CLL Global Research Foundation Virtual Town Hall | January 27, 2026

Jamie Forward: Hello, and welcome. Thank you for joining us for the first CLL Global Research Foundation virtual town hall of 2026. I'm Jamie Forward. I know you're used to seeing Jeff Folloder here. He has a conflict today, so I'm going to keep the seat warm until his return at our next event. So, today, we're going to be discussing recent news and updates in CLL research and treatment, and, of course, we'll be answering your questions. Before we get started, let's just review a few housekeeping items. We've received many questions for our experts.

We'll do our best to get to as many as possible, but keep in mind that we cannot answer specific questions about your medical treatment. Those should be discussed with your own healthcare team. You'll also receive a survey following this town hall. Please share your experience with us, so we can continue to improve our programs for you. Now, let's meet our guest for today's program.

First I want to introduce the president and CEO of CLL Global, Dr. William Wierda. Dr. Wierda, could you please welcome our audience?

Dr. William Wierda: Welcome everyone from chilly Houston, Texas, and thank you, Jamie, for filling in. It's a pleasure to see you and Dr. Ferrajoli this afternoon.

Jamie Forward: Thank you, Dr. Wierda. We're also joined by Dr. Alessandra Ferrajoli from the University of Texas MD Anderson Cancer Center. Dr. Ferrajoli, can you please introduce yourself?

Dr. Alessandra Ferrajoli: Thank you, thank you for the invitation. I'm Alessandra Ferrajoli. I'm one of the CLL physicians here at MD Anderson, and I work closely with Dr. Wierda on many aspects of the care of our patients with CLL.

Jamie Forward: Thank you so much. Okay, well, let's move right into the discussion. So, Dr. Wierda, just this last December, cancer

experts gathered from around the world to share their research at the American Society of Hematology annual meeting, also known as ASH. Can you share some of the highlights from ASH with our viewers as well as any other CLL research updates?

Dr. William Wierda: I would be happy to do that. I have some slides because most of us are most comfortable talking with slides. As you indicated, every year we have a large meeting, and I think most of the participants probably are familiar with that, that we are reviewing both benign and malignant hematology advances and research. And the most important findings are being presented at this meeting, and that's the American Society of Hematology meeting.

So, I have two slides that summarize the highlight presentations that were made at the December meeting, and I'm just going to walk through each of those to give you an idea of what was presented and what we're talking about this year, what we talked about last year, I should say, December 2025 at ASH.

And I've divided these into two slides, one for previously untreated patients and one for previously treated patients, and I'll just walk again through each of those. So, the first item there is a trial that the German CLL study group has done called CLL-17. The first time it was presented was at this last ASH meeting. That was a randomized trial of different treatments for patients with CLL, no chemotherapy and patients would receive either ibrutinib (Imbruvica), ibrutinib plus venetoclax (Venclexta) or venetoclax plus obinutuzumab (Gazyva).

This was actually a plenary presentation, meaning it was the top of the top presentations. There's a plenary session where the top of the top data is presented, and this particular abstract was presented as a plenary session, and it demonstrated the outcomes were similar in terms of progression-free survival between all three of those treatments for patients who received them in the frontline setting.

And I think it does support an approach of fixed duration treatment, meaning treatment to get patients in a

remission and get them off treatment, so they can enjoy their remission with a reasonable expectation of a long progression-free survival or long remission duration. And that you could achieve similar outcomes at least with a follow-up that we have from this study if patients receive venetoclax-obinutuzumab compared to if they receive ibrutinib continuous treatment, for example. And so that was an important trial.

I think for me it will also be important to see what the follow-up is from that trial because it's a frontline trial. In order for us to get a full understanding of the impact of a treatment and the value of a treatment in the frontline setting, we need a long follow-up to see how long those remissions last and how patients do long-term.

Moving to the next trial, this was two Phase III trials actually that looked at pirtobrutinib (Jaypirca) in previously untreated patients, and those were CLL-313 and CLL-314, both randomized Phase III trials that were done by Eli Lilly. In 313, patients were randomized to receive treatment in the frontline setting with either pirtobrutinib, which is a non-covalent BTK inhibitor that we associate with better tolerability, less side effects and toxicities, a low risk for atrial fibrillation compared to ibrutinib and the other second-generation BTK inhibitors that are covalent BTK inhibitors.

