would say, at this point in time, I do not think there's enough evidence with checkpoint inhibitors, that I would use them first. But, I think there's lots of evidence and lots of reason why we should use the other immunomodulatory therapies.

Lizette Figueroa-Rivera:
Thank you. The next question--is there something else besides Benadryl® that can help the severe itching?

Dr. Francine Foss:
The itching is a very difficult problem for most of our patients with this disease, and they go through Benadryl, Atarax®, Claritin®. Another thing that's helpful is gabapentin, and we have a number of patients on gabapentin. We have-- some of our patients are taking naloxone, and there's a clinical trial. We do need new medications for itching. That's an area of unmet medical need in this disease. Some patients require a course of steroids. So, we have patients taking low dose prednisone just to control the itching. But, we really don't like to do that because then the prednisone causes immunosuppression and increased instance of infection. So, I would have to say that, at this point in time, the state of the art for controlling itching is really not where it needs to be.

Lizette Figueroa-Rivera:
Thank you. And what precautions do I need to take in the sun as I have mycosis fungoides?

Francine Foss:
Well, sun exposure is an interesting area to discuss, for patients with mycosis fungoides because on the one hand, you know, ultraviolet light, UVA, UVB, is used as a treatment. So, for some of our patients with early stage disease, we might actually tell them to go out and get, you know, 20, 30 minutes of sun exposure without sunscreen. So, that may actually have a therapeutic effect.

But, as patients move through therapies like total skin electron beam and as they've actually had phototherapy or if they've used topical chemotherapies, their skin becomes more sensitive to the damaging effects of the sun. So, we have to tell them really to avoid the sun. So, I think that's a question where there's no right answer, and it really depends on your talking to your physician and having them look at, you know, the status of your prior therapies with skin exposure and then what therapies you're on now to give you an idea as to whether or not you'd have damage from further skin exposure to the sun.

Lizette Figueroa-Rivera:
Thank you. And next question is--what is a bleach bath, and when would I need one?

Dr. Francine Foss:
A bleach bath is a way of disinfecting your skin. So, we give you a recipe to put a certain amount of bleach into the bathtub, and that actually can help to keep the bacteria count down on your skin. Now, this is important because one of the major problems that patients have are getting skin infections and getting blood infections, such as staph, that effectively comes from your skin. So, if we can keep the bacteria count down on your skin, then, your skin, you know, is going to look better, first of all, and second of all, you're going to be less likely to get infections. This is oftentimes recommended for patients that have, you know, more extensive involvement of their skin and more advanced stage disease.

Lizette Figueroa-Rivera:
Thank you. And is the fatigue associated with the disease or with the treatments?

Dr. Francine Foss:
Well, that's another very good question, and I think it's both. And I think there are kind of three reasons to have fatigue in this disease. Number one, the disease itself. It is a cancer, and, you know, it can, in more advanced stages--it can cause fatigue.

Number two is that a lot of our treatments, such as romidepsin and some of the other treatments, can actually cause fatigue. So, there's treatment related fatigue. There's fatigue because we, lower the thyroid function with bexarotene. So, patients can be fatigued at that level as well.

But, the third thing that I think is happening--and I'm starting to recognize this more and more--is what I call treatment fatigue. Treatment fatigue occurs in patients that have to be on treatment for a long period of time, particularly when they're taking these treatments every day or three times a week, every week for years and years. That whole process by itself can cause kind of a fatigue syndrome. So, we are actually trying to address that by looking at, ways of giving patients treatment holidays, for instance. So, that's a whole area that needs to be explored. But, I think for patients with CTCL, there are many reasons to have fatigue. And oftentimes, we can't really sort out what the problem is. But, we can help patients with fatigue, and I think that's the important thing. So, we are, you know, we're working with some of our collaborators here to look at doing things like, actually giving, in some patients, antidepressants that are activating. In other patients, we might give low doses of Ritalin or a drug like that, that help the patient just to feel a little bit better, as they go through some of these treatments.

Lizette Figueroa-Rivera:
Thanks. That's actually quite insightful for the treatment fatigue, and I'm glad that you're looking into it. And hopefully other institutions will too.

The next question--are there certain skin products I should avoid?

