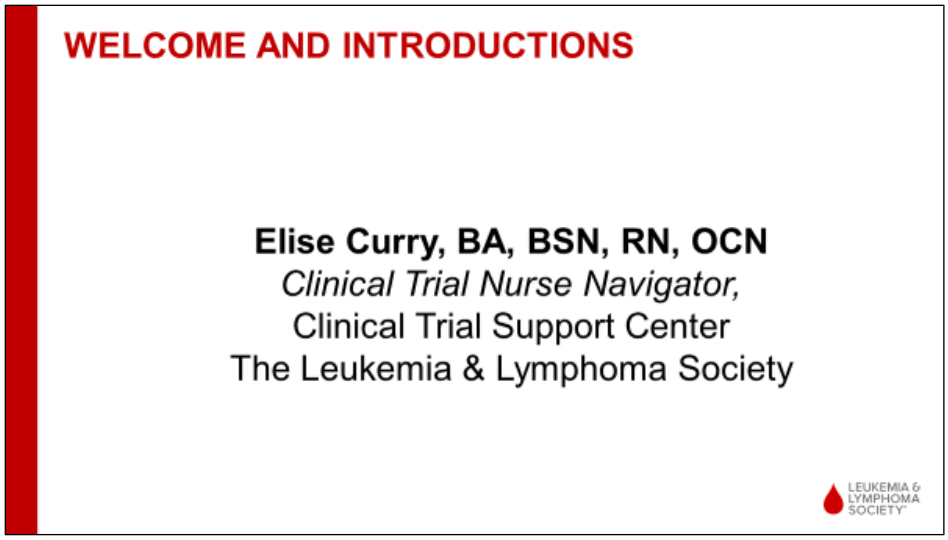
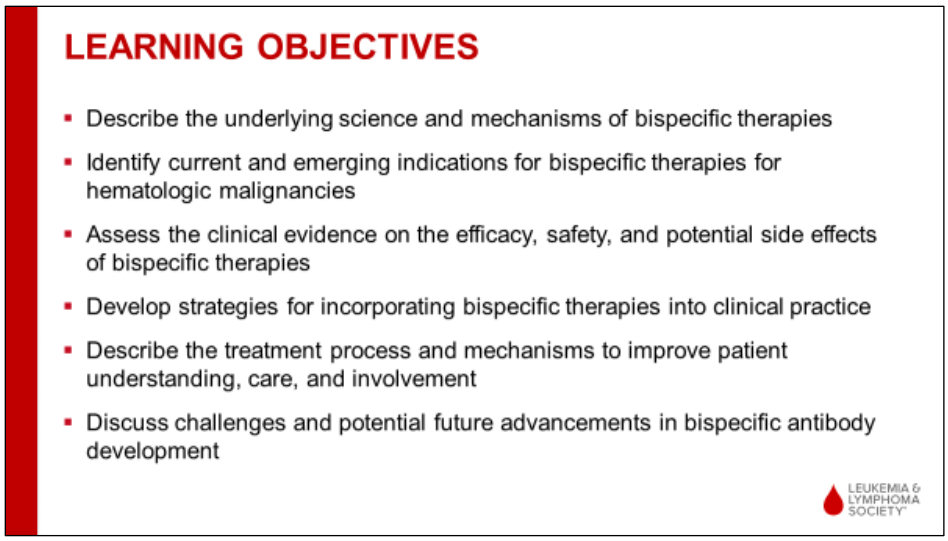
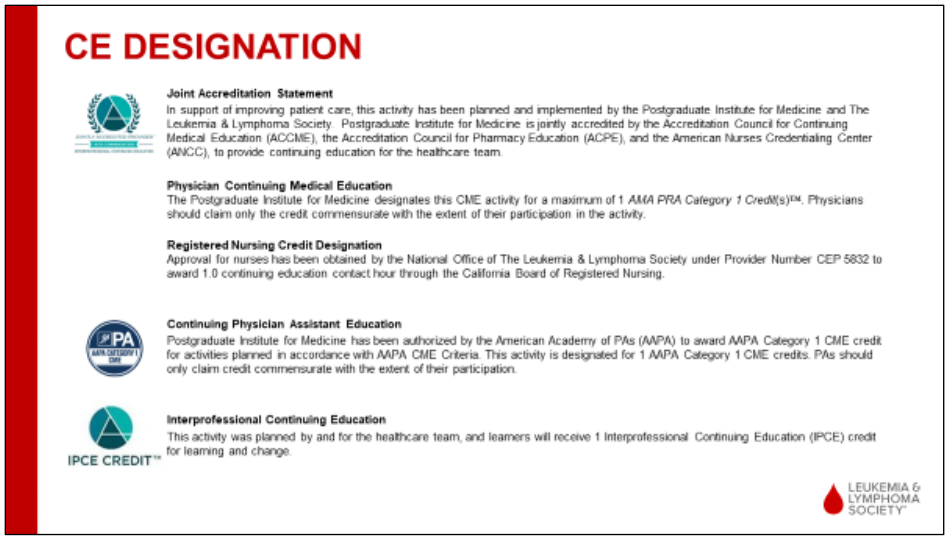
WELCOME AND INTRODUCTION



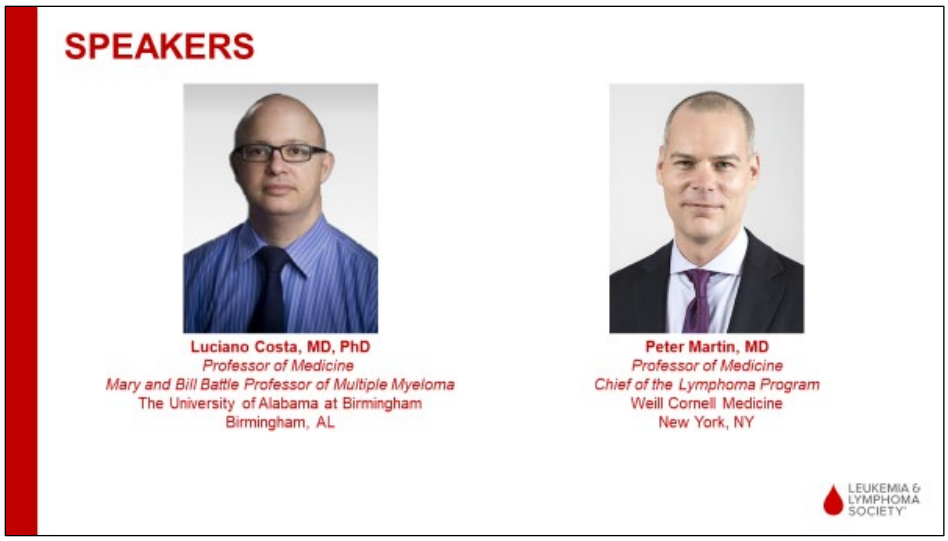
Elise Curry, BA, BSN, RN, OCN
On behalf of The Leukemia & Lymphoma Society, thank you for joining us for “Bispecific Therapy: Advancing Patient Care Through Targeted Treatment.” Through healthcare professional education, patient education, and support services, LLS is committed to improving patients’ quality of life. LLS advocates for funding to accelerate the discovery and development of blood cancer therapies and is the largest nonprofit funder of blood cancer research, investing more than $1.8 billion worldwide since 1949. Later, I will share information about education and support resources.



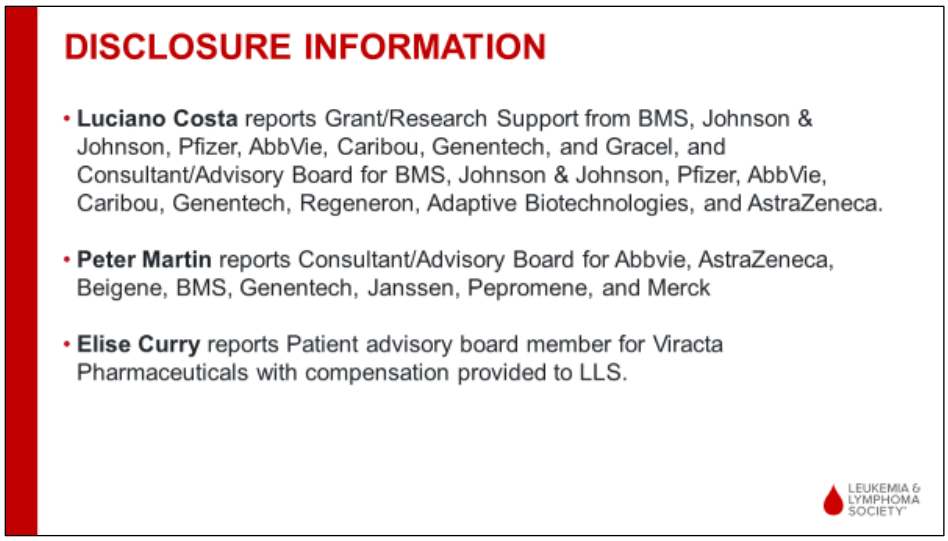
The learning objectives for today's program are listed on this slide.



Details on continuing education credit are listed here.



I am now honored to introduce our faculty. Dr. Luciano Costa is a Professor of Medicine and Multiple Myeloma at The University of Alabama at Birmingham in Birmingham, Alabama. And Dr. Peter Martin is a Professor of Medicine and Chief of the Lymphoma Program at Weill Cornell in New York City.



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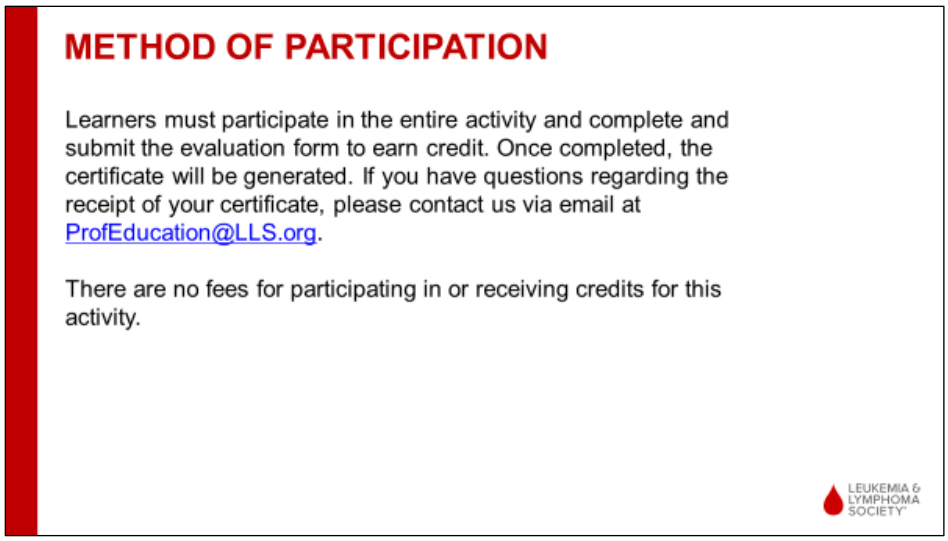
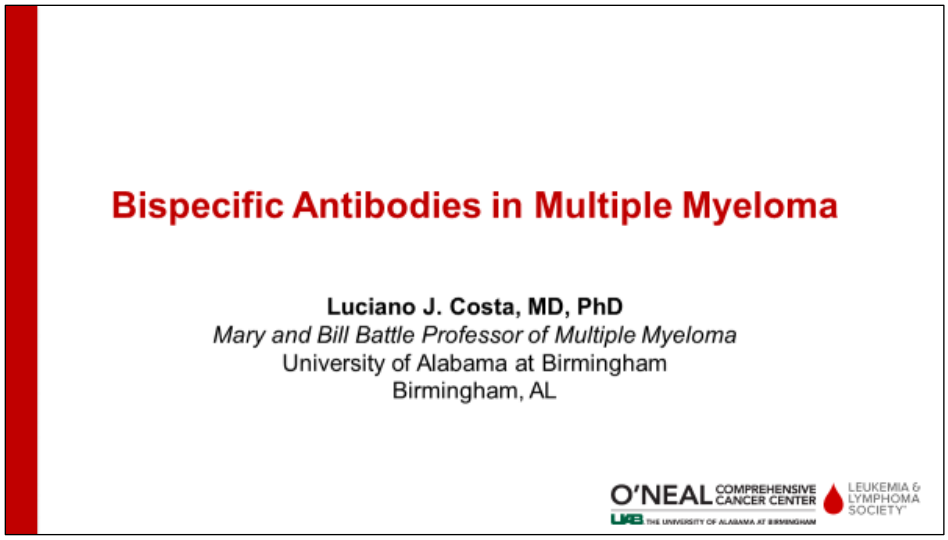
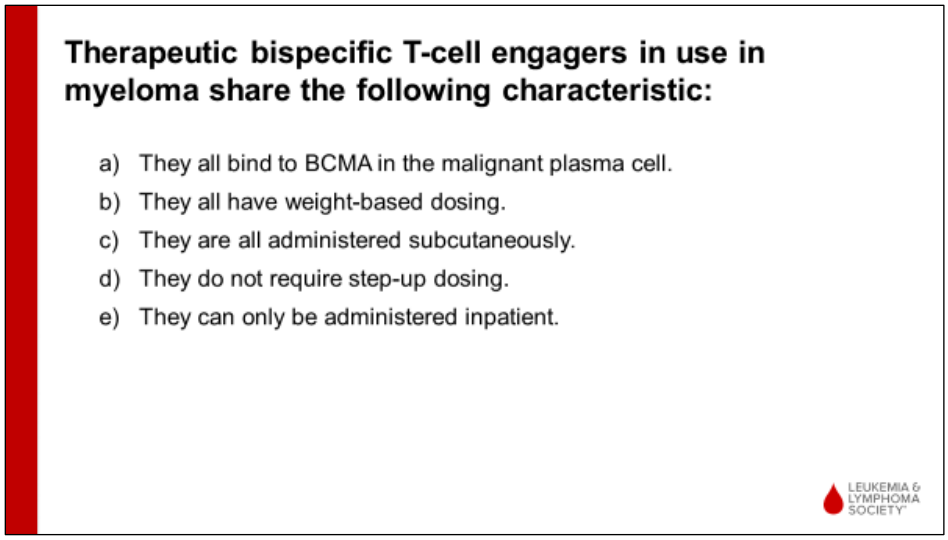


To receive credit for participating, please complete the evaluation at the end of the program. Once the evaluation is submitted, a certificate will be generated. Your feedback is important to help us plan future programs and is also required for you to receive continuing education credit. I encourage you to submit questions to the presenters as you are listening. Please type your question in the “Ask a question” box under the speaker window. We will answer questions later in the program. Dr. Costa and Dr. Martin, thank you for volunteering your time and expertise with us. It is now my pleasure to turn the program over to you.

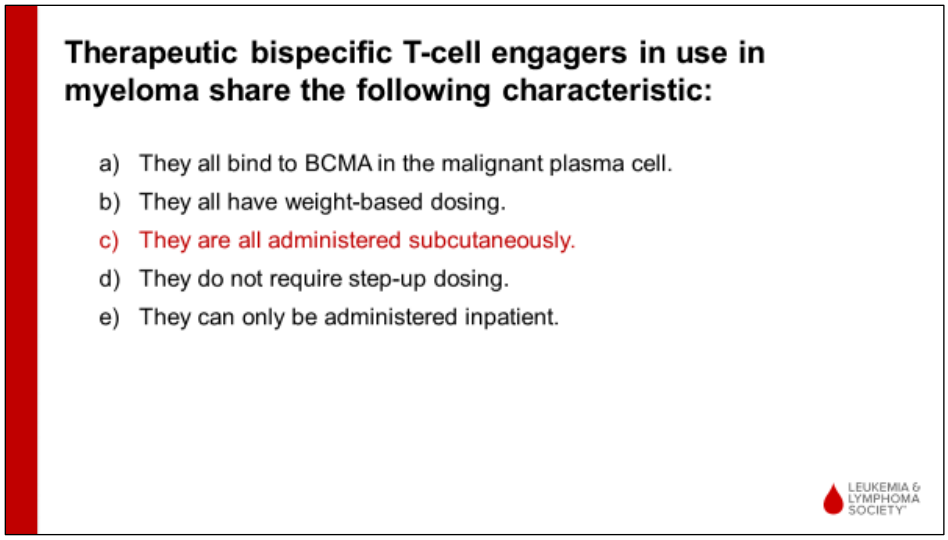


Luciano J. Costa, MD, PhD
Thank you so much and thanks for the opportunity provided by The Leukemia & Lymphoma Society to reach out to your audience and discuss a little bit about bispecific antibodies. Of course, my specialty is multiple myeloma, so I'm going to be speaking primarily about the existing clinical data for bispecific antibodies in multiple myeloma, but

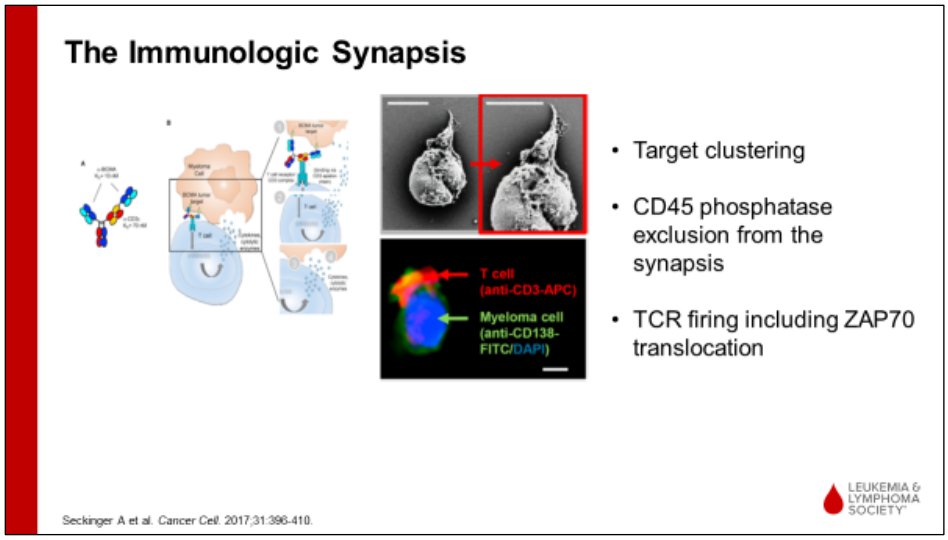
I believe some of the concepts that are going to be discussed are very much translatable to other disease settings such as lymphoma.



I'll start off with a polling question. Therapeutic bispecific T-cell engagers in using myeloma share the following characteristic: They all bind to B-cell maturation antigen (BCMA) in the malignant plasma cells; They all have weight-based dosing; They are all administered subcutaneously; They do not require step-up dosing; or they can only be administered inpatient.

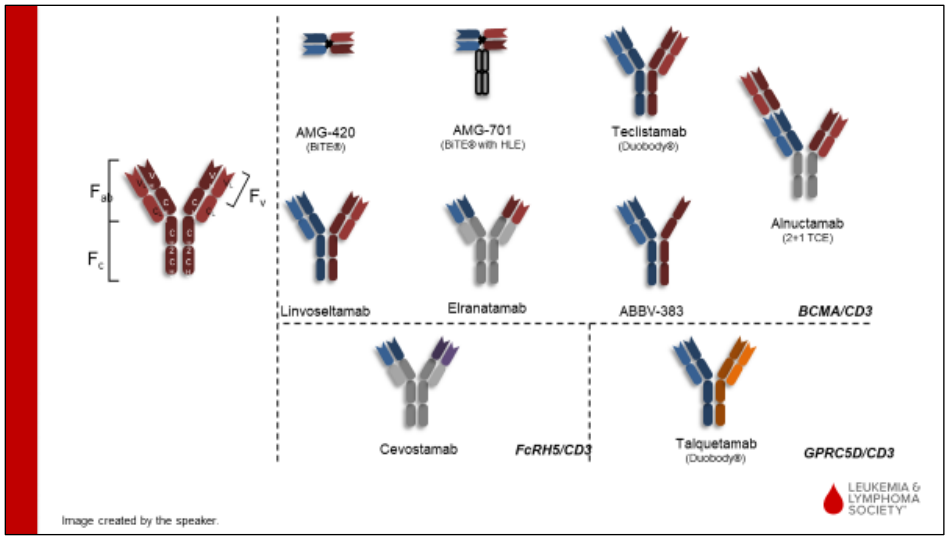


All right, so that's somewhat of a tricky question. I see most of the audience—or the most popular—was A, “They all bind BCMA in the malignant plasma cells.” But actually we're going to talk about what at least one approved T-cell engager that binds GPRC5D. But, it just so happens that all three approved are administered subcutaneously.



