Participants: Dan DeAngelo, MD, PhD, Dana Farber Cancer Center
Lindsey Roeker, MD, Mayo Clinic
Lindsey Whyte, Leukemia Research Foundation

- Thank you so much for joining us for the first of our Leukemia Q&A series. Today's topic is chronic leukemia, and we're joined today by Dr. Dan DeAngelo from Dana-Farber and Dr. Lindsey Roeker from Mayo Clinic. My name is Lindsey Whyte and I am the Director of Programs and Partnerships at the Leukemia Research Foundation. Thank you so much for joining us.

In a moment, I'll introduce our speakers and we'll begin the conversation about chronic leukemia. In contrast to our other webinars, the speakers today will not have a formal presentation, but instead we will respond to questions that have been submitted by webinar participants both live today and in advance through the registration process. Thank you all for the great questions that we received.

We would like to acknowledge the sponsors of the Leukemia Q&A series and this session in particular. Our series supporter is AstraZeneca and our sustaining supporters are Astellas, Bristol Myers Squibb, Merck, Novartis, and Taiho Oncology. Thank you all for your generous support.

The Leukemia Research Foundation's mission is to cure leukemia through innovative research funding and to support patients and families. The foundation was established in 1946 and has raised over $120 million in support of its mission since that time. We have funded research grants to over 750 researchers worldwide. Our support programs for leukemia patients and their loved ones include information and resources, education programs like today's, financial assistance, and a directory of other helpful organizations and links on our website.

During today's program, we welcome you to submit questions in the Q&A box, which is at the bottom of your Zoom screen. This is a safe space and we welcome any question. If you are wondering, chances are there are others on the call who have the same question but may be afraid to ask. Having said that, we may not be able to cover all of the questions during the time that we have. Please note that if you want your question to be anonymous, you need to check the little box that says anonymous, otherwise your name may show. And also, if you already submitted a question at registration, please know that we have those questions. We will do our best to cover as many as possible. And as I said, we may combine some questions if they're of a similar topic or nature.

After today's program, you will be sent a brief evaluation through email. Please take a moment to complete the evaluation so that we can improve future programs. Also, this webinar will be recorded. It's actually being recorded, and a link to it will be sent to all registrants for anyone who needs to leave early or who would like to watch a replay with captioning and a transcript on their own time. Please note that AI scribes and automated note-taking tools will be removed from the session.

So onto our speakers today. We are grateful to have Drs. Dan DeAngelo and Lindsey Roeker with us to respond to your questions. Dr. DeAngelo is a professor of medicine at Harvard Medical School

and the Chief of the Division of Leukemia at Dana-Farber Cancer Institute in Boston, Massachusetts. Dr. DeAngelo earned his MD and PhD in molecular genetics from Albert Einstein College of Medicine of Yeshiva University in the Bronx, New York. He completed his internship, residency in clinical fellowships in medical oncology and hematology in Boston at Mass General, the Dana-Farber Cancer Institute and Brigham and Women's Hospital. Dr. DeAngelo's clinical research focuses on optimizing therapy for adult leukemias, myelodysplastic syndromes, and other hematological malignancies. He is a co-chair emeritus of the National Cancer Institute Leukemia Steering Committee. He serves on the leukemia core committee for the Alliance Cooperative Group and is the principal and co-investigator of several ongoing clinical protocols. He serves as a member of the NCCN Guidelines Panel for Chronic Myeloid Leukemia. Dr. DeAngelo has authored and co-authored more than 250 original peer-reviewed manuscripts, review articles and book chapters, and has presented his work nationally and internationally.

Dr. Lindsey Roeker earned her medical degree from the Mayo Clinic School of Medicine. She completed her residency in internal medicine at Brigham and Women's Hospital, followed by a fellowship in hematology and medical oncology at Memorial Sloan Kettering Cancer Center in New York. Following her training, Dr. Roeker joined the faculty at MSK where she served as Director of the Chronic Lymphocytic Leukemia Program. In early 2025, Dr. Roeker returned to the Mayo Clinic and is an active clinical investigator on the CLL disease team with a research focus on measurable residual disease adapted treatment strategies, novel therapeutic development, real world evidence supporting the optimal use and sequencing of targeted agents and tumor microenvironment modifying strategies. Thank you so much both for joining us today. Please, let's get things started now with our first set of questions, which are focused on disease causes and risk factors. Did you want to just provide a quick hello while I switch over here?

- Sure. Hi everybody. This is Dan DeAngelo. We're looking forward to these questions. I don't know how you wanted to do this, Lindsey.

- Yeah, thanks so much. Excited to be here and go through some questions and chat about these chronic leukemias.

- Great. Okay. And of course, my first page is hidden for me. Here we go. Okay. So as I mentioned, the first set of questions is focused on causes and risk factors, and we're going to start actually with a CMML. Actually, I think before we start, let's make sure that we just kind of talk a little bit at a higher level about each of the indications that we're going to be covering today. So I know that we have received a lot of questions about CLL, several questions about CML, but I also want to make sure that it's recognized that several other patients and caregivers have submitted questions about some other less common diagnoses, including CMML and LGLL and MDS. So we're going to do our best to cover everything and make sure that as many of the questions that have been submitted are covered, but also I just wanted to make sure that everyone understands, we won't be spending the entire time on CLL or the entire time on CML or anything else. It's going to be spread hopefully as equally as possible. And let's start with this one.

What nationwide or other large scale efforts are being made to gather together all the genetic variants that are discovered for leukemia or other cancer patients?

- Well, that's a big question, and there's lots of efforts at the national level as well as the international level on clinical trials, which is why we encourage patients to participate in clinical trials because in addition to asking and hopefully answering a question of therapy, we are able to collect a lot of the data for patients going on to therapy in terms of the cytogenetics, that is the chromosome level, as well as the molecular mutations that have caused the various diseases for acute and chronic leukemias. And so it's very important. And then once these databases have been collected, you can go back and ask questions of who may benefit. So if it's drug A versus placebo, for example, in a particular trial, you can go in and then have a deep dive after the end of the trial to say, "Well, maybe these particular mutations, the patient may have benefited better than not." And these are incredibly important and only can be addressed with prospective clinical trials. Now, all of us, and I'm sure Lindsey will tell you as well, we all collect it on all of our patients as well, and we have institutional or collaborative efforts to try and address these, but nothing can take the part of a large national or international trial.

- Completely agree. And I think it also highlights the importance of... I talk to patients in clinic a lot about this, so we do a lot of genetic testing at diagnosis to tell us what to expect. It doesn't necessarily tell us what to do, but it does tell us what to expect in terms of trajectory, especially for CLL, but for other diseases as well. And genetic testing is kind of variably applied across the country. So there was kind of a big effort looking at how often are people actually getting genetic testing. And it's less common than I think many people who kind of subspecialize in these diseases and think a lot about them would hope that we would see, because I think there is a lot to be gained from understanding the genetics of the disease. So it is something as a patient to bring to your oncologist, have we done the genetic testing that would be helpful? What would we learn from additional genetic testing? I think obviously the clinical trial piece of this is so important, but even in routine care, sometimes these genetic pieces can be very helpful and informative as we're figuring out clinical trajectory and what to expect.

