Ask the CLL Expert LIVE From ASH 2015 Replay

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Andrew Schorr:
Hello, CLL friends. I'm Andrew Schorr, someone who has been living with CLL since 1996. I'm happy that I've been doing well. I was in the FCR Phase II trial long time ago, but other people have had, many have had a rougher go than I have, and I am excited for you as we're now at ASH in Orlando, Florida. A lot of news continues to break in CLL. We're going to be taking your questions.

I'm sitting with my friend, an expert in the field, Dr. Jeff Sharman. I want to get your titles always right, Jeff. It is, let's see. Of course, you're a medical oncologist, hematologist at Willamette Valley Cancer Institute and Research Center in Oregon. My son goes to the University of Oregon, so I'm very excited about that. Also medical director of hematology research at the US Oncology Network, in which is in about 19 states now, so all over. Jeff, thanks for being with us.

Dr. Sharman:
Thank you, Andrew. I'm happy to be here.

Andrew Schorr:
Okay. So let's get some headline news for our live audience. We're going to be taking your questions shortly, and you'll be able to just click on the question link there on Zoom, and many of you have sent in questions. And also you'll be able to pop up on the screen if you're on webcams, so that's really cool.

But, Jeff, let's start with sort of what is the news for CLL patients from ASH?

Dr. Sharman:
So quite a few stories coming out this year. I think many of them are pieces of information I think that are maturing storylines. There are some new storylines coming into play.

I think the one that may have the most immediate impact to patients is what we call the RESONATE 2 study. This is a clinical trial of previously untreated chronic lymphocytic leukemia patients, randomly assigned to chlorambucil (Leukeran) versus ibrutinib. And this study will be presented shortly. The abstract is already available online, and it shows a substantial improvement in outcome for patients treated with ibrutinib.

That's not so much of a news flash. I think we all expected that, however the—really the most important piece of that is how did people do previously untreated on ibrutinib (Imbruvica). The previous story to that was only published on 30 patients. This was a large, multi-center randomized clinical trial, and they do very well. This is a neat addition and will likely lead to FDA approval of ibrutinib for previously untreated patients.

What we don't know is what the specifics of those approvals will look like. So whether they restricted it age or functional status or whether there's no restrictions at all, it's going to upend the way we treat CLL in the previously untreated patients because it now becomes a decision point of this versus whatever else we were going to talk about.

Andrew Schorr:
Right. And, of course, people continue to look at ibrutinib being combined with other medicines to get sort of a bigger bang up front, so you don't deal with the problem of resistance, in other words, the cancer figuring out a way around that individual medicine, right?

Dr. Sharman:
Yes. So there [are] currently studies being run, two studies that I would draw attention to. One is a randomized study in high-risk chronic lymphocytic leukemia. This is defined by patients with the presence of a 17p deletion, 11q deletion, and in one of the two studies the presence of a TP53 mutation. These findings confer high risk, and there [are] actually two studies running very similar in design.

One of them, all patients receive ibrutinib and half of them receive an antibody called ublituximab. And then in the other study is actually a head-to-head study of ibrutinib versus ACP-196, which is a new BTK inhibitor that also has some very impressive data here at ASH.

Andrew Schorr:
Wow. Okay. And the other thing, just to headline, is there any news about what had been ABT-199 and venetoclax? Because people have been hearing about that as a new kind of medicine, and maybe it could be combined with others, but is it sort of giving a bigger bang?

Dr. Sharman:
Yes. So venetoclax is sort of a which one is not like the others. All of the B-cell receptor signaling inhibitors, and that includes ibrutinib, idelalisib (Zydelig), duvelisib, ACP-196, (TGR-1202) TG-1202, all these are what are called B-cell receptor signal inhibitors. And those I would say kill CLL cells slowly, and so the responses improve over long periods of time. Sometimes measured over many months, even years you'll see responses continue to improve.

Bcl-2 is a very different target in chronic lymphocytic leukemia cells. It's like the seatbelt of the car. It's the safety mechanism that keeps the CLL cell alive, maybe the B-cell receptors, the gas and the Bcl-2 is the brakes. And so if you sever the brakes, the cells die very quickly, and so this drug instead of having very slow responses has very, very fast responses.