And so that was one trial that was presented with pirtobrutinib. Frontline, it demonstrated improved progression-free survival for patients who received pirtobrutinib compared to chemotherapy or bendamustine (Treanda) plus rituximab (Rituxan).

The BRUIN CLL-314 trial was a trial that randomized patients between pirtobrutinib versus ibrutinib. And it was a mixed population, 30 percent of them had been previously untreated, 70 percent of them were previously treated, and that was a noninferiority trial that was intended to show that the outcomes were no worse with pirtobrutinib compared to ibrutinib in the frontline setting. And, in fact, there were trends of improvement in outcomes for patients who received pirtobrutinib over ibrutinib in that analysis. Again, we need longer follow-up.

The follow-up was relatively short, but these two trials are encouraging data looking at more selective BTK inhibitor, pirtobrutinib being used in the frontline setting and the impressive tolerability with that agent and efficacy. Moving down to the next trial is a Phase III trial called FLAIR.

There were several abstracts that were presented, three of them, in fact, related to the FLAIR data. The FLAIR data highlights the regimen of ibrutinib plus venetoclax where that combination is given from two to six years. It's based on MRD response, and the data continued to be impressive and confirmed the improved outcomes for patients who received the combination of ibrutinib and venetoclax. Not currently approved in the FDA, but it is on the NCCN guidelines.

I think the main concern with that regimen has been the use of ibrutinib and the toxicities we see with ibrutinib. Nevertheless, it's a very effective combination. We've done work with ibrutinib and venetoclax, and we will continue to see updates from that data that has been very positive. There's a Phase II trial with sonrotoclax, which is a newer BCL2 inhibitor that work similar to venetoclax where a combination was being tested of sonrotoclax plus obinutuzumab.

This appeared to be a well-tolerated combination. The follow-up is very short in the presentation of this Phase II data, but it is encouraging and the responses were encouraging. We'll see what the longer follow-up with that combination looks like in the frontline setting. Dr. Jain from MD Anderson presented an updated presentation on our Phase II trial with pirtobrutinib, venetoclax, and obinutuzumab, which has been evaluated in the frontline setting. He reported on the responses among 80 patients who received it as their first treatment.

It's 13 cycles of combined treatment. The outcomes have been exceptionally good where almost 90 percent of the patients consistently achieved undetectable MRD remission by the end of treatment.

And so, we're excited about this combination. It's probably the most effective combination that we've tested, and we're excited to see what the follow-up will be for those patients, but a very high undetectable MRD rate by clonoSEQ, which is the most sensitive measure of minimal residual disease, and again I mentioned that that's 90 percent MRD-undetectable by clonoSEQ. Dr. Ferrojoli, in fact, has a trial with that same combination for previously treated patients, and so far, I'm encouraged by the patients that I've treated on that combination, and we're seeing good outcomes for those patients.

The last item on that list is our Phase II trial with acalabrutinib-venetoclax (Calquence-Venclexta) with or without early obinutuzumab, and the update from that presentation that Dr. Swaminathan made on our study was that obinutuzumab could be delayed.

Administration in that combination could be delayed till later, the first six months of the second year on treatment, and if that was the case, it was equally effective and perhaps had less associated side effects and toxicities associated with it. And so, we haven't published that data yet, but we're in the process of summarizing it. Moving into relapsed and refractory disease, I mentioned the Phase III BRUIN CLL-314 trial pirtobrutinib versus ibrutinib demonstrating noninferiority of pirtobrutinib over ibrutinib, and, in fact, response and progression-free survival perhaps better for patients who received pirtobrutinib over ibrutinib.

Lisaftoclax is another BCL2 inhibitor that's been developed by a company by the name of Ascentage. There were data presented on a Phase II trial with lisaftoclax as monotherapy. We see activity with that compound in previously treated patients with CLL.

And that development continues including in combination trials, combination with acalabrutinib, for example, is being evaluated with lisaftoclax. The next item is a Phase I trial. I spelled it incorrectly. It should be rocbrutinib, R-O-C, not R-O-X. Rocbrutinib has been known previously as LP-168. That's a BTK inhibitor that works both covalently and non-covalently that's in development and Jen Woyach

presented an update on that compound.

It appears to have activity including in patients who have resistance to covalent BTK inhibitors like acalabrutinib, ibrutinib, zanubrutinib (Brukinsa) and including patients who have various mutations in BTK that have been associated with resistance to covalent BTK inhibitor. So, you'll hear more about rocbrutinib in further development. It has activity particularly in patients who are failing covalent BTK inhibitors.