Dr. Francine Foss:
Another very good question because there are lots of different skin products out there with different claims. But, generally speaking, what I tell patients is that a lot of these skin products have additives or perfumes or scents. And they can affect your skin in a number of different ways. So, I tell folks to really avoid most of those, and we recommend sticking to kind of very basic things like Cetaphil® and Aquaphor® and Eucerin®. But, I tell patients if they have something in particular that they, um, were interested in using to bring it in, and our pharmacist would look at the ingredients, and we would try to make a decision whether we think

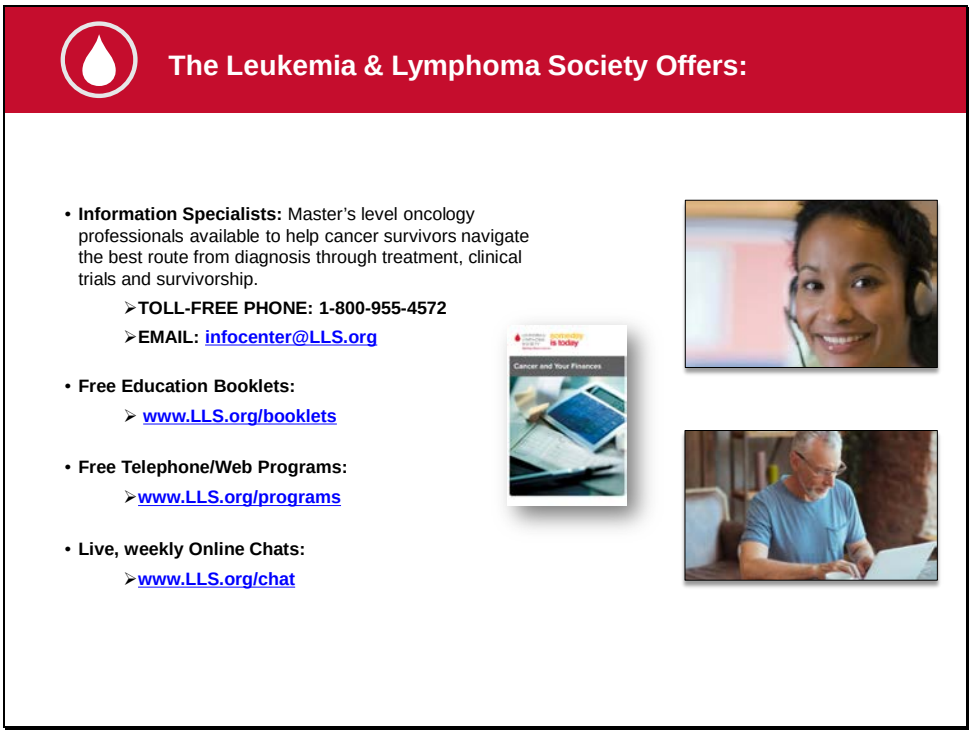
there would be any harm or not. So, generally speaking, I think what I tell patients is less is better and sticking with kind of one standard thing that helps you, whatever that cream is, is the right way to go.

Lizette Figueroa-Rivera:
Thank you. And the last question today--for low grade CTCL is watchful waiting a treatment option?

Dr. Francine Foss:
Another very good question, because you hear about watchful waiting in some patients who have B-cell lymphoma. With cutaneous T-cell lymphoma, it's really, honestly, not an option for many of our patients because they're symptomatic. They come in. They have a disfiguring rash. They have itching. And then, you know, they obviously have concern about the disease. In reality, we actually have some experience where, for the very early patch stage patients, they may actually do well without definitive therapy for a period of time. But, by the time a patient gets into our clinic, they generally have a symptom. So, I would say that, because we have so many low-level therapies nowadays, including the topical retinoids and we have topical nitrogen mustard, for instance--like we have effective therapies that are fairly easy to use, that I generally recommend a patient at least consider going on therapy.