To understand how bispecifics work, we need to understand this concept of the immunologic synapsis. And this cartoon is based on one particularly bispecific T-cell engager that is actually no longer in development, but the principle is the same. By definition, the bispecifics are an asymmetric antibody molecule that has at least one FAB portion, the lead, that binds to the target of interest on the malignant cell, in this case BCMA. And another FAB portion that binds to usually CD3 on the T cells.

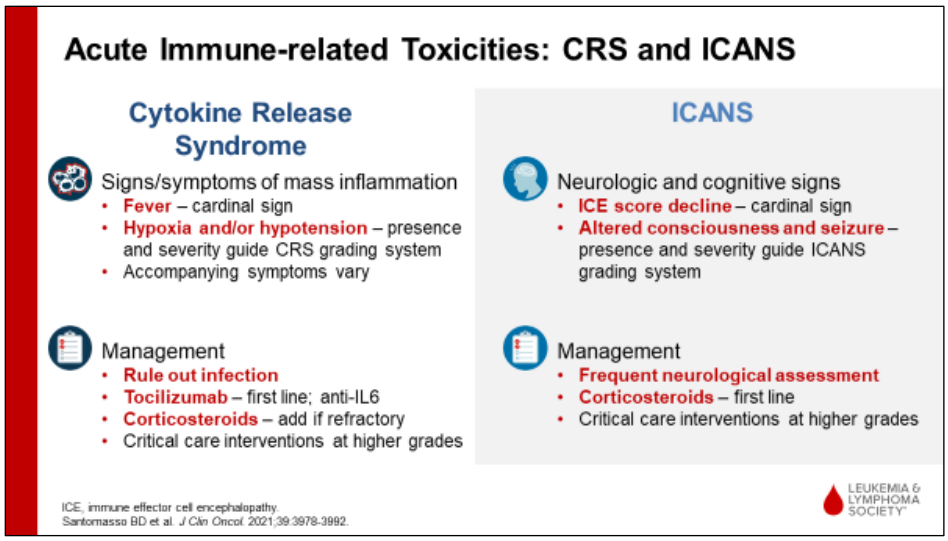
This just so happens to be a molecule that had dual binding to BCMA. And what that does, it causes this proximity between the target cell and the effector cell, in this case the plasma cells and the T cells. And that itself causes some target clustering on the T cells. This excludes CD45 from that error of the main brand and that on itself is sufficient to cause fire in the T-cell receptor through ZAP70 translocation and unleash out the intracellular signaling that are necessary for T-cell activation, including degranulation of several cytotoxic enzymes including perforin and others, ultimately causing the lysis of the target cell, in this case plasma cell.



This is an example of several bispecific antibodies that are approved in development or no longer in development in multiple myeloma. And just for reference, I have here what is a normal physiologic molecule of an intact antibody.

They vary in co-formation and their differences in structure account for some of their difference in mechanism of action, efficacy, and toxicity. The first one we had was AMG-420, no longer in development, and that's the true BiTE. So, that is essentially two very small FAB portions, one directed at the BCMA, the other directed at CD3, very much like blinatumomab that we have available for acute lymphoblastic leukemia (ALL). And even though that can get the T cells and the plasma cells together, because it's a very small molecule, it has a very short half-life and requires intravenous continuous infusion. Subsequently, there were other developments as you can see here, and, for the most part, they include the FC portion of antibody that allows those bispecific antibodies to have immunoglobulin-like pharmacokinetics with a half-life that is measured now in several days to a few weeks instead of just a few hours.

In most of those, the FC portion is inactivated. Therefore, it's enabled to trigger complement activation, therefore minimizing the toxicity related to the injection or to the infusion. And they're also silent for their ability to be recognized by, for example, macrophage and monocyte. So, essentially the FC portion is there just to give the antibody immunoglobulin-like pharmacokinetics. We currently have three that are commercially approved. One is elranatamab, the other is teclistamab, the other is talquetamab. Talquetamab is the only one that does not have a BCMA target. It instead targets a protein called GPRC5D. We're going to talk a little bit more about that.



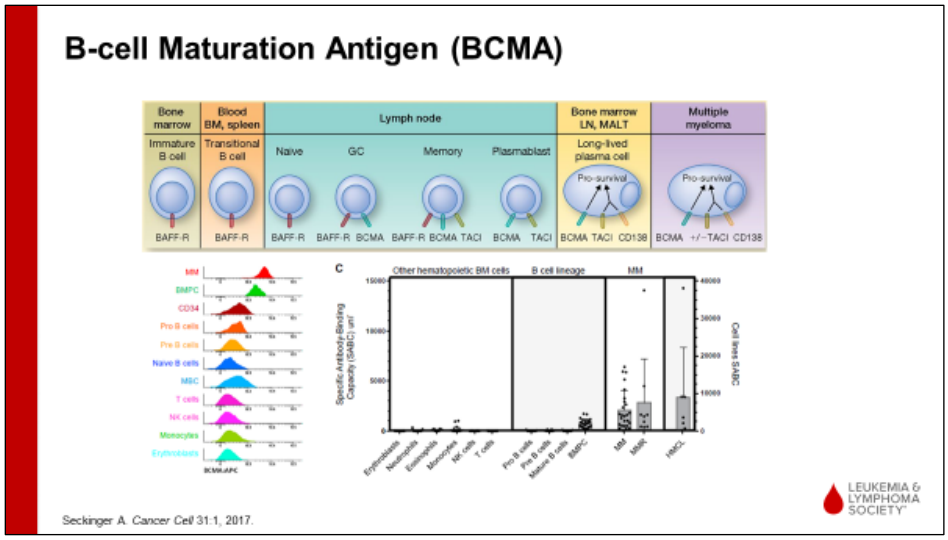
What are the signature toxicities for this class of therapy? We're essentially talking about cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (ICANS). So cytokine release syndrome, as the name suggests, develops after you have that engagement of the T cells, degranulation, and essentially overriding of several physiologic mechanism to balance immune response.

The hallmark of that cytokine release syndrome is increased production of interleukin (IL) six, but several others are part of that mediation, including IL1, and that becomes very important as we learn how to mitigate and how to manage that particular toxicity. Clinically, that manifests itself with fever as a hallmark, as a cardinal sign of cytokine release syndrome. In higher grades it can lead to hypoxia, hypotension, and several other manifestations of organ failure. The management is multipronged. It usually includes symptomatic management, usually with acetaminophen in case the manifestation is only fever. Tocilizumab is an anti-IL6 receptor and has been broadly used to abort that reaction and cause, for the most cases, resolution of the symptoms. In more extreme cases when the patient gets sicker, particularly when the patient is needing mechanical ventilation or high oxygen flow or needs vasopressors, that's when they reach out to corticosteroids or other T-cell modulators.

ICANS is really a far less common toxicity. It really became my opinion when you talk about cytokine release, we want to talk about bispecifics just because bispecifics were developed shortly after CAR T cell, whereas ICANS is a far more pronounced type of toxicity. The best understanding that we have is that ICANS is essentially triggered by the transposition of some of those cytokines, particularly IL6, across the blood/brain barrier, causing several central nervous system (CNS) manifestations. The most common is dysgraphia, the inability to write precisely or as the patient customarily does. Other manifestations can be expressed such as aphasia—in more pronounced situations, the patient can become obtundent. And, of course, mostly in the CAR T-cell literature, we have seen extreme cases with brain edema and even death. Now immune effector cell-associated encephalopathy (ICE) score is a tool for grading ICANS. It's not a diagnostic test and that's very important because, oftentimes, when we're treating an 82-year-old who happens to develop fever, and you go do an ICE score in the middle of the night,

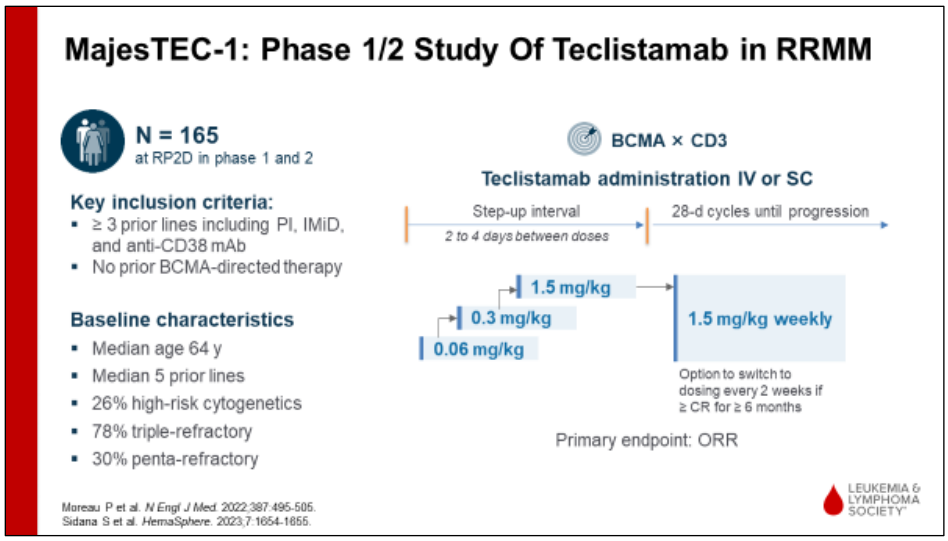
you don't expect the patient to particularly ace the math test. That does not necessarily mean the patient has ICANS. So, it's important to use that assessment very judiciously.

ICANS is fortunately rare in bispecifics, at least in myeloma, and almost never of high grade. The cornerstone of management is corticosteroids. It can occur independently or shortly after cytokine release syndrome CRS. We usually see them kind of lumped together and of course if you have the coexistence of CRS and ICANS, it's important to control the CRS and also control the ICANS. And often by doing one, you also do the other.



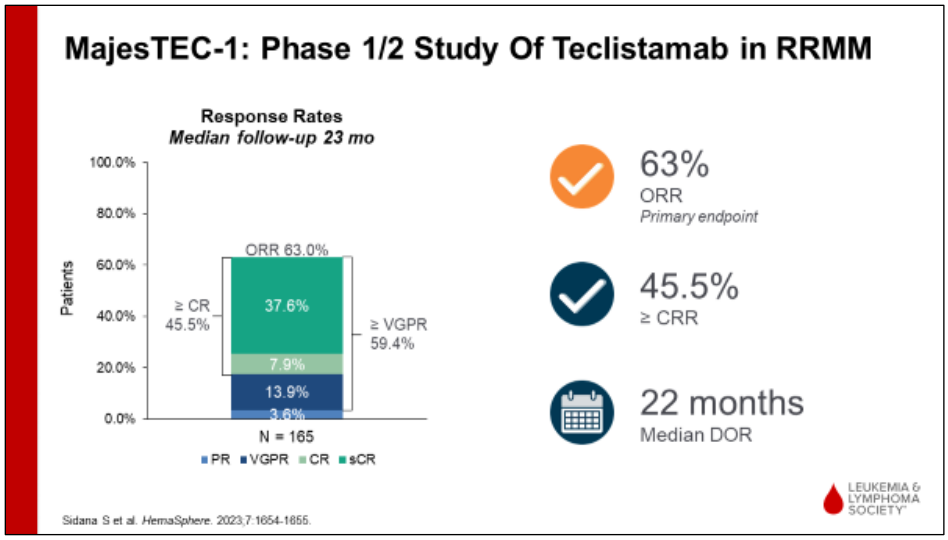
Now let's talk about our prime target in myeloma: BCMA. That stands for B-cell maturation antigen. That's a very important surface receptor in mature B cells and consequently in plasma cells. It has several physiologic ligands, including B-cell activating factor (BAFF) and A PRoliferation-Inducing Ligand (APRIL), and is essential for plasma cells survival and persistence. And that's very important because, if it's not a target, then the plasma cell can easily get rid of it without losing its ability of survival.

We see that it's very uncommon that the malignant plasma cell has already a mutation or a chromosome, a deletion that leads to complete loss of BCMA. However, that becomes increasingly more understood, a mechanism of resistance to BCMA-directed bispecific antibodies. BCMA is preserved on the malignant plasma cells and, if anything, its expression becomes more abundant as the myeloma goes through multiple lines of therapy. Because that is essential also to normal plasma cells, you're going to have universal hypogammaglobulinemia every time that you effectively target BCMA. That becomes a signature toxicity for this class of agents.

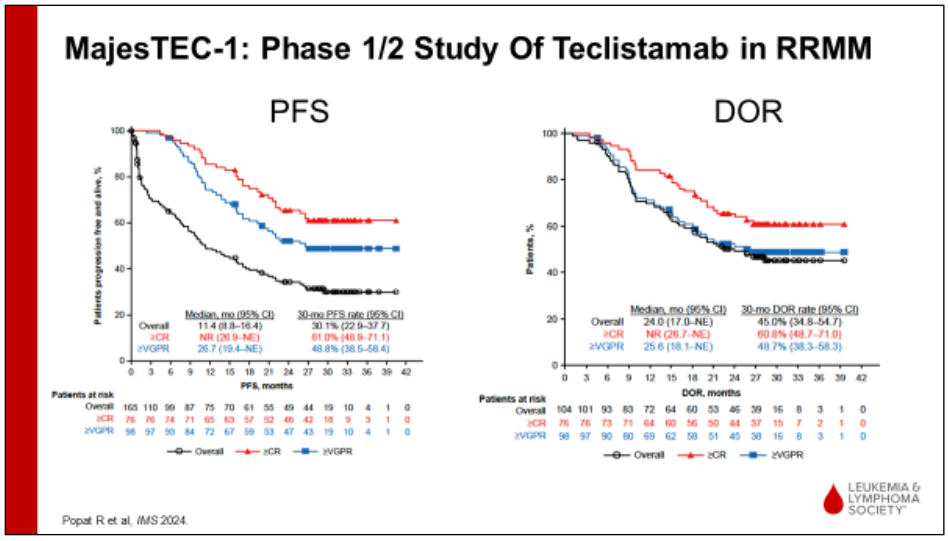


The first BCMA-directed bispecific that we had approved is teclistamab, based on MajesTEC-1 trial, which is a phase 1/2 study in a patient population that historically has a chance of response to next line of therapy of about 30% and a progression-free survival (PFS) of about four months for any combination we could pick up.

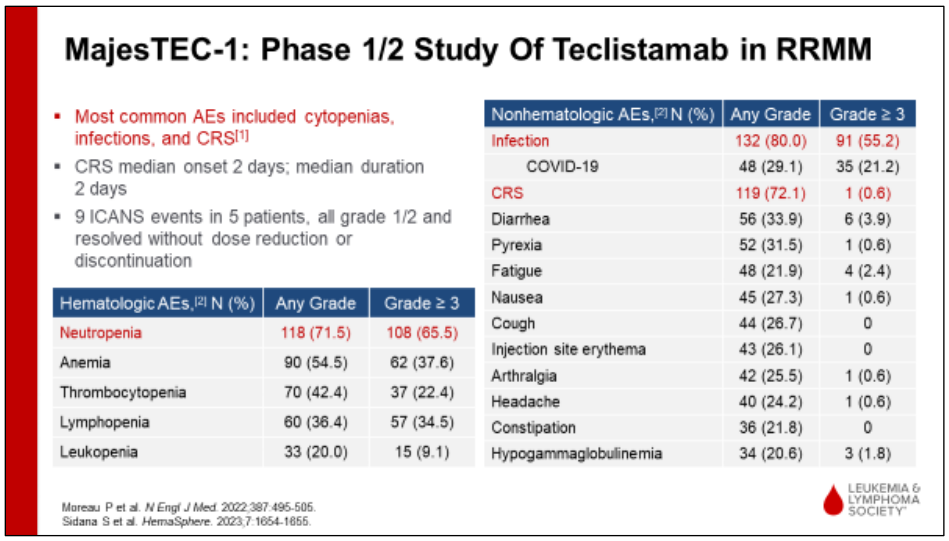
And those are patients who have received prior therapy with both an IMiD and proteasome inhibitor but also an anti-CD38 monoclonal antibody. And, on this program, we established some of fundamentals that have been later used in other programs to adjudicate cytokine release syndrome and that is the subcutaneous as opposed to intravenous (IV) administration and the use of step-up dosing–not giving the intended therapeutic dose on the first dose but working towards that, through two steps in this case, giving it over the course of one week, ultimately reaching the target dose of 1.5 milligrams weekly.



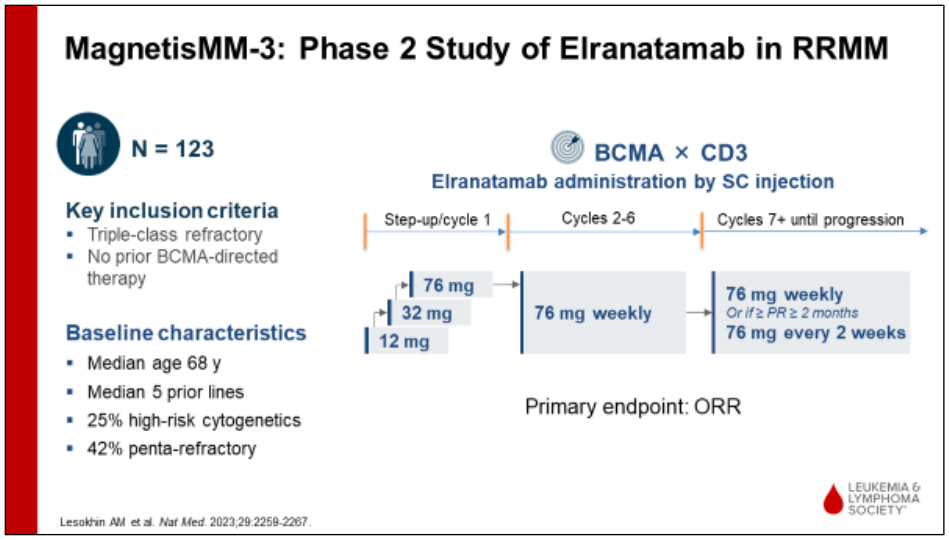
And, in this program two-thirds of the patients had a response. The majority responses are good responses, very good partial response, or complete response, and the median duration of response is 22 months.



This is the most recent update showing a median progression-free survival that is 11.4 months, but is as high as over two years for those patients who achieve very good partial response (VGPR) or better.