There are two degraders. Actually, there are three BTK degraders in development. We heard presentations on two of those, BGB-16673, which is being developed by BeOne, and bexobrutideg, which is NX-5948 being developed by Nurix. The data that were presented were expanded Phase I, cohorts of patients who received in the relapsed setting either of these two BTK degraders.

And we're seeing activity in patients who are treated with both of these agents either the BGB-16673 or the bexobrutideg particularly in patients who have failed a covalent and noncovalent BTK inhibitors and patients who have various mutations in BTK associated with resistance to the inhibitors.

The degraders work differently than the inhibitors. The inhibitors will bind to the BTK protein and block the enzymatic function of BTK. The degraders bind to the BTK and cause the cells to degrade the protein so they eliminate the protein, which is different than inhibiting the function. And I think these drugs will be very important as treatment options for patients who have had our inhibitors and have developed resistance to inhibitors.

There was an abstract presented as a real-world experience with the liso-cel (lisocaptagene maraleucel [Breyanzi]) or CD19 CAR T-cell therapy where in the real-world experience in patients who have received that treatment, the response rates have been higher than what was reported on the liso-cel TRANSCEND CLL 004 trial, and so that was encouraging data because it looks like the use is better in the hands of the community or the centers that are using it than what we have reported for the clinical

trial.

Then, there were two trials that were presented for patients with Richter transformation. The first one was one that Dr. Jain presented from our group. It was a cohort of 15 patients with Richter transformation who received combined pirtobrutinib, venetoclax, and obinutuzumab. And so far, we haven't been impressed with the response rate with that combination and the durability of the responses. The follow-up is reasonably short, and the number of patients who've been treated are limited, but we're seeing activity with the combination.

It's very well-tolerated and so our work with that combination continues, and then the CLL study group presented an update on the checkpoint inhibitor with zanubrutinib-tislelizumab (Brukinsa-Tevimbra) with zanubrutinib for patients with Richter transformation.

And that's a nonchemotherapy option, has activity in treating patients with Richter transformation, and we've done work with nivolumab (Opdivo), and there are others that have worked with other various checkpoint inhibitors which appear to have activity in treating Richter transformation, not such great activity treating the CLL. There are a number of meetings coming up where we'll hear more data. Again, the big meeting for us is the ASH meeting, but we do oftentimes hear updates at these other meetings such as the European Hematology Association, meeting ASCO, the German CLL study group meeting, etcetera.

So, with that, I'll turn it over to Jamie again, and thank you for your attention.

Jamie Forward: Thank you, Dr. Wierda. So, Dr. Ferrajoli, let's turn to you for your take on CLL research. Can you share your updates?

Dr. Alessandra Ferrajoli: So, yes, thank you for the high-level view that Dr. Wierda gave us from the results from ASH. And I was asked to focus on a couple of updates, 1.) Is work from our institution that was sponsored by the CLL Global Foundation and that was actually presented as a Purdue

presentation by one of our fellows. So, we are very proud of this work. And it focus on our efforts in improving the compliance with vaccination and cancer screening in patients with chronic lymphocytic leukemia.

The reason why we did this work is because, as is known to this community, there is a very high risk that the immunodysfunction associated with the CLL can predispose people with CLL to the development of other cancer.

And there is also concern that the immunizations that are normally given to the individual may either be omitted or may not be considered so important for people that have CLL. So, we decided to initiate what we call an improvement project, a performance improvement project that looks at how to best make sure that everyone is up to date on immunization and cancer screening. So, what we did, we really looked at this over the years, and we wanted to see our reminders that were given as part of a survey as well as important reminders when the patients came to the clinic would change over time, again, how effective this strategy is.

And we also looked at seeing whether there were certain pockets of patients, certain type of patients that maybe were particularly behind in the immunization and the cancer screening. Now, when we initiated this project, we initiated it in June of 2019, so everyone can appreciate how this was a pre-COVID era. We didn't know that we would be going through a pandemic.

And so, we didn't know that besides assessing the efficacy of our initiative, we will also be going through some times that are changing and changing in terms of also the attitude toward vaccination as well as the real physical accessibility to medical facility and the risk of being seen in a medical facility.

