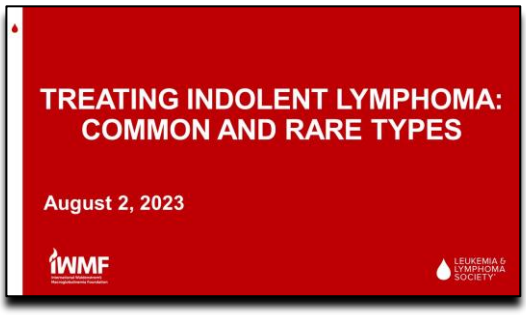
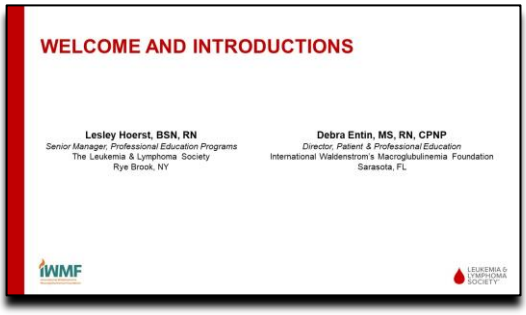


Slide 1: Treating Indolent Lymphoma: Common and Rare Types

Operator: Greetings, and welcome to Treating Indolent Lymphoma: Common and Rare Types, a web education program. At this time all participants are in a listen only mode. It is now my pleasure to introduce your moderator, Ms. Lesley Hoerst. Thank you. You may begin.



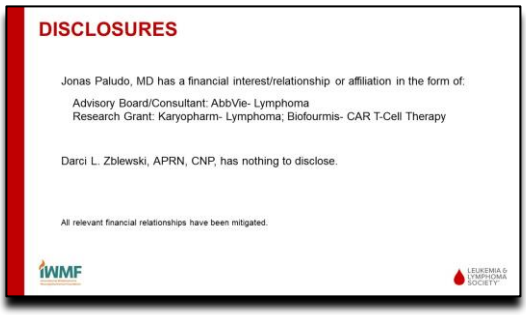
Slide 2: Welcome and Introductions

Lesley Hoerst: On behalf of The Leukemia & Lymphoma Society and the International Waldenstrom's Macroglobulinemia Foundation, thank you for joining us. Our organizations are committed to improving patients' quality of life through webinars such as this one for healthcare providers and education and support resources for patients and caregivers.

This webinar will focus on treating indolent lymphoma, including how to identify and diagnose indolent lymphoma subtypes, new and emerging treatment options, and the interprofessional healthcare team's role in managing these patients. A review of resources you can provide to your patients as well as additional education resources for you will also be provided.

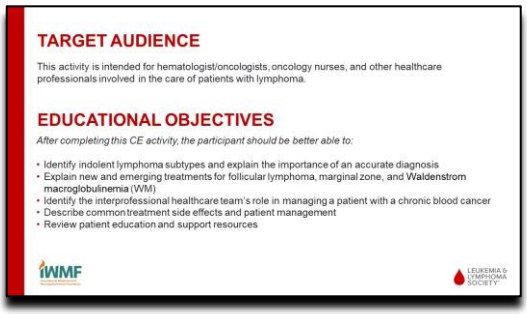
Slide 3: Speakers

I'm honored to introduce our presenters, Dr. Jonas Paludo, Assistant Professor of Medicine and Oncology at Mayo Clinic in Rochester, Minnesota, and Ms. Darci Zblewski, Department of Hematology Lymphoma at Mayo Clinic in Rochester, Minnesota. Thank you for volunteering your time and expertise with us. Following your presentations, we will share information about Resources from The Leukemia & Lymphoma Society and the International Waldenstrom's Macroglobulinemia Foundation.



Slide 4: Faculty Disclosures

Faculty and planner disclosures are listed here.



Slide 5: Educational Objectives
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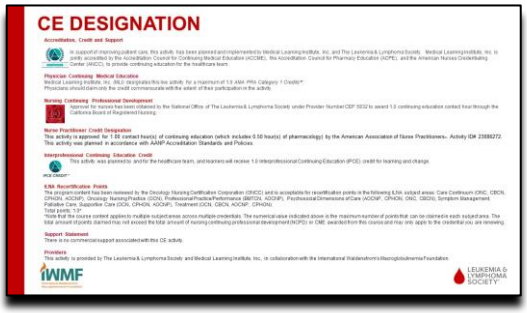
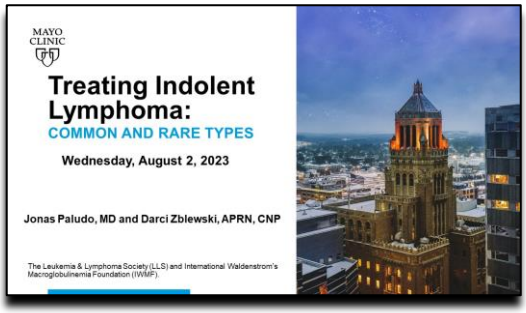
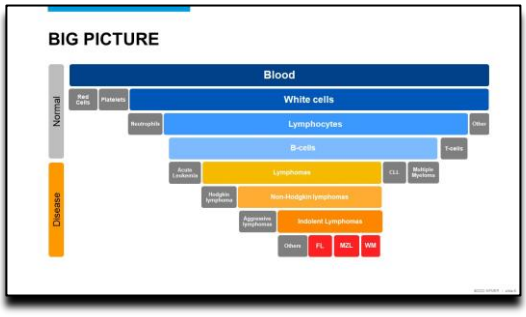


Slide 6: CE Designation
Continuing education information is listed here.



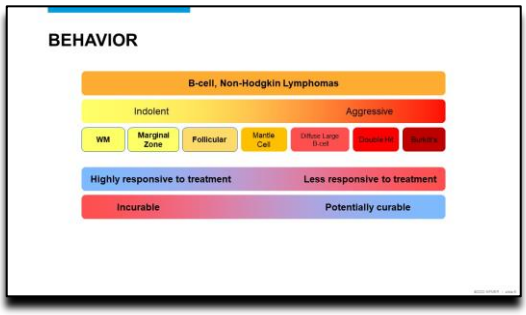
Slide 7: Treating Indolent Lymphoma: Common and Rare Types
Dr. Paludo, it is now my pleasure to turn the program over to you.

Jonas Paludo, MD: All right. Thank you for the kind introduction, and welcome, everyone, to join us today as we talk about some of the principles of indolent lymphomas.



Slide 8: Big Picture
So, I want to start from a 20,000-foot view to showcase where B-cell indolent lymphomas fit into the big picture of hematologic malignancies. Lymphomas are one category of hematologic diseases. They arise from the lymphoid lineage of the hematopoietic system. B-cells or B lymphocytes are the starting point for the B-cell lymphomas, which represent 85 percent of all the lymphoma subtypes and will be the topic of our discussion today.

Now, lymphomas are divided into Hodgkin's and non-Hodgkin's lymphoma. Non-Hodgkin's lymphoma is a category that includes more than 60 different subtypes of diseases with very different characteristics from one another. Non-Hodgkin's lymphoma can be separated also based on their behavior as aggressive or indolent. In a moment, the indolent lymphomas, follicular, marginal zone, and Waldenstrom's are some of the most common subtypes and will be the focus of the treatment section later in the presentation.

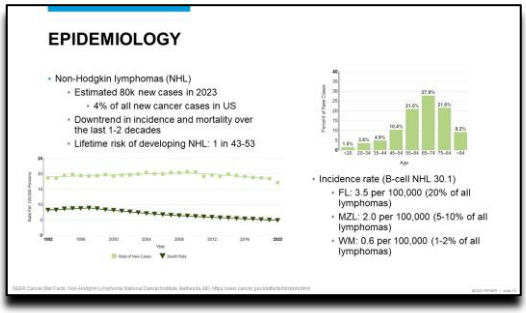


Slide 9: Behavior

So as I mentioned before here, the non-Hodgkin's lymphoma can be divided into indolent, those are slow-growing lymphomas, or aggressive, fast-growing lymphomas. Here I have a gradient on their behavior. It includes some of the examples of different subtypes of non-Hodgkin's lymphoma, with Burkitt's lymphoma, probably the most aggressive lymphoma subtype, which can double in size in a matter of a few days. Mantle cell lymphoma is kind of in the middle here with features of aggressive and indolent diseases. For the indolent lymphomas, follicular is the most common subtype.

Now, indolent lymphomas are in general very responsive to treatment. You only need one or a few drugs, and you can get very good responses in indolent lymphomas. Aggressive lymphomas, on the other hand, are much more difficult to treat. They usually need a lot more chemotherapy, multi-drug chemo regimens. And the overall response rates tend to be lower.