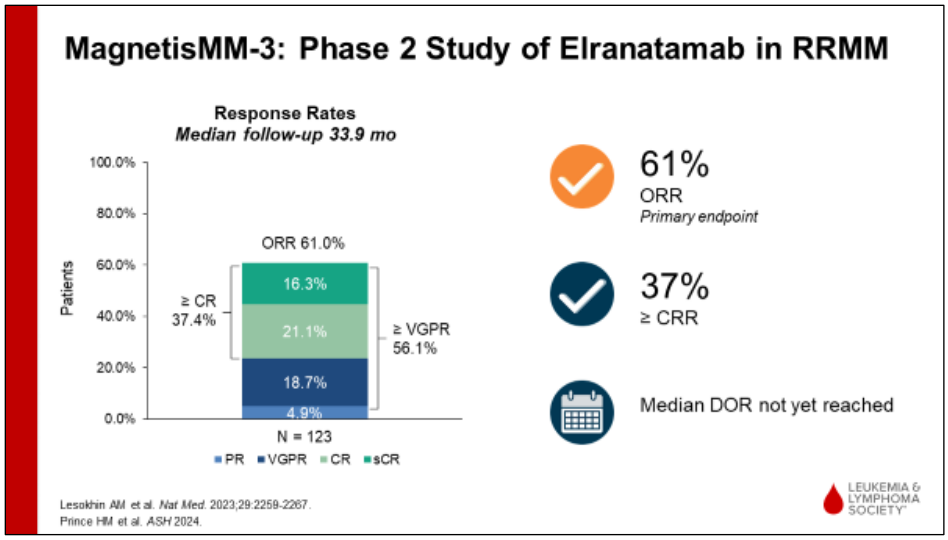


Of course, this very active therapy also has some important toxicities. It's very common to have hematologic toxicity, mostly neutropenia, mostly during the first one or two cycles, and that's easily mitigated by dose holds or use of growth factor. A lot more complicated, however, is the issue with infections. Keep in mind that this development happened on the peak of the COVID pandemic. Nevertheless, the majority of the patients develop at least one episode of grade three or higher infection, of which more than 20% were COVID-19 infections. Cytokine release syndrome is very common, about 72%, but just one single patient in the whole program had a grade three or higher cytokine release syndrome.

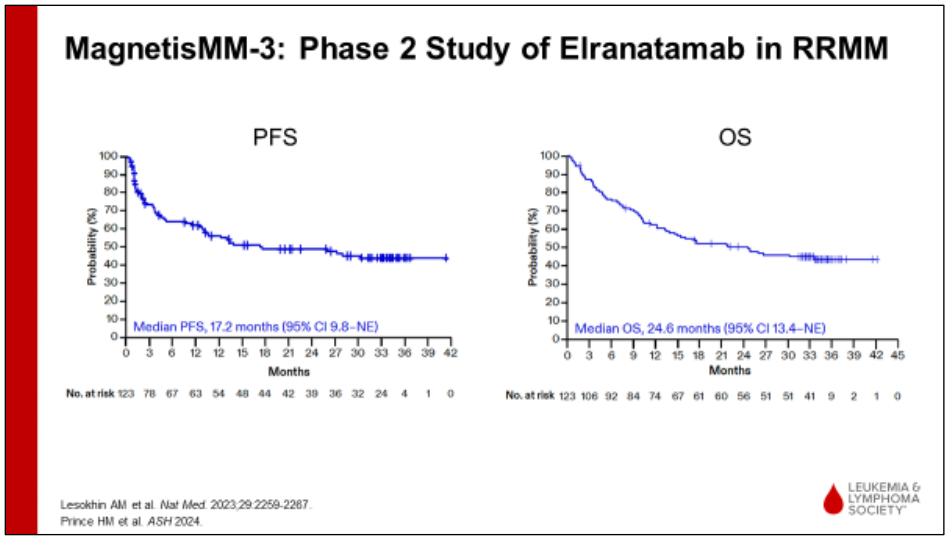


The other BCMA-directed bispecific T-cell engager that is currently approved and available is elranatamab. Elranatamab became available thanks to the MagnetisMM-3 trial that enrolled a population that was somewhat similar to MajesTEC-1, except perhaps with a few more penta-refractory patients, and has some mild differences in eligibility, tolerating somewhat sicker patients.

Here, they also employ the subcutaneous route and step-up dosing as a way to mitigate cytokine release syndrome. But instead of a weight-based dosing, it used fixed-dosing with 12 and 32 milligrams as a step up, and 76 milligrams as an intended target dose. The other thing that was important is that, after cycle six, patients who had partial response (PR) or better, which is just about everybody who reached cycle six, would change the treatment to be every other week as opposed to weekly.

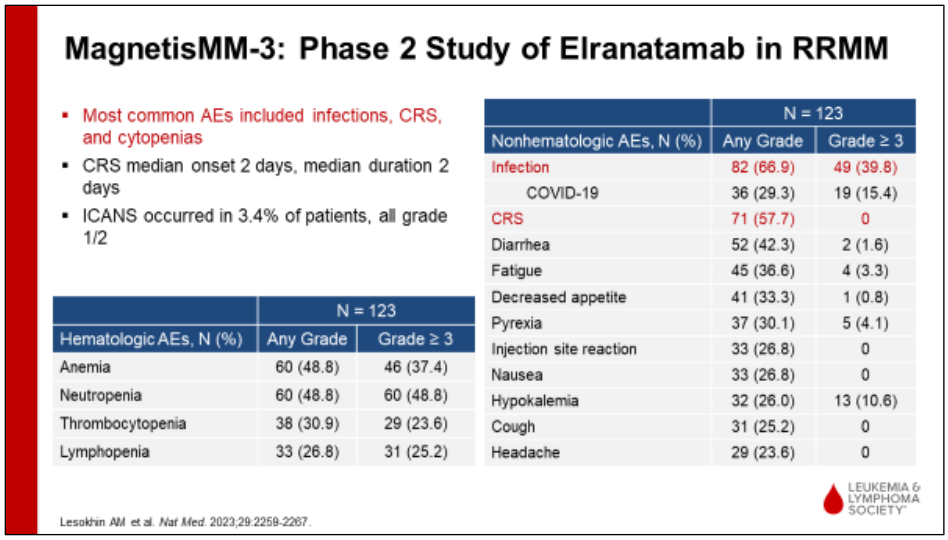


These are the efficacy responses. 61% of the patients had a response. Over a third of the patients had a complete response, and median duration of response has not been reached.



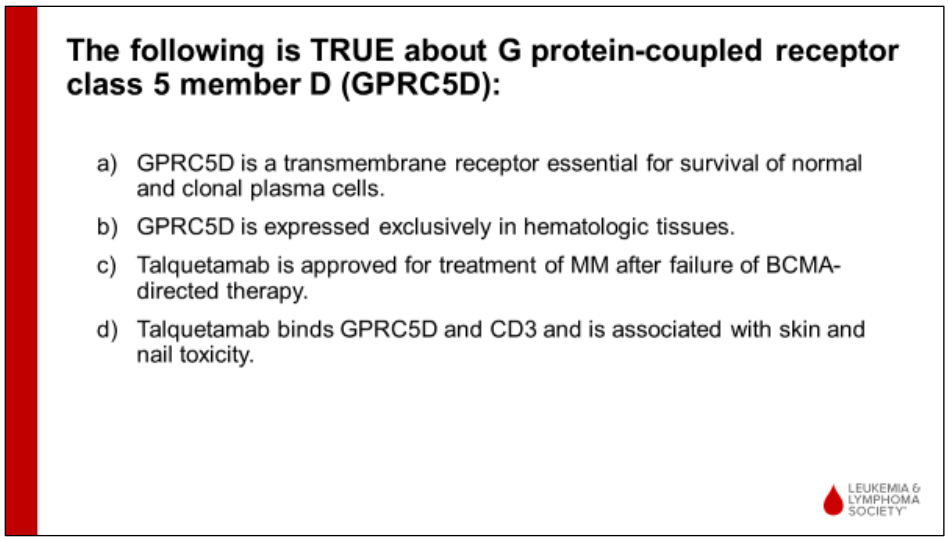
This is the most recent update in efficacy. You see a median PFS that approaches 18 months and median overall survival that is 24.6 months. Remember that the benchmark for this patient population is under one year. So, that is clearly an improvement of what

those patients could achieve before the existence of this particular drug.

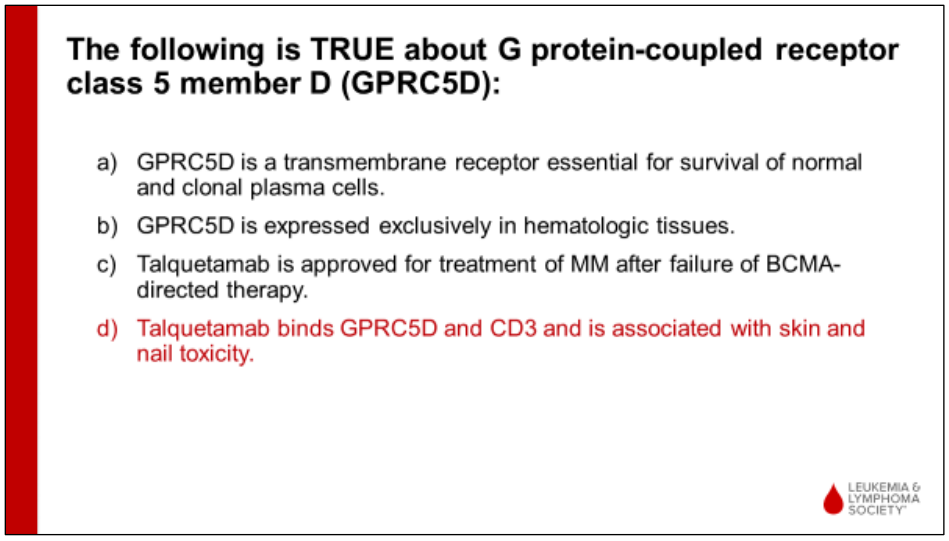


Now the toxicity profile is going to look very familiar to you because it's very similar to what we saw with teclistamab. We see here a little bit less infection, particularly high-grade infection, perhaps reflecting the fact that this was conducted a little bit later on compared to MajesTEC-1. And again, most patients had cytokine release syndrome but no single patient had grade three or higher cytokine release syndrome. And, as expected, because you have control of the reaction by using the step-up dose, most of the CRS is very short lasting. It happened after the first and the second dose. And once properly addressed, it does not repeat or does not repeat itself with the same magnitude beyond the target dose.

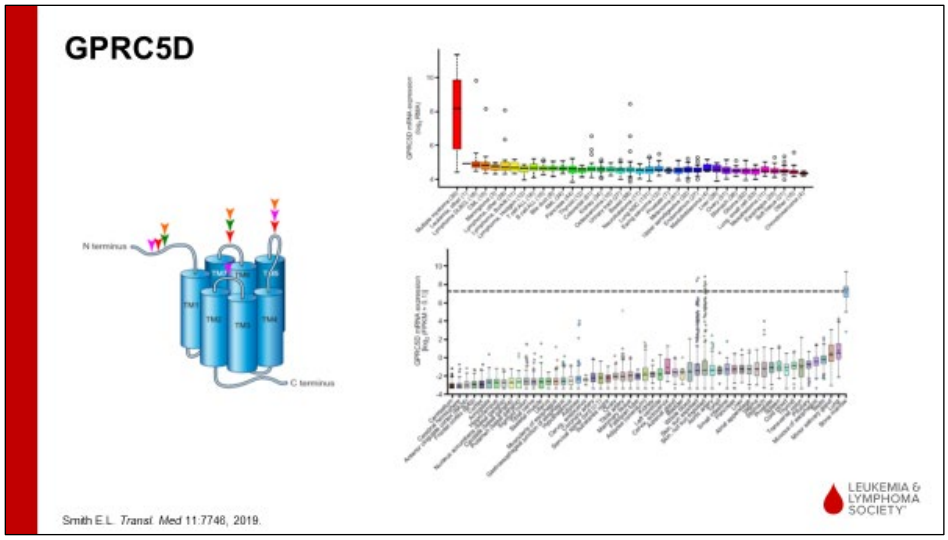
One thing that is important across all the three bispecific T-cell engagers approved in myeloma, you essentially do not see cytokine release syndrome beyond the first target dose. So any patient with fever happening on the second or third month should be approached as having most likely an infection, as opposed to a late-onset CRS.



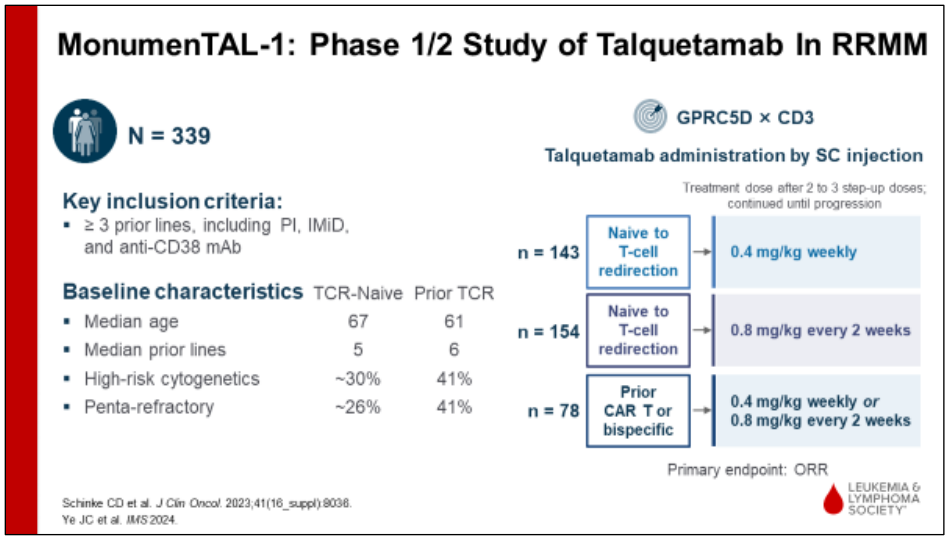
Before we change chapters to GPRC5D bispecific, let's do a brief polling question here. Which of the following is true about G-protein couple receptor class 5 member D (GPRC5D)? Is it: GPRC5D is a transmembrane receptor essential for survival of normal and clonal plasma cells; GPRC5D is expressed exclusively in hematologic tissues; Talquetamab is approved for treatment of myeloma after failure of BCMA-directed therapy; or talquetamab binds to GPRC5D and CD3 and is associated with skin and nail toxicity.



Great, I see that 70% of you chose the correct answer, which is D, it binds GPRC5D and CD3 and is associated with skin and nail toxicities.

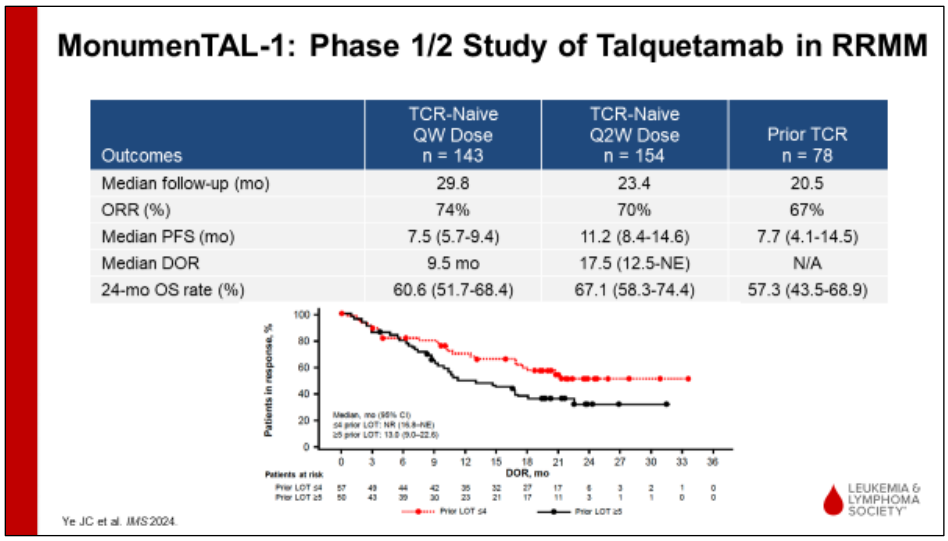


This is GPRC5D. It has a receptor-like structure and is expressed almost exclusively in hematologic tissues thanks to the expression in plasma cells, but is also expressed in other keratinized organs and tissues which, in part, account for some of its toxicity. Unlike BCMA, it does not have a known ligand, and it does not have a function for the persistence or the survival or thriving of the plasma cells, perhaps explaining why the antigenic loss through mutation or through dual deletion happens a lot more often or seems to happen a lot more often than it happens with BCMA.

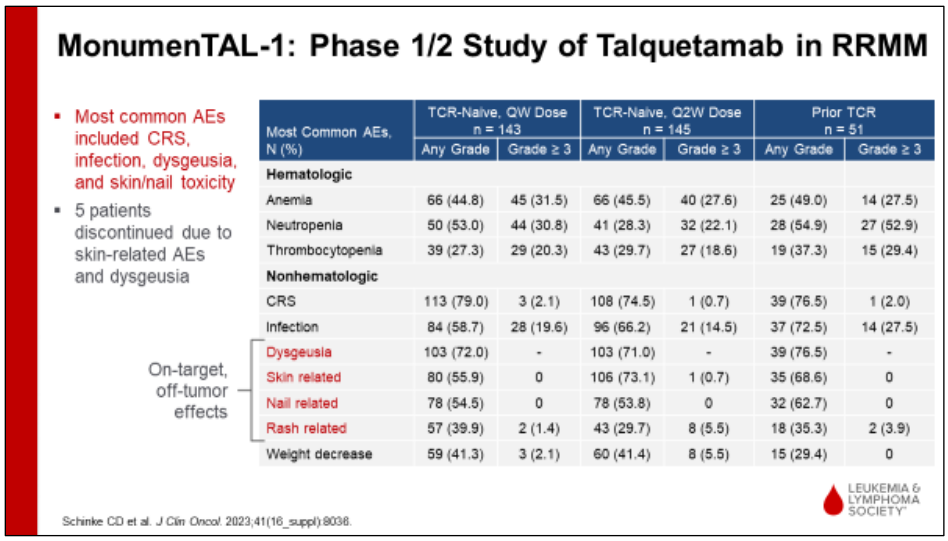


The trial that gave us talquetamab is monumenTAL-1, and is also a phase 1/2 trial, and because this was developed shortly after some of the BCMA CAR Ts that we currently have available, it was natural that some of the patients that entered this study had received prior T-cell–redirecting therapy. So when presenting the results, they chose to separate patients who were T-cell–redirecting therapy-naive or patients with prior T-cell–redirecting therapy. And here you have some characteristics of those two populations. It

was a much larger study, with about 150 patients at 0.4 milligrams per kilogram weekly of the target dose and 0.8 milligrams at every other week. And we have 78 patients who had received prior BCMA-directed CAR T or bispecific.



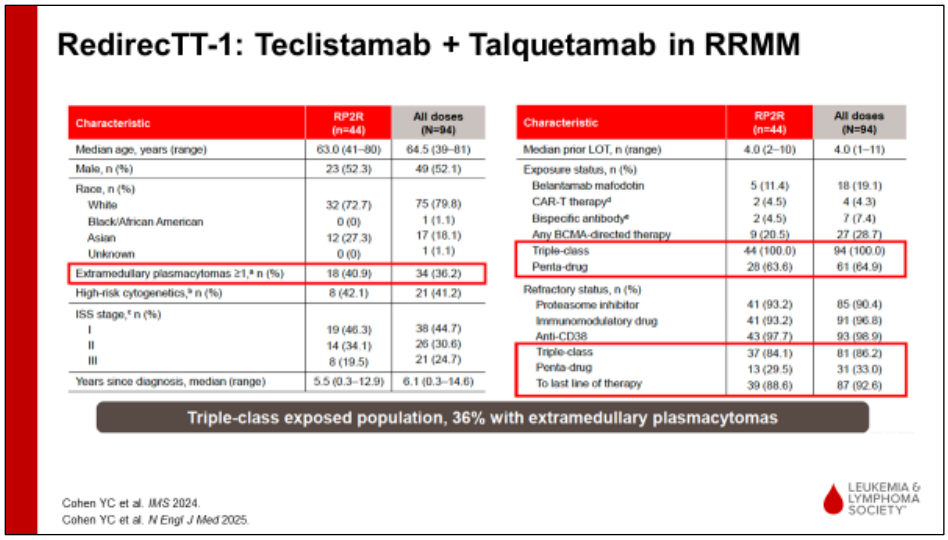
Here you have the outcomes. The overall response rate was somewhat higher than you see with BCMA-directed bispecific: 74% and 70%. And that is pretty much preserved on the patients with prior T-cell–redirecting therapy, particularly those who had received prior BCMA-directed CAR T. Median PFS is now 11.2 months among those patients who received Q2 weeks dose and 7.7 months between both scales for patients who received a prior T-cell–redirecting therapy. Not surprising, those patients who have access to talquetamab after three or four lines of therapy overall had a better PFS than those treated after five or more lines of therapy, which I believe is something that you see for just about any new therapeutics. Overall survival is in excess of two years and is 67% of two years for those receiving the drug every two weeks and 57.3% for those who have received prior T-cell–redirecting therapy.