That is both good and bad. The good is that we see patients have very deep responses at very early time points. The bad is that in some cases those response rates have been too fast…

Andrew Schorr:
It's a powerful drug.

Dr. Sharman:
…and we've run into problems called tumor lysis syndrome. But what we do see is very deep, powerful remissions, and to be presented here will be a potentially registrational study, meaning a study that will lead to FDA approval of venetoclax, a Bcl-2 inhibitor. And that's in relapse-refractory high-risk patients, and we're seeing very strong responses with that drug, also a pill, also not necessarily traditional chemotherapy.

Andrew Schorr:
Okay. Very cool. All right. Now, for people with us we've got a bunch of questions in already. And again right on Zoom if you want to ask a question, there's a link there. And then you can send it in, or you'll be able to pop up on your webcam. So we have a lot going on. We'll be able to see you if you do. Okay.

But, Dr. Sharman, let's go through some questions we've got. So you were just mentioning about this ACP-196 and hearing that it's a BTK inhibitor. Is this—having a second-generation BTK, is it a big leap forward? Is it incremental? How would you describe that?

Dr. Sharman:
It is early but very exciting. If you think about a different disease very similar to chronic lymphocytic leukemia, we'll call chronic myelogenous leukemia, CML, the first-generation drug there was a drug called imatinib, or Gleevec, and Gleevec really changed the way we think about treating cancer, because it was the first time we used these very targeted drugs that had high levels of efficacy.

But imatinib, or Gleevec, was followed shortly thereafter by two drugs, and then now actually several more, that appear to be more potent, and that appears to lead to better outcomes in chronic myelogenous leukemia. There is some optimism in the field that we may be starting to see a similar story play out with ACP-196, and I will caution it is early, really early. And some of this data is going to be presented about the time we finish here today, so I will be a little bit coy deliberately but impressive responses with this drug, and I think that we will see a second approved BTK inhibitor once we get all the appropriate data and regulatory information for ACP-196.

Andrew Schorr:
And I know people watching, my friend Lisa Weiss is in a trial with that, and she communicates with a lot of women in the CLL lymphoma community, so again, whatever developments, we always have to thank people who are in clinical trials. And thanks for Arthur with that question. Let's go on.

Johnson, in this question, he said, "I read an abstract that implied venetoclax, we just talked about, is active in patients who were relapsed or refractory to ibrutinib or idelalisib treatment, so what about that?"

Dr. Sharman:
Yeah, and forgive me for not being able to quote the specific percentages in that study. It's just kind of been a lot of data here, but yes, qualitatively very good responses even amongst patients who have previously been treated with a B-cell receptor signal inhibitor, and that would include idelalisib or ibrutinib.

Andrew Schorr:
Okay. Now we're going to buzz through a bunch of your questions. Remember, you can send some in right now. But Robert sent in this question, he said, "When CLL patients are undergoing treatment how compromised is our immune system, and can we do anything to mitigate that?"

Dr. Sharman:
Yeah. There's I think a variety of ways to think about this. Chronic lymphocytic leukemia is a cancer of the immune system, so the immune system is compromised right out the—right from the get-go, even before treatment. And there aren't simple tests that give us these binary answers of yes, no or numerical answers of 65 percent suppressed or 30 percent—we don't—it's a qualitative, subjective type measurement, but we do see unusual infections in patients with CLL. We do see infections that are common, can become considerably more severe in patients with CLL even before treatment.

Now, treatment itself, lots of different treatments, some more immunosuppressive than others. The traditional fludarabine-based regimens were most often the hardest on the immune system.

Andrew Schorr:
I always got sinus infections with that.

Dr. Sharman:
Yeah. And rituximab (Rituxan) itself is depleting B cells, which is one component of the immune system. So it's a little bit hard to disentangle what's the disease and what's the treatment, particularly in the setting where there [are] multiple different treatments available.

One question I think we'll probably get to here in a little bit is a medication called IVIG. And IVIG stands for intravenous, that's the IV, immunoglobulin, IG—so intravenous immunoglobulin, IVIG. And this is essentially a pooled blood product, so from blood donations they extract the serum and obtain all the antibodies. They pull those together and then give antibodies to patients.