- Great, thank you. And I think that it's exciting that we've gotten to this point, right? Because 15 years ago, probably not all patients did have genetic testing done. And so not only is the testing done across the board with all patients as they're diagnosed and sometimes even repeated, but also it's as the original person that asked the question suggested it is being shared more widely now.

- Oh no, absolutely. And the cost of the screens has decreased and the rapidity for which you get the results has increased. So now when I started, I'm older, so when I started medical school in 85, we weren't sequencing anything. But even when I was a first year fellow in 96, I mean, it was AML or CML or MD. I mean, we just qualitatively, based on the bone marrow, looked at patients. And now you can't, just as Lindsey said, we don't treat a patient until we know the molecular and the genetic landscape of the patient because we can individualize the data and we've only been able to do that over the last decade or so. And in the future, we're going to have a lot more data because the rapidity for which you can get these assays completed and interpreted is increasing.

- Absolutely.

- Wonderful. Thank you. Okay. I'm going to move on to another question before I go to... Well, let's start with this one. Will I have CLL for the rest of my life?

- Yeah, great question. So maybe just stepping back one step, so CLL is chronic lymphocytic leukemia. It's a chronic, meaning lifelong blood cancer that tends to be slow growing. So when we talk about chronic leukemias, what we mean there is in many cases, these are slower growing processes and ones that we're able to manage very, very well over time, but ones that we often don't have a cure for. And that is the case in CLL. We have tools that work incredibly well if and when we need them, but with the tools that we currently have, we are not able to cure CLL. So we think about first, what symptoms is a person having and when are we going to need to treat? And then once we treat, how are we going to sequence these treatments so that we can kind of maximize the benefit over the long term so that it's something that we're able to deal with well and is kind of dealt with as we need to deal with it, but we're not able to totally eradicate it with the technologies we have available in 2026. We're hopeful that that will change over time, but reassuringly, we do have really good tools for managing CLL in many, many cases.

- Great. I'm going to, even though it wasn't asked, I'm going to ask the same question for CML. And if you would like to respond to the same general concept for other types of leukemias, like the ones that I mentioned where we've received questions, that would be great.

- You want me to start with CML-1 "M"?

- Correct.

- Thank you. So just as Lindsey said, chronic myeloid leukemia, I mean the chronicity means that these are slow growing, they're chronic. And the difference can be, is this something you have for life? Now that we're in the 25th anniversary, 25th year of imatinib or Gleevec being approved, so this is a big year, as I remember when it wasn't. And before 2001, the only treatment for CML was stem cell transplant. Now, very few patients get stem cell transplant. We put patients on oral therapies. And if you treat a hundred patients, about 50 patients will go into a molecular remission. That means you can't detect any evidence of CML in the bone marrow, which we don't necessarily need to repeat, or in the blood, or by genetic testing. And in those patients or many of those patients, we may even try discontinuing the therapy. And then half of those, or about 25 out of 100 patients, they can stay off therapy. It's kind of crazy now. We used to think that was impossible. Are those patients cured? I think so, but they can have at least a treatment-free window for many patients. As I said, one in two, 50 out of 100 can enter that era, and about half of those can even discontinue. And for the treatment of chronic myeloid leukemia, the future is really bright. We have six FDA approved drugs and three that are in clinical testing, and so we have lots of different options for patients who may or may not have some side effects, if you will, or some intolerance issues to one or another drug. There's lots of choices.

- Okay, great. And for LGLL patients and CMML patients, can you just kind of share at an overview what things look like for those patients as well, please?

- Did you want to take the LGL?

- Absolutely. So LGL is another slow-growing blood cancer that tends to have more autoimmune effects. So we think a lot about the low blood counts associated with LGL leukemia as being kind of driven by the immune system. And this is, again, a lifelong cancer, but one that we are able to treat to either modify the immune system so that the blood counts are not affected by the cells, or we

use medications that do kind of get rid of that clone. And when we look at long-term outcomes from clinical trials, people have very extended periods where their disease can remain in remission. So while we're not curing it, and we do think that there's a risk of the disease coming back, similar to CML, we are able to kind of achieve these long treatment-free remissions for many patients with LGL leukemia.

- Great.

- And Dr. DeAngelo, do you want to do CMML?

- I'm trying to think about how to approach chronic myelomonocytic leukemia or CMML. I mean, chronic, so because it's slow growing and it lasts for a while. When I was in med school and a fellow, CMML was classified under the group of disorders called myelodysplastic syndromes. It was one of the subtypes. And because it has a slightly different feel for it, it was removed into its own classification. When I talk to my patients, it makes it a little confusing for them. So myelodysplastic syndrome, very simplistically, these are patients who have... Their bone marrow's not working. They're not making the white cells, they're not making the red cells, they're not making the platelets, the cells that help clot the blood. So those three cell lines are often low. Every patient's a little different. So some patients are just anemic, some patients just have a low platelet count or a low white count, but many patients will have two low counts or all three. CMML is a little different. Many patients, in addition to having anemia, low red count and low platelet count, they'll have an elevated white count, specifically monocytes, and that's where the chronic leukemia word comes. But really, it is a disease of chronicity, but it's a disease of marrow failure, and these patients do have a risk for converting to acute leukemia. We'll talk about that probably in another question, but that's kind of an overview. It is a form of, or very similar to patients with myelodysplastic syndrome.

- Great. Thank you. That was very helpful. I actually had never heard the two described together, so that was... And I also noted that in the NCCN guidelines for patients, which I refer patients to often, CMML is only mentioned in the MDS guideline.

- Well, because it used to be part of MDS historically, but then because it has different features and we're trying to treat it differently as it was removed out, that's good and/or bad because it's often not included in some of the current studies. It's separate, so it seems to be a little bit of an orphan disease now, whereas historically it was just incorporated into the MDS trials.

- Yeah. Very good. Thank you. Okay. One person asked, this is a CLL patient- they asked, "Does a 13-year watch and wait ever morph into AML or one of the other more serious types of leukemia?"

- Great question. So CLL, chronic lymphocytic leukemia, is... When I think about disease course for people, about a third of people need to be treated right when they're diagnosed. So they come in because they're having symptoms, because they have low blood counts or big lymph nodes. That's a third of people. A third of people never need to be treated, so they live out their entire normal lifespan. CLL never causes symptoms or problems that need therapy, and a third are somewhere in between. So they have this watch and wait period where we're watching blood counts, we're looking for symptoms, we're meeting with people in clinic regularly, and based on that, they're in this observation period. The risk of CLL becoming a more aggressive cancer is something called Richter transformation, which is where it goes from being a chronic leukemia, chronic lymphocytic

leukemia, and becomes a more aggressive lymphoma. So that is most often diffuse large B-cell lymphoma, so that's the most common form of Richter transformation. We can rarely see that CLL can become a Hodgkin's lymphoma, so that's called a Hodgkin's transformation. That's very rare, but these are the more aggressive lymphomas that CLL can turn into. We do not see CLL turn into an acute leukemia, so an AML or ALL. The risk is really turning into one of the more aggressive lymphomas, large cell lymphoma or Hodgkin's. And that overall is very rare. So it's probably around 5% of people have their CLL become a more aggressive lymphoma, and it tends to be people who have had previously treated CLL. So seeing CLL turn into a Richter's transformation when it hasn't been treated is a rare form of a rare event, if you will, so something that we see infrequently. It's something that we think about and is the reason that we see people regularly and tell people in clinic if you're experiencing symptoms that are really different, so you're noticing quickly growing lymph nodes. I tell people if you are noticing small grapes in your neck and all of a sudden you've got a Clementine, that's a big problem, you got to call me. We look at blood counts, and if we're seeing quick declines in blood counts, that can be an indication that we need to look for something more aggressive. And then we look for "B" symptoms, so drenching night sweats, unexplained weight loss, fevers without an infection. These are some of the symptoms associated with a more aggressive lymphoma and things that would prompt us to do some additional testing to look for that Richter transformation event.

