Transcript | Living With Chronic Lymphocytic Leukemia

Andrew Schorr: Greetings from Southern California, San Diego, actually. I'm Andrew Schorr from Patient Power. I've got my copilot who's asleep. Thank you so much for joining us for this Evening with the Docs program for people like me and like you, or your loved one dealing with CLL. I've been living with CLL for 25 years and I'm doing well, and I lead a full life. That's my dream for you. We have a wonderful partner, Nebraska Medicine, the University of Nebraska Cancer Center. With us, are two leading experts from there, Dr. Julie Vose, who is the Chief of Oncology and Hematology there, and really a world-renowned hematologist. Julie, thank you so much for being with us.

Dr. Vose: Thank you for the invitation.

Andrew Schorr: Then also Dr. Chris D'Angelo, who is a scientist and physician also treating CLL patients at the University of Nebraska. Chris, thank you for being with us.

Dr. D'Angelo: Thank you very much for letting me be with you, looking forward to it.

Poll One: How Long Have You Been Living With CLL?

Andrew Schorr: We've got a lot to do. We're going to pop a poll up very quickly. We want to know, who's in the audience, how long have you been living with CLL? Just click on that. Are you a newbie? You've been living with CLL for a little while. You still could be in the watch and wait phase. I was for four and a half years, five to 10 years, there are a lot of people like that. Some people like me, many actually, more than 10 years. That's very encouraging. We'll give you the results in just a minute. There we go. Okay. Less than a year, we don't have newbies, it looks like. I was in watch and wait for four and a half years, one to five years. Some people, long time. It's that middle ground. I think what you're going to hear today is there're going to be a lot more people like me even if you've been diagnosed at a later age because we have lots of treatments. Okay. You ready to go? Okay. Folks, we need to just understand, what is CLL? Chris, I'm going to go to you first. You probably do this every time there's a new patient. How do you explain what it is?

Dr. D'Angelo: Basically, in some ways I think discussing a cancer like a lymphoma or like CLL is unique compared to the general understanding of cancers. When you think of lung cancer, for example, it makes sense. It's a cancer that's in your lungs and you can understand that you treat it differently when it's in there and it has a different prognosis when it spreads outside of it. CLL is different in that sense because it's a cancer of the blood and a cancer of the lymph system. In many ways, that's part of our immune system. That's a system that's present not just in one organ location but throughout the body. We think about that a little bit differently. We think about that not only with respect to prognosis but also with respect to treatments where a

lot of our treatments are more either chemotherapy-based or use agents that target the whole body with drugs that don't just stay in one spot but go throughout the body to treat it.

Andrew Schorr: Now, Dr. Vose, we saw a lot of the people are in that one-to-five-year category. Some are wondering if they've been in watch and wait, what's going to be an indication for treatment. What are the symptoms you're looking for with your patients to say, "We need to start treatment?"

Dr. Vose: A lot of people are worried just about what their total white count is but that's actually not an indication for treatment. It's if there's a total white count that causes problems with anemia. That's different from person to person, what the magic number is, but typically would be a hemoglobin less than 10 or if the platelet count is less than 75. Seventy to 80, for example, that would be an indication for treatment. Or if the patient has very enlarged lymph nodes that are pressing on organs or causing problems or pain or a large spleen is causing pain. There are a number of different indications but it's definitely different patient to patient. It has to be individualized.

Andrew Schorr: One person might have what would be described as a way out of whack white count but feel pretty good. Another person might have just a little bit over normal and have quite the symptoms.

Dr. Vose: Right. Exactly. People can have as high a white count as I've seen over 500,000 but they still don't have any symptoms or problems that would need indication for treatment. It's highly variable.

Andrew Schorr: People wonder then when you start treatment... We're going to get to this in a minute. We're going to go through the treatments, Dr. D'Angelo. You're following somebody in that watch and wait. This is a discussion you're having with them when they get to a certain point. A lot of it has to do with, “How are they living their life?” It's quality of life.

Christopher D'Angelo: Absolutely. The management of this disease is, again, unique in that it's very much a marathon and not a sprint. Everything that we're trying to do in this situation is either to improve quality of life and how you're feeling while you're on treatment but also how many days, longevity, trying to extend that as long as possible too. I think our long-term survivors that have been living with this disease for a long time can probably attest to this more so than even me for that matter on how the paradigms have changed over time, too. The longer things are going, the new drugs that are available, the new types of therapies, and that's why managing both of these things are important.

Andrew Schorr: Let's talk about the elephant in the room, if you will. I'm sure your patients ask you every day whether they're in Nebraska, the Dakotas, your whole region there. They say, "Okay. Well, we had this pandemic, and now more and more people are getting vaccinated." I'm a fan of that but we're going to ask you what you're telling your patients. Then, "Are we, with an immune illness, if you will..." You mentioned it, Chris. "Are we going to get a response?" First of

all, Julie, when your patients ask, are you telling them, your CLL patients, that they should be vaccinated?

Dr. Vose: Absolutely, 100%. I'm telling them they should be vaccinated. However, you hit the nail on the head there that we're not sure if they're going to respond the same way that a normal person might respond. If the CLL patient is not on therapy, I think the chances that they will respond [are] certainly higher if they are on therapy that attacks the B lymphocytes, which all of our therapies do, particularly monoclonal antibodies. They may certainly not respond as well to the vaccination but that doesn't mean that they shouldn't take it. You try to perhaps time that around their therapies, if that's possible, to hold their therapies for a period of time, but again, it has to be an individualized decision with your doctor.

Andrew Schorr: Chris D'Angelo, what are you telling your patients? They say, "Okay. I've been cooped up for a year and I've been afraid to go out of the house or I'd been really limited. I can't hug my grandchildren." What are you telling people now about how to live their life?

Dr. D'Angelo: We're getting back to that quality-of-life importance of things too. I'd say I'd still exercise safety and caution with respect to large social gatherings. I think outdoors is better. I think where you can, mask wearing, I think, is still important, particularly if you're interacting with large groups of people that you haven't seen in a long time. If you're wanting to hug your grand kids or your family again, and they've been vaccinated, I think you should really feel encouraged about that. You yourself, if you've had the opportunity to be vaccinated, we think any immune response that you get, even if it might be diminished is better than no response at all. I think these are all important factors.

Andrew Schorr: Okay, Julie, I just have a question for you about this last weekend. There was a lot of discussion about whether the general population will need a booster shot but there are some patients who wonder, "Well, should we get not one shot or two shots but three shots. In other words, should we be vaccinated more? It's like, we know that if we are older and we get a lung cancer vaccine, we get a higher dose." You are the scientist too. What's the thinking about that now for CLL patients?

Dr. Vose: I would say the answer to that is unknown, but I imagine we will be seeing some clinical trials regarding that relatively soon. Currently, we really don't have a way to get extra vaccine… goes to this for anybody. I know that there are the initial two or the initial one, and that's really all there is because most physician offices don't have the vaccine. It's really not possible now but I imagine soon we're going to be seeing clinical trials in our patients with CLL and other lymphomas or other key malignancies because it is such a problem. I'm sure all of us are going to need boosters sometime in the fall or the winter.