If you look at patients with chronic lymphocytic leukemia, they typically will have lower levels of antibodies, whether they're treated or untreated because of that cancer of the immune system, this is one where we can get some numerical readout, but again numbers don't tell the whole story. So we can give IVIG, and in some patients it is appropriate, in some patients it can be life-altering, and in some patients it's overtreatment.

So how do we decide? We get a little bit concerned when somebody's antibody levels, their IgG levels are lower than 400 milligrams per deciliter, but that as a number doesn't tell us we have to do anything. If they're low and are having frequent infections, frequent sinusitis, hospital admissions for pneumonia, that's a time we may use IVIG.

Some of the things we're seeing with some of the other drugs, though, is that immune system and immune function is even starting to improve on some of these novel agents.

Andrew Schorr:
But should I go to the health food store or eat some vegetable or something that's going to inoculate me, if you will, something you know about?

Dr. Sharman:
You know, I think a lot of patients, very understandably, want to do whatever they can to control their situation, and I think one of the ways that finds an outlet is various supplements and things like that. Very few of these have documented scientific claims to show that immunity is ideal. I think that healthy levels of vitamin D are probably beneficial, but even that is based upon understanding of T-cell function. And where I live up in Oregon vitamin D deficiency is very common, so at least try and get people into the normal range.

People have talked about others, but I think there are very few. And specifically I'll say that marijuana doesn't work. I tell my patients in Oregon.

Andrew Schorr:
Okay. Well, I want to thank Robert for that question. Also about IVIG, we've gotten a question in about that, so I want to thank for that submission. Just one thing is, you know, many people with CLL are older. They have grandchildren who have colds and things like that. Either during treatment or at other times you say, well, grandpa has CLL and shouldn't be around little Suzie who has a cold or things like that. Anything about relationships people have they have to be careful about?

Dr. Sharman:
You know, I think it's hard to make a sweeping proclamation with everybody, and I try to tailor that to the patient who is with me. Some patient who has a track record of frequent upper respiratory infections may be on treatment and sickly, I might tell them to stay away from Suzie, but outside of that scenario I kind of oftentimes tell my patients about a neck check. If people have sniffles and stuff like that, well, it's probably not going to get you into trouble. It might make you uncomfortable.

But if somebody's feverish and coughing and, you know, possible pneumonia, stuff like that, I might give them a wider berth while you're on immunosuppressive treatment. But again not all treatments are the same.

Andrew Schorr:
I want you to know I've been on some long flights. We went to a wedding in India. I thought should I wear a mask? And I always said no, like, don't worry about it, no. I'm fine. I came back fine. All right. Let's go on, and if you have questions I want to thank you. We won't get to all of them, but we're going to buzz through a bunch. And again you can submit questions now. Here [are] some that we've received.

This one is from Richard. So he said—you know, things have changed now—he said, "For patients who are on inhibitor treatments who still have some minimal residual disease should transplant be considered?" And again knowing transplant has been the big gun, if you will, with toxicity.

Dr. Sharman:
Yeah. Boy, I think that that is one where—very difficult discussions. I think you could find experts in the field with differences of opinion. The only place where I would be trying to get somebody to transplant currently would be in somebody either intolerant or refractory to a BTK inhibitor if I couldn't get them on a Bcl-2 inhibitor, who is also young enough to get the therapy. And if I could just back up there.

Transplant is the big gun, as you said, and the challenge is you will have a substantial number of patients not survive the treatment itself. And so it's a very high-risk proposition, certainly not one that I would use MRD as a guide point, because, you know, this is somebody who you're struggling to control that might be appropriate. Because if maybe one out of five patients doesn't survive the treatment, it's not like we're talking about a 1 to 2 percent mortality from that. So very high risk, and even if you do survive it, oftentimes you'll survive it with life-altering side effects…

Andrew Schorr:
Yeah.

Dr. Sharman:
…chronic graft-versus-host disease and so forth. So I would have to have a pretty strong reason to be sending somebody to transplant.

Andrew Schorr:
Okay. Let's go on. Barry sent in this question. He said, "I was diagnosed with CLL in mid-2009 and I'm still in stage I, but at the time I was told the average CLL patient lived eight-and-a-half years. Is this true?" Or basically, are we rewriting the natural history of CLL?