Most Common AEs, N (%)	TCR-Naive, QW Dose n = 143		TCR-Naive, Q2W Dose n = 145		Prior TCR n = 51	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Hematologic						
Anemia	66 (44.8)	45 (31.5)	66 (45.5)	40 (27.6)	25 (49.0)	14 (27.5)
Neutropenia	50 (53.0)	44 (30.8)	41 (28.3)	32 (22.1)	28 (54.9)	27 (52.9)
Thrombocytopenia	39 (27.3)	29 (20.3)	43 (29.7)	27 (18.6)	19 (37.3)	15 (29.4)
Nonhematologic						
CRS	113 (79.0)	3 (2.1)	108 (74.5)	1 (0.7)	39 (76.5)	1 (2.0)
Infection	84 (58.7)	28 (19.6)	96 (66.2)	21 (14.5)	37 (72.5)	14 (27.5)
Dysgeusia	103 (72.0)	-	103 (71.0)	-	39 (76.5)	-
Skin related	80 (55.9)	0	106 (73.1)	1 (0.7)	35 (68.6)	0
Nail related	78 (54.5)	0	78 (53.8)	0	32 (62.7)	0
Rash related	57 (39.9)	2 (1.4)	43 (29.7)	8 (5.5)	18 (35.3)	2 (3.9)
Weight decrease	59 (41.3)	3 (2.1)	60 (41.4)	8 (5.5)	15 (29.4)	0

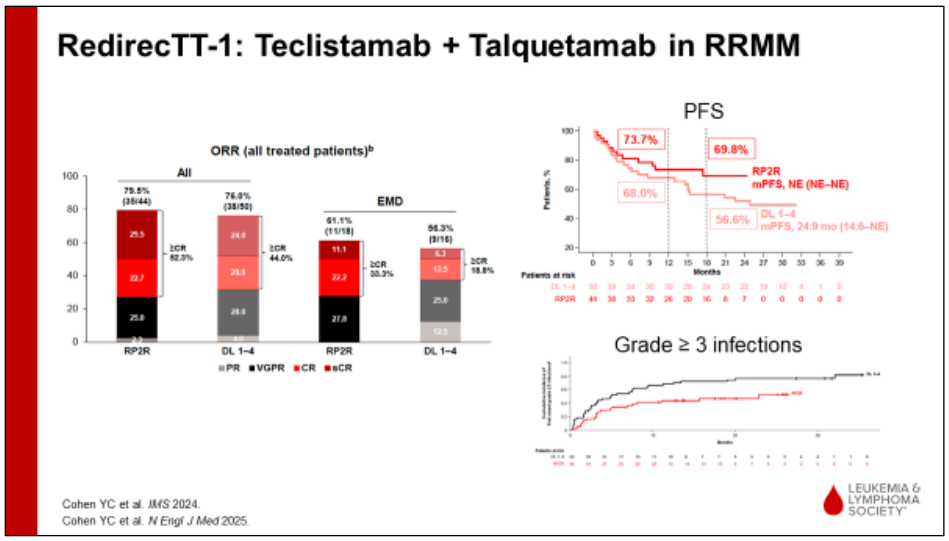
When you look at toxicity, we see somewhat of a different picture than we see with teclistamab and elranatamab. Hematologic toxicities are also common but mostly grade one and grade two, or they're brief neutropenia or thrombocytopenia that occurs during the first few cycles. Infections are less common, particularly high-grade infection. That is seen in less than 20% of the patients without pre/prior T-cell–redirecting therapy and close to 30% of those with prior T-cell–redirecting therapy. What we have here instead is what we call "on-target off-tumor effect," something that we still do not fully understand, but is believed to be related to the expression of the GPRC5D in some normal tissues in the oropharynx, skin, and nail bed. And that accounts for rash, in some cases really extreme inflammation, some nail dystrophy, that is not particularly dangerous or painful but can be very disturbing to patients.

Dysgeusia can be a major issue. It affects the patient quality of life. I think all of us enjoy tasting good food, but it also has sometimes some tangible impact on the patient's weight. It's not uncommon to see weight drops particularly during the first five or six months of therapy.



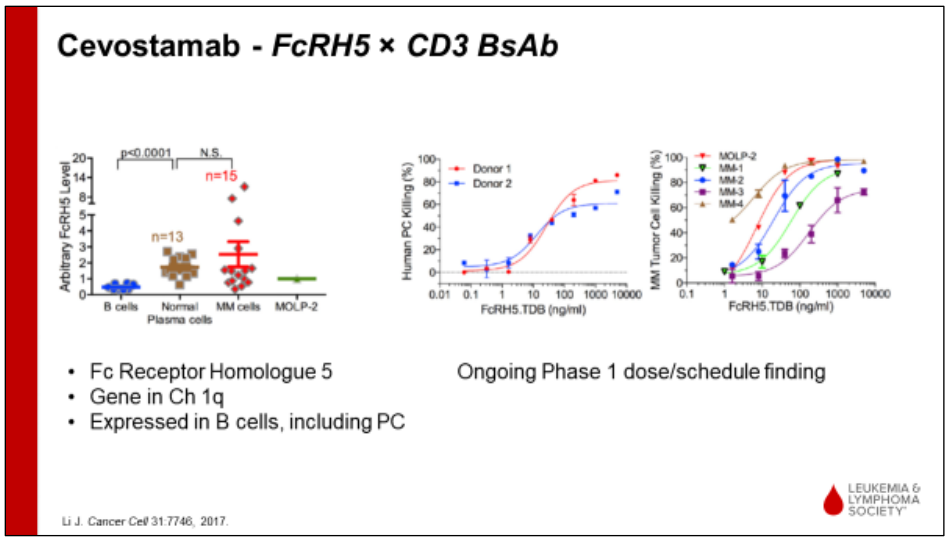
Now we often have those patients in front of us and have to make a choice between a BCMA-directed and or a GPRC5G-directed bispecific T-cell engager. This clinical trial, recently presented and published, brings us the opportunity of doing both. Perhaps capitalizing on the strong effect of each of those bispecifics alone, but also the fact that the expression of the target can be somewhat heterogeneous and loss of target can be a mechanism of resistance. So, that just becomes less likely if you're targeting two different proteins at the same time.

This is the regimen one that combined teclistamab and talquetamab on a patient population with prior triple class–exposed disease, including some very high-risk patients, including patients with extra middle or plasmacytoma, seeing in about 40% of those patients treated at a recommended phase 2 dose. Some patients with high-risk other than genetics and patients with penta-exposed disease.



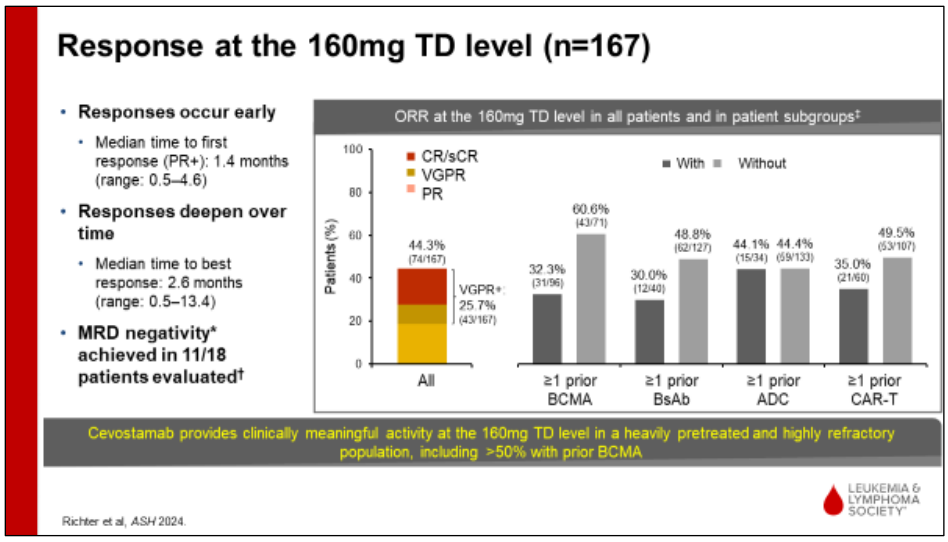
If we just take each one of those bispecifics and, using patients with extramedullary disease, you expect to get a response of about 30% to 40%. Extramedullary disease is really an element that seems to affect the efficacy of those agents. Here you see that, across the cohort, we had close to 80% overall response rate, more than 50% complete response (CR), and an overall response rate of over 60% for those very hard-to-treat patients with extramedullary disease. Responses are not only frequent, they are profound and can be lasting, as you see at 69.8% progression-free survival at 18 months.

Infections of course becomes the biggest problem with this type of therapy. As you can see here, approaching 40% of patients with grade three or higher infection after two years in the program.

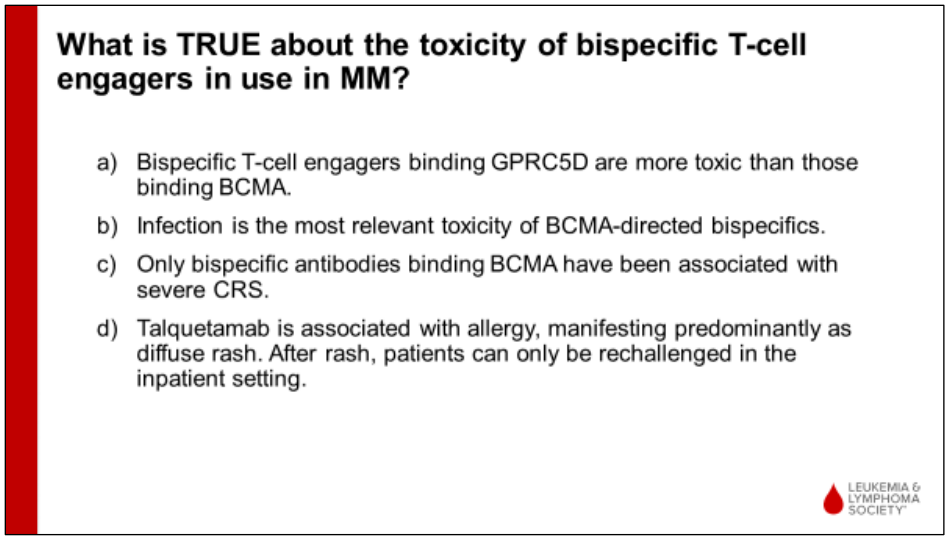


Now we are grateful for the targets we have, but we always find circumstances where we need newer targets and one that has been explored for quite some time now in clinical trials (we hope it's going to come to clinic eventually) is cevostamab that targets FcRH5.

FC receptor homolog five is a family of receptors presence on B cells that is coated on chromosome five Q and that expression maintains in plasma cells and maintains in as they become malignant and also when they become a multi-resistant malignancy.

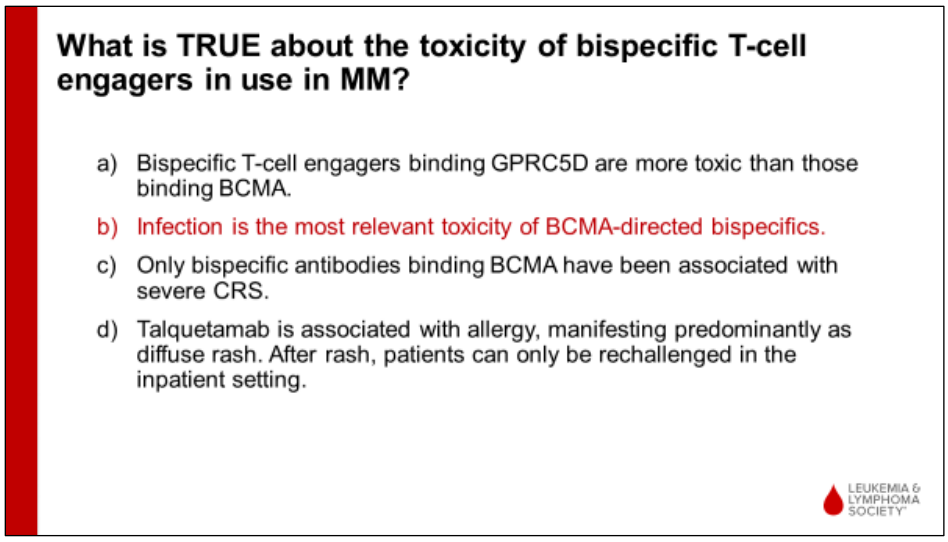


Cevostamab has been phase one for a long time. We have worked on different schedules of administration, different doses. This is the most recent update provided at the 2024 American Society of Hematology annual meeting (ASH) showing that about 44% overall response rate, including responses in patients with prior BCMA-directed bispecific antibodies or CAR T-cell therapy.

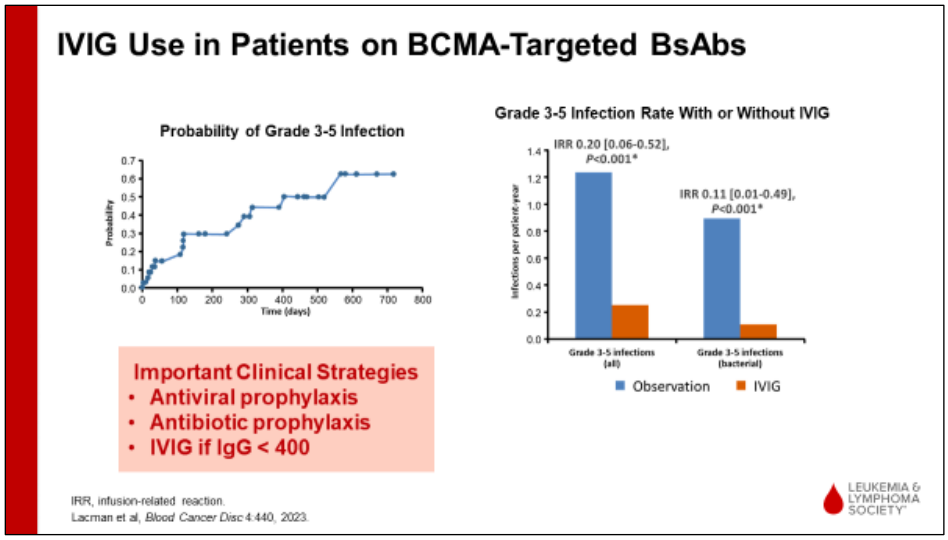


My last poll of this session, what is true about toxicity of bispecific T-cell engagers in use in myeloma? Is the answer: The ones binding GPRC5D are more toxic than those binding BCMA; Infection is the most relevant toxicity of BCMA-directed bispecifics; Only bispecific antibodies binding to BCMA have been associated with severe CRS; or

Talquetamab is associated with allergy, manifesting predominantly as diffuse rash. After rash, patients can only be rechallenged in the inpatient setting.

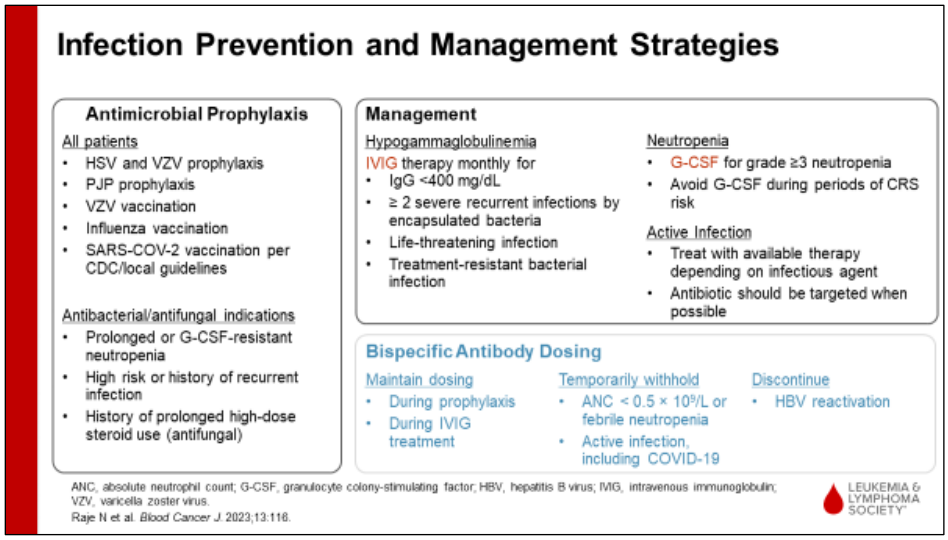


Okay, well it looks like my effort was fruitful because 80% of you got the right answer, which the infection is the most relevant toxicity associated with the BCMA-directed bispecifics.

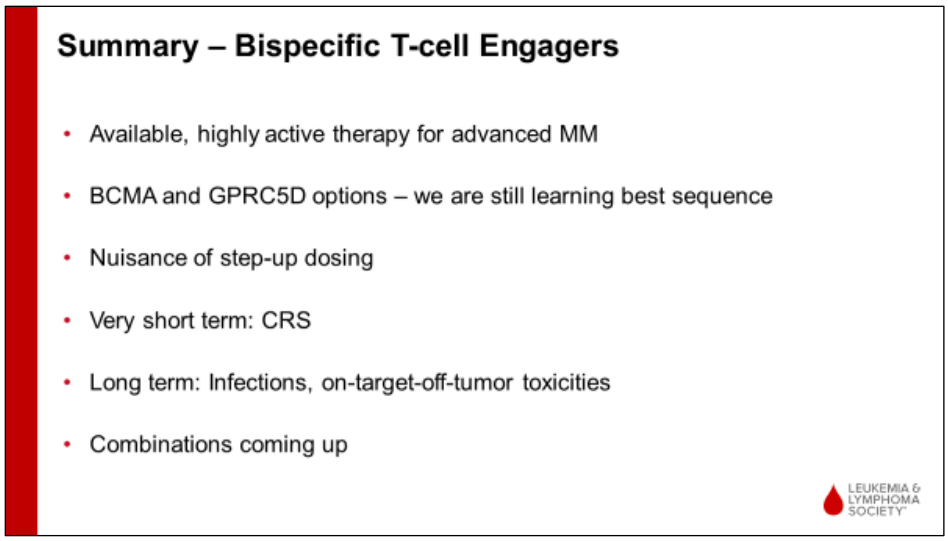


So, how do we mitigate that infection? Now of course it's not as simple as the patients do not produce antibodies. So the type of infections we see is mostly bacterial infection, particularly for encapsulated pathogens that can be mitigated, for example with intravenous immunoglobulin (IVIG). But we also see other types of infections, particularly viral infections or infections by pathogens that we usually see in very immunosuppressive patients, for example, pneumocystis jirovecii pneumonia (PJP). After a very hard awakening we had around the COVID pandemic, many of us have adopted

prophylactic use of IVIG. We seem to have made a tremendous difference. This is one publication where the use of prophylactic IVIG—well, technically not prophylaxis—patients under 400 of IVIG, which everybody's going to be at this point. It seems to be greatly associated with reduction in risk of infections, particularly grade three or higher infections.