Andrew Schorr: One last thing for you, Dr. Vose, and that is many of us had various tests, did we get antibodies from the vaccine? I know there's been a debate among physicians, should you even do the test? Many of us still got low numbers, if you will. I know I got really low. I know the immune system is more complicated than just an antibody response. First of all, do you

encourage people to have an antibody test or not? And based on if it's lower, how do you tell them not to be depressed about it, if you will?

Dr. Vose: We've been doing some trials to try to look at antibodies in patients who are on treatment or off treatment with key malignancies and have been tested after they've gotten... Originally, we did it if they got infected but now after they got the vaccine. Unfortunately, we don't have those results. In clinical practice, we have been testing patients if they ask for it, but I haven't been testing them on a prospective basis. There's also some controversy about which tests to order. There's lots of different antibody tests. Some are semi-quantitative. Some give you a titer. They're quantitative. Some do IgM, IgG. There's a variety of different tests to do. The one I have been using is a IgM and IgG antibody test that supposedly is the best one to do.

Unfortunately, most of my patients that I have that have requested to be tested have been negative as you said. That doesn't necessarily mean they're not immune. They could have other antibodies that we're not able to test with some of these tests, or they may be low titers that are below the threshold. It is concerning and I do tell all of my patients to continue to be extra cautious because of some of these issues. I think that we're going to probably have to face this with further information and probably further vaccines down the line.

Andrew Schorr: Chris, this whole thing, and it's moved really fast – a vaccine in less than a year, really – but for science and you're a scientist, this is like, “Stay tuned.” There’re so many answers you don't know yet.

Christopher D'Angelo: Everything that we do is, you move forward, you take a cautious step forward and then you look around and re-examine the situation. You try to learn from that. Then you take the next step forward based off of that. It's like designing a machine and then turning it on, finding where the problems are, turning it off, fixing that, turning it back on. That's how we move forward. I think we've been very excited with how we've done that in the last year, I think, as a scientific community. That doesn't mean that there aren't challenges there. There certainly are, but I really like the trajectory where we're heading. I'd love to see how we start to take the next step as far as clinical trials and testing our more at-risk populations. How do we best vaccinate them? I think this is a great question that we need to answer over the next year.

Poll Two: What Stage of the CLL Journey Are You In?

Andrew Schorr: I know we like definitive answers on a lot of things. We do have some more definitive answers on CLL, the disease and the management of it. We're going to talk about that in just a second. Let's pop up that poll. We want to know where you are in your journey. There could be those people in one-to-five years who are in watch and wait. I was four-and-a-half, or you've started your first CLL therapy. You got a remission from that. I got a 17-year remission from my therapy, which will be one of the ones we'll mention. Then did you relapse and you're back in treatment or you relapsed and now you're worked, and you stopped again? If there's another, you can tell us what that is. Okay, we'll have that in a second. We're going to start, first

of all, just an overview, Dr. Vose, CLL is one of the malignancies where we have made a tremendous amount of progress, haven't we?

Dr. Vose: Absolutely. There're all kinds of new therapies we didn't have just a few years ago. We're understanding the disease better, which of course leads to better therapies. We have clinical trials where we are testing one therapy against another and trying to put different patients in different situations on the best therapy. We also have a lot of information on the genetics of CLL, which we didn't have a few years ago, which has also been quite helpful. Yes, understanding it and choosing the right therapy for patients, very important.

Andrew Schorr: Well, we're going to talk about that. Let's look who we have. Thirty-eight percent are still in watch and wait, Chris. We saw that some people though are one-to-five years, so it's gone on for a while. Then we have most people have moved on, so relapsed, and relapsed and watch and wait again. Chris, let me ask you about that. The people who are in watch and wait, for some people, that can go on for a really long time. I have a friend diagnosed when I was in 1996 and he's never been treated. You've probably seen it all over the map?

Dr. D'Angelo: Yes. We certainly see a lot of people that are in watch and wait. That's what I tell patients in clinic too. It's really hard to know how long people will stay that way. Sometimes you start to get a sense of a disease is starting to move along a little bit but at the end of the day, you really don't know. Many people can go a very long time. Just as Dr. Vose was pointing out, major changes in treatment even in the last decade or so. All that time is time well-served for lack of a better word, on many ways. Just being around and watching how the treatments can change and see what is newly available where it wasn't before can also be a very encouraging thing.

Andrew Schorr: Alright. Well, let's take a look at what the treatments are. Nate is our director. Nate, I think you've got a slide you can pop up there and we can see the different treatments. Here we go. Okay. Our understanding is these are the current treatments. Dr. Vose helped us understand this. BTK, Bruton's tyrosine kinase inhibitors. A lot of people are on those. I believe we've got two that are approved. We've got one that's approved, not for CLL, but is sometimes used for CLL. These are pills you take every day.

Dr. Vose: Bruton's tyrosine kinase inhibitors, a pill that you take every day. Some of them are twice a day pills. It basically targets a pathway in B lymphocytes and doesn't allow this pathway to continue to proliferate so that that pathway, when blocked and the CLL-side cells gradually will die off. It's a very interesting class of agents. When we did some of those original trials, it was interesting that the patients with lymph nodes after they started the therapy a few days or a week later, the lymph nodes would shrink down very rapidly but their white count in the blood would actually go up.

That's related to the fact that all the cells that were trapped in the lymph nodes then are released into the blood. The body's natural way of killing those cells called apoptosis or programmed cell death took care of those cells over time. We originally couldn't figure out if the

drug was actually working or not, but because the lymph nodes had all gone down, we kept the patients on the agents, and they continued to be very successful. Now, we're just trying to work with modifications of those agents. It's like freaking of them, adding them to other therapies and combination therapies.

Andrew Schorr: We're going to talk more about that particularly related to trials. Let's go back to the slide. Actually Nate, you can leave it up because we're going to go through the different categories. That other category there was the Bcl-2 inhibitors. Dr. D'Angelo, let's talk about that. venetoclax (Venclexta) is an approved Bcl-2 inhibitor. Tell us what that is. Is that just going after the CLL cell in a whole different way?

Dr. D'Angelo: Yeah. You hit the nail on the head there. This is a little bit of an understatement, but a cancer cell is good at one or two or both, a couple of different things. One is it's good at just growing. That's part of the challenge there. That's where BTK inhibitors are really successful. They shut that signal off. The other thing that cancer cells can do that can cause trouble is they resist those signals that tell the normal cell to die and go away. That's where these Bcl-2 inhibitors come in is they block that pathway that the CLL cell has learned to use and restore that normal mechanism that tells a cell, it's time to go away and time to die through apoptosis as Dr. Vose was suggesting. These work through an entirely different mechanism to treat cancer and have honestly been revolutionary in the therapy for this disease.

Andrew Schorr: The idea there is that rather than take the pills every day or have the Gazyva, obinutuzumab, for a while and then the pills and you continue on, you might be able to stop for some time.