Dr. Sharman:
How long ago was he diagnosed?

Andrew Schorr:
2009. That's what he was told.

Dr. Sharman:
Well, he's only got about two years left, so we better move fast, right?

Andrew Schorr:
Yeah.

Dr. Sharman:
No. You know, those numbers are inherently retrospective, so that is based upon data look backwards. You say when were patients diagnosed, how long did they survive? And virtually all of those numbers are based upon the pre-inhibitor

era, if you will. The pre-BTK, the pre-Bcl-2, the pre-CAR-T, pre—you know, any of this, such that if I meet a patient today, I can't tell them what their survival is.

It's no longer—I mean 8.5 would be pretty much a worst-case scenario. There are patients who do worse, really ultra high-risk disease, but in the era of new drugs we are rewriting these rules, because we won't know average survival until we've incorporated all these new therapies into the natural treatment history for patients.

Andrew Schorr:
Jeff, I've been talking to a number of CLL folks here, and they're starting to use this C word we haven't heard before, and that is can they see with everything coming together and new combinations that may be tried in clinical trials, etc., where we can knock this disease back, maybe immunotherapy on top of it, where we can actually have C mean not cancer but cure?

Dr. Sharman:
Yeah. I thought you were going to say carrots.

Andrew Schorr:
No, no I'm saying cure.

Dr. Sharman:
So let me take you a slightly different direction with that answer. It's hard to know what cure is until it's been proven for a long time, right? And so with these new agents the best we can say are rates of minimal residual disease, which you got to get there before you get to cure, but we will not know about cure based on novel agents for a decade. It may be that we can get there, and maybe if not cure, maybe control.

I don't think we are curing patients with BTK inhibitors, I don't think we're curing patients with PI3 inhibitors, but start adding them together in appropriate patients I would say I think we're starting to ask those questions.

But let me—let me go to the harder part. It's easy in the excitement of all of the new drugs to throw the baby out with the bath water, and good old-fashioned FCR, a drug combination that has sort of held the high grounds for 10 to 15 years…

Andrew Schorr:
I've had no treatment for 15 years…

Dr. Sharman:
Yeah.

Andrew Schorr:
…with FCR.

Dr. Sharman:
A drug combination that held the high grounds has been falling. However, there have been two publications within the last several months to show in appropriately molecularly selected patients rates of 8-, 10-, 12-, 14-year minimal disease negativity is obtainable. And at some point, you start asking is this a cure because it does—there's this feature called a Kaplan Meier curve, and the Kaplan Meier curve shows rates of progression over time. And every time there's progression the curve goes down, and add enough patients and you see a line that comes like this. When we begin to see a plateau in the curve, meaning it levels out, there are no more events dropping, that's our scientific clue that we're seeing a cure.

Now, in the MD Anderson group, that rate was maybe only about 30 percent of patients. Although 30 percent is a big number, what's more important is if you look at the molecular sub-groups, those patients who have IgVH mutated do much better than those who are unmutated, and those patients with favorable FISH changes, 13q, trisomy 12, these patients have the best outcome. And, in fact, in the German CLL 8 study they're reporting 8-year survival rates of 100 percent

following FCR in a large study in patients with some of these favorable risk groups. So I think cure is not only possible but in the right patients with the right treatment probable.

Andrew Schorr:
My wife is listening to that carefully, I'm sure.

Dr. Sharman:
Yeah.

Andrew Schorr:
All right. Let's go on. And, Barry, hopefully you got your answer, and hopefully you'll have a long life and not be concerned about what you've been told about that eight-and-a-half year number.

All right. Here's a question from Colin, and Colin wrote in and said, "Can the markers resulting from a FISH test change over a period of watch and wait?" I know they can change as treatment happens, but during watch and wait time or during treatment as well, and he says that FISH testing results are becoming more important in treatment decisions. So talk about FISH and where that test comes in.

Dr. Sharman:
So IgVH—not what you're asking me about—but IgVH is constant. Is does not change except under vanishingly rare circumstances where maybe there [are] two different diseases and so forth. For the most part, IgVH once there is always stable.