- Okay, great. Thank you. Okay. How much... Let's stay on the CLL topic for a moment, and this is under the treatment category. How much progress is being made in CLL research?

- So much. CLL is a disease that has really, over the last 12 years, just radically transformed. So it went from being a disease where we use chemo-immunotherapy that worked okay but not great, to a drug where we have had many approvals of agents that work incredibly well. So with research, we have developed three major classes of medications and we have more underway. The major classes are BTK inhibitors. So BTK is a protein that I think of CLL cells as kind of getting this chronic signal that says grow, divide, grow, divide, grow, divide, and BTK inhibitors basically cut that signal off. So rather than being a cell that is growing and dividing, it's kind of moving out of its protected little nest and moving into the blood, living out a normal lifespan, and then dying off. BTK inhibitors, we currently have four approved. So we have covalent inhibitors including ibrutinib, that was the first approved, acalabrutinib and zanubrutinib, which are covalent inhibitors that we use really broadly now in clinical practice. And then we most recently have a non-covalent BTK inhibitor approved that's called pirtobrutinib that works even when these other ones have stopped working. We're also developing BTK degraders that are ongoing clinical trials looking at this class of medications, which we think is going to be very effective and probably an important tool in the future of CLL. So that's a BTK class. We have BCL-2 inhibitors, which are medicines that go into the CLL cells and basically flip a kill switch so that the cell pops open. Those are incredibly effective medicines and have allowed us to really convert many people into using time-limited therapy, meaning you're able to be on treatment for a short period of time and then don't need therapy afterward. You have a time where your disease is under control and is kind of in remission. The FDA approved one is venetoclax. We have others in development. And then we also have immunotherapies. So right now we have approved anti-CD20 antibodies. Obinutuzumab is probably our most widely used. We also have rituximab as an approved option and ofatumumab, which is used much less frequently now. But these are medicines that basically harness the immune system to come in and fight off the CLL cells. We have other cellular therapies in development. So CAR T-cell is FDA approved. Liso-cel is FDA approved for the treatment of CLL,

and that was just a recent approval based on research that's been done. We're also developing bispecific T-cell engagers, which are medicines that grab the cancer cell, grab the immune system, and bring it together to tell the cells to fight off the cancer cells. So this is a long-winded answer to say that this is a disease that has benefited from a ton of advancement through research, and we are still developing new drugs for people who have their disease come back and need new strategies. And there are lots of clinical trials looking at how we optimize these therapies, how we go about developing new medicines. So clinical trials are a really important part of hematology care, and I encourage anybody thinking about treatment to seek out what are my clinical trial options? Is this something I might benefit from?

- Great. Thank you. Okay, let's switch over to CML. So Dr. DeAngelo, we just kind of went through a little bit of the pharmacy options for CLL. Let's maybe talk about CML. Someone asked specifically what are the latest best drugs to treat CML? You mentioned previously that there are, I think it was five FDA approved. Did I get that right?

- There's six.

- Six, sorry.

- Yeah. I don't know that there's a best drug because they all work incredibly well, and they may be best for an individual patient, but you have really tremendous choices even with the original imatinib or Gleevec, which is still used in a lot of patients. But we have what we call first generation, which was imatinib or Gleevec, and then we have three second generation. We have a third generation called ponatinib or oclusig, which is typically reserved third line with some minor exceptions. And then asciminib, which used to be third line, now it's agnostic. So we have five different drugs that could be used upfront or second line. And each individual, depending upon their age, their goals, their other medical conditions, other medications that they may be taking, all of these are outstanding choices that have really resulted in chronic myelogenous leukemia or CML 2026 to have a life expectancy of the general population without CML. You really can't say that with many diseases. Even high blood pressure, for example, there's a certain issue that we all have, but CML, by and large, has a normal life expectancy nowadays, and we have outstanding choices. I don't know that there is one best drug. There may be a certain choice that's best for the individual, and that's the discussion between the patient and their physician.

- Good. Thank you. So this question, very thoughtful question that kind of builds onto that last question. While there are many good therapies available in CML, we see an astonishingly poor level of medical knowledge around their effective and sometimes safe use outside of CML specialists such as yourself. So in other words, maybe in non-academic medical center settings or other hospital settings where patients aren't experts on CML per se or CLL, et cetera, what can be done to improve the situation for the safety of patients?

- That's a phenomenal question and a complicated question, and I would say you can take the CML out of the question and rephrase it. I mean, we could spend an hour on this topic. There's a lot of disparities, socioeconomic, ethnic, things like that. But one of the disparities in the country is urban rural. We talk about this all the time. I'm fortunate to work in a big city with lots of other physicians, and I'm able to really focus on my disease of interest, and I'm sure Lindsey will tell you the same. I

see about 3% of cancer, that's what acute leukemias are, and chronic leukemias. My wife reminds me that all the time. You only know 3%.

- Got to keep you humble, apparently.

- You know them really well.

- You know 3% really well.

- And I don't focus on the lung cancer, breast cancer, GI cancers that the rest of the world needs to focus on because those are the more common diseases. But then the person who asked the question is right. If you only see, this is a one in 200,000 frequency. So a new CML patient may occur in a busy general oncologist, maybe one a year, maybe one every 18 months. And I'm seeing two or three new cases a month. And so that's just what it is. I think that we all do medical education. We all go to scientific meetings. There are American Society of Hematology meets in December. There's a European meeting. And these are all education where we all try to learn. A lot of the CML questions are being incorporated into the maintenance of certification and the boards that Lindsey and I have to take, which tries to educate. So there's constant education, so you should be reaffirmed with that. People are doing their best. I know most people have my cell number or email. I'm sure Lindsey says the same thing. Call me if you have a question. I'm happy to answer it or see your patient. So we're all doing our best out there, but it's tough. I mean, if you're eight hours away from where I work in Boston, it may be hard for the patient to come down and it's inappropriate. That's why God gave us cell phones and email addresses so that we can help. But we're all available and it's okay for the patient to ask a question because if you were getting your kitchen redone, you'd ask for three different opinions. So it's okay to do that. Nobody's going to be offended. I think people are afraid. I talked to a patient yesterday who said he felt like he felt that he was offending the person who was taking care of him by seeking a second opinion. I said, "That's crazy. Your physician is more than happy to do that. We'll work together to make sure that whatever questions you have could be addressed." And I'm sure Lindsey does this all the time. So we're working hard on medical education, trust me, and we're all available to anybody who has a question.