Dr. D'Angelo: The initial study that took a look at this combination therapy of obinutuzumab, venetoclax, treated for a fixed duration. That's the terminology that we're starting to get used to as we're thinking about these new therapies with CLL. One of the advantages is that this therapy was continued for about a year or so and then stopped. Patients had various sustained remissions following that completion. It's an emerging idea. I guess, in some ways it's an oldie coming back around as we did chemotherapy for a few cycles and then stopped too.

Andrew Schorr: Well, that is the old. Dr. Vose, let's go to that third column chemotherapy. That's what I had. A lot of people who were treated years ago had FCR. The R not being a chemotherapy but fludarabine (Fludara), cyclophosphamide (Cytoxan) were. Bendamustine (Bendeka and Treanda), yes. Even the older drugs like chlorambucil (Leukeran). That was the idea though, that we could have a course of therapy maybe six months and stopped. For me, it worked 17 years. I'm very grateful for that but I did develop a second cancer. Is that the concern about chemo or is it the toxicity? Why have we moved away from that?

Dr. Vose: Yeah, all the above. Chemotherapy does work quite well for CLL in many cases. Specifically for patients that have certain genetic subtypes of CLL that we test in all patients now, chemotherapy works the best. Those are really the patients that we're trying to use chemotherapy and especially, the FCR regimen, which can have some excess toxicity. We always test the patient for these genetic abnormalities by FISH testing and by IGHV mutational

status. If they are mutated and if they have certain FISH that we test for, then those make good patients for FCR regimen. Usually patients that are younger, underage, 50-ish, I make it a little bit older as I get older, but 50-ish are good candidates for the FCR regimen.

But patients that are a little bit older, renal function, kidney function may be an issue with that regimen as well as other toxicity and infections. BR is still very popular and is used in patients with CLL in certain circumstances. We can talk about that a little bit later too, but it also is fixed duration that is not necessarily thought to be as good as FCR for that certain subtype of patient. If the patient can take the FCR, that is something that we do consider in those young, good prognosis patients when they need treatment.

Andrew Schorr: What about the risk for a second cancer? For instance, I remember vividly talking to Dr. Steve Rosen one day, who's at City of Hope. He just doesn't believe in chemo because he worries about setting up for a cancer down the road.

Dr. Vose: No, I think that's very valid. FCR in particular can cause secondary malignancies unfortunately, as you know. It can also cause quite a bit of problems with normal tissues and organs. That is a very selective group of patients that we now use it on. To be honest with you, I can't remember the last time I used FCR. Most patients just don't fit in that category.

Andrew Schorr: We're going to look at that slide again because I want to talk about relapse. There are a lot of people in that category who are with us tonight. Well, some people might stay on ibrutinib (Imbruvica) or acalabrutinib (Calquence) or you mentioned BR, Dr. Vose. Now, here in the relapse setting, Dr. D'Angelo, Bcl-2 inhibitor, there was a different study, not with obinutuzumab or Gazyva but with rituximab, or Rituxan. In other words, so tell us where that would fit in for a relapsed patient.

Dr. D'Angelo: I think the combination of venetoclax and rituximab is a wonderful option for someone that hasn't received a venetoclax in the first line at the time of relapse. That had a pretty good track record on the study that was conducted using this combination of therapy that induced a very nice remission and a very nice response. There's data that is still coming out from the initial study that looked at that combination that continues to demonstrate that those on it that were on it for a fixed duration and eventually stopped it have responses that last for a long time afterwards that are durable.

Andrew Schorr: Dr. Vose, this other category, PI3K inhibitors. I don't believe these medicines are used as much but where do they fit in?

Dr. Vose: PI3-Kinase inhibitors. Idelalisib (Zydelig) was the first one that you see there. Usually, it was combined with rituximab. Then a newer one, duvelisib (Copiktra) also. These are usually used when the patient has failed two or three prior lines of therapy, usually, three lines of therapy, so chemotherapy, a BTK inhibitor and a venetoclax containing regimen typically before we go to the PI3-Kinase inhibitors. That's for couple of reasons. One is that it just doesn't work as well as some of these others do. They can have some excess toxicities. When the first one came out, idelalisib, we didn't really understand as much. Now, we understand a little better how

to prevent or to treat these types of side effects. It is useful in some patients but just not used as often as the others.

Andrew Schorr: You said that BR, Dr. Vose, is still used sometimes though for some groups of patients.

Dr. Vose: Sometimes that's the right thing to do. I'll give you some examples. Sometimes there's older patients who have trouble with copays for oral medications. They just are not able to take these expensive oral medications even when they get some help for that. On some patients that may be an opportunity to use that, or if they failed the other therapies and they haven't had chemotherapy before, that is also an option to consider.

Andrew Schorr: In a little while we're going to talk about clinical trials including CAR T-cell therapy and other CARs, if you will. We'll explain that. Julie, you've been at this a long time. You recall that stem cell transplant was used for some people in CLL. Where does that stand now?

Dr. Vose: It's still used occasionally but not used very much anymore. These patients of course have to be younger patients. They have to have failed all the other therapies. By the time you get to that point, often patients are not allogenic stem cell transplant candidates. Plus, we have all these other options for patients nowadays. I would say the allogeneic transplants arena has really decreased quite a bit for CLL patients.

Andrew Schorr: Thank you for the slide. We'll just talk to the doctors now. Chris, so here comes a patient where there's indications of retrieval. You've got these different choices, walk us through the thinking of how you and the patient decide what you're going to do.

Dr. D'Angelo: What's important in thinking about treatment is it's important about thinking about how that treatment would work in somebody's quality of life and in somebody's lifestyle. One of the first things I ask somebody is what their goals are. Some cases, that's pretty straight forward. It's what we all want. We want to live as long as we can within reason. We want to have a really good quality of life. Then when you're thinking about that, you're thinking about some of the other diseases they might have that require therapy or other kinds of treatments. You're thinking about how robust they are, what their quality of life is like currently. They run in marathons still and stuff like that? Are they mostly spending time in the company of loved ones, but mostly maybe sitting down and watching TV or having conversations, but not a lot of physical activity anymore.

Based on those two things, that can help us start to think about treatments that make sense, that later maybe being an example where chemotherapy might not be the most straight, easiest option anymore, but still an option depending on what we're dealing with. Getting to the point that treatment is very individualized. One example that's coming up is when do you use these BTK inhibitors if you're using them in the front line versus one of these Bcl-2 inhibitors, venetoclax for example. Some of that is based on goals. Some of that is based on therapies that they're taking. For example, there can be a bleeding risk that's associated with BTK inhibitors. If somebody is on anticoagulation already, where that can't safely be stopped, if you have another

option like venetoclax, maybe that's the one that you start with, then you use the BTK inhibitors, you keep them down the road for if you need them later, as one example.

Andrew Schorr: Dr. Vose, some people have atrial fibrillation. My understanding is that can be an issue if you're on a BTK, certainly ibrutinib. Where does that come in? Does that rule you out from ibrutinib or you just have to watch it? How does that work?