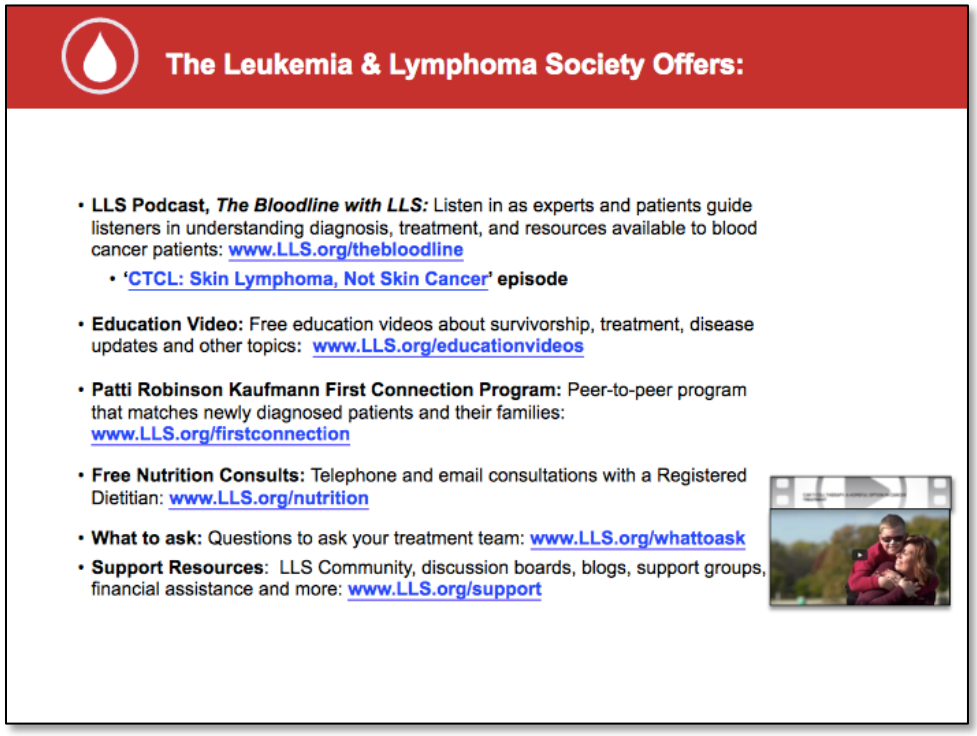
But, on the flip side, you know, if a patient is really averse to doing it and they want to wait and see what the progression of their disease is, as long as they're being followed by a disease expert who's monitoring the situation, I would not be averse to that. But, again, it goes back to whether or not a patient is symptomatic.

Lizette Figueroa-Rivera:
Well, thank you, doctor. And that concludes the question and answer portion for our program. Again, Dr. Foss, thank you for sharing your time and knowledge with us. And, again, thank you to Seattle Genetics for support of this program.



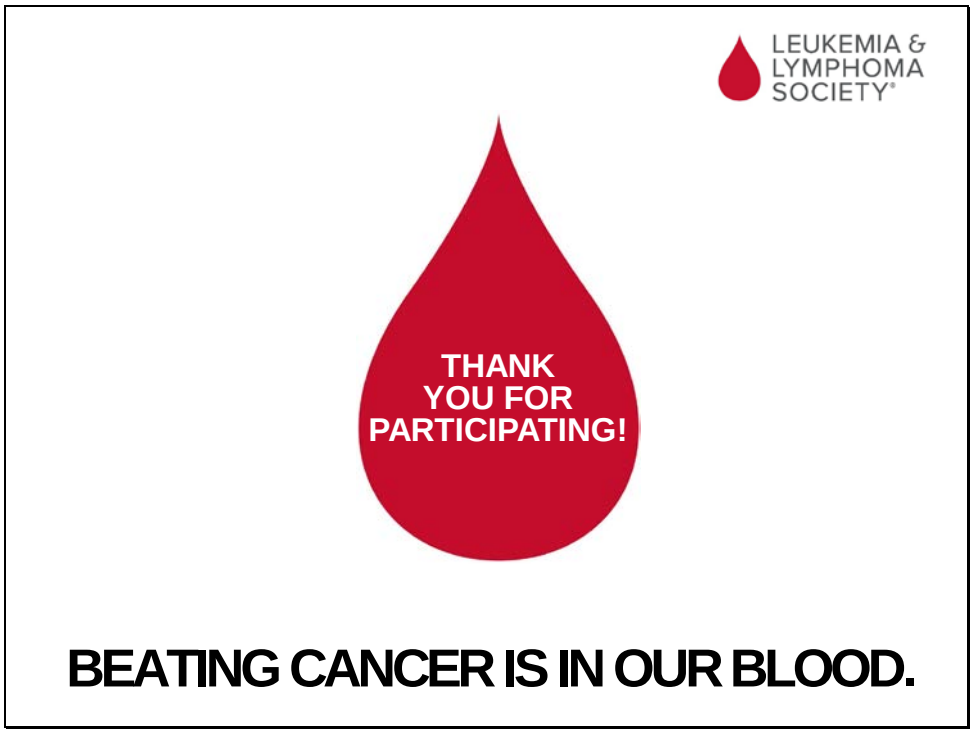
Slide 43- The Leukemia & Lymphoma Society Offers:

If you have additional questions, please call a Leukemia & Lymphoma Society Information Specialist at 1-800-955-4572. Information Specialists are available to speak with you from 9:00 AM to 9:00 PM Eastern time, or you can reach us by email at infocenter@LLS.org.



Slide 44- The Leukemia & Lymphoma Society Offers

We can provide information about treatment, including clinical trials or answer other questions you may have about support, including questions about financial assistance, such as transportation or copay assistance. Also, please visit our online *LLS Community* to connect with our other CTCL patients and caregivers at www.LLS.org/community.



Slide 45- Thank You

On behalf of The Leukemia & Lymphoma Society, thank you for listening, and we wish you well.