FISH changes. The most common time FISH changes is following treatment. So if you eradicate 99 percent of the disease with some sort of therapy, that 1 percent that survived is selected for, and whatever the FISH characteristics that percentage may then go on to repopulate the—relapse.

Andrew Schorr:
Those molecular survivors..

Dr. Sharman:
Those are the survivals, survivors, yeah. And so there is sort of survival of the fittest, and so generally we see higher rates of adverse features with relapse disease than previously untreated. 17p for instance in frontline is 5, 6, 7 percent. In relapse studies, it's as high as 30 percent, because it enriches over time.

The question this individual is asking is a little bit different, can it evolve during watch and wait? The answer is yes. It's not as common to happen, and for that reason there can be some variation in practice patterns amongst thought leaders. Some will do it right before they treat somebody, some will do it maybe when it's diagnosed and then redo it later, but I will tell you in community practice, where I practice, we've looked across practice patterns, and FISH is significantly underperformed. Meaning prior to first-line therapy it's only about 65 percent of patients get it done, and in second- and third-line, going out to third-line it's perhaps one out of three patients is getting it redone. So we're not doing FISH enough as a practicing community.

Andrew Schorr:
Okay. So ask for your FISH test. There are other tests that are more just research oriented, but FISH throughout the CLL world, people should be asking for that.

Dr. Sharman:
Yeah.

Andrew Schorr:
Okay. Now, we were talking about FCR a minute ago, and our friend Michelle wrote in. She's actually going through a trial now, FCR plus ibrutinib, I think. She's in a clinical trial.

Dr. Sharman:
Yeah.

Andrew Schorr:
But the point is what we've wondered about FCR, and I had it, and I did, maybe not connected at all, years later developed a second cancer, myelofibrosis. People with any kind of chemo-based treatment, am I at a higher risk for a second cancer? Or because I'm a cancer patient to begin with, am I at risk of a second cancer?

Dr. Sharman:
Yes, which is—which is…

Andrew Schorr:
Okay.

Dr. Sharman:
It's a complex question. I say that sort of yes to multiple questions in there, because the subtleties are worth getting into. Patients with chronic lymphocytic leukemia even untreated are at higher risk of developing second cancers. It is probable, however, that certain treatment combinations may render patients more at risk for secondary malignancies of which FCR is probably one of them. We see with long-term follow-up rates of secondary cancers along the order of 5 to 10 percent, which is actually not a trivial number.

Now, have anybody in their 60s and 70s survive another 10 years, and you're going to see cancers just because cancers happen. So how much of that is attributable to the treatment versus natural history versus complications of CLL I think can be a little bit difficult to disentangle, but I think amongst practitioners in the field the thought is FCR may be higher risk/higher reward, and therefore most appropriate for those patients who are molecularly selected.

Andrew Schorr:
Okay. William sent in a question. He says—well, actually we're going to not do this one.

We're going to go Eileen, says, “Is a drop in platelets a normal side effect of ibrutinib, and if so how do you handle that?”

Dr. Sharman:
So it is not a common side effect, however it has been seen. And remembering that the Btk enzyme is within platelets as well, the mechanism by which Btk can lower—BTK inhibitors can lower platelets is not well characterized. We've always thought that perhaps it may qualitatively affect the way platelets function, but not quantitatively, although there are some patients who clearly do.

How do you manage it? There are not clear guidelines. I think a lot can vary based on the individual. Are they on aspirin, are they on Plavix, are they on Coumadin, anything else that would potentially lower bleeding. We also don't like to do treatment interruptions in ibrutinib if we can avoid it, or very importantly we try not to do dose reductions in ibrutinib if we can avoid it because we know that that's not good either. So we may start to be sort of trying to pick amongst the lesser of two evils. And with a specific patient like that I can't make a recommendation. I would sort of have to qualitatively see, but it has been reported amongst Btk inhibitors.

Andrew Schorr:
Okay. Here's a question we got from someone who is watching on line now. They didn't want to give their name, but they said if their spleen is enlarged, which happens in CLL, what happens if the spleen is removed, to the CLL? So you take the spleen out, does it make the CLL worse, better, what does it do?