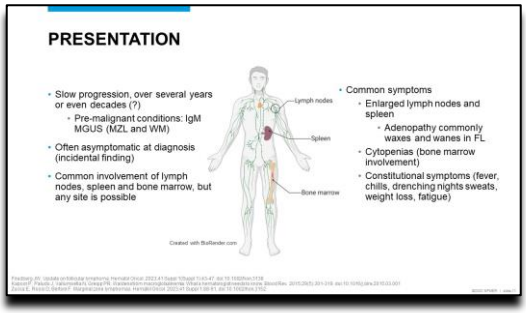
But on the other hand, those aggressive lymphomas that respond well, they are potentially curable diseases, while indolent lymphomas are considered incurable. Of course, there are always exceptions to the rule, but that's the reason why we consider indolent lymphomas a treatable but incurable disease.



Slide 10: Epidemiology

Now in the next slide here, I have an estimate on the numbers. And we estimate about 80,000 new cases of non-Hodgkin's lymphoma in the U.S. in 2023. And if you look at the figure at the bottom here, the incidence of non-Hodgkin's lymphoma is in light green, and the mortality rate is in dark green. It is encouraging to see a downtrend in the incidence over the last 10 years or so, but most importantly, there has been a downtrend in mortality over the last 20 to 25 years. Now, I don't think we have a specific explanation for the improving mortality, but it does coincide with the approval of the first anti-CD20 monoclonal antibody, rituximab, in the mid-90s.

In the next figure here, you can see the distribution of cases based on age. While lymphomas, or non-Hodgkin's lymphoma, is often a disease of older patients, 20 percent of those patients are actually younger than 55 at diagnosis, so not an insignificant proportion of younger patients overall. The incidence of follicular lymphoma, it's about 3.5 cases per 100,000 people. For marginal zone, it's about 2 cases per 100,000. For Waldenstrom's, we are talking about 0.6 cases per 100,000.



Slide 11: Presentation

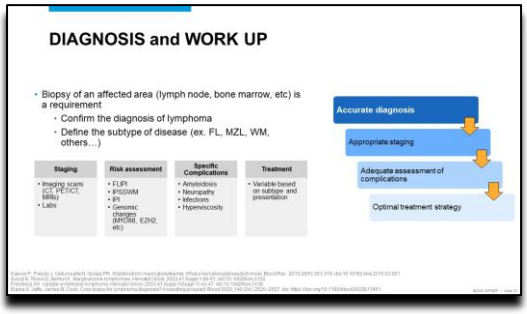
The indolent lymphomas, they usually present as slowly progressive adenopathy, usually over several months to even a few years. IgM MGUS, which is a pre-malignant condition, always precedes the development of Waldenstrom's, sometimes, I'll say rarely, precedes development of marginal zone lymphoma as well.

It's also not uncommon for patients to be diagnosed incidentally while being asymptomatic. And the most common sites of involvement for the indolent lymphomas are the lymph nodes, the spleen, the bone marrow, the bone marrow being seen in 40 percent of patients with follicular, and all patients with Waldenstrom's by definition. However, the lymphoma cells can go anywhere in the body essentially.

The most common symptoms that we see is lymphodenopathy, which can actually wax and wane in follicular cases. Splendomegaly is also common. Cytopenias are often secondary to bone marrow involvement and can be seen now especially in Waldenstrom's, since bone marrow involvement is universal

in this disease. Constitutional symptoms, which arise from the increased inflammatory state, are seen across the board in all different lymphomas.

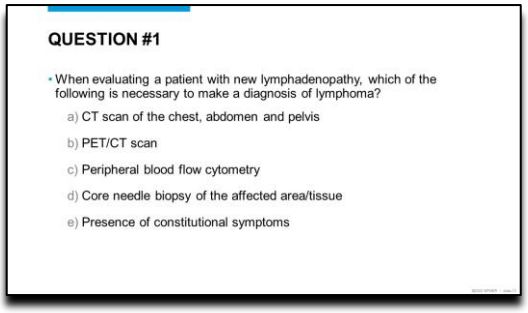
Now specific subtypes of lymphoma can also have specific symptoms. Now, Waldenstrom's is a great example here as it's producing that IgM monoclonal protein, which can itself cause specific symptoms such as hemolytic anemia, peripheral neuropathy, or even hyperviscosity syndrome, if at very high levels, something that you would never in follicular lymphoma, for example.



Slide 12: Diagnosis and Work Up

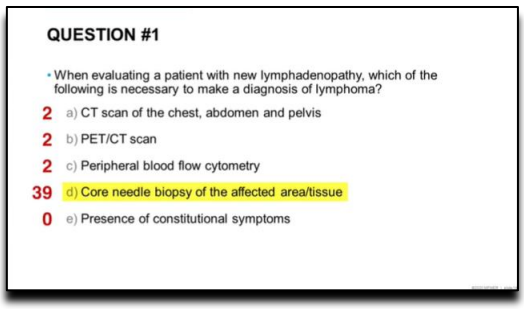
For the diagnosis of lymphoma, diagnosis of lymphoma can only be made through a biopsy of the affected organ or tissue or site, usually a lymph node or a bone marrow, but it can be from any site that's involved. An excisional biopsy is the preferred method to make a diagnosis of lymphoma, but core needle biopsies are also very decent. And you can make a diagnosis in more than 90 percent of the cases.

Fine needle aspirations, or fine needle biopsies, are not enough for lymphomas or for a lymphoma diagnosis. The biopsy is important to confirm the diagnosis and also to tell us what subtype of lymphoma we're dealing with. That is very important as almost everything else depends on one specific subtype. The subsequent staging tests that we choose, the risk assessment scores, specific workup for some complications that are seen more commonly in one or the other, and, most important, a treatment strategy, all of that depending on having a specific diagnosis and accurate diagnosis.



Slide 13: Polling Question 1

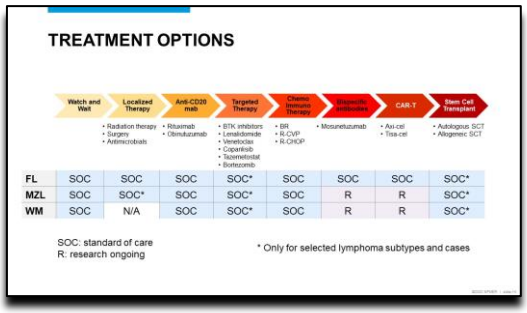
Before we go to the next section of the talk, we have a question here that we want the audience to participate. So, the question here that I have is, when you are evaluating a patient with lymphodenopathy, which of the following is necessary to make a diagnosis of lymphoma, a CT scan of the abdomen, chest, and pelvis; PET scan; peripheral blood flow cytometry; core biopsy of the affected tissue or area; or presence of constitutional symptoms?



Slide 14: Polling Response

The majority of the responders selected choice, or option D, according to the biopsy. And that's absolutely right.

We do need a biopsy. As I mentioned, an excisional biopsy is preferred. Core needle biopsy does usually a pretty good job at making a diagnosis. Fine needle biopsy or aspiration is not enough. Thank you for answering the question.



Slide 15: Treatment Options

I will move forward now to the next section, which is to talk about different treatment options.

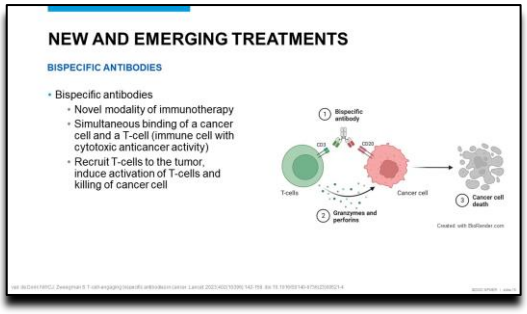
So, what I have here is, I have a list of different treatment modalities loosely in order of--the list intends to the most aggressive options. For indolent lymphomas, treatment options include watch-and-wait, localized therapy with radiation, or surgery for some very specific circumstances.

Then you have the anti-CD20 monoclonal antibody, rituximab and obinutuzumab, then target therapy, a very large and a very important group of drugs for this disease, a combination therapy with chemoimmunotherapy regimens. Then here, you have the bispecific antibodies and CAR T, which are newer treatment options, and finally, the stem cell transplantation, autologous or allogeneic.

In the table below here, you can see that there is a considerable amount of overlap of options across follicular, marginal zone, and the Waldenstrom's. Please keep in mind this is just a simplified way of bundling the treatments, as not every treatment here is approved for every lymphoma subtype I have included.