So, we really didn't expect to conduct the survey during this time. But this gave us additional information and I think valuable information. So, the group is pretty large, more than 1,000 patients, and those are the characteristics of the people that received at least one of

our surveys. And just to summarize, I brought some examples. For example, we looked at the compliance with the influenza vaccination and as we can see, we had very high compliance prior in the year 2019 to 2020.

However, the compliance decreased a little bit to a lower level in 2023 and 2024, and we attributed this to a general maybe skepticism and tendency to not want to receive vaccination unless absolutely necessary.

So, what we see is that it ran over time for influenza vaccination is toward a decline in the use of this vaccination. Very different was what we saw with the COVID-19 vaccination where we had a very high vaccination rate when the disease initially presented, obviously, because this is a way to assist in building the herd immunity and in really increasing the ability to defend against the vaccination. And then, we have seen a decline and kind of a plateau reached in COVID vaccinations.

So, I would say that the COVID pandemic has had an effect pretty large on vaccination, however, when we looked at the influenza vaccination, we did see that our strategy of administering a series of surveys and mostly reminding the patient about the importance of this vaccination, did improve the compliance and the completeness of the influenza vaccination.

So, I would say this demonstrated that adding attention in the clinic and discussing vaccination gives results with improved vaccination, which was something very different instead with the cancer screening trends. What we see is we look at the mammogram on the top and the colonoscopy on the bottom, and we were able to note that while during the COVID pandemic, there was a decline in the completeness of the cancer screening. This rebounded to values that are similar to pre-COVID or even higher.

So, this in terms of cancer screening was really related to accessibility and the risk to be in a medical facility and undergo testing. So, there was more a delay related to the pandemic rather than a decrease in the use. And also, for

this, we noted that repeating a series of surveys really improved, as we can see, improved the number of patients that undergo screening. Examples of this are the skin cancer screening and the PSA screening.

So, basically, what we concluded was that a very simple health maintenance survey that can be repeated at every visit and a particular attention to focusing during the visit carving out a little portion of the visit to review what we call health maintenance will improve the vaccination rate and the cancer screening rate.

We also noticed though that there were some differences according to the characteristics of the patient. The older patients tended to have a better adherence with these recommendations. And we also noticed that even if in CLL, we see that the majority of the patients tend to be white, there was a lower skin cancer screening and a lower rate obtaining PSA screening for the patients that were of different ethnicity. So, this is particularly important to be reminded.

So, again, this was presented as a part of my presentation and its work sponsored by the CLL Global Research Foundation that we are very proud of. And we are going to take this concept of improving health maintenance, improving cancer screening to a higher level.

We were able to receive funds from the National Cancer Center Institute to allow us to test if using a test that is called multi-cancer early detection test. That is a test based on molecular sequences that are present in the blood and they can be used to identify up to 50 different types of cancer. This is, of course, due to the advances that are being in much learning in medicine, and so we will be offering to our patients with CLL to give us an additional blood sample. This will be analyzed for the presence of any cancer signal, and then we will be recommending additional testing as needed.

The reason why we want to do this, this is an example of a case, is because this multicancer screening test have been particularly useful in identifying cancer at early stage and particularly cancers that tend to be aggressive in nature.

So, we will like to be able to identify any potentially aggressive cancer very early in our patients as it was done on these patients where a cancer of the tonsil was identified very early, and therefore could be treated in a much earlier phase than if we wait for that cancer to become manifest and give symptoms.

And then to conclude the part that was assigned, I was assigned to again highlight important studies at ASH.

And the one that made the plenary session and we were all very proud of seeing this study in the plenary session is the CLL17 trials. We were proud not only because it's a study in patients with CLL and sometimes CLL doesn't get necessary as much of the spotlight as some other condition, but also because confirmed the validity of some of the strategies that our institution has implemented for quite some time.

And that Dr. Wierda already reviewed with you using combination of ibrutinib and venetoclax, using triple combination with newer BTK inhibitors. So, what the CLL17 compared was the strategy of continuous therapy with BTK inhibitor toward the fixed duration therapy that the fixed duration therapy was the combination of a BCL2 inhibitor with an anti-CD20 monoclonal antibody or combining the two targeted therapies.

And as we can see, this as a very large study. Patients were randomized in two to three arms, and actually it was quite impressive that they were able to enroll almost 1,000 patients in less than two years. And it was mostly in Europe with some participation outside of Europe. Those were the hypotheses to see if fixed duration therapy would be as good as continuous therapy with ibrutinib, and the response to treatment that are in the slides, I think we all are aware and very happy that whatever strategy we use, we're going to see a very high response rate in excess of 80 percent for all the three arms.