Dr. Vose: I think each individual patient is different. If a patient already has atrial fibrillation, then that's a consideration when we choose these medications, there are some of the BTK inhibitors that newer generations that may have less atrial fibrillation. That should be a consideration. However, if they develop atrial fibrillation on the medication and they have trouble controlling the atrial fibrillation, that may be an indication to stop that particular medicine. It depends on the situation. A lot of the patients who do have atrial fibrillation are also on anticoagulation, which is another issue that you have to be very careful about. Originally, the ibrutinib trials didn't really understand that. Some of the patients originally were on Coumadin, or warfarin. That is a severe contraindication for being on the BTK inhibitor. The other anticoagulants, less so, but if they're on warfarin, they probably should not be on a BTK inhibitor.

Andrew Schorr: If you are on, let's say, ibrutinib and you've been doing well in the BTK though, I imagine BTKs are not exactly alike. You've got the acalabrutinib and then zanubrutinib (Brukinsa) off-label that's been approved for other blood conditions. Are there nuances between them where somebody might switch from one to another, Dr. Vose?

Dr. Vose: Yes. They all have slightly different side effect profiles. In the individual patient, take that into consideration. Couple of other issues, the acalabrutinib is given twice a day, whereas ibrutinib is given once a day. Even though that sounds trivial to patients, that's actually not trivial. That's one issue. They do have different side effect profiles. They all cause some issues with bleeding but some of the trials have suggested that the second generation of acalabrutinib or zanubrutinib is less stick that in the leading category and possibly less than that atrial fibrillation category. They do have potentially different profiles. You have to really know the patient and try to talk [to] them about these things of choosing these agents.

Andrew Schorr: Let's go on to the venetoclax-based regimes, Dr. D'Angelo. You're watching people and there's this concept called MRD, minimal residual disease or measurable residual disease. Where does that testing come in to let you and the patient know, maybe at some point you can stop.

Dr. D'Angelo: MRD testing is something that's being actively studied and investigated in clinical trials and using that as a deeper way, for lack of a better word, of understanding exactly where your remission status is, where we know the traditional ways of assessing a disease can be tricky. This is one way to maybe look at a little level deeper. A lot of the trials that are incorporating that, a lot of the Bcl-2 inhibitor studies combinations, venetoclax and obinutuzumab or venetoclax and rituximab that have looked at that have included MRD testing as a surrogate endpoint to see if these regimens are inducing better rates of MRD negativity.

They are pretty successful with that, which again is a good sign that these therapies are very effective and is one example of how they're inducing long remissions by not only making long but also deep. That deepening helps contribute to the lengthening of response. As far as active testing, I'm not sure quite standardized just yet where that's recommended for every patient that as part of their treatment panel. It depends on what the [inaudible 00:35:11]. It depends a little bit at the discretion of the physician taking care of them but that's not quite something that's made it out into a standard of care yet.

Andrew Schorr: Dr. Vose, we got a question in, someone said, well, if you take a vacation from venetoclax. You and your doctor agree you can stop. Are you penalized if at some point you need to go back, or will it work again?

Dr. Vose: That same thing could be said for the BTK inhibitors as well. Sometimes we need to have patients take a little vacation from that too. Especially with the venetoclax, you do have to be a little careful because if they have their white counts go back up so it's quite high, then we have to go back and start at a lower dose again and build that patient back up on the dosing. It's possible to be done. It just has to be done carefully.

Andrew Schorr: You can switch from one category, the BTK to the Bcl-2, is there a washout period, or how does that transition happen if you switch somebody?

Dr. Vose: You would be able to switch between those two pretty easily, but again, depending on what the white count is, when you switch to venetoclax, you do have to be careful about the ramp up dosing on that.

Andrew Schorr: Dr. D'Angelo, monitoring. I come see you over time. You're checking my lymph nodes. Maybe I'm getting blood tests, things like that, but what other testing are you going to do? Am I going to need a bone marrow biopsy sometime? Or if you're thinking of changing therapy, what's in store for me on the testing front?

Dr. D'Angelo: Monitoring and testing wise, it's a great question. I think the most important thing I'm checking in on when I'm seeing you in clinic is how you're feeling. Symptoms guide so much of the decision as far as when is the next time to be considering therapy and often herald and correlate to when a disease has progressed to the point where it might need more therapy. That's why I like to clarify that as I think one of the most important parts of the follow-up visit. Checking the lymph nodes is important too. The testing is important as well. Don't get me wrong. If someone has circulated a lot of CLL in the past on their blood, that's a test that can simply be monitored and watched.

If you're starting to see it rise, it's certainly not a reason to panic just yet or anything, but it's a sign of something that we might be watching you on. As far as bone marrow biopsies go, I will consider those if you start seeing changes in the blood counts if they're dropping. CLL is a disease that sometimes has some funky immune phenomenon where they can trigger auto-immune destruction of some of the other cell lines. A bone marrow biopsy can be very helpful in figuring out if that's what's going on or if something else is going on.

Andrew Schorr: I recall years ago my platelets went down precipitously. They did do a bone marrow biopsy then. They were worried about my myelodysplastic syndrome. Fortunately, I didn't have it. Even before I started taking prednisone (Rayos, Prednisone Intensol, and Deltasone) or anything, they just started to go up. They went down and they went back up and that was the last I ever heard of it. Here's a question for you, Dr. Vose, this came in. It says, can you please give your opinion, which first treatment is state-of-the-art at the moment? For instance, would it be ibrutinib or ibrutinib, venetoclax combos? Where would you start?

Dr. Vose: Sure. As Dr. D'Angelo was talking about, we have to individualize this with the patient. I talk about the pros and the cons of all these different options, including potential clinical trials. A lot of these combinations aren't necessarily available but they're available in clinical trials. You have to talk about all the different possibilities and again, what medical issues the patient might have, or do they have to travel long distances or lots of different things that need to come into the decision about that and offer them all these different options. I try to be very thorough when I'm discussing different options with those patients.

Andrew Schorr: Just one last thing about transplant, Dr. Vose, you mentioned this. It sounds like stem cell transplant is in the background now. You're probably superseded completely by these other immunological approaches.

Dr. Vose: I wouldn't say that it's completely gone, but it's a very special patient whose kind of failed all these other options we're talking about including clinical trials that you would consider that on. Sometimes the patients, however, have CLL plus another cancer that may be appropriate for treatment with an allogeneic transplant. Sometimes as you will know, some of our treatments cause another cancer, for example, if it causes acute myelogenous leukemia, or if it causes MDS, that may be an indication for an allo transplant that could potentially fix both of those problems. There are certain patients where that's still appropriate.