Now in reality, while different lymphomas may be treated with the same drugs, the actual sequence and rationale to select one treatment over another can be quite different when you consider follicular, marginal zone, or Waldenstrom's.

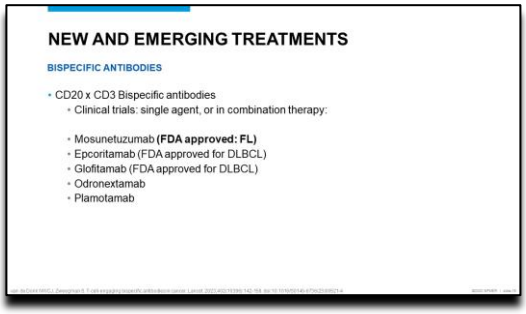
So next, I have selected three of the recent treatment options that became available to review more details.



Slide 16: New and Emerging Treatments

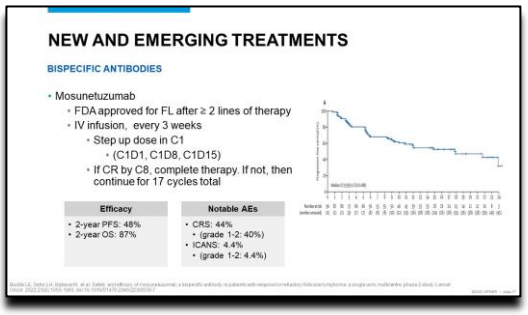
And we'll start here with the bispecific antibodies. So, a bispecific antibody is designed to bind two different targets, one in the cancer cell, one in a T-cell. The T-cell--the normal T-cells are chosen because they have--it's all natural ctyotoxic activity in a natural anti-cancer role in the immunosystem.

In a nutshell, is you bring the two cells together by binding the cancer cell and the T-cell. You induce activation of the T-cell, which will then destroy the cancer cell.



Slide 17: New and Emerging Treatments

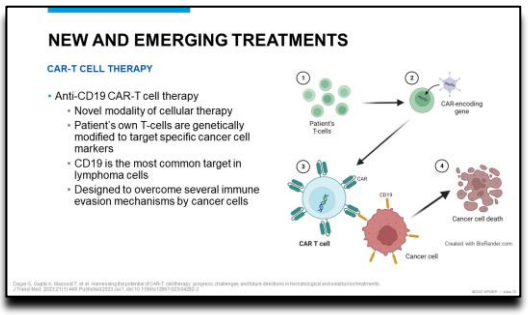
Wea do have several bispecific antibodies already available. They do have different targets based on the different diseases. In lymphoma, the target cells in the cancer cell, its usually CD19 or C20. In the list here, as you can see the difference in CD20 x CD3 bispecific antibodies, including mosunetuzumab, which was recently approved by the FDA for treatment of follicular lymphoma.



Slide 18: New and Emerging Treatments

Now, diving a little deeper into mosunetuzumab approved for follicular after at least two prior lines of therapy, it's given as an IV fusion. Initially, you have a weekly step-up dosing for three weeks, then once every three weeks. In the pivotal trial of mosunetuzumab, patients that achieved a complete remission by cycle 8, the treatment had stopped at that time. Those that did not achieve complete remission continued for a total of 17 cycles, which is about a year of treatment.

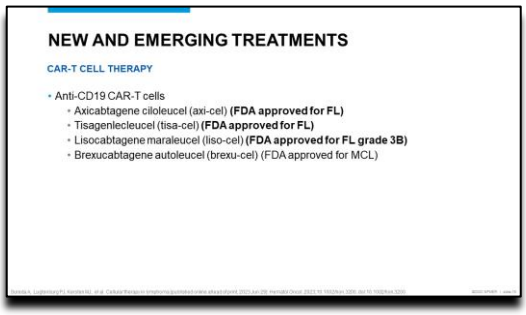
About 63 percent of patients had a complete remission with mosunetuzumab, and just under half were seeing remission after two years. Now, cytokine release syndrome, or CRS, was a potential severe complication that was seen in 44 percent of patients. But, the majority of those patients had only mild to moderate CRS. Neurotoxicity was not very common, only about 4 percent to 5 percent of patients. And all of those were mild forms of neurotoxicity as well.



Slide 19: New and Emerging Treatments

The next one here to highlight is CAR T-cell therapy, which is a novel form of cell therapy. Since we're focusing on lymphoma, we'll talk about anti-CD19 CAR T-cell therapy. Autologous CAR T products are FDA approved. And they are manufactured from the patients' own T-cells, the reason why they are called autologous.

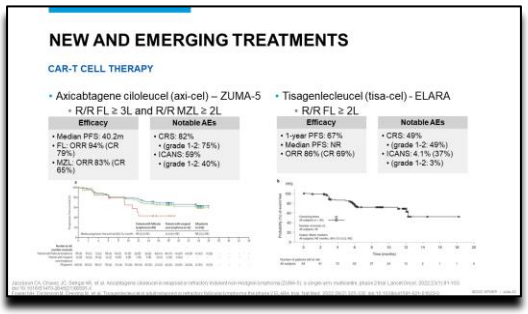
The T-cells, they are collected from the patient through apheresis, sent in for manufacturing. That's using a viral vector to introduce the engineered gene for the chimeric antigen receptor, CAR. That gene includes a monoclonal antibody that's taken to the outside of the CAR T-cell to bind the cancer target, CD-19 is the case here. The inside, we have the activated domain, CD28 or 4-1BB. And once the CAR T-cells are infused back to the patient, they can identify the cancer cells and eliminate them with the assistance of the other immune system cells.



Slide 20: New and Emerging Treatments

Now similar to bispecifics, there are several different CAR T-cells of products available. Axi-Cel and Tisa-Cel are approved for follicular lymphoma after two or more lines of therapy. Liso-cel is only approved for follicular lymphoma grade 3B. And CAR T-cells are being investigated for other indolent lymphomas, including marginal zone and Waldenstrom's.

The CAR T treatment is a one-time deal, is a one-time treatment but it's a long process. It takes about a month from the apheresis to the CAR T-cell infusion and at least another month of monitoring for those acute complications of cytokine release syndrome and neurotoxicity. And there could be continued complications longer that after that, but overall, it's about two months where the patient has to be with us in our center before they can return home.

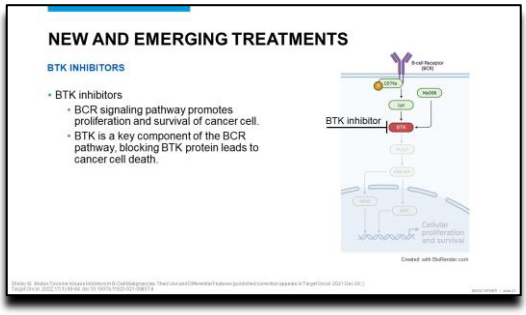


Slide 21: New and Emerging Treatments

Looking into the details of both the Axi-Cel and Tisa-Cel, those are approved for all types of follicular lymphoma. In the ZUMA-5 clinical trial, Axi-Cel included both follicular and marginal zone. The ELARA clinical trial only got follicular lymphoma patients. Overall, 80 to 90 percent of patients with follicular marginal zone responded to CAR T. Most patients, 65 to 80 percent, had a complete remission.

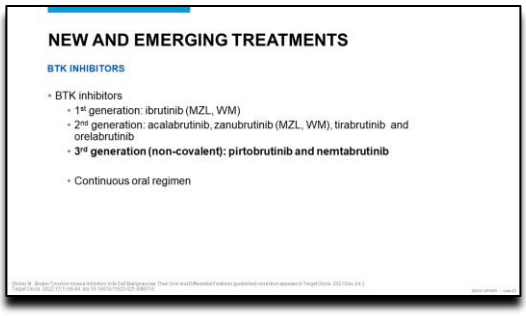
Most importantly, I think, is that a good proportion of those patients responding to it had a prolonged remission. Now, CRS

and neurotoxicity were common side effects, which is expected with CAR T, but most of those patients had a mild to moderate form of CRS, grade 1 or grade 2.



Slide 22: New and Emerging Treatments

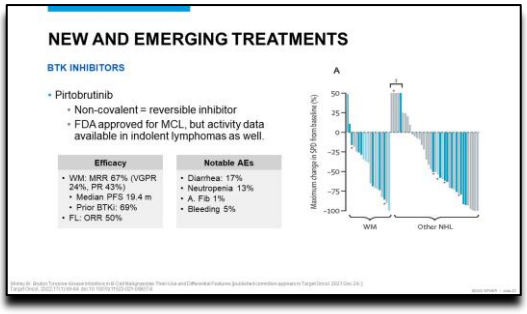
And then finally, I want to review the BTK inhibitors, now not necessarily a new treatment class. But, a new generation of BTK inhibitor was recently approved for mantle cell lymphoma and hopefully will make its way to other indolent lymphomas in the near future. Now, BTK inhibitors, as the name suggests, they block the BTK protein, which is an important component of the B-cell receptor pathway, playing a very important role in cancer, proliferating cancer cells and facilitating the survival of those cancer cells.