And as Dr. Wierda mentioned before, some studies give us even response rate in the 90 percent and those treatments in particular when we look at the one that we are proposing as fixed duration, a combination of venetoclax

and obinutuzumab, and venetoclax and ibrutinib are able to give us undetectable measurable residual disease. That means we can really achieve deep remissions, a remission that can be sustained for quite a long time.

The results that were presented are actually quite early because for a study of this type, we already know that we will need a follow-up of at least nine years before we can see really more final results. And we can declare maybe one of the combinations superior, but that's nearly up to three years all the three strategies are very valid and effective.

And we notice our high is the overall survival and again, overall survival very similar for the three approaches. So, this concludes the presentation that I have.

Jamie Forward: Well, thank you, Dr. Ferrajoli. So, before we move on, Dr. Wierda, is there anything, additional information you'd like to share with the audience before we go to Q&A?

Dr. William Wierda: I don't think so. I think we can move to the questions.

Jamie Forward: Sure. Well, I want to mention to the audience that if you missed anything presented by the panelists today, the slides and a replay of this town hall will be made available on the CLL Global website at cllglobal.org in just a few days. So, let's move on to Q&A. As I said at the beginning of the program, we've received quite a few questions, and we're going to try to get to as many as possible. If you'd like to send a question in now, you can send an email to production@thehccollective.com.

So, let's start with this one. Dr. Wierda, what do we know about the impact of the COVID vaccine on CLL?

Dr. William Wierda: What do we know about the impact of the vaccine on CLL? We know that patients do get an immune response when they receive the vaccine. There are two vaccines that have been the predominant vaccines in use for most of the time during the pandemic and in the short period after the pandemic. Those are the Moderna and the Pfizer vaccine. Those are the mRNA vaccines. That’s a new vaccine strategy. We don’t have much long-term understanding of

complications and side effects and toxicities that patients and normal individuals, individuals who don't have CLL can have.

And so, I think repeated vaccination and long-term follow-up is a question that most of us are thinking about and are considering in our current strategy of what we recommend for our patients. Again, this is the first mRNA vaccine that we've had. The traditional type of vaccine that we have had has been the one similar, that's the strategy with the influenza vaccine, the flu shot. That's a protein-based vaccine.

Right now, there is a protein vaccine available for COVID-19, that's the Novavax. And so, for patients who are interested in boosters and revaccinating, my recommendation recently has been to transition more into the more transitional strategy of vaccination with the protein-based vaccine.

And again, that's the Novavax in preference over the mRNA vaccines. The other thing I would mention is that we have treatments for active COVID-19 infections. We have remdesivir (Veklury) and we have nirmatrelvir (Paxlovid), and so while it was initially a life-threatening diagnosis and illness, our patients do relatively well, in my opinion, these days with the vaccine strategies that we've implemented and the treatments that we have for patients who develop those infections.

Dr. Alessandra Ferrajoli: I may add that there were also studies looking at how the COVID vaccines work in patients according to what treatment they are receiving. Definitely, we see better responses in terms of antibody response for patients that received the vaccine before they start any treatment.

The lower level of responses are seen for the patients that are receiving monoclonal antibodies or they have received monoclonal antibodies recently. There were studies done looking at whether taking a pause on the treatment for CLL, in particular those studies were done with Bruton's tyrosine kinase inhibitors, would improve the response of the vaccination, and that was demonstrated not to be the case. So, it's important to remember that there is no need

to stop the treatment for receiving the vaccination because that did not make a difference.

But yes, being vaccinated, using the vaccine that is the best match for the current COVID strain is what we recommend. I agree with Dr. Wierda, we will like to keep receiving boosters and being vaccinated as much as possible.

Jamie Forward: Okay. That's great advice. So, there's a large cohort of patients who were on FCR trials. For those patients who had deep remissions but relapsed after many years, do you have any updates on the relapsed patients or basically how long does disease burden stay low? How many convert to high-risk CLL? Kind of a long question. Dr. Wierda, do you want to start?

Dr. William Wierda: Sure. So, we have a lot of experience with FCR. Dr. Keating developed the FCR regimen. The first trial with FCR was started in the 1990s, and so we have nearly 30 years of follow-up for some of those early patients who went on the FCR regimen. We know that it has a high response rate, a high complete remission rate, and a mediocre MRD-undetectable rate. The MRD-undetectable rate with six cycles of FCR is about 50 percent in the bone marrow.