- Yeah, I think those are all fabulous points. I think the other piece is, as Dr. DeAngelo pointed out, there are people who spend a lot of time thinking about a very narrow field and there are in many disease patient advocacy groups where you can access subspecialty care even outside of the typical clinical infrastructure. So for CLL at least, there's opportunities to engage specialists if something feels like a second opinion would be helpful. And we are more than here to play whatever role is helpful to people. I tell my patients that all the time and agree, we talk to doctors about this too. I'm here to support in whatever way is helpful. So if going to your local doctor is just significantly easier and that feels good, and then if a question is arising, I'm here as a backup, more than happy to do that. And I think ultimately those of us who really spend a lot of time thinking about niche areas just want what's best for people who have this disease and we're all here to help in whatever way we can be.

- Yeah. Thank you. Yeah, I appreciate that. And I just want to say that having worked in the rare disease space now for 15, almost 20 years, it's so important because doctors can't be experts on everything as you pointed out. And I'm happy to help as well. As you mentioned, nonprofits and

advocacy organizations are sometimes able to make connections. And so if folks are looking for some sort of a second opinion or would like some sort of question answered or connection made, they're welcome to reach out to us as well here. Okay. I wanted to come back to the CMML question that we did not address earlier. This is, are there newer tests that can identify CMML progression before it shows up on a CBC?

- Yeah, so this is another great question actually. It's kind of insightful in a way and it backlogs into some of the questions that were addressed earlier, maybe with the first question about large scale efforts to understand genetic variants. And so in patients with MDS and CMML, as we said, they're kind of cousins to each other, a little bit different, but they're similar cousins. The biggest area in terms of progression is looking at the blood counts and seeing how they change and/or the bone marrow. But to the person who asked the question, oftentimes what we'll do is look at the genetics and you can obtain that from the peripheral blood just as easy as you can from the bone marrow. So in a patient who has relatively stable disease, I'll often check what we call the next generation sequencing or just the genetic markers. Because if I start seeing new mutations that is genetic evolution, then I'm more concerned. And you can do that just from the blood. Even in a patient with stable counts, they often go together that a newer mutation will accompany a change in the clinical status that is white count goes up, red count go down or something like that, but not always. And that's a way of just keeping tabs on it and really parlays into the first few questions that were addressed.

- Great. Thank you. Okay. We're going to switch gears here and get into some specific cases which have been submitted in the registration. And then I know that we have at least one question in the Q&A that I'll turn to as well. So this is a CLL patient, 34-year-old female. What are the risks, benefits of starting treatment while still in the observation period and asymptomatic? My doctor said they would be okay with starting zanubrutinib in hopes of controlling the disease while burden is low. How concerned should we be if we're notch one? I'm not sure what notch one is.

- Yeah, so notch one. Yeah. Okay. So a really good question. This is the question of early intervention. Should we be treating CLL before it's causing symptoms? There are five symptoms that we think about that tell us whether we need to treat CLLs. Two are based on blood counts, two based on exam, and one based on symptoms. So based on blood counts, we're looking at low hemoglobin and low platelets. So hemoglobin under 10, platelets under 100. We look for bigger bothersome lymph nodes, a bigger bothersome spleen, and then symptoms like fevers, drenching night sweats, weight loss without trying. And in the absence of any of those symptoms, we've done clinical trials looking at early intervention. And the major studies that have been done have looked at chemo-immunotherapy approaches, which as I said earlier, we really don't use anymore chemo-immunotherapy. And then we've also done a study looking at early intervention with ibrutinib, which is a first-generation BTK inhibitor. Again, not broadly used in clinical practice, but a drug that is effective, has a bit more side effects than many of the medicines we use. And we've proven that with those kinds of studies, early intervention doesn't help people live better, live longer. So because of that, the standard of care is watch and wait until symptoms arise. There are ongoing clinical trials looking at early intervention. So there is a strategy looking at venetoclax and obinutuzumab as an early intervention, and it's a SWOG study, so a cooperative group study that's available across the country. It looks at early intervention for patients with higher risk disease as compared to delayed standard initiation timing for venetoclax and obinutuzumab. That's a combination strategy that's time limited. As a clinical trial strategy, I think it's a very reasonable

thing to do. So let's look at whether treating early with a time-limited strategy where we can get the disease into remission and hopefully when there's less disease around, limit what we call clonal evolution, meaning this disease kind of slowly morphs over time and changes and maybe becomes a little bit harder to deal with. I think in a clinical trial context totally makes sense. The strategy of using zanubrutinib early, which is what the question was, I think is a little bit more questionable just because now we have pretty long-term outcomes from the early intervention with ibrutinib study, and it really has shown that it isn't helping people live longer in any way. And in high risk disease, specifically those who have TP53 changes, which is different than the NOTCH1 mutation that was mentioned, but is kind of a higher risk disease feature, we've actually proven that not only does it not improve survival, but it also doesn't improve event-free survival, meaning the idea that the disease is coming back, needing to be treated, those kind of things. So in that context, I think there really is not any data supporting that early intervention strategy. So I guess I would say if you have a real desire to explore that early intervention strategy, I'd maybe seek out the clinical trial option, understanding that the SWOG study is available across the country. And as we talked about earlier, there are access issues with inability to get to a academic center, but it is worth checking that out. It's called the SWOG study that it's S1925 is the number. So if you Google SWOG S1925, you'll be able to come up with it and see where it's open. But the approach of using zanubrutinib early is one that I'd probably be pretty cautious about. That might not be something that's really very data-driven.

- Okay. Thank you for that. We have a question. I'm going to go to a question that's in the Q&A real quick that was also asked through registration, and I think we have enough information to get through it, but let's see. How common is having CLL on ibrutinib white blood cell count normal four years? White blood cell starts rising, the doctor okays stopping treatment. Then the white cell count drops to 40% and remains stable, but elevated nine months. We're going back and forth a little bit on there, but maybe if anyone can make heads or tails of that, and then I will also go to the other question the same person submitted.

- So what this sounds like is potentially there was some early indication that maybe there was progression on ibrutinib with a rising white blood count. And then after stopping drug, we're seeing some fall of the white blood count. I think there are a couple of pieces here. The first is in the setting of ongoing BTK inhibitor therapy, we can sometimes see fluctuations in white blood counts, particularly if people have infections or inflammatory conditions, surgeries, those kind of things. We can often see that quick elevation of white blood count. I don't know what the context was here around that rise in the white blood count, but those would be things that I'm thinking of. If we are seeing lymphocyte counts kind of rising over time along with falling of other counts, that often does suggest progression. The question about it dropping after stopping ibrutinib, there are a lot of... It's kind of hard to know without having the specifics of the clinical context, but one thing that ibrutinib and other BTK inhibitors does is it moves cells in the lymph node niches into the peripheral blood. So sometimes we can see sort of this redistribution of cells from the lymph nodes into the blood because a lot of the ability to stay kind of safe and protected in lymph node is BTK dependent. So if we use a BTK inhibitor, we're kind of shoving those cells into the blood. And sometimes as we stop ibrutinib, we can see that those cells retreat back into the lymph nodes and that might cause kind of a drop in the white blood count. The other thing that I think is worth mentioning here is we've looked at patients treated with ibrutinib who have stopped for a reason other than progression, so side effects, decision to stop by a patient or a provider. And in that context, when you stop ibrutinib and you've had some response, the average time off therapy before disease comes back and needs

to be treated is about two years. So while BTK inhibitors really have been developed as continuous treatments, meaning those that you take for as long as they're working, there are people for whom if they're stopping these medications and there isn't signs of rapid progression, you might have some time where you actually don't need treatment and we should kind of watch and wait until a need for therapy arises.