Slide 23: New and Emerging Treatments

Now, multiple BTK inhibitors are available. They've been used in practice for a while. Ibrutinib has been available for a long time. It is FDA approved for Waldenstrom's and marginal zone lymphoma. Zanubrutinib is also approved for marginal zone lymphoma and Waldenstrom's.

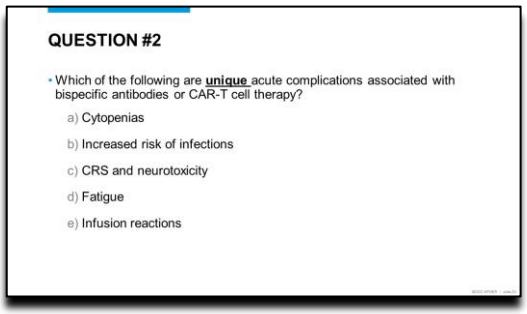
But early this year, pirtobrutinib was approved for mantle cell lymphoma. Pirtobrutinib, which is a third-generation BTK inhibitor, is a non-covalent form of a BTK inhibitor. All of these drugs are oral treatments. They are taken daily or twice a day for as long as they're working and as long as they are tolerated.



Slide 24: New and Emerging Treatments

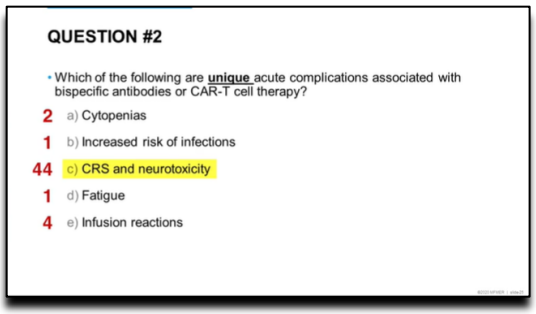
And if we look a little bit more into the details of the pirtobrutinib clinical trial, for Waldenstrom's and other non-Hodgkin's lymphoma, the BRUIN trial, two-thirds of patients with Waldenstrom's treated with pirtobrutinib achieved a major response and remained in remission for an average of 19 months.

When you look at the other indolent lymphomas, 50 percent also responded to pirtobrutinib. But, I think the most remarkable feature here of this drug is that pirtobrutinib seemed to work well even in those patients that had lymphoma progressing after a prior oral generation BTK inhibitor. So, overall a well-tolerated treatment. Fatigue, diarrhea, neutropenia would be some of the common side effects. AFib and bleeding was also noted, although less common than in other BTK inhibitors.



Slide 25: Polling Question 2

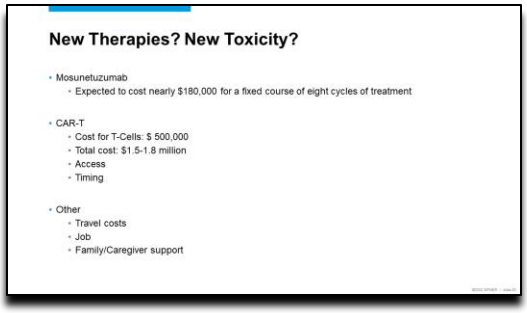
So, moving on to the next question that I want to share with the audience here. The question that I have here is, which of the following is a unique complication, acute complication, associated with bispecific antibodies or CAR T-cell therapy? So, the terms we have here is cytopenias; increased risk of infections; CRS, neurotoxicity; fatigue; and infusion reactions. So again, which of the following is a unique complication of bispecific antibodies in CAR T-cell therapy?



Slide 26: Polling Response

The majority of you got the correct answer, which is alternative C, CRS and neurotoxicity. Those are unique complications of bispecifics and CAR T. The other options we have, they are also common complications, but they can be seen with chemotherapy and immunotherapy as well.

So, this actually concludes the initial part of the presentation, talking about some of the indolent lymphomas and the new and emerging treatment options. I'll hand it over to Darci now to take it from here. Thank you so much for your attention.



Slide 27: New Therapies? New Toxicity?

Darci Zblewski, APRN: Thank you, Jonas. So moving into the second portion of our presentation, I will be covering some of the toxicity and then talking about care teams and the importance of care teams within cancer care.

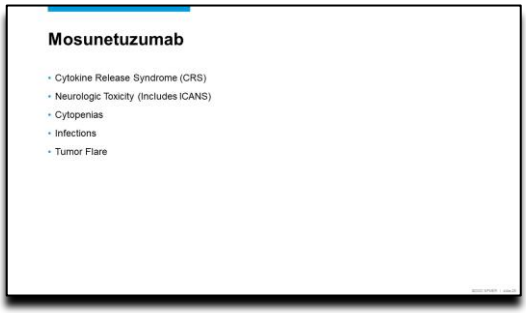
So, new toxicities--or new therapies, are there new toxicities? The answer is yes and no. We've seen all of these toxicities, like cost, access, timing, all of those things with a lot of the other medications and therapies that have been approved.

But at the same time, we're now looking at a little bit different toxicities. Some of that is the excessive cost. I remember when Rituxan started and how expensive it was. But, when we're looking at mosunetuzumab, it's about $180,000 for a fixed course. And that's just the medication. That's not including all of the other built-in costs of administration and pharmacy costs and labs and visits, etc.

And then, CAR T, we have had a patient tell us that just the cost that they were billed for was $500,000 for the CAR T-cells alone. And then, their total cost was $1.5 to $1.8 million. The other thing, too, is our access. There's only certain institutions, and there's not as many institutions out there doing CAR T. And as we're getting more and more institutions that will be a better access, that people do need to travel in some areas long distance and then excessive amounts of time spent in that city.

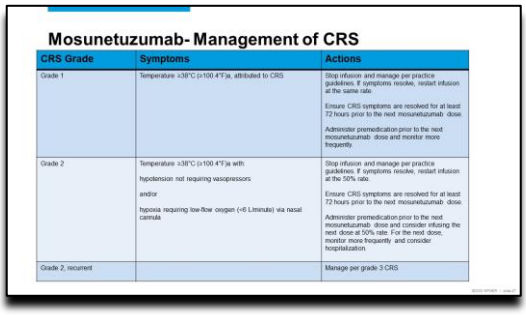
Timing. We do need insurance approval as well as then harvesting the cells, sending them off. There's about a three-week lag time in between the collection and then infusion. Other costs in other types of cities, the travel cost, like I mentioned above, people traveling long distances. This is available for younger people as well, jobs, family members, et cetera.

And then, family caregiver support. One of the things, as we talk about CRS and ICANS, in the next coming slides, these are new side effects that are much different than what we typically see. And it is very hard for family members and caregivers to watch their loved ones go through some of these. And we actually want them to experience, and we just need to support them through, but it is a big change for some of their personalities, et cetera. So, it is difficult for family and caregiver support.



Slide 28: Mosunetuzumab

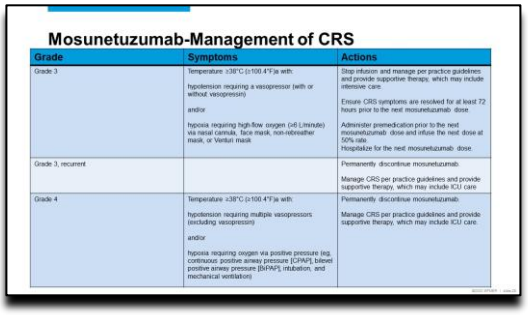
For mosunetuzumab, we do see cytokine release syndrome. We see the neurological toxicity, include ICANS. We see cytopenias, infections, and tumor flares.



Slide 29: Mosunetuzumab- Management of CRS

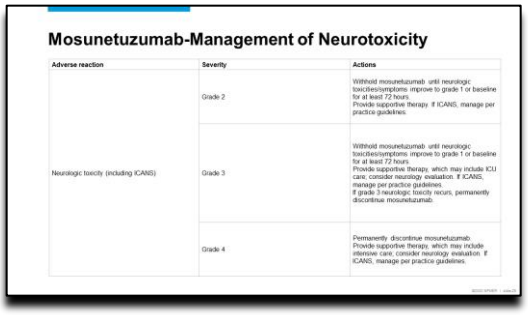
So, the management of cytokine release syndrome, which is an acute systemic inflammatory syndrome, characterized by fevers an multiple organs dysfunction that's associated with the bispecifics as well as our CAR T product.