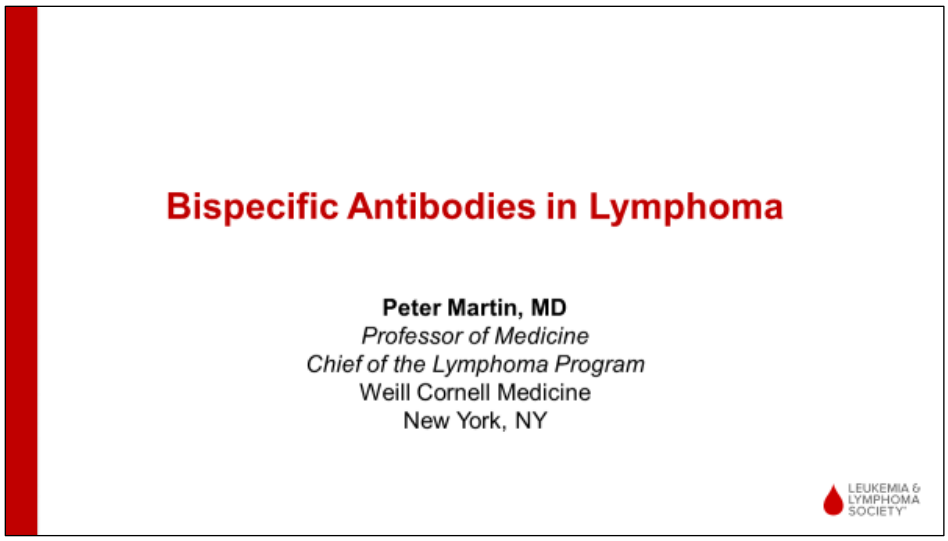
There are several published guidelines. They essentially can be summarized by IVIG replacement for those who are hypogammaglobulinemia, which is going to be everybody, universal VZV (Varicella-Zoster Virus) prophylaxis with acyclovir or valacyclovir use of PJP prophylaxis; we usually went with Bactrim three times a week. Growth factors for neutropenia were seen mostly during the first few months. Surveillance for patients who are HBV carriers and discontinue or stopping therapy if any infection is present. But I would recommend you to consult those guidelines for more details about mitigating infections.



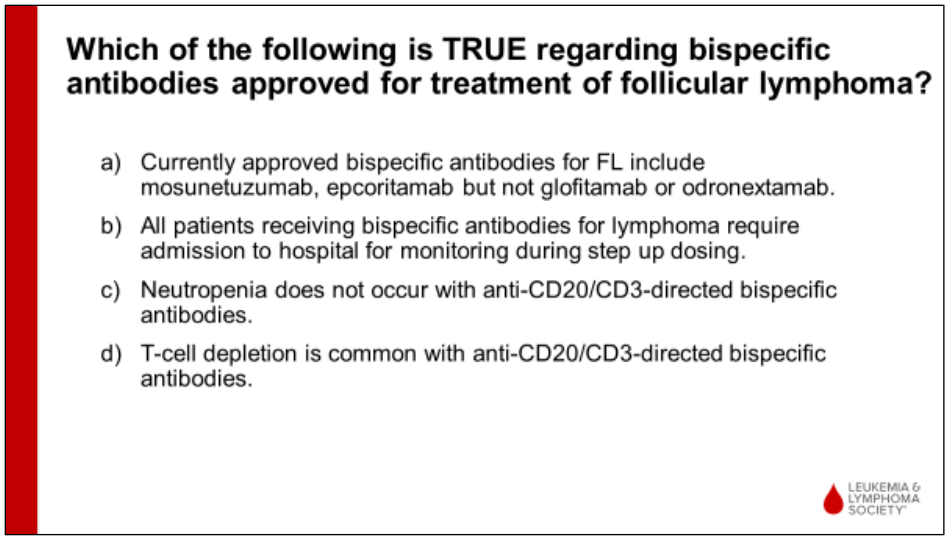
In summary today I discussed with you that bispecific T-cell engagers are available, highly active therapies for advanced multiple myeloma. We have options directed to BCMA and GPRC5D and we're still learning how to best sequence those targets. But there's no wrong answer as long as you reach out to an effective and safe therapy for your patients.

There are nuisances of step-up dosing. Our institutions have found different ways to cope and work around it. The CRS is a very short-term problem. It is a problem of the first week. It's not a problem of the second month or the third month or the patient who has been on therapy for several months. The key thing that everybody needs to be aware of are the infections because mitigating those is the responsibility of everybody who is part of the care of those patients. And be aware of the on-target-off-tumor toxicities of GPRC5D and that there are a series of suggestions about how to manage that skin and nail toxicity. And be prepared because I think we're going to have combinations with those agents in a very close future.

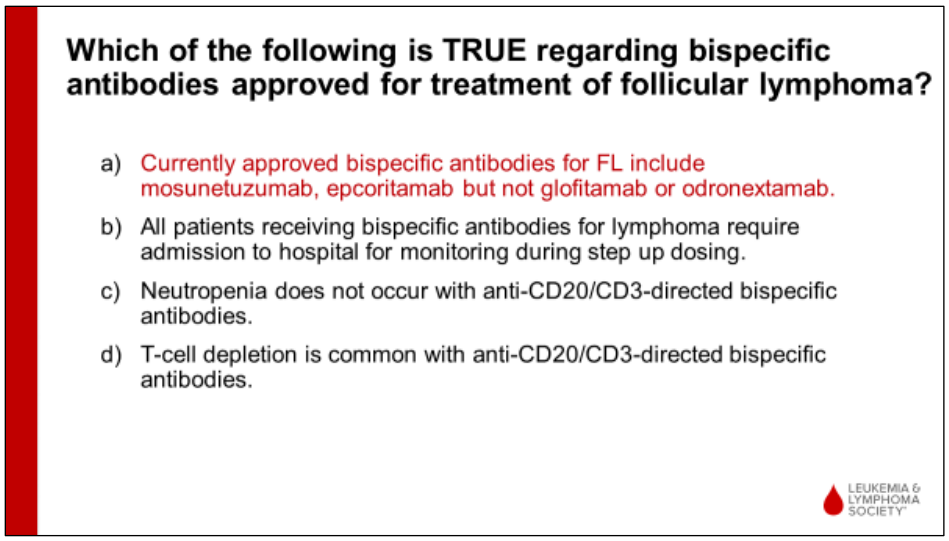
I'd like to again thank for your attention and pass the virtual stage to Dr. Martin.



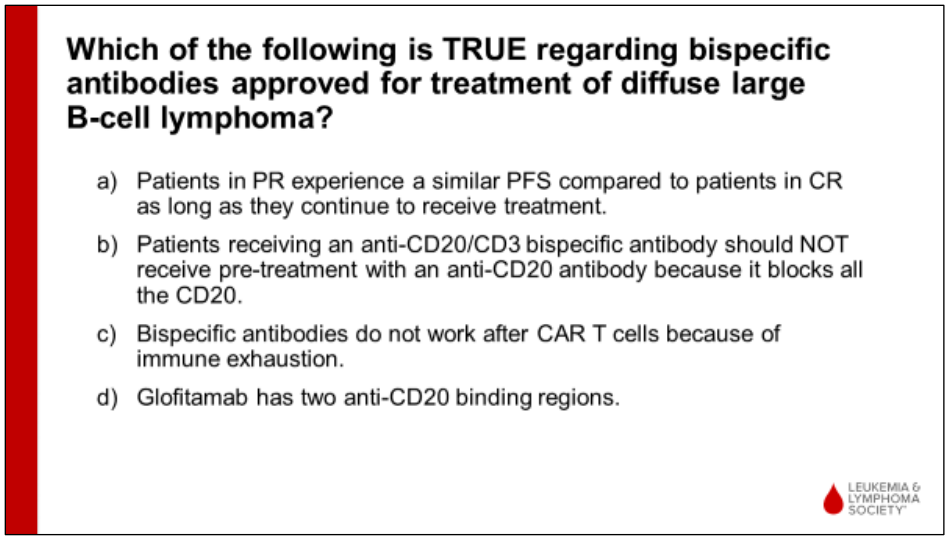
Peter Martin, MD
Thank you, Dr. Costa. I'm Peter Martin from Cornell in New York.



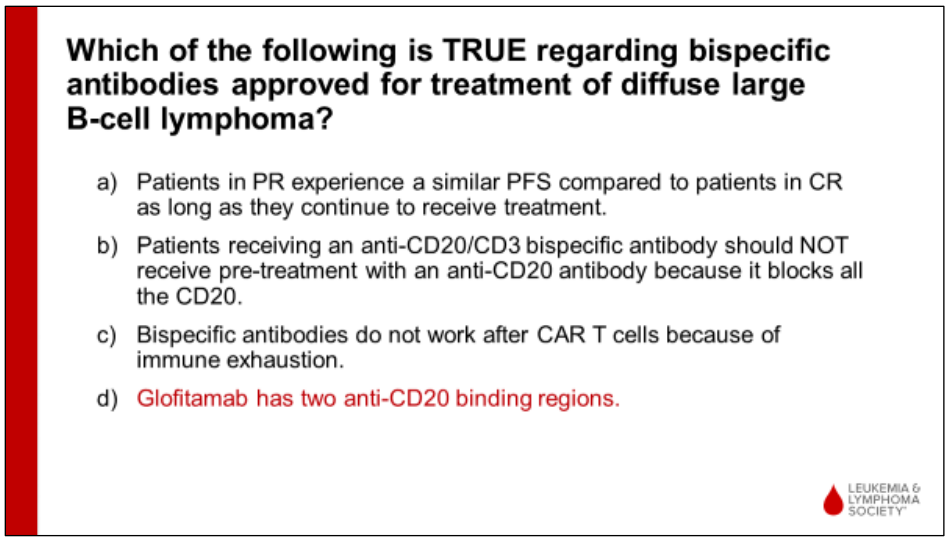
Here are the questions that I'll introduce. Which of the following is true regarding bispecific antibodies approved for the treatment of follicular lymphoma? Is the answer: Currently approved bispecific antibodies for follicular lymphoma include mosunetuzumab, epicoritamab but not glofitamab or odronextamab; All patients receiving bispecific antibodies for lymphoma require admission for monitoring; Neutropenia does not occur with anti-CD20/anti-CD3-directed bispecific antibodies; or lastly, T-cell depletion is common with anti-CD20/anti-CD3-directed bispecific antibodies.



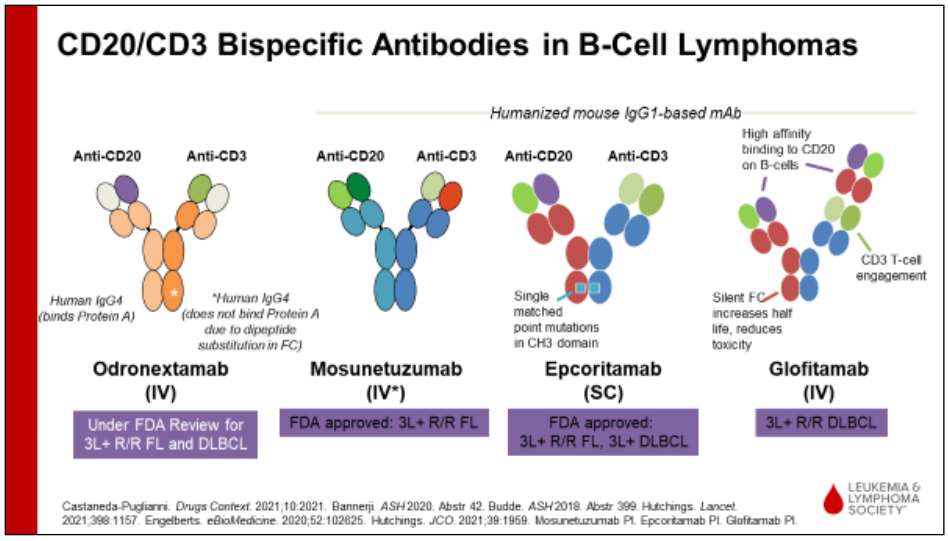
All right, the answer here is A, and we will go into that in a little bit of detail in a few minutes.



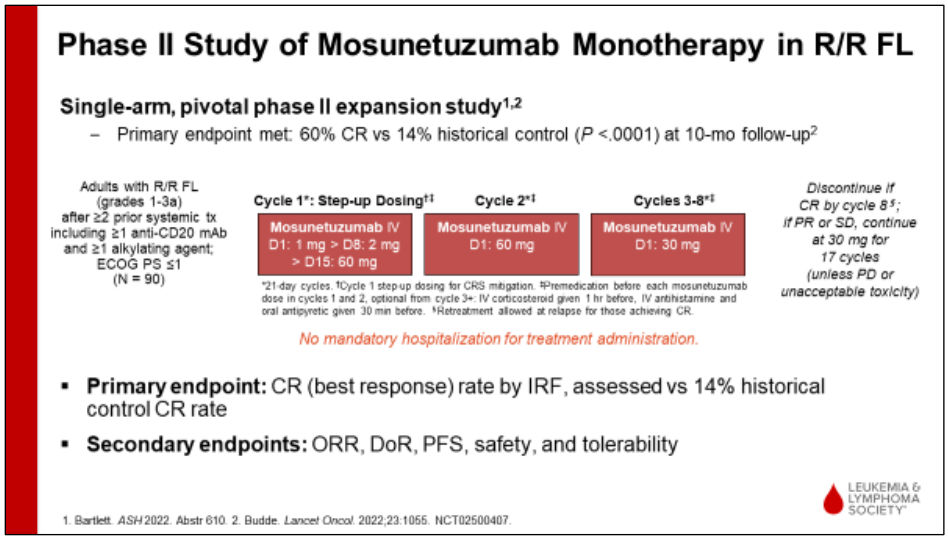
And my second question, our last question, is, “Which of the following is true regarding bispecific antibodies for diffuse large B-cell lymphoma, not follicular lymphoma like the last question?” Is the answer: Patients who experience a partial response or patients in a partial response experience a similar progression-free survival compared to a complete response as long as they continue to receive treatment; Patients receiving bispecific antibodies should not receive pre-treatment with an anti-CD20 antibody because it blocks all of the CD20; Bispecific antibodies do not work after CAR T cells because of immune exhaustion; or glofitamab has two anti-CD20 binding regions.



All right, I think several of you got this one, so we'll see that as well.

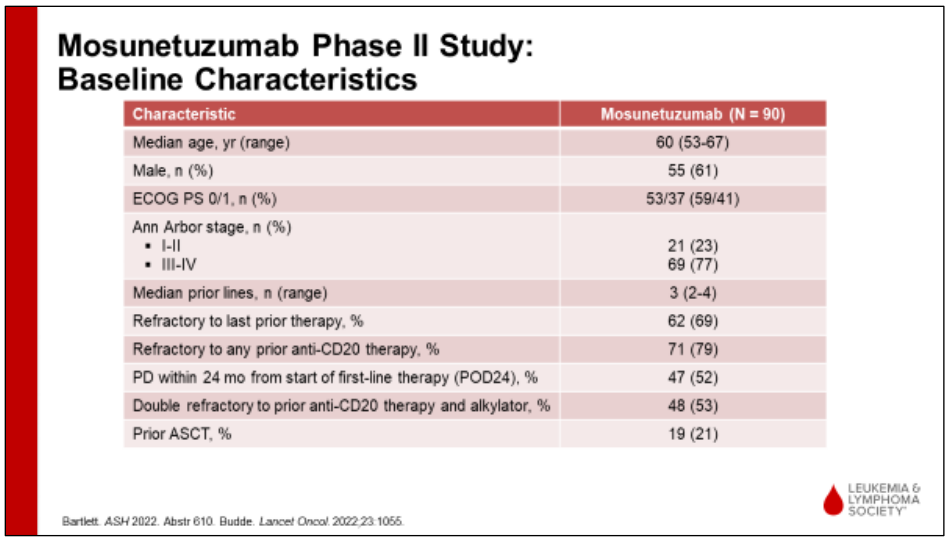


So we're just talking specifically about diffuse large B-cell lymphoma and follicular lymphoma. All of these antibodies as well as others are in clinical trials in other forms of B-cell non-Hodgkin lymphomas, including mantle cell lymphoma (a study was recently published there) and marginal cell lymphoma, but the ones that are approved are approved specifically for follicular and diffuse large B-cell lymphoma. I've got odronextamab on the slide because it is under review for follicular lymphoma and diffuse large B-cell lymphoma, and we may see it approved in the near future. And you can see the structure of the antibodies there, including two anti-CD20 binding regions for glofitamab with one anti-CD3 binding region, which is interestingly tuned down a little bit to have a little bit less affinity for CD3, ideally mitigating some of the cytokine release syndrome.

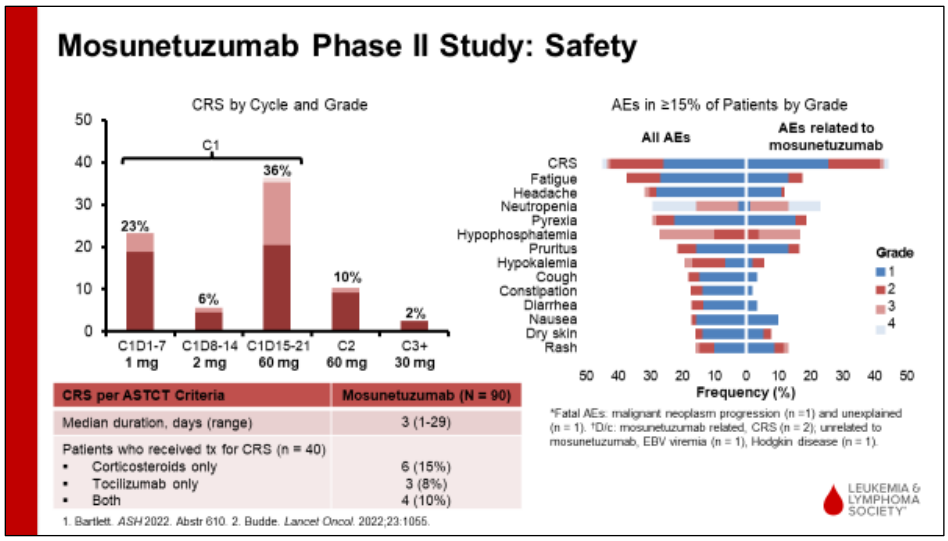


Let's talk a little about mosunetuzumab in relapsed follicular lymphoma. Specifically, I'm just going to go over the pivotal trials that got these drugs approved. There are a number of other trials that are ongoing or presented or published. I'll highlight some of the key similarities behind these trials as we go along and you'll see that they, in many cases, are very similar to what Dr. Costa presented in multiple myeloma. Mosunetuzumab in this trial is administered to patients with relapsed/refractory follicular lymphoma following at least two prior lines of therapy that included anti-CD20 and an alkylating agent. The eligibility criteria there may look familiar to some of you. Those are the same criteria that were used to get accelerated approval for the PI3 kinase inhibitors you'll remember from a few years ago.

There was already a strategy for accelerated approval in follicular lymphoma and they basically followed the same strategy here looking at the same population. And that's pretty similar for all of the trials with these drugs in follicular lymphoma. Like multiple myeloma, all of these bispecific antibodies include a typical step-up dosing followed by continuous dosing. Perhaps unique to mosunetuzumab is that treatment goes for eight cycles in patients who achieve a complete response and up to 17 cycles after that. So, a total of somewhere between six to 12 months of therapy, time-limited therapy, unless patients experience progressive disease or unacceptable toxicity in the interim.