Andrew Schorr: Dr. D'Angelo, a question you must get all the time with new patients is, "How serious is my version of CLL?" And you have all these tests you can do now. Tell us about prognostic factors. We used to talk a lot about different chromosomal abnormalities, 17p as being one that was less good, but with these med -

Dr. D'Angelo: A lot of the testing that you said, a lot of the genetic testing that we'll do at diagnosis can inform us about what options are available. The nice thing about BTK inhibitors and Bcl-2 inhibitors is they both seem to be effective in treating that higher risk 17p deleted CLL version. Understanding if that mutation is present or not, kind of helps you think immediately if these are going to be the drugs you're going to move forward with or if chemotherapies remain an option. Dr. Vose had suggested the IGHV mutation status. That's another important factor in figuring out somebody's prognosis, as well as somebody's treatment options.

That's a situation where in the right patient FCR still may be a very good option. It's still individualized for different people, but I think those prognostic factors are important.

Understanding somebody's comorbidities in general too and somebody's functional status is also a very important part in thinking about prognostic factors as well.

Andrew Schorr: Let me just summarize a couple of things before we go to our break. You have these pills now, or sometimes pills with some monoclonal antibodies that are giving people good quality of life, and whether they go for daily pills or fixed duration, that's a discussion and what other conditions they have. Then as we get into clinical trials, we're going to talk about, could we do better where if these medicines kind of poop out on you, do we have yet another class or new improvements to go to? It seems like you both are pretty encouraged. If I come to you as a new CLL patient and I'm depressed, you give me reason for hope, right, Chris?

Dr. D'Angelo: A lot of my visits reinforce that idea. There is plenty of room for help in this disease. I think many patients have lived that as their own experience. I tend to be very positive on the outlook of things. Even looking at the last 10 years or so, we use therapies that weren't available before. Who knows what will happen 10 years from now, but you can imagine we're pretty optimistic. That's really what I try to communicate to anybody coming here, especially as scary as a new diagnosis can be.

Andrew Schorr: Dr. Vose, just a little teaser for where we're headed. You've been a university expert for a long time. You were president of ASCO and you dealt with doctors from around the world. Knowing where research is headed, which we'll talk about in greater detail, do you tell your patients that the odds are they're going to have a pretty long life?

Dr. Vose: Again, some of these factors that we're testing can help with that a little bit, but compared to even just a few years ago, we have so many options for these patients and even if they don't respond or fail one, there's so many other options that I think I'm much more optimistic now than I was even less than 10 years ago. I think there's so much we can do now.

Andrew Schorr: That's where I am, 25 years folks, living with CLL. I'm leading a pretty good life, I'm very grateful. I mentioned this early on that I've been living a long time with CLL. I was in the phase two trial. We're going to learn about clinical trials for FCR, fludarabine, cyclophosphamide, rituximab, and it led to wrong long remission. I actually got that combination 10 years before it was approved by the FDA. I think it made a huge difference for me, and that was after four and a half years of watch and wait. I'm a big believer in clinical trials, and we're going to be talking about that now. Welcome back to the doctors.

Poll Three: Have You Participated in a Clinical Trial? Would You Like To?

Andrew Schorr: We're going to do a quick poll to just find out where you're coming from related to clinical trials. We have two university doctors with us. First of all, would you like to participate in a clinical trial? Are you currently in a trial or have you been in one like me? Let us know, but let's talk about that progress. First of all, Dr. D'Angelo, where would we be without clinical trials?

Dr. D'Angelo: I think if this pandemic has taught us anything, it's something from a vaccine perspective of how important these clinical trials were in moving us forward and demonstrating not only the safety of it, but also the efficacy. That's just one point, but heck we don't need the COVID pandemic to teach us that. Everything we've learned about how to take care of this disease really starts and ends with clinical trials.

Andrew Schorr: Dr. Vose, when someone's in a clinical trial, I know my experience was I was monitored really carefully. I like the attention, I did, but safety is a big issue for us, and people are afraid of being part of an experiment. How do you explain that to patients about the opportunity that they may get something better, they'll help advance science, and their safety is protected?

Dr. Vose: Now, as Dr. D'Angelo said, basically every therapy we have for not only CLL, but every cancer today is therapy, but yesterday it was a clinical trial. That's how we learned. That's also how we're able to advance the science and advance treatments for patients. We really wouldn't be where we are today without that. Patients in clinical trials are monitored very carefully for, they often have extra blood tests, extra scans, extra whatever we need to monitor the patient after exams. They really are able to benefit from that not only themselves, but to help the patients of tomorrow. I really encourage patients to consider that. Sometimes it seems like it's an extra burden, but it's really something that can be beneficial.

Andrew Schorr: I think you sold it, Julie, would you like to participate in the trial? For you all at the University of Nebraska where you do a lot of research, that's good news that people would consider that. Dr. D'Angelo, with a patient how do you weigh, we have good, approved therapies. How do you talk about here's what we've gotten approved, here's what we're looking at that could be better, how do you discuss it all together?

Dr. D'Angelo: I think you try to put it in context for that person and try to... In some ways it's very similar to how you do it without a clinical trial. You're really trying to find something that matches what their goals are, what their quality of life is, how you can work it in to their daily life. Honestly, I think trials are surprisingly flexible. There’re obviously some parts that really can't be changed, but we're actually pretty good at customizing them, I think, and making them work in somebody's life within the parameters and guidance set by that trial. I'm bringing out the option, I'm discussing the alternatives and I'm trying to describe what life might look like on that trial compared to what it wouldn't look like without and what advantages you get from it.

Sometimes that's new access to therapy that you wouldn't get otherwise. Sometimes as Dr. Vose had mentioned before, some insurance companies won't immediately cover medicines or will cover them but leave a pretty hefty copay there and clinical trials may sometimes be an opportunity to get access to medicines that you might not otherwise. Something that I bring up.

Andrew Schorr: Julie, you used a word earlier, you used the word distance. In your part of the country there's some big distances. You've got big states and people come to the University of Nebraska from far and wide, right?

Dr. Vose: Yes, we have patients that come from really all over the U.S. but mostly in our five-state region.

Andrew Schorr: In that region though, can I be in a trial with you but have some collaboration with a general hematologist-oncologist? In other words, can there be some teamwork where some of the stuff can happen closer to home?

Dr. Vose: We absolutely always try to work with a local oncologist if that's something that where the patient comes from if they're very available. However, some of these clinical trials are very specific about what they allow and don't allow. Many times, a lot of the the tests and visits need to be done at the center where the clinical trial is from, and don't allow that type of thing. A lot of that's kind of mandated by the FDA because they need to know exactly what the data is and make sure that it's the same across the board for that patient and for that trial at that center but wherever possible, we absolutely try to do that.

Andrew Schorr: Let's go on and talk about what's in research. I'll stick with you for this one to begin with Dr. Vose. We talked about the BTK inhibitors, and we talked about first-generation like ibrutinib, second-generation you referred to acalabrutinib, but I understand there are drugs in trials now that maybe are third-generation, how will they be different?