- Okay. I did want to say two other questions he asked, what's next? More watch and wait, which it sounds like maybe if he's stable, that may be the next step, right?

- Yep, exactly. - Until the counts kind of start to change. And then he also asked how normal is the sequence? Roughly, I guess.

- Yeah, I guess it's hard to know without the specifics and understanding what the context had been around the rise and fall of white blood counts. But I think that it is fairly common that if people are coming off of ibrutinib and their symptoms are well controlled, that you can have a period of watch and wait that can last years. So I think that continuing to observe if the blood counts are okay, there's no growth of lymph nodes or spleen and you're feeling okay is a reasonable strategy.

- Okay, great. I wanted to point out that one person who is an LGL patient on the Q&A, the live Q&A, specifically pointed out T-cell LGL. So I'm not sure if you have anything to add with regards specifically to T-cell LGL in terms of availability of treatment or the approach to treatment. And then we do have a question, how do I balance being careful with just living life? That person has T-cell LGL. So I don't know if you wanted to take a stab at that one right now.

- Did you want -

- Yeah, I'm happy to take that. So LGL leukemia is kind of a blanket, an umbrella term that most commonly means T-cell LGL, so that's the most common version of LGL leukemia. There's a rarer form of LGL leukemia called NK cell LGL leukemia, but everything I said earlier about LGL leukemia probably most broadly applies to T-cell LGL. And in terms of this question about how much do I balance living my life versus being careful, I think it's a really important question and one that really does affect people who have diseases that are affecting their immune systems. So I talk to my patients a lot about these are cancers that increase your risk of infection. That's definitely true. And also the point of living or being alive is living, so we've got to do that too. So we talk a lot about what can we do proactively to protect you from infections. Some of the best tools that we have are vaccines. So flu shot is a great idea, staying up to date on your pneumonia vaccines, your shingles vaccine, the RSV vaccine. These are some things that can prevent common infections that can be really problematic and drive need for hospitalizations and things like that. So I encourage everybody to be up to date on vaccines. For CLL specifically and also some of these other diseases, we check the protein part of your immune system, so immunoglobulin levels. If those levels are low, sometimes we use additional tools to prop it up and prevent infections. And then I tell people every interaction has a benefit and a risk, right? That's just part of being human. If you're in a context where everyone around you is hacking and seems to have a cold or a flu or whatever, probably better to be wearing a mask in that context because you're probably more likely to protect yourself if you're being careful. And also, there's still benefit to seeing your family, seeing your friends, going to church, going out to eat, doing all of those things. So I do encourage people to continue living your life, just being a little bit aware of what's happening around you so that if there is a higher risk

exposure, you can maybe move yourself away from it. And with family and friends, when they're really sick, it's maybe time to give you a little bit of space and then come back when you're feeling better.

- Great. There was a question submitted live, and I also received questions about the COVID vaccine. In this case, it's specifically for CLL patients. I know there's a lot of concern about different vaccines for CLL specifically, so maybe we could get that one.

- We recommend COVID vaccines in terms of comparative efficacy in this context of CLL, so mRNA versus non - MRNA vaccines. They actually haven't been compared head-to-head. So I encourage people to stay up to date on their vaccines. We reassuringly are seeing that people are, even if exposed to COVID-19, we're seeing less hospitalizations and less bad outcomes than we did historically, but you're likely to protect yourself well if you're vaccinated. And in general, we don't have a strong preference about which type of vaccine that is.

- Great. I have a question for you, Lindsey, on that. Do you see a... Because I know after CD20 monoclonal antibody, you got a muted response to vaccine. Is it true? So do you try to get your patients vaccinated before, for example, if you're going to give obinutuzumab, and then what about the BTK inhibitors? Is it the same thing?

- Such a good question. So in general, if we're about to start therapy, I tell everybody now's a good time to get vaccinated. So it's really easy in the fall because if I'm about to start therapy now, I want you vaccinated now so that we can head into therapy while vaccinated. And we talk to people before treatment about making sure that we're as up-to-date as possible on vaccines. Beautiful point. We learned in the early COVID days about immune response to COVID vaccines after CD20 antibodies. In that first six months, it's relatively rare to see an antibody response. So really kind of a protein part of your immune system producing these proteins that are protecting you from the infection. And that's fairly... After obinutuzumab finishes, for instance, it's fairly common that for the first six months, we're not going to see a huge response. If you just finished obinutuzumab in September and you're deciding whether to get the flu shot now, my advice would be to get it because we do see T-cell responses even if we don't see antibody responses, and that T-cell response can be helpful. Something's better than nothing is kind of my approach there. So I do encourage people to be vaccinated, understanding that some of the longer term vaccines, so non-seasonal ones, not flu and COVID, but pneumonia, shingles, those kind of vaccines, probably better to wait six months after you've completed obinutuzumab. BTK inhibitors don't seem to have the same impact on vaccine efficacy, so while you're on a BTK inhibitor, totally fine to get vaccinated. We think that there's going to be a good response, although if you're about to start, now's a good time to get vaccinated.

- Okay. I'm going to move to a question that was submitted live, and this person is diagnosed with CML just two years ago when he was 38 years old. He had stem cell transplant a few months after diagnosis, along with oral medicines and chemotherapy. Since then, he has relapsed three times with tumors growing on his bones. And he mentioned, we talked about how CML generally is easy to contain and is questioning why is he not having that experience? And he's said in a separate comment that he needs a second opinion, it sounds like. So can you just comment a little bit about if you have anything you can share on this specific case, but also on the tumors on the bones? I know that that is something that happens from time to time.

- Yeah, it's exceedingly rare in CML. You see it in more advanced phases of CML. And so this is unfortunately one that I would be loathe to really make specific comments without more details. There are patients specifically post-transplant. As I mentioned earlier, we don't transplant a lot of patients with CML anymore, but there are reasons to, so I'm not sure exactly the timing or the era that this individual was transplanted. And when the disease comes back, sometimes it can acquire some resistance mutations, so that might be an issue. Really, more devil's in the details and obviously a recurrence after transplant really should be seen in an academic center. So I'm sure that somebody would be happy to see this individual.

- Yeah. And if that individual wants to contact me, I'm happy to talk through some options based on where they're located. Okay. So I wanted to go back to CLL treatment, and specifically you mentioned immunotherapy, and one specific question was, is ongoing immunotherapy better than other treatments? And then the second was, have CAR-T side effects gotten any better?