We do have them graded. And I'm not going to go through all the details because a lot of this comes from the ACTCT 2019 guidelines. And then, there are also institutional guidelines that each institution adds or subtracts and makes their own additional changes to it. The big thing we do need to make sure when we're looking at the CRS event is that they're not related to any other concerns, any other comorbidities, or like a COPD, and that's why they're hypoxic, or some other infection that's creating the fever versus it being a CRS.



Slide 30: Mosunetuzumab-Management of CRS

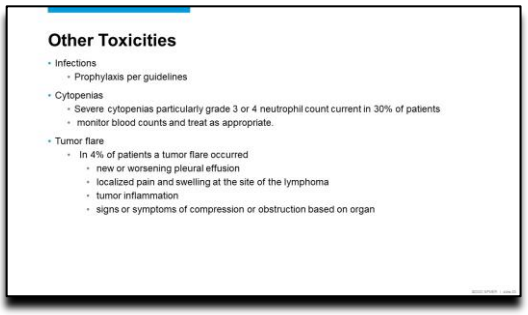
So, it goes through the grade score. And it gives you all of the, this is the symptoms, and then these are the actions. And like I said, moving forward, these are all the ACTCT guidelines. There's also a step-up dosing that's available to try to prevent CRS.



Slide 31: Mosunetuzumab-Management of Neurotoxicity

So, there's also in the package insert--there's a management of the neuroxicity and the ICANS. And from the ICANS, it's an immune effector cell-associated neurotoxicity syndrome. And it's a neuropsychiatric syndrome that can occur in some patients that are treated with these immunotherapies. And it may or may not be accompanied by CRS. So, that's really important to also know is that if they have CRS, it doesn't mean they're going to have neuroxicity or vice versa.

Some of the symptoms that we see with these neurotoxicity is memory loss, slow reaction time, hallucinations, difficulty concentrating. And we do ask that people don't drive for eight hours after receiving the medication because there is an increased risk for seizures.



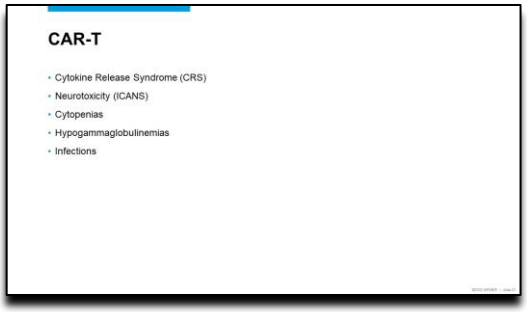
Slide 32: Other Toxicities

So, other toxicities that we can see with mosunetuzumab~~.~~ So from an infectious standpoint, the prophylaxis is per guidelines. Sometimes, that's institutional guidelines, and others it's very bispecific recommendations. So, ~~each one--~~each bispecific has a recommendation on what they would like prophylactically given.

In this particular medication, hepatitis B screening is recommended. Chronic or past HPV infections will help us determine if there's an antiviral need and then what the therapy and follow-up will be. We do see cytopenias at grade 3 or grade 4 neutropenia in approximately 30 percent to 40 percent of the patients. So, we do need to know that there are dose modifications for the grade 3 and 4 neutropenia.

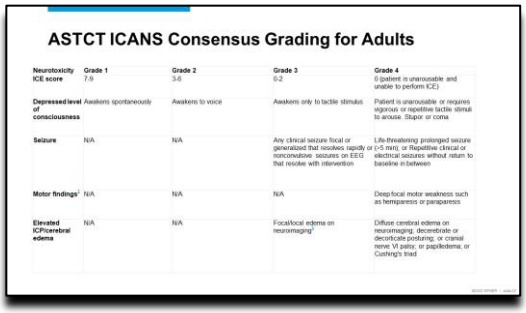
There's also a lymphopenia noted in about 100 percent of the patients, which is expected. And thats grade 3 or 4, it's about 98 percent. In other cell lines, at grade 3 or 4, we're seeing about 10 to 13 percent, so making sure we're monitoring their blood counts and treating, as appropriate.

In about 4 percent of patients, they have seen tumor flares in studies. So we, of course, are treating them based on the symptoms and whatever is based on the tumor, where it is, if they have pleural effusion worsening, doing--signs and symptoms of compression that we can see tumor inflammation, pain, so just basically treating and supporting these individuals throughout the process.



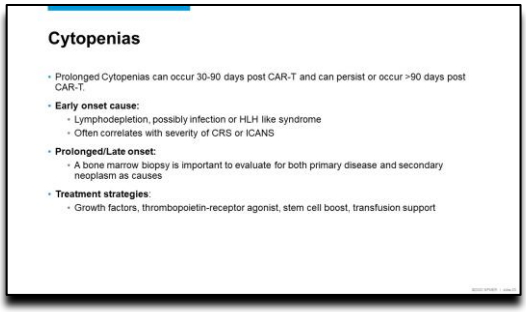
Slide 33: CAR-T

So, we'll move on to CAR T, which, again, has the cytokine release syndrome, neurotoxicity, the ICANS. We can see cytopenias, hypogammaglobulinemias, and infections.



Slide 34: ASTCT ICANS Consensus Grading for Adults

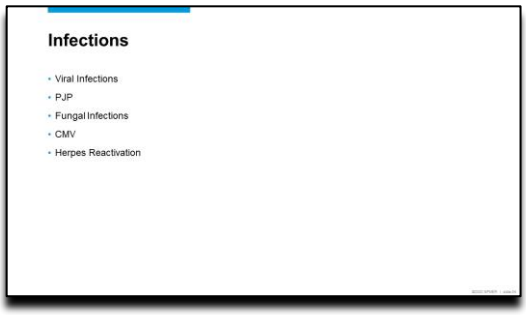
So, with the ICANS, I put in another consensus grading to this one because in the previous slide, they did not start out with grade 1 either. But, we do prefer that you use the same grading system as the ASTCT versus some of the other grading systems. But, there are other institutions that do grade it differently, but this is the grading system that is preferred.



Slide 35: Cytopenias

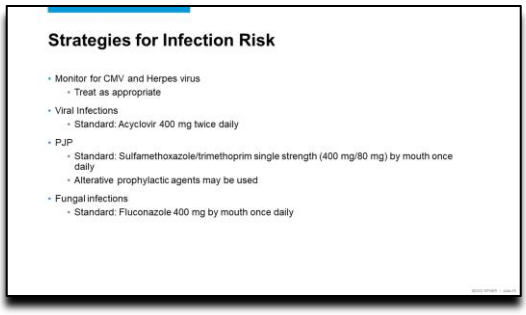
So, cytopenias, we've got prolonged cytopenias, which can occur with 30 to 90 days post-CAR T and can persist or occur greater than 90 days post-CAR T. We see the early onset cause can be the lymphodepletion, possibly infections or HLH like symptoms. It often correlates with the severity of the CRS or the ICANS. We do see prolonged or late onset. A bone marrow biopsy is really important to evaluate for both primary disease and secondary neoplasms it causes. This is the gold standard for finding secondary myeloproliferative disorders or myeloid disorders.

And then, strategy from treatment option, growth factors, thrombopoietin receptor agonists. Sometimes stem cell boost can occur. That's only if they have a stem cell product. And sometimes people collect in-store. So, some people may have a product that could be utilized first for a stem cell boost. The benefits, though, of growth factors and thrombopoietic receptor agonists are unclear, so it's very much per institutional guidelines on whether that's utilized.



Slide 36: Infections

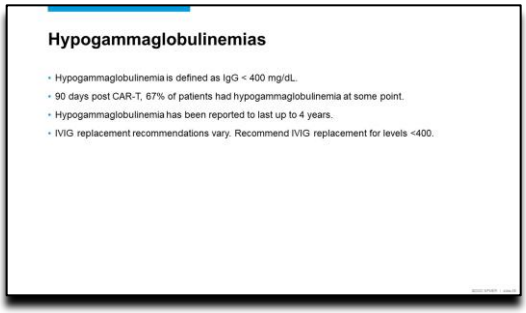
From infection standpoints, we can see viral infections, PJP, fungal infections, CMV, and herpes reactivation.