Dr. Vose: There are some patients who are resistant to BTK inhibitors, and there's a certain known resistance molecule, if you will. If the lymphoma has that particular abnormality, then the patient becomes resistant to the first and second generation BTK inhibitor. The next generation actually is by a slightly different mechanism and that resistance mutation that can be overcome by that next generation and then a BTK inhibitor could in that case work again. That's something that's not normally tested for, the mutation, but if we are suspicious about it, there is a potential test that we can send off to get that. In those cases, then that resistant new BTK that potentially overcomes that resistance can actually be useful.

Andrew Schorr: Let me see if I get it right. If I've been on the BTK inhibitor, but it appears that sort of my CLL is kind of outsmarting the drug resistance, you may have another BTK inhibitor in trials that might not have that same issue. Did I get it right?

Dr. Vose: That's right. Not all BTK failures are from that, but a certain percentage are.

Andrew Schorr: Those are, I think they're… Chris going into phase three trials. I know there are at least two, anyway, that I've heard about. That's something to be discussed. Let's go on to CAR T, let me see if I have this right. Chimeric antigen receptor T-cell therapy. It's approved in some lymphoma. Now one's approved in multiple myeloma, but not in CLL. Dr. D'Angelo, where are we with that with CLL?

Dr. D'Angelo: Correct. I would say this is a good example of how clinical trials will hopefully help us eventually cross this finish line for CAR T therapy and maybe another example of emerging cellular therapies that may sort of butt into that space where the allo stem cell transplants used to be. Some of the initial studies that have taken a look at that can

demonstrate that the CAR T works and can control the CLL, but in some cases, the durability is the part that has been a little bit more of a sticky wicket to crack, so to speak. Some of what we're learning and some of what we have clinical trials that we're actively working on are designs that sort of incorporate other therapies in combination with the CAR T to kind of improve, augment, that response and sort of maintain it a little bit longer. That's one strategy that we're looking at. Other strategies use sort of different CAR mechanisms, either different cells or different targets.

Andrew Schorr: I'll stick with you for that. I interviewed someone from MD Anderson who's been working on CAR NK treatment, and I know it's early, but I think there's this effort to have things that don't take as long to develop what they're going to infuse back in here. Maybe whether it could be less expensive, I don't know, or off-the-shelf CARs, do you see this in our future? Where do you think we're going?

Dr. D'Angelo: I think that absolutely has an opportunity to grow in the future. One of the advantages for off-the-shelf therapy, so to speak, is it sort of shortens that window of time. There is a couple of week delay in manufacturing somebody's cells. What CAR T does is it takes your own lymphocytes out of your bloodstream, incorporates that new CAR structure that allows them to sort of re-target, re-engage against that, bring your immune system back in touch with that cancer cell and really work to achieve phenomenal responses. The problem is manufacturing. Sometimes it takes a couple of weeks to make that, and sometimes that's time that a patient doesn't have.

These types of lymphomas and CLL is an example of them having a possibility of growing very quickly. That might not be available to everybody, that waiting period. Off-the-shelfs could really work here in that you don't have to wait for that, or if maybe your own lymphocytes don't work as well anymore after receiving different treatments for different things or as a consequence of CLL, maybe it wouldn't even be possible to manufacture them. Another advantage of off-the-shelf is that you wouldn't need to, you can just pull it off the shelf.

Andrew Schorr: Dr. Vose, you've been around transplant for years in a variety of different immunological approaches. How do you feel about this whole CAR approach as far as CLL?

Dr. Vose: The preliminary studies actually look quite promising. We have a CAR CLL study at our place too. In fact, if anybody's interested, please let us know. I think it is promising and it's sort of a way to do an allo transplant without doing an allo transplant without having some of those complications. We're trying to use the immune system to fight the CLL, yet we don't have some of the other complications of graft-versus-host disease, or other things you see with an allo transplant. I do think there's promise there, if we could have an off the shelf one to do that same treatment structure but yet be able to pull it off the shelf, that would be even better. We have a lot of research to do.

Andrew Schorr: Where does this fit in sort of the treatment paradigm though? We talked about some people, Dr. D'Angelo said it might be on watch and wait for a really long time. Some

people not as long, but still four-or five-years type of long, then you have BTKs, and even new ones that may for a long time or venetoclax regimens that work then you can go back to it, have it again if you need it. Who would need a CAR T? Or is it just if we live long enough, we might?

Dr. Vose: Most of the patients that are on these clinical trials right now have already been through all the standard treatments. This is sort of their fourth, fifth, sixth option or they're patients who have had some of these bad genetic markers. Perhaps even if they were on these other therapies, they just didn't last very long. It's not for every patient, but it's something certainly that is of consideration for some patients.

Andrew Schorr: Dr. D'Angelo, here's a question we got in earlier, and I meant to ask you this, and that is with the new novel agents in clinical trials, are you CLL doctors starting treatment sooner so that the watch and wait period is less, whereas there's still an argument watch and wait for as long as you can?

Dr. D'Angelo: Great question. In general, I would say watch and wait still remains a great option that most of the criteria that would be an indication to treat sort of still follows as far as clinical trials go, even on the frontline studies. I would say never say never though. Historically when we studied these and we studied looking at therapy versus waiting, we didn't see any survival advantages. People weren't living longer because we started treatment sooner. All that we're really doing is exposing people to potential side effects earlier on, rather than waiting and producing, honestly, what remained very good quality of life years. Watch and wait works very well for many people since you don't get any side effects if you're not on any therapy and if you're not symptomatic from your disease well, hey that makes sense. It might be a question that gets picked up again in the future, and there are other blood cancers that are starting to look at at that kind of question, but I don't know just yet about CLL on that matter.

Andrew Schorr: When I was on Facebook earlier today in one of the CLL groups they were talking about particularly GI problems from some of the medicines they were taking. Let's stick with you on that. Dr. D'Angelo, can that be managed? People worry about diarrhea, they have other nausea issues, whatever, with different treatments. How do you help people so that they have that quality of life?

Dr. D'Angelo: You're right. That's a very important thing on a therapy that you may be on for a very long period of time. Coming up with ways to optimize that are important, ideally you would try to treat the symptoms so to speak. Sometimes these are symptoms that show up early on and then sort of quiet down the longer you stay on therapy. Depending on where you're at on this, if this is a relatively new medicine for you, and you're seeing some side effects, I'd say stick with it and listen to your doctor and with management and with time, sometimes they just get better on their own. For those that are on it and need some relief in the meantime, a lot of the agents that we use can still be effective here, anti-diarrheal agents, things that you can even pick up over the counter with your doctor's advice can be useful. Imodium (loperamide), for example, can be helpful in slowing down the diarrhea in that regard and nowadays there's lots of nausea medicines that can work very well in trying to achieve that good quality of life.

Andrew Schorr: One other question for you. One of the big things that people worry about is fatigue. Even though some patients who've been on Ritalin (methylphenidate), so what's your thought about fatigue? I know for instance, exercise is a good thing, but what do you tell people about fatigue?