Dr. Sharman:
I wouldn't ever use that specifically as a treatment of CLL. Although the enlarged spleen is undoubtedly a home to a lot of CLL, removing it doesn't do anything to treat the marrow and the lymph nodes and so forth. And the spleen, even if compromised, probably does have some residual immunologic function and support, so I wouldn't do it just for the sake of doing it.

If somebody needs their spleen out sometimes perhaps because they have ITP, which is an immune-mediated attack on the platelets, or trauma, people can injure their spleen, it needs to be removed, you treat it—use it for those reasons. But in terms of how a spleen removal in somebody with CLL affects the natural history of the disease we don't think it has much of a role.

Andrew Schorr:
I want to mention—we just have a little bit more time. Someone just sent in a question now, from William, but if you have a question send it real quick on the Zoom page there, and also you can do it where you're popped up on your webcam as well. Okay.

So William sent in this question. I'm 11q—I guess he meant…

Dr. Sharman:
11q deleted, yeah.

Andrew Schorr:
…11q deleted, so one of the subtypes of CLL, 72 years old and I'm relapsing after having a remission from FCR. Can you give me advice, in his situation, as to Phase II or III trials that he maybe should be discussing or seeking?

Dr. Sharman:
Yeah. This is a perfect patient for either of those two high-risk studies we talked about. The TG therapeutic study, ibrutinib plus or minus ublituximab would be a great option for such a patient.

For somebody who is relapsing with 11q, I don't think that chemotherapy is the right answer, and we do know that patients with 11q, they do better on ibrutinib than anything they've done historically. But amongst patients with 11q, they don't do as well on ibrutinib as they would if they didn't have 11q. Does that make sense?

Andrew Schorr:
Yeah.

Dr. Sharman:
So that would be a patient who would be perfect for the TG therapeutic study if somebody was in that. That's a study open really broadly throughout the United States. Similarly another study that we talked about previously also in the high risk is ibrutinib versus ACP-196. Both of those would be great studies for a patient similar to that.

Andrew Schorr:
Okay. We're going to close in just a minute. I want to put in a plug for clinical trials and also seeing a CLL specialist. So, Dr. Sharman obviously is, and he helps educate physicians around the world as well. Here at ASH, we've been interviewing your colleagues as well, but these are all CLL subspecialists. And I think, wouldn't you agree, that with the pace of change it's really good to check in with somebody like you? You know about the trials, you're seeing the changing landscape. I know you're counselling your colleagues throughout US Oncology as well so that what you're learning helps them.

Dr. Sharman:
I mean, I think that this is a very dynamic field, and I think that it is very hard as a patient to evaluate the ability of your own physician to render knowledge in this field. It is a hard thing, and I don't even know how to tell you to evaluate your own doctors. I think some very—if you're concerned or uncertain that your doc has that knowledge, I don't think it's wrong to ask questions. If I think if they're not ordering FISH, I think it's fair to request FISH. And if they're not getting FISH or they're dismissing it, maybe that's a clue that—you know, that might be a concern.

You know, I work in a community practice network, and so I'm a community practice doctor. I see my own patients in Eugene, and I know that many of the research-oriented physicians that I work with throughout the country within community practice can do a fantastic job. But I also acknowledge that there are a lot of docs out there who may only treat a small number of CLL patients in a year.

And maybe that's the question to ask. How many CLL patients do you treat per year? Hopefully, you get an honest answer. But if that number is less than, say, six to 10, that might be a good clue that somebody might be—have their treatment interests elsewhere.

Andrew Schorr:
Okay. As always, Dr. Jeff Sharman from US Oncology, thank you for being with us. I will be doing an interview with Dr. Sharman you'll be able to see on Patient Power. We have interviews with a number of other CLL specialists. We recorded a roundtable today with Dr. Wierda, Dr. Tam from Australia, who was very involved in venetoclax early on, and also Dr. John Gribben from England. So wherever you're from we're gathering this news, and we'll be bringing it to you. It will be posted on Patient Power.

Also there's a live update today at 5:30 Eastern and also tomorrow so tune in for that. So thank you for being with us. We'll post a replay of this. You can share it with others you know, your support group, and even maybe with your doctor. Thank you for joining us. And, Jeff, thanks once again.

I'm Andrew Schorr on location in Orlando at the ASH meeting. Remember, knowledge can be the best medicine of all.