Slide 37: Strategies for Infection Risk

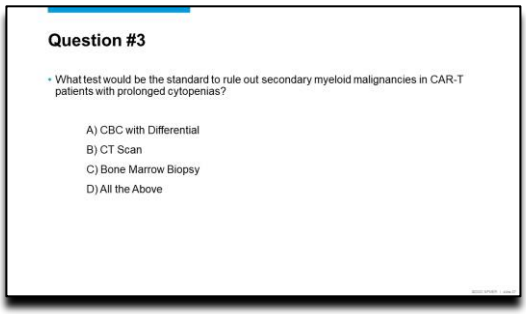
So, I didn't talk about too much the acute and the first 30-day infections because it's very much similar to transplant recommendations. But, bacterial infections are very common in those first 30 days. So, Levaquin is utilized along with any other prophylactic that's required, including the viral infection for acyclovir or PJP, etc.

So, we do monitor for CMV. Monthly, we do the CMV. And viral infections, the standard we use is acyclovir 400 mg twice daily. And we use that because we also check the CD4 count on a monthly basis. And we keep individuals on the acyclovir for as long as it takes for their CD4 count to get up to above 200. PJP prophylaxis is once daily by mouth. And again, we do keep those from a lymphopenia standpoint. We can use pentamidine if there is a Bactrim allergy or an intolerance. And then, standard fungal is fluconazole 400 mg by mouth once daily. We do utilize other antifungals based on institutional guidelines. Or if there's prolonged cytopenias, we may need to change that fluconazole to voriconazole or one of the other antifungal therapies.



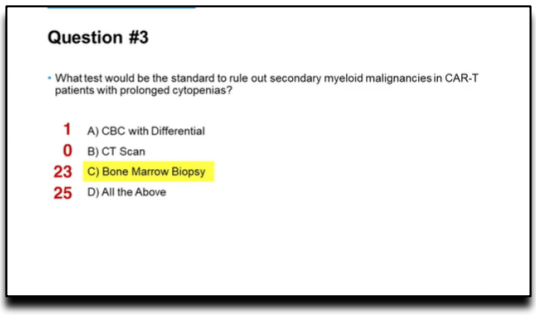
Slide 38: Hypogammaglobulinemias

So, hypogammaglobulinemia is very common to see in CAR T patients. About 67 percent of patients will have a hypogammaglobulinemia at some point. ~~We do see--~~we define it as an IgG level of less than 400. And 90 days post-CAR T is typically when we're seeing it. But, hypogammaglobulinemia has been reported to last up to four years in individuals. We do IVIG replacement. And we do recommend that with levels less than 400. Or it can be greater than 400 if they have recurrent infection.



Slide 39: Polling Question 3

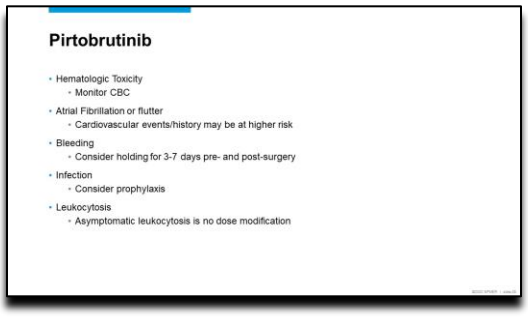
So, for our next question, what test would be the standard to rule out secondary myeloid malignancies in CAR T patients with prolonged cytopenia, A, CBC with differential; B, CT scan; C, bone marrow biopsy; or, D, all the above?



Slide 40: Response

So, it's very interesting because we did get about--we had 45-46 percent do C and 52 percent do D. So, it's actually C, a bone marrow biopsy. CBC with differential will give us information on whether they have cytopenias that are unexplained. But, you can see the cytopenias that are prolonged from the CAR T, so it doesn't really tell you 100 percent whether you have the secondary myeloid malignancy.

CT scans we actually don't do in myeloid malignancies. And then, bone marrow biopsies will be able to tell us if there is an underlying myeloid malignancy like in myelodysplastic syndrome where we may not see blast or changes on the different--so that would indicate there is a myeloid malignancy. So, the answer is C.



Slide 41: Pirtobrutinib

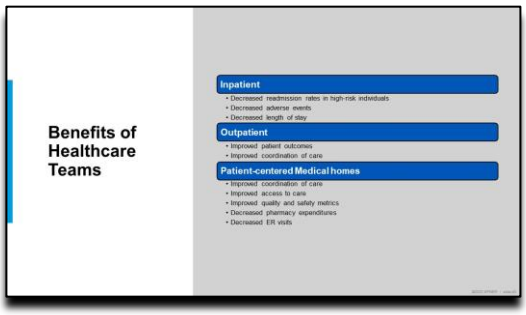
So, pirtobrutinib does have some CBC, so hematologic toxicity, so we do need to monitor those upfront. Atrial fibrillation, or flutter, cardiac events, or a history may be at a higher risk for having atrial fibrillation or flutter. But, as Dr. Paludo mentioned, this is less than in ibrutinib. From a bleeding standpoint, we do consider holding for three to seven days pre- and post-surgery. This is very dependent on the procedure or the surgical intervention that the individual will be undergoing.

Infection, sometimes we do consider prophylaxis with PJP or viral prophylaxis. And then, we do see a leukocytosis, but this is an asymptomatic leukocytosis, so there is no dose modifications required.

Slide 42 Healthcare Team

So, now, I'll just switch into healthcare teams. So, healthcare teams, by definition, is professionals from various roles who enter a collaborative relationship with the patient to deliver coordinated high-value and patient-centered healthcare. Qualities of a healthcare team is mutual accountability, working closely together to solve the problem, shared goals, clear role, and roles and responsibility outlined, mutual trust, the ability to adapt quickly, continuous learning, and individualized coaching.

And according to the agency, of the healthcare research and quality. The primary goal of medical teamwork is to optimize the timely and effective use of information, skills, and resources by teams of healthcare professionals for the purpose of enhancing the quality and safety of patient care.



Slide 43: Benefits of Healthcare Teams

So, some of the benefits that we found in research from an inpatient standpoint would be utilization of healthcare teams as a decrease in readmission rates in high-risk individuals. We've also seen a decrease in the adverse events as well as a decrease in the length of stay. From an outpatient perspective, we have also showed an improved patient outcome and improved coordination of care.

Patient-centered medical homes have also showed improved coordination of care, improved access to care, as well as improved quality and safety metrics, and then decreased pharmacy expenditures and a decrease in emergency room visits.

Slide 44: Individuals in Care Team

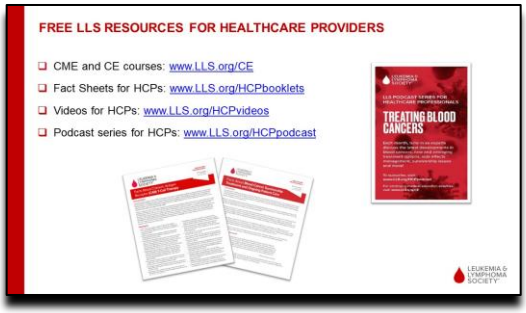
So, the importance of our team--as you can see, this is a slide filled with many different aspects of the care team. But, one of the things we do need to make sure we don't lose sight of is that the family, the patients, and the caregivers are of number-one important in that care team. We've got our physicians, our hematologists, radiation, oncologists, pathologists. One thing I came across that's kind of eye-opening is that about 30 percent of cancer diagnoses can be misdiagnosed or not diagnosed at all, so our pathologists obviously are really important as well--surgeons, fellows, residents, and the list goes on and on.

We have advanced practice providers, and each individual institution utilizes differently based on the state and their practice agreements. Pharmacists, we utilize as coming in and seeing patients. They can be utilized in so many different aspects. Then, we've got nursing with our triage nurses in the clinic. We've got chemotherapy inpatient and outpatient nurses. Clinical research coordinators are a huge--important role of helping us get patients on clinical trials and then the follow-up for them.

We have our desk staff, our schedulers. They're sometimes the first touch point for patients, so they're a huge benefit to us in our care team. Social workers help with things which will segue nicely into the next thing, like those that are traveling long distance. Social workers are really beneficial in helping with financial commitments and then also helping pay for some of the medications with all of these new massive price tags that we are seeing on them.

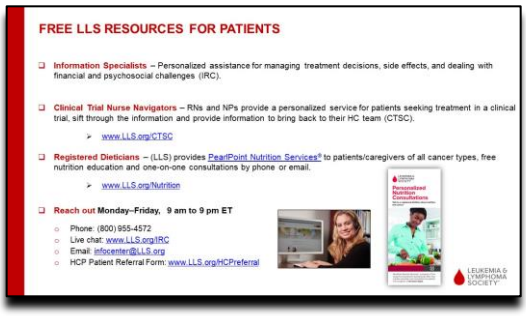
And then, there are other people that I have not mentioned on the slide, such as our nutritionists and physical therapy, occupational therapy, et cetera. And the list can go on and on. And the benefit of us having care teams does improve quality, improve outcomes, and can improve the accuracy of our care as well as decreasing the expenditures to patients.