Dr. D'Angelo: Yes, that's a great question too. I think when it comes to fatigue, some of it is, are you treating the symptom of it versus getting at kind of the cause of it? One of the things that I'm doing for anybody that's experiencing fatigue on any of the medicines I'm treating them with is really evaluating all options. We know that these diseases don't exist in a vacuum and that patients may have more than one thing going on. That's a good example of where it's important to try to figure that out. Some things that can be tricky and subtle, if you're not looking for it can be infection. There are infections on these drugs that are worth looking for.

The other one can even be things like depression and stuff. Those are hard illnesses if you're not looking for them to pick up and sometimes co-management of that can be actually very effective. Not to mention the sort of standard tried and true things that you hear us say a lot remain effective. Exercise is a very good way of improving fatigue. It's certainly not one of those you aren't exercising and then you exercise and then are expecting immediate benefits from that. It does take a little bit of working with it to really get that response.

Poll Four: Are You Concerned About Second Cancers? Have You Developed One?

Andrew Schorr: The thing that people worry about big time is might they be at risk for a second cancer? We have another poll about that and let's pop it up on the screen, Nate. This is about, are you worried about second cancer? Tell us if you've developed a second cancer or if CLL is your second cancer. We'll look for those results in a minute. I'm going to ask about one Dr. Vose, skin cancer, my understanding is that CLL patients should have a regular consultation with a dermatologist, and I do, and I have developed, and here I am in Southern California, a basal cell right on my nose. I'm actually going to have a mast surgery for a squamous cell they found over here, I'm pretty public about my condition and I get monitored carefully, but what about that? About a worry about skin cancer and why would that be a concern particularly for CLL patients?

Dr. Vose: For reasons we don't a hundred percent understand patients with CLL, and some other indolent lymphomas as well do have increased risk for skin cancers of all type. Of course, the skin cancer we worry about the most is melanoma. The others are perhaps a little bit easier to treat, but I agree that it would be good to have a dermatologist or a very good primary care physician to check your skin at least yearly when you have CLL. Of course, you can do a lot of that yourself too because there is that increased incidence and you do have to be very careful and in the same vein, some of our treatments appear to slightly increase the risk of some of these skin cancers too. That's another issue that needs to be considered.

Andrew Schorr: Worried about it, 40%, not worried about it, 40%, it's pretty split. Some people like me have developed a second cancer. Are there other cancers we need to watch out for, Dr. Vose, that a CLL patient might be at risk for?

Dr. Vose: Yes. Mostly those we talked about earlier, secondary malignancies related to the treatments, a lot of that's related to the issues with the two chemotherapies, so MDS, acute myelogenous leukemia, other blood cancers can be at increased risk. Those are the majority of ones that are of concern.

Andrew Schorr: Can you explain something to us as well? Richter's transformation, how often does that happen for CLL patients? What is it and what do you do about it?

Dr. Vose: Richter's transformation is when a person's had CLL and they change or transform to a more aggressive type of lymphoma, typically diffuse large B-cell lymphoma, which is a faster growing type of lymphoma. What happens is that the cells that form the CLL are actually genetically changed or modified, and then they stop growing at this slow rate and start growing at a very fast rate. They also become much more difficult to treat, a lot of the regular CLL treatments that we use do not work on these Richter's transformation. That's where, especially those patients need to be in clinical trials and look at new therapy options.

Andrew Schorr: What is the incidence of that among all CLL patients?

Dr. Vose: It's fairly low, it's probably in the five percent range, and it typically happens after you've had CLL for a while, but doesn't have to, it can be de novo at the time of diagnosis.

Andrew Schorr: Dr. D'Angelo, here's a question that came in from the audience. This person wrote in, my husband is in watch and weight, but has an extreme problem with itching and sores on the skin. He's had tests that indicate no skin cancer. Is this a big issue with CLL? If so, could this be a cause for treatment? It is so bad. He has trouble sleeping. Dr. D'Angelo.

Dr. D'Angelo: Pruritus or skin itching is a symptom that does come up in non-Hodgkin's lymphomas and CLL we can see that too. It is certainly something that comes up and I think the most important part is evaluating for other causes. It sounds like he's been evaluated for those. That's where dermatology management making sure there's not a new infection that's possibly coming up or even something separate as with respect to any other kind of skin diseases. If that evaluation has happened and there's not a whole lot of other options, but accepting CLL as a possibility, then I would consider that as something to be bearing in mind as far as treatment goes. Some of it might do with how much disease is present too. If there's only a little bit of CLL, maybe not that high of a white blood cell count, for example but a large effect of symptoms that's something that kind of weighs in, but I certainly think that's worthy of a conversation as far as whether or not to treat.

Andrew Schorr: I was looking at some postings by different CLL patients. Somebody wondered whether they had brittle fingernails related to one of the medicines. If you encountered that Chris, and what did you do about it, or if did you do anything?

Dr. D'Angelo: In general, chemotherapy damages some body tissues a little bit more often than others, especially the ones that sort of rapidly grow. Skin hair, for example, GI, all of those are our body areas that have a high amount of cell turnover and are more susceptible to these agents, but in particular there are brittle nails that can develop with some BTK inhibitors. I don't know if it's a one size fit all thing, but some things that have been tried and there was not a great level of evidence to support them, but also relatively safe would be sort of nail oil that you can apply on the cuticle bed. Sometimes nutritional supplements. Biotin is a vitamin that you can try to take and see if that helps a lot. Then honestly, depending on sort of where you're coming from, even painting your nails can help kind of take care of that, but obviously that might not be an option for everybody.

Andrew Schorr: Dr. Vose, I bet you've been asked a hundred times, is there a CLL diet or an anti-cancer diet? What do you tell people? Different regions of the country people eat different things. I'm here in California, we eat fruits and nuts but maybe it's different where you are, but what about a diet that you would recommend for people?

Dr. Vose: I wish I could say that there was a magic diet, but unfortunately there's not. Typically, I just tell patients when they ask that question that they should try to do a typical healthy bite, which would be fruits, vegetables, lean proteins, and to try to keep the sugars down, but not necessarily for the CLL, but just their overall health and trying to maintain a good weight and that sort of thing. Unfortunately, there's no magic diet.

Dr. D'Angelo: Just to piggyback on that, sorry, Andrew. Absolutely everything Dr. Vose said is a hundred percent correct, but that's a question that we hear about a lot as specialists here and as cancer doctors in general. There's actually a study that we're looking at opening up here. It's not a clinical trial, but it's a study that's intended to capture this diet question. We'll be serving patients with CLL that have what their diets look like. We're also looking at that with respect to this concept of the gut microbiome, or sort of the bacteria that live in your gut and sort of how these things might all relate with each other and if whether or not they relate to CLL. That's a big if right now, we really don't know if that's happening or not, but that's an example of research that's just asking the question.

Andrew Schorr: We talked at the beginning of the program really about COVID. We were talking about our immune systems. If you go to a shop, if we go back to a shopping mall, many of us haven't, but if you did and there's a vitamin store there, they have the big posters about immune boosting this or that, or TV commercials now too. Is there anything of Dr. D'Angelo that I could take as a CLL patient that's going to boost my immunity?