- Great questions. So ongoing immunotherapy, let me take that in a couple of different ways. So the first is, most of the time, if we're using immunotherapy like anti-CD20 antibodies, we do it for a time limited strategy. So usually it's six cycles of obinutuzumab in combination with venetoclax is when we use it most often. So a pill-based therapy plus obinutuzumab, you get that IV component for six months and then continue with just the pill part venetoclax for the completion of one year if it's being used as the first treatment for CLL. That kind of balances the benefit of using immunotherapy and getting control of the disease with the risk because immunotherapy, anti-CD20 antibodies specifically also wipe out some of the healthy normal immune systems. So when we were talking about the lack of vaccine response, the other thing we see with immunotherapy is you can have increased risk of infections. So we want to make sure that we're balancing disease control with not putting people at such risk of infection that that really impacts how they do overall. So from that perspective, I guess ongoing immunotherapy really isn't very common. It's kind of used in a shorter period of time, and then people have kind of treatment-free observation periods, meaning time where their disease is under control and they're not needing therapy. In terms of CAR-T, CAR-T is an interesting tool for CLL because used alone, the response rate is pretty low. It's like one in five. So it's not a slam dunk or a home run, if you will. We are figuring out strategies as to how to use it better. So it's been studied in combination with ibrutinib, the BTK inhibitor. And with that, the response rate is much higher and people, the chance of achieving a complete response is much higher. So we often aim for that using CAR T-cells in combination with BTK inhibitors. It's been studied with ibrutinib in practice. Many people use pirtobrutinib, the non-covalent BTK inhibitor, as a kind of sidekick for CAR T therapy. And the added advantage of using these BTK inhibitors along with CAR T is not only does it seem to make them more effective, but it also seems to decrease the risk of cytokine release syndrome, which is the major side effect that we see with CAR T-cells. And cytokine release syndrome is basically the idea that you're putting a T cell that's been basically retaught or retrained to fight cancer cells into your body. That cell is going and fighting these cancer cells and fighting them off. It's an amazing tool, but also comes with kicking up some dust as you're using that tool. So we often see that people can have fevers or low blood pressure or need oxygen or have kind of inflammation with that process, and sometimes we need to use additional tools to calm down that inflammation. It seems that BTK inhibitors make it much less likely that we see some of those inflammatory side effects. So I guess we are learning more and more about how to use CAR T-cells well. We're also doing a lot to develop bispecific T-cell engagers, which are medicines that kind of come off the shelf, if you will, so they don't require the manufacturing

process of CAR T-cells. And we think we are hopeful that that's going to be in the future a really effective class of medicines for CLL.

- Great. Okay. I'm going to take this question from the live submissions. "I am a 77-year-old with CML for 12 years. Initially, I took Sprycel for about a year, but kept getting pleural effusion, which required amniocentesis to take out one liter of fluid from my right lung each time. I switched to Gleevec about 10 years ago. I am still bothered by a repeat of pleural effusion treatment about every two years. I have two questions. One, why is it always the right lung? And would you recommend trying a different TKI given that I need to do amniocentesis every two years? "And then he also asked regarding the Gleevec treatment," Been on Gleevec for 10 years, white blood cell and BCR- ABL results under control. However, for the past four years, red blood cells gone on a downward slope and now about 3.4. Have you seen Gleevec cause red blood cell drop over time?"

- Yeah, so these are good questions. So all of the TKIs can cause pleural effusions, and it's interesting, they're usually bilateral, but they can be unilateral, right or left. It's unclear why that is. I don't really have a good explanation. Dasatinib is the most common, and there's reasons for that because it hits other targets, but imatinib and all the other TKIs, asciminib or Scemblix is actually less likely than dasatinib or imatinib to cause pleural effusions. Sometimes you can mitigate the pleural effusions by reducing the dose as opposed to changing. So if the CML is under excellent control, and it depends on what excellent means. So for example, if the BCR- ABL transcript level is barely detectable or undetectable, I'll often just reduce the dose of the imatinib or dasatinib, depending on what the patient's on before switching to an alternative. But sometimes even lowering the dose, the pleural effusion can come back, which would require or necessitate switching. So again, there's some issues there, but all of the TKIs can cause dasatinib is just the most common, but imatinib and nilotinib and ponatinib can also cause them. But Scemblix is a little bit lower. So either reducing the dose if the BCR - ABL transcript level's very low or switching to an alternative TKI may be an option. And then of course, trying to make sure that it really is the TKI and it's not something else. There are alternative reasons why patients get pleural effusion, so it may be worthwhile just making sure the Is are dotted, Ts are crossed, the heart function's normal, there's nothing else going on in the lungs, just to make sure that everything's okay and that we're not just putting the blame on the imatinib. But if this has been going on for many, many years, it probably just is the CML. But again, make sure that everything is checked.

- Okay. Okay. CLL patient. I would like to know if ongoing CLL four and a half years can cause hearing loss and severe tinnitus. Could it be the leukemia causing it or a BTK drug Calquence that is causing these issues? I'm also having vision issues after cataract surgery in 2019. The surgery was successful, but the vision in my left eye is minimal and there may be a pool of blood behind my eye.

- Okay, so let's take it one piece at a time. So from the hearing perspective, BTK inhibitors have not been associated with hearing loss or tinnitus, so not kind of a common effect of a BTK inhibitor. I think there are a couple of things to think about with the hearing loss. The first is BTK inhibitors do increase bleeding risk. So one of the things I think about when people describe hearing loss is making sure that there has not been any bleeding either behind the eardrum or in the structures in the inner ear. So that would be one thing to consider. The other piece is thinking about other medications that you're taking. So there are some medications that are more commonly associated with tinnitus, specifically NSAIDs. So ibuprofen is one, Benadryl is another, and then chloroquine or hydroxychloroquine is another. So thinking about the other medications and whether there might be

some other medication effect there. The last piece that I'll mention is these are very rare but can be manifestations of stroke. One of the things to think about is that BTK inhibitors can increase the risk of atrial fibrillation. Atrial fibrillation is associated with stroke. So I would want to make sure that we've really done a good workup to understand whether there was any bleeding within the ear system or any evidence of anything going on in the brain that might be related. But then if not, I would kind of manage these as separate problems that happen to come up when there's CLL and a BTK inhibitor around. In terms of the eye piece of this, I think... So the first piece is if you're going to have any procedures, we always want to make sure that we're holding BTK inhibitors before and after because there is a bleeding risk associated with them. So not all people doing procedures know that BTK inhibitors cause bleeding. So I talk to people about if anyone's talking about putting a needle or a knife anywhere near you, call me first that we make sure we know what's going on there. With the bleeding behind the eye, I guess that would be a question. Was this an unforeseen complication of a surgery that has led to decreased vision or might this be a manifestation of some underlying comorbidities? So we do see pooling of blood behind the eyes in people with diabetes, high blood pressure, those kind of things. So making sure that other risk factors are accounted for and mitigated, I think would be the other piece here. And then finally, the last piece is that BTK inhibitors can also be associated with high blood pressure. So thinking about blood pressure monitoring and making sure that high blood pressure hasn't contributed would be another piece here. So I guess the answer is no clear like, oh yes, this is definitely because of drug, but there are a lot of other things I would want to be thinking about to understand if there might be a risk here.

- Great. And I just wanted to recognize there was one other question on that general topic as well, so I'm not going to bring that up again, but yeah, there's definitely a couple of folks who are dealing with vision or hearing issues. This one is, what is the relationship between CLL, Brukinsa and central retinal vein occlusion or macular edema? Probably the same answer, I'm guessing.

- Yeah, so central vein occlusion, so whoa, sorry, central vein occlusion is a disorder that's often associated with diabetes and hypertension. So thinking about the effect of zanubrutinib or a BTK inhibitor on the blood pressure would be an important piece of this, but not directly linked, I think, in this context.

- Great. Okay. I have moved into the lifestyle, supportive care, diet and exercise section of questions because we have gotten one live and we have a couple on this list as well. So this one I love. I love the ocean. Is it safe to swim in the ocean with CML? I'm afraid of getting an infection of some kind.