Thank you.



Slide 45: Free LLS Resources for Healthcare Providers

Lesley Hoerst: Thank you, Dr. Paludo and Nurse Practitioner Zblewski for your very informative and comprehensive presentation. I am now pleased to share free resources from The Leukemia & Lymphoma Society for you and your patients. The Leukemia & Lymphoma Society offers free CE and CME online courses as well as a podcast channel, where you can listen to healthcare professionals discuss treatment, side effect management, and strategies to support your patients. New and interesting topics are added every few weeks. To access these as well as our videos and fact sheets on a variety of topics, please visit LLS.org/CE.

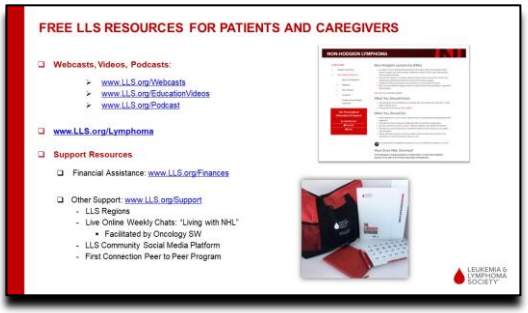


Slide 46: Free LLS Resources for Patients

The Leukemia & Lymphoma Society Information Specialists are highly trained oncology social workers and nurses who provide accurate, up-to-date disease treatment and support information, including financial. Patients can contact them directly, or you can complete a referral form.

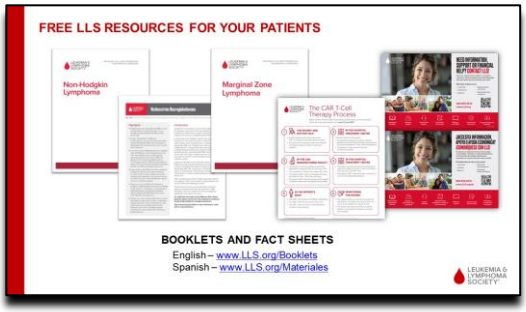
Information Specialists can also help you access or order multiple free copies of booklets to give to your patients. Our Clinical Trial Support Center Nurse Navigators are registered nurses and nurse practitioners with expertise in blood cancers. They work one-on-one with patients via telephone to provide user-friendly information, help find appropriate clinical trials, personally assist them through the clinical trial process, and provide information for the patient to bring back to their healthcare provider. This is a unique service from LLS.

For information or to refer and connect a patient with an Information Specialist or a Nurse Navigator, use the URL listed here. Refer your patients for a free one-on-one nutrition consultation with one of our registered dietitians through The Leukemia & Lymphoma Society's PearlPoint nutrition services. Consultations are by phone, are available for patients of all cancer types and all ages and are available in many languages using our interpretation service. I hope you will consider all of these specialists an extension of your healthcare team.



Slide 47: Free LLS Resources for Patients and Caregivers

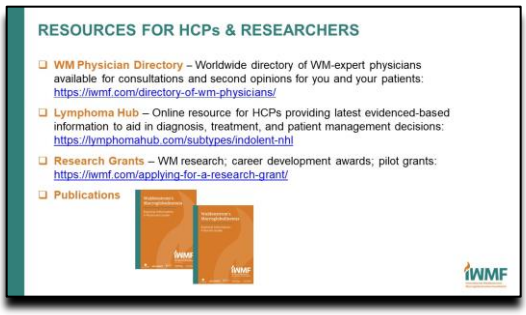
LLS offers blood cancer disease-specific information and support resources for patients and caregivers, including telephone and web education programs, videos, podcasts, and booklets. You may know about LLS' financial assistance program, and I encourage you to stay up-to-date on the availability of funds as well as additional support resources using the links on this slide.



Slide 48: Free LLS Resources For Your Patients

Here are examples of booklets and informational cards you can order from LLS at no charge to give to your patients, or they can access them on the LLS website. If you have questions on any LLS resources, please contact an Information Specialist.

I will now turn the program over to Debra Entin to present resources from the International Waldenstrom's Macroglobulinemia Foundation.

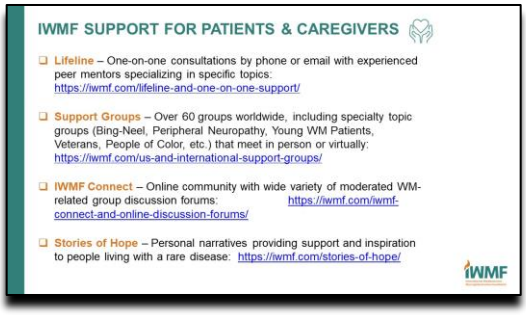


Slide 49: Resources for HCPs & Researchers

Debra Entin: Thank you, Lesley I'm pleased to have the opportunity to share free resources from the International Waldenstrom's Macroglobulinemia Foundation. On this slide, I'd like to highlight two of the resources. Since WM is such a rare disease, people often want to seek a second opinion from a WM expert. At the IWMF, we maintain a physician directory that lists WM expert physicians who have agreed to be available for consultations for you and/or your patients. So, please take advantage of this valuable resource.

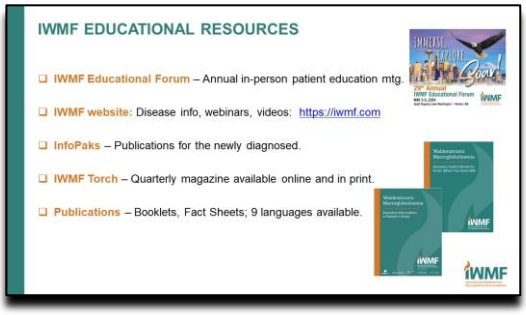
Moving on, some of you may already be familiar with the Lymphoma Hub, an online resource providing healthcare professionals with information on lymphoma and CLL. This past year, we partnered with the Lymphoma Hub to provide a dedicated section on WM, where you can access the latest news regarding WM research, treatments, and patient management. I'm happy to say this has become one of their most highly viewed sections, and I encourage you to take a look at it.

If you're interested in conducting WM research or seeking a career development award, please take a look at the many grant opportunities listed on our website. And lastly, I'd like to point out that we've recently started to expand our portfolio of publications, which traditionally were targeted solely with patients, but now do include ones meant for a healthcare professional audience.



Slide 50: IWMF Support for Patient & Caregivers

And living with a rare disease can be very difficult. However, I'll promise to people with WM is that with the IWMF, they are never alone. And this slide lists a number of our support programs from one-on-one consultation with peer mentors to online communities and in-person support groups. We offer a variety of programs, so patients can find one that matches their needs and their preferred style of communication. And more information about each of these programs can be found using the links provided.



Slide 51: IWMF Educational Resources

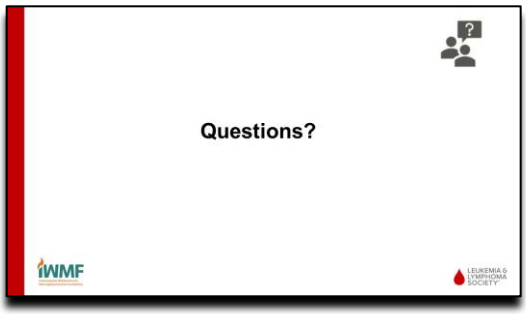
The IWMF has a myriad of educational resources, including a variety of publications offered in nine languages, disease information on our website, a quarterly magazine called The Torch, and our premier annual patient education conference that brings together people affected by WM and the expert healthcare professionals that treat them. It's really a wonderful community-building experience that your patients can participate in, either online or in-person. And the next conference is being held in Seattle in May 2024.

Slide 52: IWMF and Partner Resources

Here I've listed a number of resources offered by the IWMF and our partner organizations. Our financial resource section was recently updated and expanded to be a very comprehensive listing, and I'm confident it would be a welcome resource to any of your patients seeking financial assistance. One program I'd like to point out is the travel and lodging assistance program we recently started with NORD to support patients traveling to get a second opinion, which links back to the physician directory I had mentioned on the first slide.

And lastly, I want to remind any audience member who is joining us from outside the U.S. that the IWMF has affiliates in 22 countries should they want to connect on a local level. If you have questions about any IWMF resource, you can connect with staff at our headquarter office at the contact information listed here.

And now, I'll turn the program back over to Lesley from LLS to moderate our Q&A session. Thank you.