Dr. D'Angelo: I think these supplements can be tricky because the messaging behind them sort of makes a lot of logical sense if you're trying to think of any options. The thought here is that okay, well, they're relatively safe. Maybe I'll give them a shot and that's where it's kind of tricky. These supplements don't get quite the same rigorous study that the FDA gives when we're looking at new medicines for CLL, for example. That's a little bit why when we get that we are so careful in our clinical trials, as far as safety goes, but also very confident in the results when we

publish them. It's a little bit harder to say that sort of supplement wise whether or not that track record's there.

In general, I don't discourage patients from trying, and it's always very good to have a conversation with your doctor about that, because sometimes they might actually interact with some of the medicines that you're on and could actually cause more harm than good in that situation. Good communication is an important thing there. As someone who's willing to try I'm always willing to listen as long as we're keeping an eye on things, and if we see some new lab abnormalities on blood work or a new symptom or something like that, very carefully reevaluating the medicines that you're taking, including supplements and stuff to try to figure that out.

Andrew Schorr: Just a word about communication. I would just say it is so important to have an honest relationship with your provider, the physician, the nurse, the nurse practitioner, the physician assistant, the whole team. When they say, what are you putting in your body? Basically, tell them everything. If you're taking some unusual thing that you got over the counter, tell them. That's the communication and the other thing is many CLL patients are older, many are male. Sometimes we don't always speak up. Whether it's the spouse and I'm sure you both, you physicians have heard this, "How are you doing?" The guy says, "Fine." The wife or partner is saying, "No, you got to share." We got this question in, Julie, a COVID question. It is if one of us may be vaccinated or not develop COVID we know it was bad news earlier, and let's face it. There're still people passing away. How can you help me as a CLL patient early where my prognosis won't be so bad?

Dr. Vose: Obviously, we still want to be on the lookout for symptoms related to that and to get tested as soon as possible, if that's the case vaccinated or not, because as we talked about, don't know if the vaccine works as well. There are certainly the monoclonal antibodies that can be given when the patient is not as sick, if they're not in the hospital. Once they're in the hospital we understand a lot more about supportive care now trying to start some steroids on patients, giving them [inaudible 01:14:58] We usually are stopping their CLL therapy during that time period to try to reduce that as an indication of problems too. Especially if it's a monoclonal antibody. Obviously try to support them through whatever we need to. We have learned a lot more about how to take care of patients than we did a year ago for example.

Andrew Schorr: I hope so. Obviously, we've seen the mortality going down. A couple of quick questions now wrote in on Facebook, Dr. D'Angelo can a patient who is in watch and wait be in a clinical trial or their trials for them always you're going to have to start at therapy?

Dr. D'Angelo: Clinical trials often are testing sort of medicines or one medicine against another, but sometimes there are situations where you're testing a strategy. One, it's not too difficult to think of a trial where somebody could be in the watch and wait arm so to speak versus an early intervention arm or something. While I am not aware of that trial right here or anything like that right now, that is certainly something that could be conceivable. If it's not a trial, there are sometimes what we call just sort of prospective studies, for lack of a better word, where we want

to understand somebody's what the biology and what the clinical experience and what the patient experience quality of life getting to again is like on this.

If it's not directly testing a strategy or a therapy, it's gaining insight into what a patient's experience is with this and those trials are very important, I think in understanding how we care for patients, not just from the medicines we prescribe, but some of the sort of whole base communication or monitoring or any of the other care strategies that are a form of more comprehensive plan in somebody's management.

Andrew Schorr: We'll try to buzz through some questions quickly. Wendy wrote in Dr. Vose, and you've done a lot of lymphoma treatment, of course CHOP-R is used for some of the lymphomas. Wendy wants to know, does CHOP-R, that combination have a role in CLL?

Dr. Vose: CHOP-R or R-CHOP typically does not have very much of a role in CLL unless the patient has transformed in the Richter's transformation then that is a regimen that we use for those patients, but it's not as effective as some of these other agents we've talked about for CLL.

Andrew Schorr: Dr. D'Angelo we've been doing some programs in multiple myeloma, another blood cancer. As you know they're working on BiTE therapy there, Bi-specific T-cell engagers. The question is, is that similar to CAR T or is it different?

Dr. D'Angelo: I would say similar in some ways. It's sort of using the power of your immune system and kind of targeting and using a strategy to sort of better paint and sort of target the lymphoma and sort of bring your immune system kind of into context and nearby that cancer and having your immune system sort of help play in the disease control. Some of the side effects that can come up with these kinds of therapies are similar to some of the side effects that we see with CAR T. I think one difference is there's still very much research in clinical trials right now versus CAR Ts, which are in clinical trials but then for lymphoma have some commercial approvals. The other thing is that much of the strategies for these BiTE therapies are sort of regular infusions. You're getting it dosed on a regular interval. Maybe say every two weeks, every three weeks, there are some BiTEs that require a continuous infusion where people are hooked up on a pump. The difference with CAR T, many CAR T strategies are really just a one-time therapy,

Andrew Schorr: I know we have programs for young adolescents who were on an approved BiTE therapy for acute lymphoblastic leukemia, and they wore a little fanny pack, and they get that going on. I want to just get a final comment. Dr. Vose, let's start with you, and then we'll go to Dr. D'Angelo. You seem pretty hopeful. You seem like most patients, there are lots of lines of therapy and we can live a long time and live pretty well. Are you optimistic for our future? What about a cure, Julie? How about that?

Dr. Vose: Yes, I am very optimistic. There’re so many different options that we can have even just a few years ago. We're learning how to sequence those options in which patients are going to respond best to what options. I am very hopeful; I think compared to just really a short time

ago we have so many different therapies. Cure, I don't know, but I'm always hopeful and I continue to do clinical trials so I can try to find that cure.

Andrew Schorr: Thank you for your devotion, really Dr. Julie Vose for being with us and Dr. Christopher D'Angelo, what's your final comment you want to leave us with tonight?

Dr. D'Angelo: I like everything that Dr. Vose just said with respect to hope. I think one sort of the hallmark blood cancer that we look to when we're thinking of our futures too is something called CML. That is a very distinct disease with a very distinct biology and analogies there. Once we found these therapies that work and target the specific problem with CML, patients stay on those, but they go on in many cases to live normal, healthy lives.

I think that's very much the sort of hope that we're trying to get towards with CLL and cure hopeful about that. If not a cure, if we could come up with a regimen that induced such a deep response incorporating MRD testing, for example, incorporating clinical trials, incorporating the new breakthrough drugs that we've really had in recent years for them, and really trying to find a way to bring it all together maybe we paint a situation that becomes very like what we see in CML where a disease that might require continuous therapy, but in a way that you can kind of do it that patients are living well into the ages that they want to live. Then with a disease that is well-managed.

Andrew Schorr: That's what I want. I want to keep hugging those grandchildren. I got my first hug from a two-and-a-half-year-old, just the other day. Then we have a two-months-old, we got to pinch her cheeks for the first time. That was thrilling. Thank you so much for everyone and for your dedication, Chris and Julie and really being with us tonight.