- Yes, it's safe to... I mean, as long as the blood counts are okay, it's absolutely safe to swim in the ocean unless there's something else going on that I'm not aware of, red tide or something else that's there. But I mean, patients with CML, their immune system may not quite be normal, but it's not like my colleagues' CLL and therapies. Patients typically do well. They respond to vaccines was the question, and their lifestyle changes in terms of avoidance of certain activities really is not necessary. And that is because all patients with CML are on some form of therapy. The one exception would be post-transplant. Again, I mentioned this earlier, we don't transplant very many patients with CML, but if you've had a stem cell transplant, at least for the first year after transplant, then there's some precautions. But outside of that, really nothing.

- Okay. This one is a very common question about fatigue. "My CLL specialist tells me he can treat me, but he doesn't think that will cure my extreme fatigue. Does CLL cause fatigue? I'm confused

because I have seen others with CLL complain of the exact same fatigue I experience, but the specialist seems to think my fatigue is not CLL related."

- Fatigue is the trickiest symptom of CLL, and it's the one that I probably talk to people about the most, but it's the trickiest to deal with. I think of energy levels or fatigue as being sort of one of the most multifactorial things that we experience as humans. So part of it is that, yes, I think CLL is probably contributing to fatigue, totally. And so is other medical problems, other medicines, stress, and a new CLL diagnosis or even an old CLL diagnosis can certainly be a stressful thing that can drain energy levels. Those are some of the pieces. So I talk to people a lot about how do we optimize these things? And the reason I say that is when we treat CLL, one of the common side effects of a lot of the treatments we use is fatigue. So I would say about a third of the time we make it better, a third of the time it stays the same, and a third of the time it gets worse. So fatigue is a hard symptom to treat CLL on just as the only indication. If there are other indications, then I think it's different. And if the fatigue is related to low hemoglobin, that often does get better with treatment. But if it's fatigue as the only manifestation of the disease, I talk to people a lot about what can we do to optimize everything else in order to make sure that we're kind of doing right by you. So the first piece is no one wants to hear this when they're tired, but the single best thing to help people deal with fatigue related to CLL is exercise. So I tell people the most common thing we see is that I just late afternoon totally lose my steam. At three o'clock, I need to nap every day. That's probably the most common thing I hear in clinic. And I tell everybody, if this is happening at a stable time every day, an hour before that, go outside, walk fast enough that your heart is pumping and you have sunshine on your eyeballs. I know that sounds really simple, but that is probably the single best thing you can do to try to reset and have your endorphin levels supplementing your energy level through that kind of known lull that tends to happen late afternoon. The second is if CLL really is causing a lot of stress or if there's a lot of stress in other parts of your life causing mood disruptions, feeling like your mood is low, causing anxiety where you're spending a lot of time thinking about it, these are things that your CLL specialist or your doctor really want to hear about because we're here to support people in all the ways and we really only can help if we know about it. So I tell people, if you're feeling like any of these things are happening, your mood is low, you're feeling hopeless, you're feeling anxious, I want to know about it so that I can support you. Sometimes that is non-medicine kind of interventions, thinking about counseling, thinking about support systems, thinking about support groups. Sometimes that is a medication effect, a medication that might be short-term, might be long-term, but can be really helpful in people's lives. So that's the second thing. And then the third thing is making sure that we're not missing something else. So let's check for diabetes. Let's make sure that your thyroid looks okay. Let's make sure you don't have a chronic infection that may be causing you to feel fatigued. These are other things that we should be thinking about and looking for. So those were some of the things that I talk to people about.

- Great. Thank you. Okay. CML patient question, "Can Bosulif cause shortness of breath? I am 78. Some days I can hardly hold up my head while other people say they're working full-time jobs. Is it my age?"

- Yeah, so I'm going to follow that up on what Lindsey had said. The CML drugs as a class can all cause fatigue, and I'm wondering whether shortness of breath here is really a manifestation of fatigue, and sometimes these can be mitigated by reducing the dose if that's an option, depending on how one is responding or sometimes switching. Of course, shortness of breath, one of the other

questions that you had asked or that had been asked is pleural effusions. Bosutinib is actually not commonly associated with pleural effusions as some of the other TKIs, but as I alluded to, many of them can. So just to make sure if this is really a breathing issue or is this a fatigue issue? Part of the question made it sound like a breathing and the other part of the question made it sound more fatigue. I'm assuming it's more fatigue. Age does play a factor, but there may be other issues and it could be multifactorial. Lindsey had gone through a nice discussion, making sure there's nothing else going on there, making sure you stay active, but also making sure the thyroid tests and some of the other things are checked just to make sure one doesn't just have the blinders on and just saying it is. So this could be clearly related to the bosulif, but it's important to make sure there's not anything else going on. And then depending on how you're responding, you may be able to mitigate it by reducing the dose of the bosulif or switching to an alternative drug if that's not possible. But this is a very important issue, unbelievably important. And this is one of the things that we always talk about in clinic is the fatigue and some of these side effects that for some people can be very debilitating and for other people not so. And there's a lot of individuality here.

- Okay. We have a couple of questions on natural supplements and foods, diet, that kind of thing that kind of play nicely off of the previous discussion about exercise. So specifically, are there any natural things that can help CLL such as soursop, turmeric, apricot seeds? Another question, are there any natural treatments, foods, or supplements that are promising? And then one person asked, "Does alcohol consumption affect CLL or affect the treatment of CLL?"

- So many good questions there. So the first question is about supplements. The tricky piece about supplements is that they're not studied in the same way that medicines are. So they're not regulated, they're not well studied. In general, my advice to people is supplements tend to come with some toxicity and we've really never proven that they help in any substantial way, so I tend to ask people to avoid them. There have been some early data for the use of green tea supplements. There's also toxicity associated with that, so it can cause liver problems. If you're thinking about using supplements, it's important that you talk to your medical team about it so that they can monitor you in the right way and make sure that they're not causing side effects. So that's a supplement piece. In general, I talk to people about let's kind of optimize your diet, make sure that you're kind of doing the right things there, let's optimize your other medical problems, and let's keep all of your organs as healthy as possible. So let's keep your liver healthy, your kidneys healthy, your blood pressure under good control so that your heart stays healthy. Let's do all these things so that if and when we need to do something about CLL, we have all of our tools available to us. So that's kind of my approach there, especially some of the medications that can almost act like anti-inflammatory medicines like turmeric or curcumin can actually cause kidney dysfunction. So it's just important that we're watching these things if you're going to choose to use these. But in general, if people are open to avoiding the supplements, I do tend to do that. The diet question is a great one. We don't have data to say that one diet is better than another in CLL or really in any blood cancer actually. In general, the diet that we have the best data for is probably the Mediterranean diet. So focusing on fruits, vegetables, lean protein, olive oil rather than animal fats and trying to minimize processed foods is probably, if you're looking for an overall advice on healthy living, that's probably the best data that we have.

- And alcohol.

- Alcohol. In moderation, totally fine. We do want to make sure that your liver stays healthy so that if down the road we need to do something, we have our tools available to us. So I talk to people about what is kind of the upper limit of what we would consider normal use. So it's a drink a day for women, two for men. Anything above that does put you at risk. So moderation is key here.