Slide 53: Question and Answer Session

Lesley Hoerst: Thank you. We will take our first question. The first question is, what is the likelihood of follicular lymphoma returning 12 years after a complete remission following six cycles of bendamustine and Rituxan? Does the risk increase much if the dose was cut in half of the last two cycles due to severe neutropenia?

Jonas Paludo, MD: I can chime in on that one. So, follicular lymphoma, as the other indolent non-Hodgkin's lymphoma, it's an incurable disease. So, we know it can come back even 10, 15, or even longer after the first treatment. So, it's very likely that lymphoma, the follicular lymphoma, will come back with time. Twelve years is a long time, and that's great. I know that bendamustine and Rituxan treatment works better on average in a situation like that.

We don't think, or we don't know, how much the effect of the dose reductions are in the course and the effects of the treatment. Minor dose reductions and only the last couple cycles probably have no or very

minimal effect on the efficacy. So, I don't think the treatment changes would make any significant difference. Twelve years after bendamustine and Rituxan is an excellent interval or remission. And we know follicular lymphoma does come back, even after 10, 15, or even 20 years later.

Lesley Hoerst: Okay. Our next question is, if both spouses have NHL, one with follicular lymphoma and the other with DLBCL, could that suggest they could have been caused environmentally, by environmental causes?

Jonas Paludo, MD: Well, that's a great question. And it's a very challenging one as well. The cause of lymphoma is not well understood yet. We know there are different factors. There are congenital factors. There are some familial predispositions to develop lymphoma. Waldenstrom's is a good example, as you can have familial disposition for Waldenstrom's. We know environmental factors are also important. Some are better defined than others.

Two people having the same lymphoma--I mean, you could say having lymphoma is just two unlucky people. Having lymphoma can happen. I guess it could be a coincidence. But, you also have to think about the potential environmental exposures. Now, do keep in mind that environmental exposures and development of malignancies, there's about a 10- to 20-year lag from that environmental exposure to the development of the malignancy.

So, it's really difficult to know for sure if the environmental exposure had an influence there or not, but it's possible. It's also possible that it's just a really bad coincidence that two people that know each other have developed similar diseases, even though the subtype of lymphoma is different. So, I don't have a good answer. It's possible environmental exposure is a risk factor. But, we don't know for sure.

Lesley Hoerst: The next question is, how often does an indolent lymphoma turn into a more aggressive form of lymphoma, such as diffuse large B-cell?

Jonas Paludo, MD
So, we know better--there's more data, and we know more about follicular, risk of transforming to DLBCL. That risk is approximately 1 percent per year of transformation from follicular to DLBCL.

Lesley Hoerst: Next question. How have patient outcomes improved in WM over the last decade?

Jonas Paludo, MD: That's a great question. Most of the data out there, especially population studies, are usually focused on follicular lymphoma because of the number of patients there. We know based on certain data basis that there has been some improvement in survival of patients with Waldenstrom's over the last several decades, some over the last 10 years but over the last 20, 30 years as well. That's more pronounced in older patients.

So, we know there has been some improvement in survival of Waldenstrom's patients as well and not just follicular. It's just that the studies are just not as large or powerful as the other ones, just based on the severity of the disease. And that's a great question.

Lesley Hoerst: Next question is, does Burkitt's lymphoma always start with a diagnosis of Burkitt's, or can it start with another lymphoma diagnosis?

Jonas Paludo, MD: It can start either way. So, all the aggressive lymphomas can start as the normal. So, Burkitt's can start as Burkitt's lymphoma. But, any aggressive lymphoma can start as a transformation of an indolent lymphoma. So, a patient with follicular lymphoma could transform to DLBCL but could also transform to Burkitt's lymphoma. So, it can happen.

It's very uncommon. Usually, a transformation is to DLBCL, but it can happen to an aggressive lymphoma. And honestly, I have even seen patients with an indolent non-Hodgkin's lymphoma developing--potentially transforming to Hodgkin's lymphoma.

Lesley Hoerst: Okay. What percentage of WM patients are in watch-and-wait when first diagnosed?

Jonas Paludo, MD
Another great question. I believe that is about 20-25 percent of patients with Waldenstrom's. Maybe even 30 percent of patients with Waldenstrom's, when they are diagnosed, they have no specific symptoms from Waldenstrom's or not enough cytopenias that will require treatment. So, you can say about a quarter of the patients with Waldenstrom's usually don't require any treatment, are asymptomatic at the time of diagnosis.

Diagnosis is usually incidental. You are looking for something else. You are looking--you are having a test done for a different reason. And then, you stumble upon that abnormal IgM protein or the cancer cells, and you make a diagnosis of Waldenstrom's. Something very similar, a very similar proportion of patients is also for follicular and marginal zone. They are diagnosed, and they are asymptomatic at the time of diagnosis. It's about a third to a quarter of the patients.

Lesley Hoerst: Our next question is, are gene mutations taken into consideration when deciding on what treatment choice is best for a patient? Are there drugs that specifically target these mutations?

Jonas Paludo, MD: There are. There are some gene mutations. But, that's not for every lymphoma subtype. Waldenstrom's is a good example because the MYD88 mutation can undermine the potential response rate to BTK inhibitors. They have an influence on the BTK inhibitor response, especially ibrutinib. So, for Waldenstrom's MYD88 mutation has an influence on the treatment selection.

Patients with follicular lymphoma with EZH2 mutations that may have an influence on selecting some target therapies. But, that's a much smaller part of the overall treatment strategy for follicular as it is the MYD88 mutation in the overall treatment strategy for Waldenstrom's.

Lesley Hoerst: Okay. Would mosunetuzumab ever be discontinued due to severe or recurring infections or cytopenia?

Darci Zblewski, APRN: Yes. Actually, there is--when you look at their insert--the package insert, but you look at CRS and recurrent infections and neutropenias and step-wise instructions, how to do it. But, we most certainly would discontinue the medication if we were seeing really severe infections or CRS that we are just not being able to manage, or having a lot of long-term side effects from it. So yes, we would discontinue it.

Lesley Hoerst: Okay. Our next question is, how do you feel about using the word remission with cancers such as WM as they are incurable?

Jonas Paludo, MD: A good one. When I think about remission, I think of remission as not being able to detect cancer cells. It doesn't mean they are not there. It's just that the tests that we have available, they are not able to detect. PET scan or CT scan need to have a certain amount of lymphoma before you are able to detect and see that as abnormal. Same with blood tests. You need to have a certain amount.

So sometimes, when we give treatment to patients, like the first question about follicular and bendamustine and Rituxan, they go into remission. We call it remission. What that means is that we just--the response is so deep that the tests we have available today are not able to detect it.

We know the cancer cells are still there. They may be dormant. They are somewhere there in very small amounts. And at some time, or given enough time, they will grow again, and they will be seen again. So, when I look at remission, I think of it as not being able to detect cancer, not necessarily the same as being cured of cancer where we think we have completely eradicated all the cancer cells, and the cancer will not come back, even if you wait 10, 15, 20, 30 years in the future.

Lesley Hoerst: Okay. What is the average age of diagnosis for WM? Are you seeing more younger patients?

Jonas Paludo, MD
The average age is around 70 to 72 years of diagnose for Waldenstrom's. About 10 percent of Waldenstrom's patients are younger than 50. About 20 percent are younger than 60. I don't have data to say or support if we are saying more younger patients. It's becoming more--is it that we're more aware of?

So, we may be finding more younger patients a year. But, I don't think we have specific data to support that we are seeing more--an increased incidence in patients that are younger with Waldenstrom's. That's an excellent question.

Lesley Hoerst: Okay. And we'll take one final question. If a patient's lymphoma recurs, can they go back on the treatment that previously worked for them?

Jonas Paludo, MD: It depends. It depends on the subtype of lymphoma, and it depends on how the lymphoma progressed and how--the response to the previous treatment. That's a long way to say that it's possible sometimes. And we do that mostly in patients with Waldenstrom's. We sometime may repeat a previous treatment if it worked very well, and it worked for a long time.

The exception here is rituximab. Rituximab as an immunotherapy is a very well-tolerated treatment. We tend to repeat that very often, either as a single agent or in combination with other drugs. And that's across the board in all lymphomas, not just Waldenstrom's but follicular, marginal zone, and sometimes DLBCL, and so forth.

Slide 54: Thank You!

Lesley Hoerst: Thank you to the audience for all of your questions. Again, thank you, Dr. Paludo and Ms. Zblewski for your continued dedication to patients and fellow healthcare professionals. This concludes our program.

Thank you all for participating. We hope the information presented will be useful in your work with patients and families. And we look forward to your participation on future LLS programs.