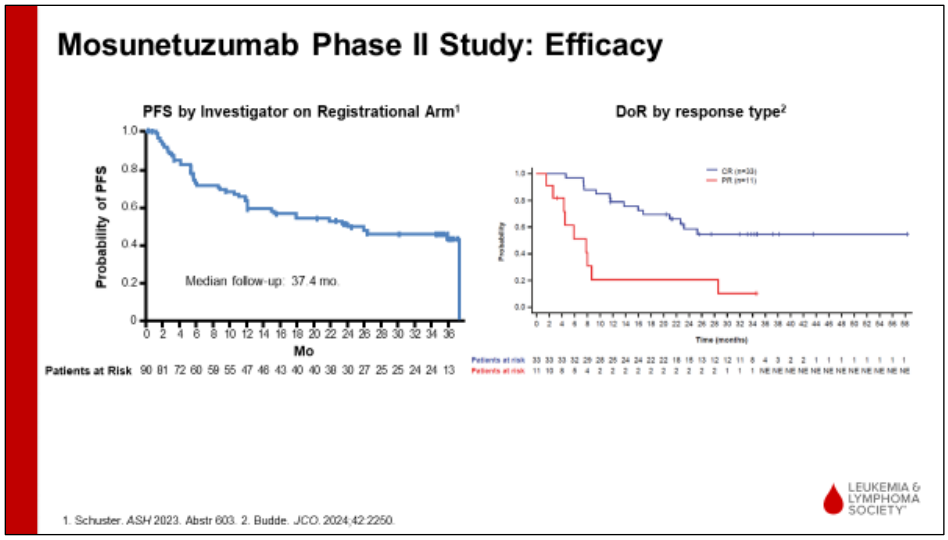


And these are the patients. You can see, similar to other trials, there are a number of patients who are refractory to their prior anti-CD20 or last line of treatment, including patients who are double refractory to CD20 and alkylator and a number of patients who had had prior autologous stem cell transplant.

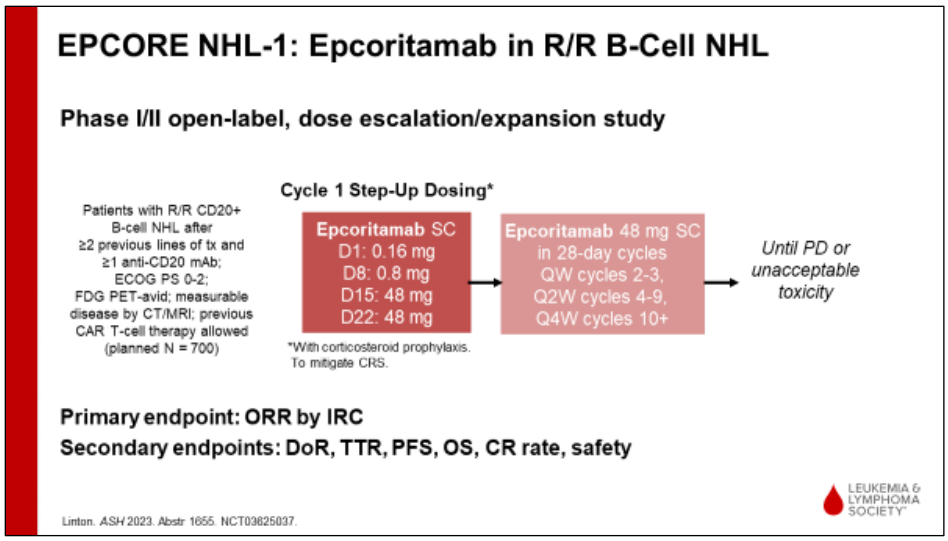


These are the adverse event data or safety data, and you can see that the highest rate of cytokine release syndrome in fact happens on day 15 at the first full dose administration or for 60-milligram dose administration of mosunetuzumab. You can see that, in all cases, rates of cytokine release syndrome are typically grade one and two with a very low rate of grade three/four to cytokine release syndrome happening specifically on day 15. On the right side of the slide you can see adverse events attributed to mosunetuzumab. I will say that, as somebody who's involved in clinical trials, I always view these data a little bit skeptically. I'm not sure that it's always easy to determine the attribution of an adverse event. For example, you'll see a pretty high rate of headache in terms of all AEs without very many headaches attributed to mosunetuzumab after giving a bunch of bispecific

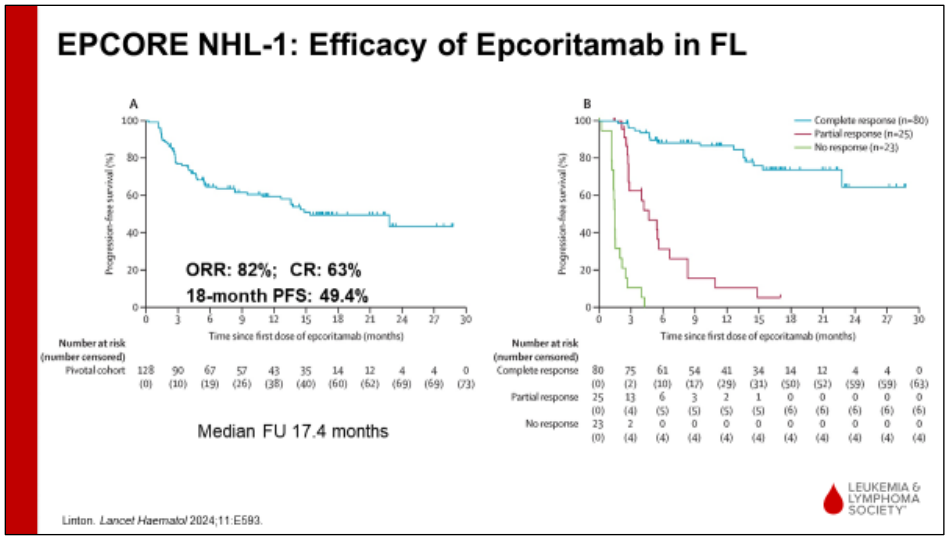
antibodies. My impression is that the headaches are probably often due to bispecific antibodies. So, when you read these tables, I would suggest that you look at all adverse events and maybe ignore, a little bit, the adverse events that are attributed to the drug because you're relying on somebody else to make that call. But you can see that these adverse events are pretty similar to what Dr. Costa presented with multiple myeloma, including neutropenia, which was in one of the questions that I mentioned earlier.



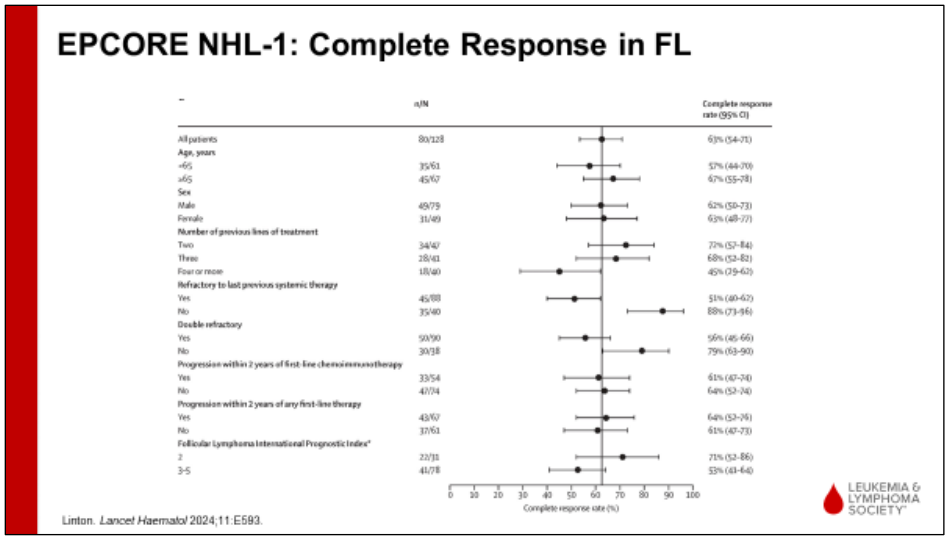
And these efficacy data come from two arms of the same trial, the registrational arm as well as. On the right-hand side of the slide, there are actually a bunch of patients who were treated in an expansion following the dose escalation, all similar eligibility criteria, all roughly at the same dose, all with a similar follow-up. But, on the left-hand side, you can see with 90 patients with a median follow-up of 37 months that the median progression-free survival is close to about 50%. And you can see on the right-hand side of the screen what I think is particularly interesting and not unique to mosunetuzumab is the significant duration of response based on whether patients are in a complete response or partial response. This is of course not really that surprising and is probably true of many therapies, but it's quite striking the difference between complete and partial responses. Remember that those patients who achieved a complete response could receive as few as eight cycles of treatment or six months of therapy. And in fact, although there are a few patients who evolve in their response from partial to complete response beyond six months of therapy, most of those complete responses will actually happen pretty early on.



Epcoritamab is the other approved antibody in follicular lymphoma, but it's also approved in diffuse large B-cell lymphoma. And so you can see the eligibility of this clinical trial was fairly broad and included a variety of B-cell non-Hodgkin lymphomas. And then there were separate cohorts specifically for follicular lymphoma and diffuse large B-cell lymphoma. It started out with standard step-up dosing as you can see here on days 1, 8, 15, and 22, achieving the full dose on day 15 in the majority of patients. Then what's different about epcoritamab versus mosunetuzumab is epcoritamab is administered subcutaneously, and it's administered until toxicity or progressive disease, not at time-limited therapy as mosunetuzumab is. There may be advantages or disadvantages to that approach depending on your perspective. Epcoritamab is administered subcutaneously in part because it's a very small volume and the excipients in which it's constituted make it amenable for subcutaneous injection. It does not have hyaluronidase, similar to other subcutaneous antibodies like rituximab hycela.



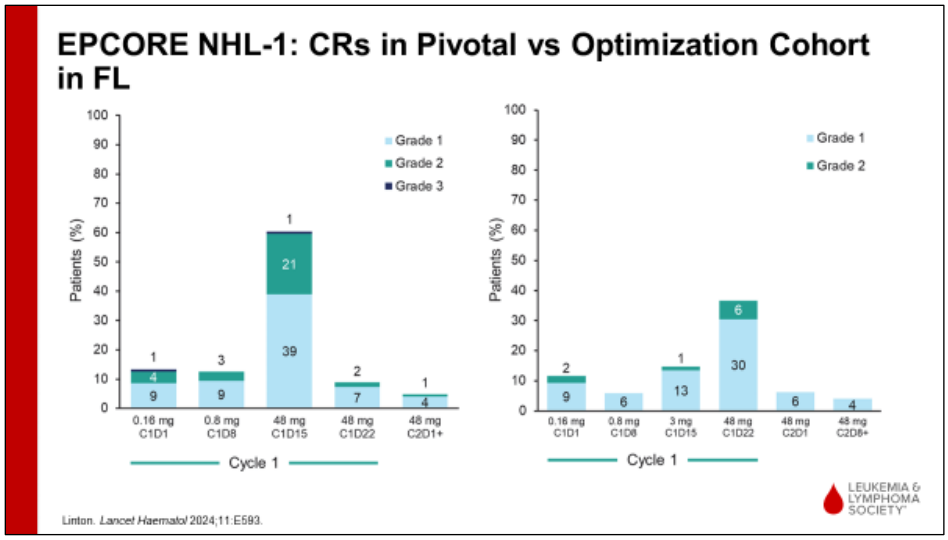
These are the efficacy in follicular lymphoma, and you can see a really pretty similar progression-free survival curve relative to mosunetuzumab. I think it's very difficult to compare across clinical trials, but you can see the gist is that things are pretty similar. And again, you can see on the right-hand side that there's a pretty significant difference between complete and partial responders in terms of their duration of response.



The interesting thing here is I think (I like to pick apart some of the data that get presented and every paper presents data in a little bit different way), but what I think is interesting about this slide is, if you know who's most likely to achieve a complete response, you can guess at who's going to have these long duration benefits from them as opposed to people who have maybe a shorter duration. Not to say that they have no benefit, but their benefit might be a little bit shorter. You can see that, on average, the complete response rate is in the 60% range. So, even in people who have higher risk disease, they're still doing quite well, but there are some people with complete response

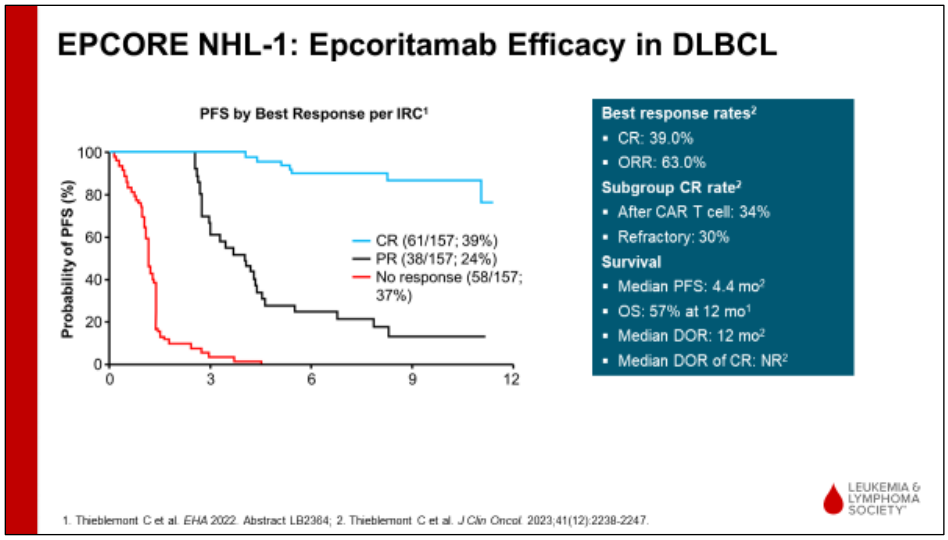
rates above 80%-90% and those are specifically people who were not refractory to their prior therapy, their previous therapy, whereas other groups tended to do pretty similarly.

If we pick people who are pretty low risk and have responded well to prior therapies, there's a very good chance that they'll achieve a complete response and have these very durable responses that go for years. Unfortunately, those are not the people who most need these new therapies, but those are the data.



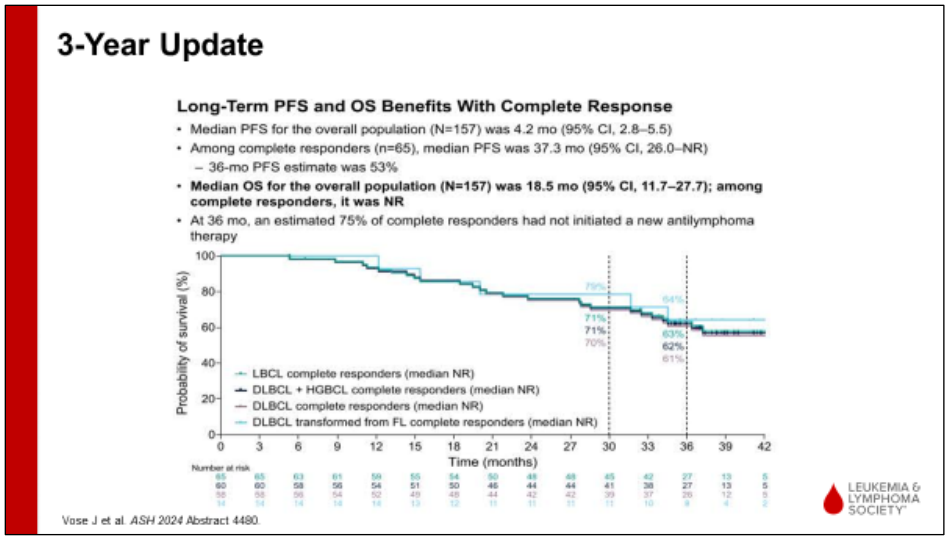
Epcoritamab, interestingly, because of this high rate of cytokine release syndrome on day 15 with the first full-dose administration, the investigators and company went back to the drawing board to look at adding an extra day in of dose escalation. And you can see that, on the dose optimization cohort on the right-hand side, they went from 0.16 to 0.8 to three milligrams, so there's an extra dose-escalation step before day 22 achieving the 48-milligram cohort. The other things that they changed there were to add mandatory dexamethasone premedication, as opposed to methylprednisolone injection, as well as intravenous fluids.

And those three changes, the additional step-up dosing, dexamethasone, and the IV fluids, prior to the administration of the drug, significantly reduced the rate of cytokine release syndrome at the first full-dose administration, making it possible for patients in this clinical trial to potentially avoid hospitalization entirely. Whereas, administered at the recommended on-label administration schedule, people are recommended to be admitted for observation at that first dose. This has been submitted to the US Food and Drug Administration (FDA) and may be incorporated in future product labels. As a result of this, we've changed our order set at Cornell. Again, this is specific to follicular lymphoma and diffuse large B-cell lymphoma, where maybe there's a little bit more urgency to get up to the full dose. We still use the standard dose-escalation schema.

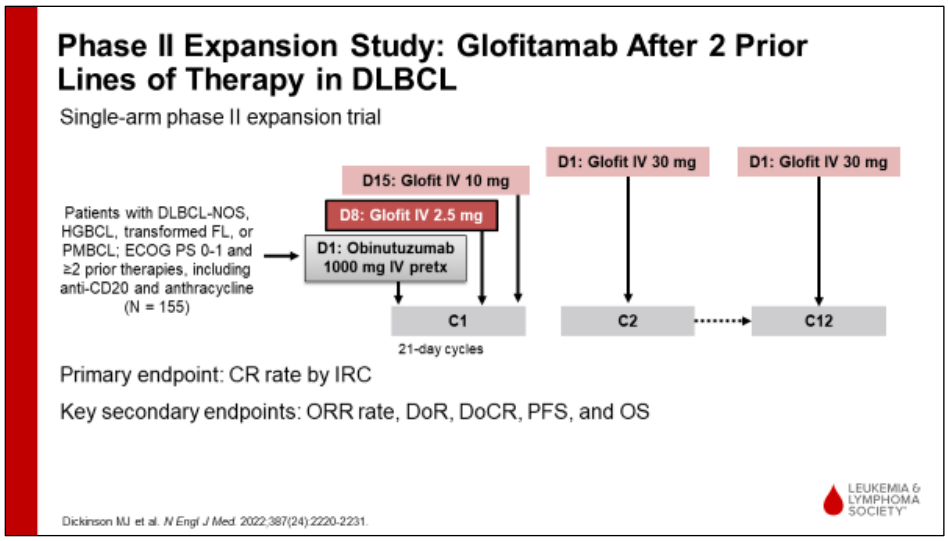


These are the efficacy data in epcoritamab, and the key differences here you see relative to follicular lymphoma are a lower complete response rate with a lower median progression-free survival of only four months.

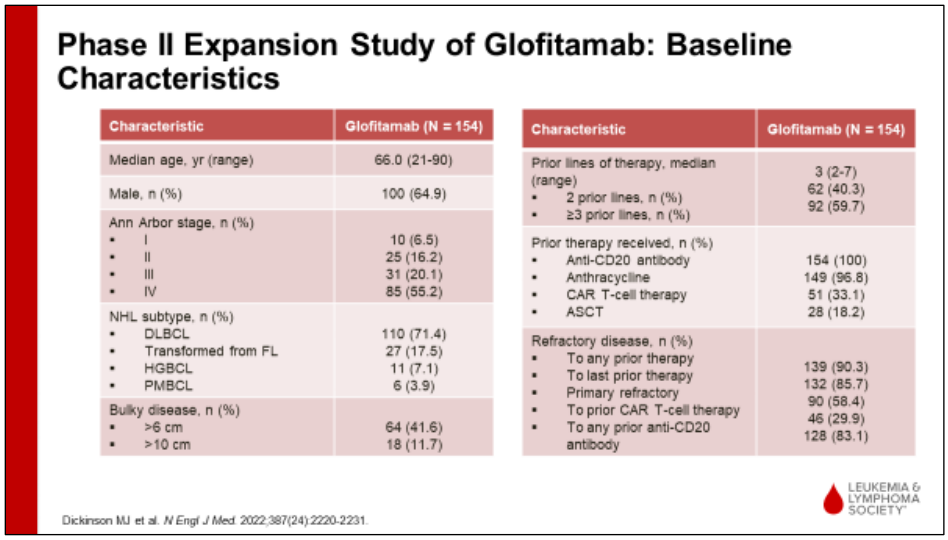
But you can see that, of those patients who achieve those complete responses, they can be remarkably durable, far more than anything that we typically see with other approved therapies in diffuse large B-cell lymphoma in this third-line and beyond setting.