- Okay. Yeah, this all applies to CML and other diseases as well, so it's important. Although I'm a little bit less generous with the alcohol consumption, it can suppress the marrow. And so I usually say not every day and not a lot if you choose, but it's okay once in a while. And remember, I don't know about the BTK inhibitors, Lindsey, but at least in CML, some of the supplements can interact with the medication, so you always want to make sure. And as you said, they're not very well regulated and they're not very well studied. And so there are some examples where there are some drug-drug interactions with some of the supplements that could be detrimental, and so it's just safer not to go down that rabbit hole.

- Yeah, completely agree. The drug-drug interaction piece is important, and that even extends to other medications. So if you're starting a new medicine, letting your doctor know that you're on a cancer therapy and saying, "Are we sure this is good with my cancer therapy," is important too. That's something anybody prescribing a new medicine should be looking for, but it's important to bring it up because there are lots of drug-drug interactions.

- Okay. Quick time check. We have about five to seven minutes left for questions, and so we're unfortunately not going to get through everything, but I'm going to pick a couple more to go through. We have one that was submitted live. This is a T-cell LGL patient. I'm on my third type of treatment in a year since diagnosis. Nothing has worked well yet, and I've had bad side effects. Could a combination treatment be prudent to try at this point? If not, what might work?

- I will assume that this means that we have tried cyclophosphamide, methotrexate, and cyclosporine, since those are the three most common types of therapy that we use early on. If that's not right, go ahead and correct me in the chat because I'm happy to adjust based on that. After we use those three medications, we're kind of in the zone of less robust clinical trial data and non-approved options, but things that are in NCCN guidelines. So some of the agents that might be worth considering are ruxolitinib is a medication that has some data in TLGL leukemia. Venetoclax has some data in TLGL leukemia. And then the other piece is that there are clinical trials available. So this might be a context where thinking about clinical trials, if you do have access to a medical center that might have a trial, is a reasonable strategy. And then even if clinical trials are not available, seeing somebody who is an expert in TLGL leukemia when you've kind of gone through the more common medications might be a reasonable thing to consider. So this might be another context where connecting with somebody at Leukemia Research Foundation might be helpful to find a good contact for you.

- Another LGL question, "This person does biweekly injections of Nplate to regulate platelets and occasionally takes Neupogen. I was able to handle cytotoxigen when first diagnosed. I do not take traditional chemo. What treatment options are there?"

- So that's kind of maybe the same answer as before. So it sounds like using some growth factors and some medications to try to support blood counts, but perhaps the disease is still active, and it kind of depends on the context and what has been tried and what's been used. But this is another

context where seeing somebody who's a subspecialist in TLGL leukemia might be worthwhile now if you haven't yet, and thinking about what clinical trial options might exist if this is actually just disease that hasn't been well controlled. And then the other piece is anytime things are really not responding the way we would expect to medications that should be working the way with pretty high response rates for TLGL leukemia. The other piece is let's make sure we're not missing something. So if you haven't had a bone marrow biopsy in a long time, that might be the thing to do. Let's make sure, especially with prior cyclophosphamide exposure that we haven't come up with a new type of leukemia. So cyclophosphamide is unfortunately associated with myelodysplastic syndrome and other leukemias. So making sure that we're not missing something here is another context, another important piece.

- I'm glad you mentioned that because I was just going to say that sometimes you have to go back to the drawing board and just make sure we're dealing with the disease that we started with.

- Okay. A CML question. I have CML. I've been on asciminib at 40 milligrams daily for the first 40 days and at 80 milligrams now for another 40 days, total of 80 days of treatment so far. Is it less likely I will hit the less than 10 or greater than 10% BCR ABL threshold at the three-month check? Apparently the lab my oncologist uses will not give more details for the 10%, so my percentage could be 11 or 99. Is this industry standard?

- Yeah, I mean the FDA approved dose is either 40 milligrams twice a day or 80 milligrams once a day. There are reasons, so I would stick to the, unless there's a reason not to, 80 milligrams a day, however you want to do that, either once or split. The 10% is a rough guess at three months, which is this early molecular response that we use. It's not an end-all be-all. There are patients who are just lower responders and still end up doing well by the one-year mark is really the importance. The early molecular mark was to identify patients who may not be responding as well as you would hope. And I use that more for when I see that is the patient really compliant? Is there a drug-drug interaction I may have missed? I go back over the medication list, the supplement list, if the patient's doing that. I don't know that I would worry. I would make one statement that in terms of following patients with CML, most labs should be using international standardized units. These are called IS units, and if the lab that your physician's not using, then there are a lot of other reference labs out there, but they really should be using IS units. These are international standardized units. Mayo Clinic, I know does. We do here at the Dana-Farber. We have our own lab, but we make every effort to make sure they're IS. And so you really shouldn't be getting laboratory assessments in a lab that doesn't use IS because it can't be followed as accurately.

- Okay. It breaks my heart that we're not going to get to every question, but there's a couple of questions on pain, and so I wanted to get to those real quick. Can CLL stage zero affect vertebrae with extraordinary pain? Can CLL spread to the bones? And then another person asks specifically, "My pain doctor wants to give me shots to relieve my back pain. Should I refuse due to CLL?"

- All good questions. CLL often involves the bone marrow, less likely to involve the structural part of the bones. So I think of bones as being like Klondike bars. The chocolate part is the part that keeps you upright, right? That's the strong part of the bones. The vanilla ice cream is the bone marrow where the blood cells are made. It's uncommon for CLL to involve the chocolate. It's almost always in the vanilla ice cream. So if you are having issues with your vertebrae, that's worth talking to your doctor about and making sure that you've done imaging, that there's not something going on where

there's destruction of the chocolate part, which very rarely could be CLL, but could also be something else. So I think getting imaging to make sure that you're not missing something is an important piece of this. The other piece is infections are fairly common in CLL, so let's make sure we're not missing some infectious process there. But in the absence of those things, unfortunately, back pain is incredibly common. So I think managing back pain according to how your doctor is thinking about it is totally reasonable. If you're on a BTK inhibitor and they're talking about putting a needle in your spine, make sure you talk to your oncologist about stopping your BTK inhibitor so you don't run into bleeding problems. But I have no issues with my patients proceeding with procedures on their spine for back pain if we are appropriately managing our medications around it, and we're sure that we're not missing something.

- Great.

- I think you just sparked my ability to have a Klondike bar now.

- I know, right? Now, clearly we need to break now because I'm going to have to go get myself some ice cream.

- Sorry.

- Okay. I want to apologize to anyone whose question was not answered. We just got so many great ones. I wish we could do this for another hour, but this is all the time we have for today. But thank you so much everyone for your questions, and thank you so much, Doctors DeAngelo and Dr. Roeker for all of your time and expertise. I also want to quickly thank our sponsors once again, this year's supporter AstraZeneca and Sustaining Supporters. And thank you again to everyone for your thoughtful questions and your participation today. Any last final thoughts to share?

- No, this was wonderful. Thank you so much for inviting me. I really enjoyed it.

- Yeah, thank you so much. Really appreciate all of it.

- Yeah. And just to remind everyone, the video and the transcript will be made available on our website. If you missed something or you need to go back and listen to it again two or three times, please, please do that. And we'll be sending the link out to all those who've registered, and I invite anybody who needs to ask a follow-up question, just give me a shout out and hopefully we can get you connected or do whatever we can to help. Okay. Thank you so much, everyone.

- Thank you.

- Have a great day. Bye.