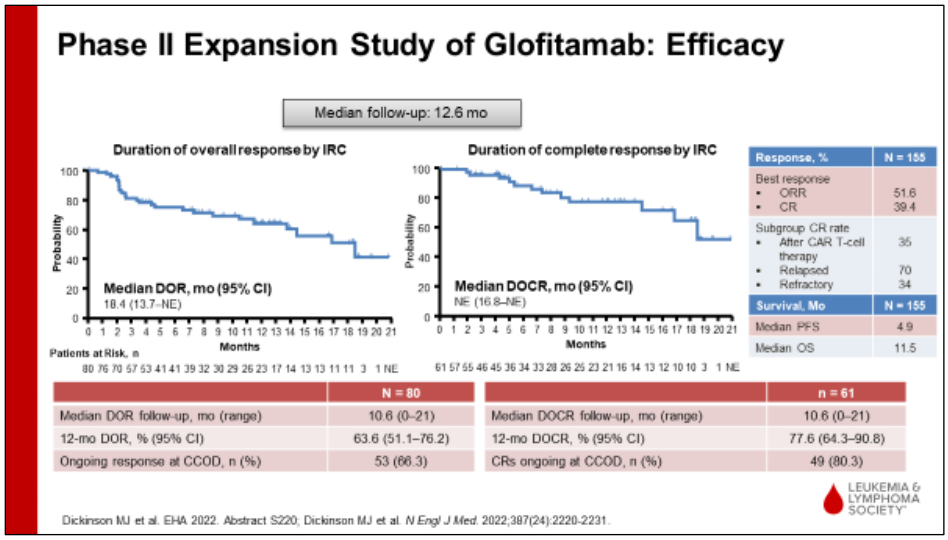
This is the three-year update, recently presented at ASH in December with follow-up, and you can see that these are multiple different subgroups, including high-grade B-cell lymphoma (that is, double hit, etc), and transformed diffuse large B-cell lymphoma transformed from follicular lymphoma. All of these outcomes are pretty good, particularly for patients who achieve a complete response.



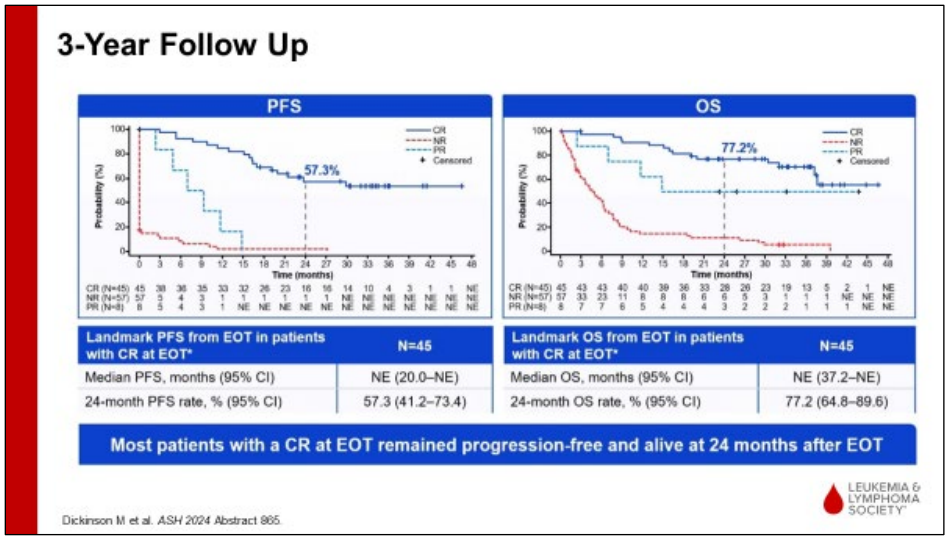
Glofitamab is the third approved antibody that I'll mention. Differences with glofitamab relative to the other antibodies include premedication with obinutuzumab. This is an anti-CD20 antibody that's administered one week prior to the first dose of the bispecific antibody with the goal of blocking circulating CD20, thereby reducing the likelihood of cytokine release syndrome when the glofitamab is administered. This was one of the questions initially. There's the same step-up dosing 2.5 and 10 milligrams with 30 milligrams starting on cycle two, and this is a similar eligibility criteria in relapsed/refractory diffuse large B-cell lymphoma, high-grade B-cell lymphoma, transformed lymphomas.



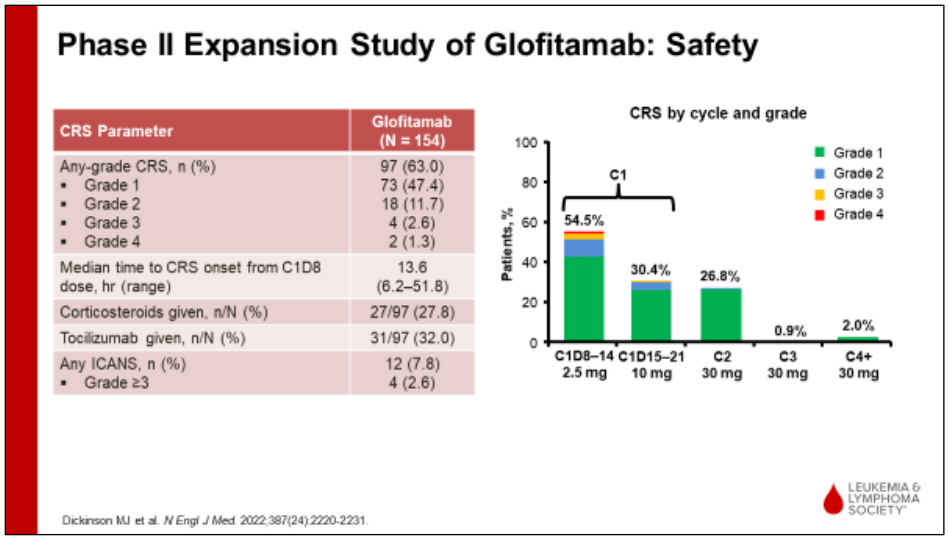
And these are the patients who went on the study. It's pretty similar to what you would expect in this population. I'll highlight one thing, however: a third of patients were post-CAR T-cell therapy. This was one of the questions that I had asked earlier–can bispecific antibodies work post-CAR T-cell therapy? So, let's see what the answer is.



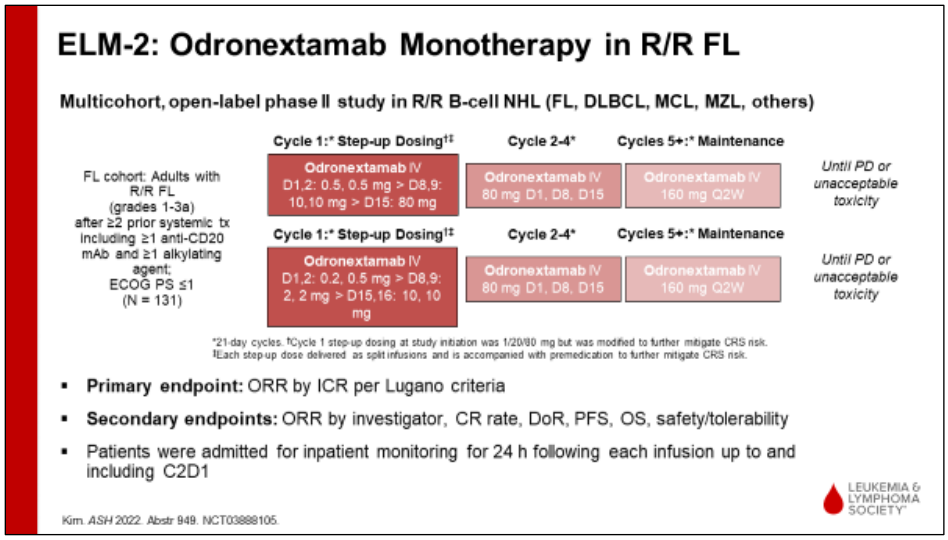
These are the efficacy data for glofitamab, and you can see that the median duration of response here is 18 months, which is quite remarkable in a population of people refractory to their prior therapies. And, interestingly, you can see in the small table on the right-hand side, in a subgroup analysis, 35% of people after CAR T-cell therapy continue to achieve a complete response.



And again, with three-year follow-up what you see is this strong difference between complete responders and partial responders, showing again that patients who achieve a complete response really can have remarkably durable treatment responses. Again, with glofitamab, treatment goes out to one year and you can see that these responses, although if you look at the PFS curve carefully, you can see that there's a small drop off in progression at about 15 months, suggesting that these people were getting scanned after stopping therapy and there was a small increase in progression. But with a median follow-up of three years, you can see that a number of patients still here are in a complete response for over a year after stopping therapy, which is quite remarkable.

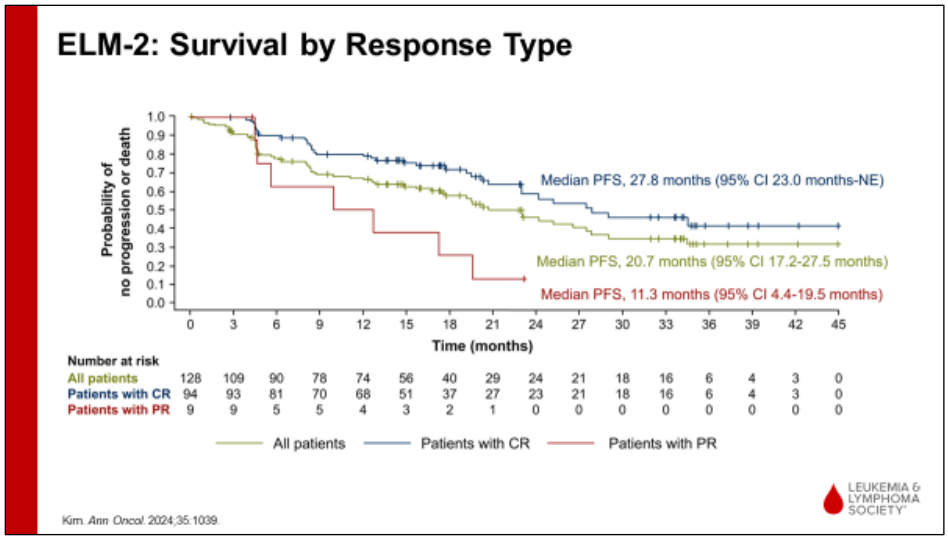


Unlike other bispecific antibodies, you can see that many of the cytokine release syndrome events with glofitamab happened in the first day of the glofitamab. This is on day eight of the administration, with day 1 being the obinutuzumab. We do typically admit people for the initial dose and observe them for 24 hours. One of the questions that was asked is why is it a mandatory four-hour observation period when the median time to cytokine release syndrome is about 12 to 14 hours? And the answer to that is that some cytokine release syndrome can occur earlier, as early as about an hour after the infusion. And in general, earlier time to onsite of cytokine release syndrome tends to be associated with a worse subform of cytokine release syndrome. So, by watching them for a period of time, we're more likely to catch the really bad cytokine release syndromes. Less significant forms of cytokine release syndrome can often be managed pretty easily as an outpatient.

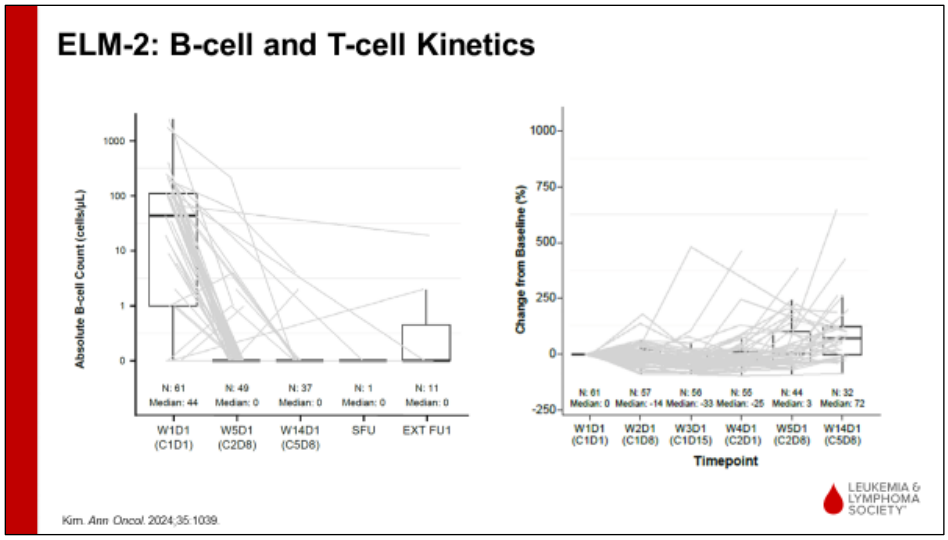


Lastly, I'll get to odronextamab. Again, this is not approved for follicular lymphoma or diffuse large B-cell lymphoma, but it is likely to be approved in the near future. Again,

step-up dosing odronextamab is administered intravenously. And again, it's administered until time of progression or unacceptable toxicity.

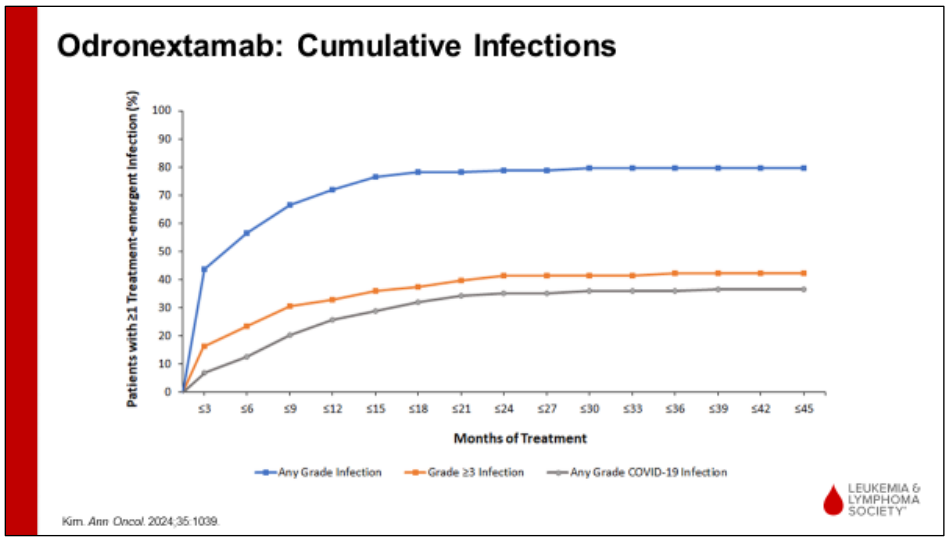


In the ELM-2 trial, which included follicular lymphoma, you can see a pretty attractive median progression-free survival of 28 months. That's longer with the other antibodies, but again, I'm loathe to compare across clinical trials. Let's just say that it is clearly effective, particularly in people who achieve a complete response.

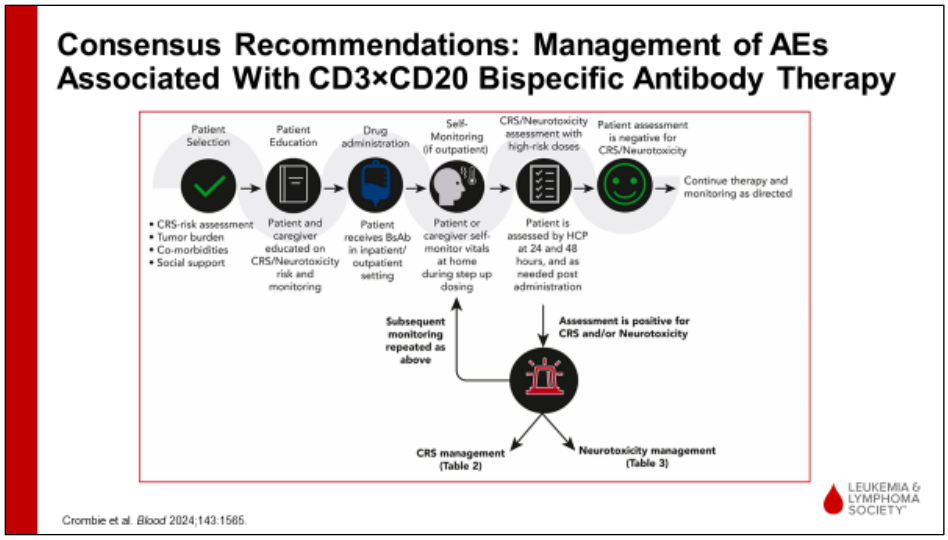


I like this publication very much because it included a number of interesting data in the supplemental part of the paper, including time to B-cell aplasia, and you can see on the left side basically all patients achieve B-cell aplasia very quickly. And interestingly, on the right side, what you can see are changes in T cells from baseline and, effectively, there are very small changes in T-cell numbers from baseline. And over the course of 14 weeks, there may actually be a trend towards an increase in T-cell numbers from baseline.

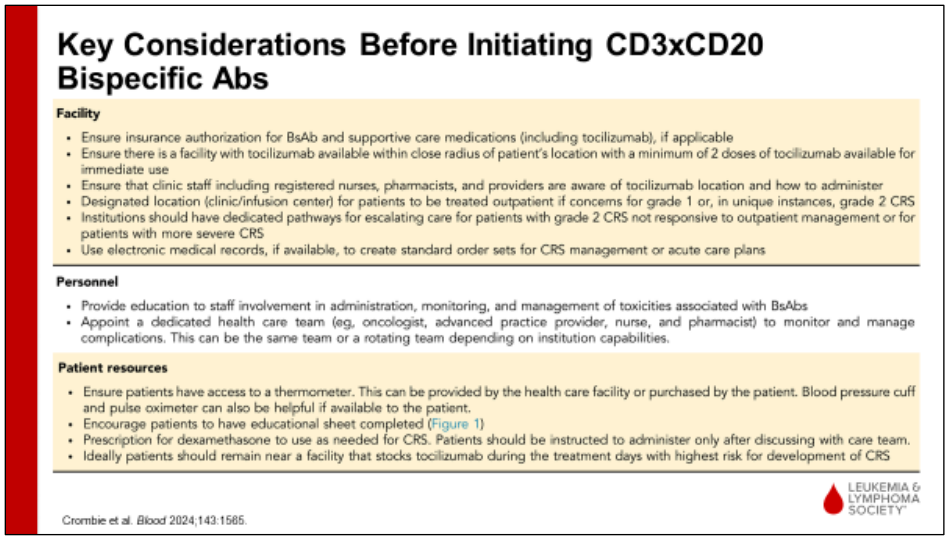
This was one of the questions I asked. Really, the immunosuppressive effects that we're seeing from bispecific antibodies is primarily due to severe and significant B-cell aplasia, not really due to major changes in T-cell numbers.



But we do see significant infections. It's interesting to me after seeing Dr. Costa's presentation that there are significant infections with the anti-BCMA antibodies in multiple myeloma. Maybe this is an interesting thing for discussion. It looks to me like the infections are a little bit worse with the anti-BCMA antibodies than the bispecific antibodies in lymphoma. But you can see that grade three/four infections are up to 30%-40% of patients with odronextamab cumulatively over the course of about a year. And so this is, I think, potentially the Achilles heel of these treatments, particularly in indolent lymphomas like follicular lymphoma where we have to be really careful about balancing the good and the bad of all of these treatments.

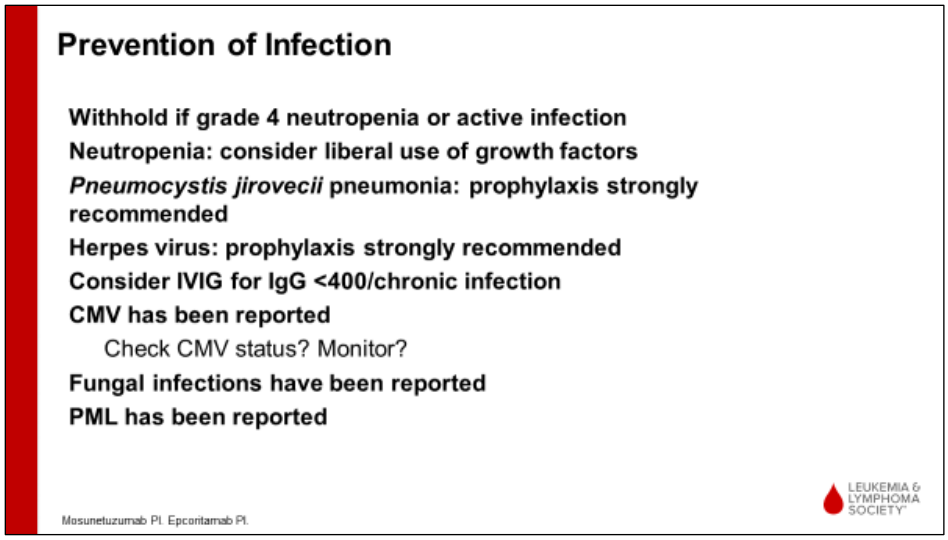


That brings us to consensus recommendations regarding the management of adverse events. I don't think it's significantly different than multiple myeloma. I will say that this paper by Crombie et al. published in *Blood* recently is a very nice consensus recommendation from multiple physicians who were involved in clinical trials using bispecific antibodies, and I highly recommend reading it as well as taking a look at the package insert for all of the antibodies. They're all a little bit different, but this guideline has a very nice summary of how to consider managing any of these adverse events. I think that, in general, we focus a lot on this red bell on the bottom, which is the management of CRS and neurotoxicity. Whereas the truth is we probably need to spend less energy on that and more energy on the top part of the figure, which is more around patient selection, patient education, and, in particular, preparation of the facility where the antibody is going to be administered.

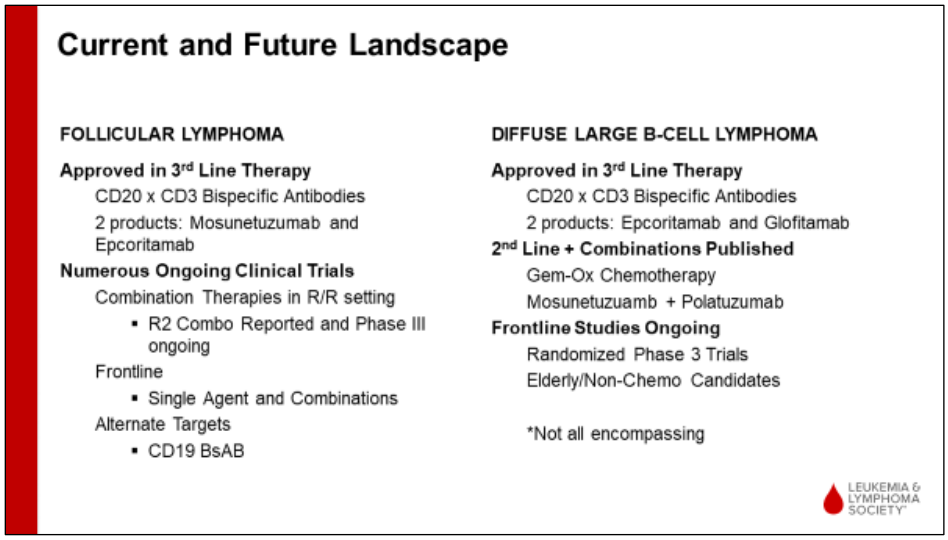


And so I just wanted to highlight that part of it and, in particular, making sure that all of the staff are trained to deal with cytokine release syndrome, that tocilizumab is available

and on hand, that patients are told who to call, where to call, that the people who are answering the phone know to take these things seriously. And I think that, in general, the kinds of adverse events that people experience are pretty manageable often in the outpatient setting provided that we have prepared the facility, the staff, and the patients with the resources necessary to deal with those issues.



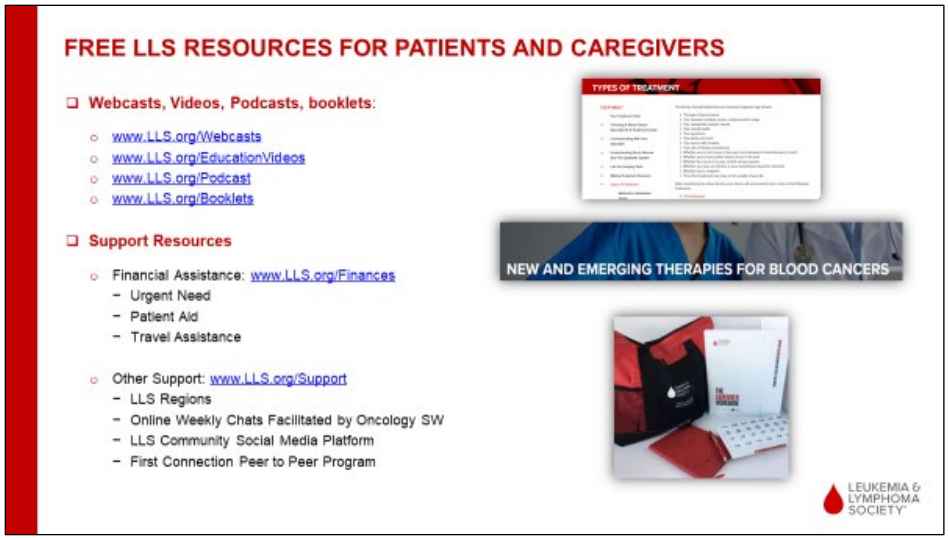
I mentioned a little bit about infection. We do see unusual infections, including PCP. We've seen cytomegalovirus (CMV) for example. IVIG is definitely for consideration for people with low immunoglobulin G (IgG) levels. There have been reports of fungal infections and even progressive multifocal leukoencephalopathy (PML), so this is something to consider and, in particular, liberal use of growth factors in patients who experience neutropenia.



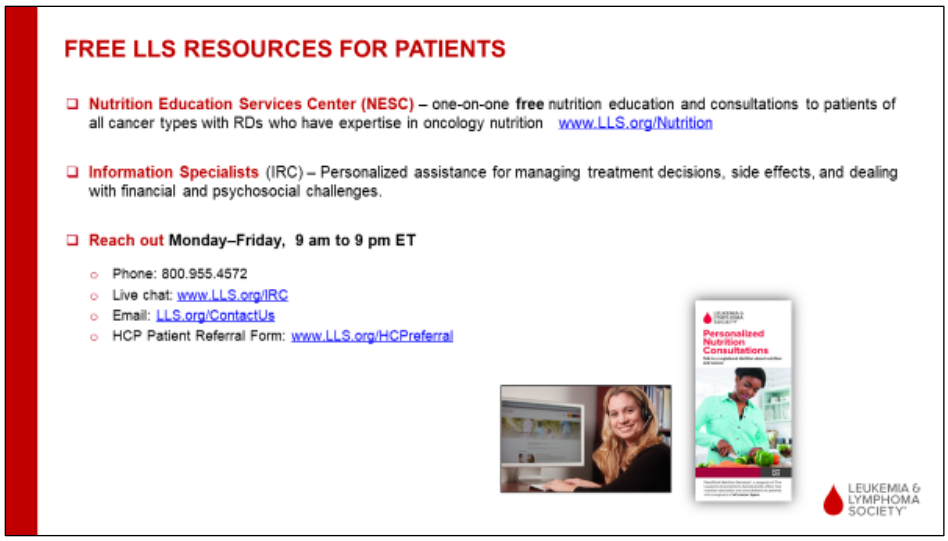
These are the current and future landscapes in follicular lymphoma and diffuse large B-cell lymphoma. Just note that there are a number of ongoing clinical trials. Remember

these are all approved with accelerated approval. And so, in general, the pivotal trials that are going to achieve full approval in follicular lymphoma tend to be based around R2 (lenalidomide-rituximab) plus or minus bispecific antibodies. There are a number of clinical trials that have been undertaken in second-line and are ongoing and frontline therapy and diffuse large B-cell lymphoma. This one with GemOx plus or minus bispecific antibodies. There have been two of those with epcoritamab and glofitamab. They've been presented and are interesting data. So, that's it for me. I'm hopefully just finishing on time and happy to invite everybody for discussion and questions.

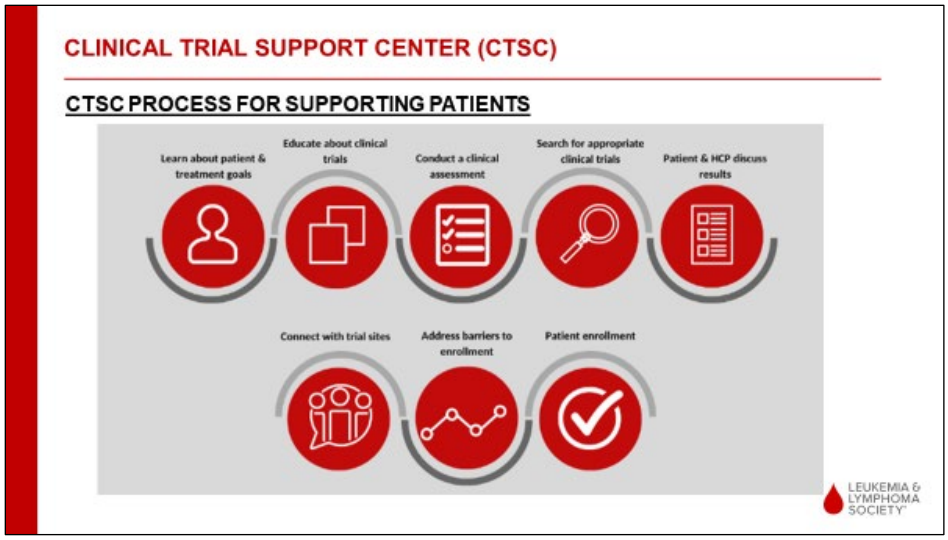
Elise Curry, BA, BSN, RN, OCN
Thank you, Dr. Costa and Dr. Martin, for your very informative and comprehensive presentations. I'll quickly go through some of LLS' resources. You can access LLS' professional education webpage, where we offer free CE, CME, live-recorded programs, and podcast channels. You can listen to healthcare professionals discuss treating blood cancers and side effects, and new and interesting topics are added every few weeks. To access these, visit LLS.org.



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

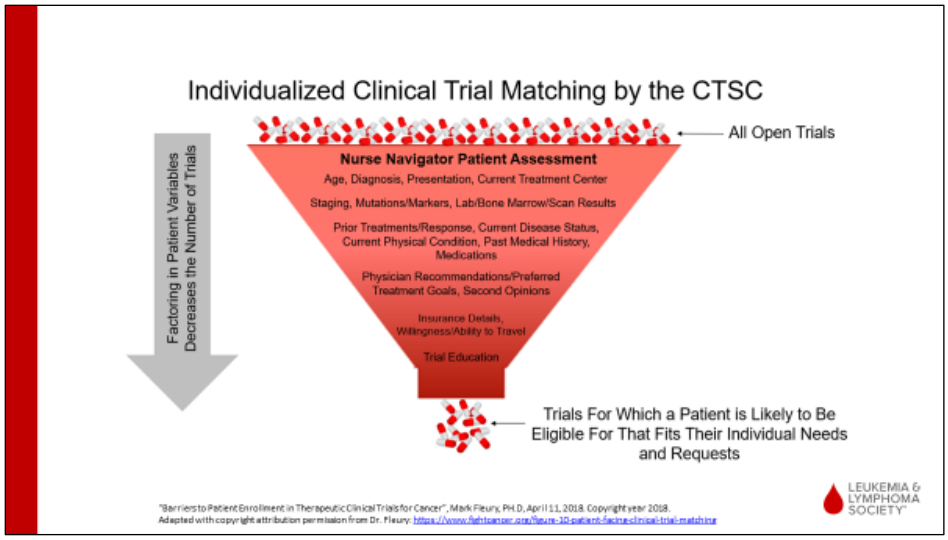


LLS offers free one-on-one support to blood cancer patients in several ways. Nutrition consultations with our registered dietitians are available by phone and for patients and caregivers of all types, ages, and languages.



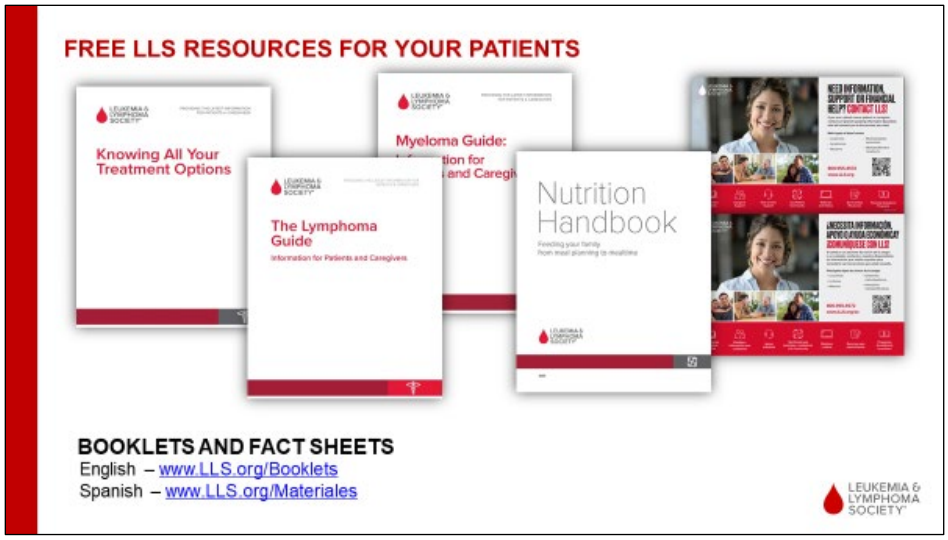
The LLS Information Specialists are highly trained oncology social workers and nurses who provide accurate up-to-date disease treatment and support information. The LLS Clinical Trial Support Center (CTSC), my home, is comprised of 12 nurse navigators who are registered nurses and nurse practitioners with expertise in blood cancers. We work one-on-one with patients of the healthcare team via telephone to provide user-friendly information, help fund appropriate clinical trials, personally assist them through the clinical trials process, and provide information for the patient to bring back to their healthcare provider. Our goal is not to enroll every patient in a clinical trial, but rather educate, support, and empower patients to be active participants in and have control over their treatment decisions.

We work closely with the patient's healthcare team to help decide if a clinical trial is right for them, emphasizing the importance of shared decision-making. To gain an idea of our impact, in 2024, the CTSC assisted 1,142 patients and caregivers and had over 10,454 interactions with patients, caregivers, and medical professionals. 20% of eligible patients enrolled in a clinical trial, well over the eight percent to 10% nationwide enrollment average.

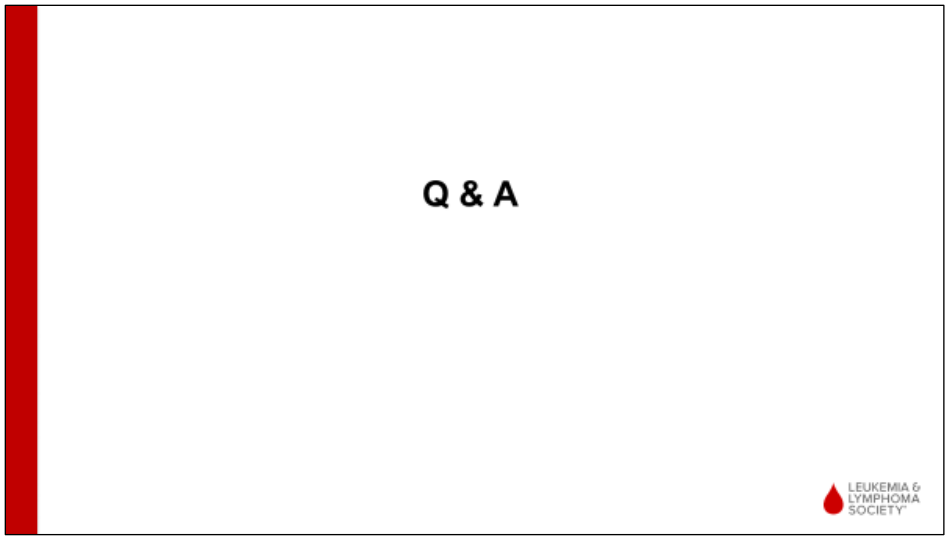


Nurse navigators begin our relationship with patients and caregivers by engaging in an initial phone conversation, where we conduct clinical assessment to learn about the patient's treatment goals, provide education, and, if appropriate, conduct a trial search for the patient. The search is based on information discussed during the assessment, taking into consideration the patient's treatment situation, willingness and ability to travel, and some other considerations. We then encourage patients to bring the trial list to their healthcare team and, if an appropriate trial is identified, the navigator can continue to help overcome barriers to enrollment by reaching out to the sponsor or specific site with any questions (for example, to find out the next steps to enroll), and we remain available for supporting questions throughout the experience.

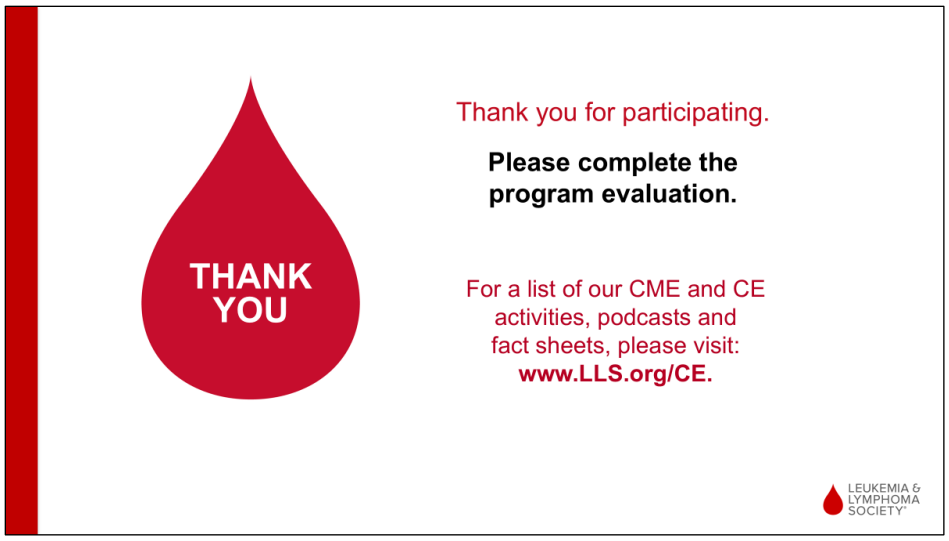
To take advantage of this unique service offered free from LLS, patients, caregivers, and healthcare providers can refer patients to the CTSC in several ways. We can be reached through our Information Resource Center at 1-800-955-4572, through our online referral form at the link above, or simply by emailing us at CTSC@LLS.org.



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



Unfortunately, we're out of time for our Q & A. Dr. Martin and Dr. Costa kindly answered some of the questions in the chat.



Here you can access your CE information. We hope the information presented here will be useful to your practice. Thank you again so much, Dr. Costa and Dr. Martin, for your continued dedication to patients and fellow healthcare professionals. The slides for today's program are available for download at LLS.org/CE. This program will also be available as a recorded enduring webinar offering CE credit in the coming weeks.