We know from our long-term follow-up that we think about patients in terms of their IGHV mutation status where patients who have an unmutated immunoglobulin gene will generally be in remission for a reasonable period of time, but their disease pretty consistently will return and they'll need subsequent therapy. Like more than 90 percent of patients with an unmutated immunoglobulin gene will have their disease relapse and need subsequent therapy. And there is some variability in the length of that remission.

That's a little bit different than what we saw in patients who have a mutated immunoglobulin gene where about 50 percent of them will remain without relapse of their disease more than 10 years. And that's the group of patients that we've talked about potentially being cured with FCR because their disease isn't coming back for more than 10 years, and we're doing follow-up for those

patients now looking for MRD by flow cytometry as well as by clonoSEQ, the MRD-6 assay.

And we're in the process of summarizing some data that we've generated recently. I don't want to discuss that data yet. It's not published yet, but it should be coming out soon. It's interesting and gives some interesting insights I think into what remission means and what MRD means and its additional data that gives some insights into that aspect. Realizing that that's chemoimmunotherapy-based treatment, we don't use chemoimmunotherapy-based treatment any longer. We use targeted therapy.

And so, one question is: Will we see the same observations with the targeted therapy, the BCL2 inhibitor based fixed-duration treatment like venetoclax and sonrotoclax and lisaftoclax as we have seen with the chemoimmunotherapy?

So, it's been a very effective treatment, but chemotherapy in my mind is something that we should be avoiding because it has side effects and toxicities that we don't want to expose our patients to.

Jamie Forward: Sure, that makes sense. So, here's another question we received. A recent paper reported significant lower rates of AFib for patients on BTK inhibitors and GLP-1 agonists. What are the potential benefits of GLP-1 agonist for the CLL patient? Could there be a favorable improvement in the microenvironment that may discourage CLL growth?

Dr. Alessandra Ferrajoli: I can take this. I mean I'm not aware of any specific research that has demonstrated any **[inaudible] [00:39:54]** action; however, we do have a lot of experience with exercise. And the benefit that exercise does to patients with CLL not only improves the performance by reducing the level of fatigue, but it also helps the immune system, and we see better T-cell function and therefore it seems to be beneficial.

And by reflection, we have added it to our initiative for CLL that focus not only on exercise, but also on diet and maintaining a body weight that is as ideal as possible, and we have seen a significant improvement in the patients

that have been able to achieve those goals. So, I think I see those medications, at least the present time, as tools that can help the patient to reach a body weight that allows them to be more active.

And therefore, by being more active, there is a lot of benefit, not only in your cardiovascular system, but there is also a benefit from an immunological point of view and also from a point of view of any symptoms like fatigue that may be associated with your disease.

But I'll be interested in seeing if Dr. Wierda has anything to add to this.

Dr. William Wierda: I don't. I'm glad you took that question. That was a great answer. I liked it.

Dr. Alessandra Ferrajoli: So far, we've only had one patient that had an immune-mediated reduction in the number of platelets after starting one of those GLP-1 inhibitors. And many patients are using those agents. So, they seem to be reasonably safe.

Jamie Forward: Okay, that's good to know. So, Dr. Ferrajoli, this one's for you. This is from Michael. He says: How does a patient participate in the CLL survivorship program at MD Anderson. What trials can you share on survivorship and CLL?

Dr. Alessandra Ferrajoli: So, to participate, all our patients are invited to participate.

Then we do some selection where we have patients that have a particularly indolent disease where we want the focus on the visit to be more on health maintenance. So, we interact with these patients, and we have them to meet also with our nurse practitioner, Jackie, that is wonderful in focusing on all those points. So, there is no special requirements to participate. As far as initiatives, we have two initiatives right now. 1.) Is Health4CLL2. That is our second program that focuses on diet and exercise. And we have almost completed, but we are going to have a few more openings, maybe four or five openings.

So, reach out to us, reach out to me, and we will do all we can to enroll you, and then we have the testing with the CMED, the Multi-Cancer Early Detection testing that is our next initiative to improve the health of our patients and diagnose any possible other cancer early.

And this will also be offered to the patients that come to our clinic.

Jamie Forward: Okay, that's great information. So, Dr. Wierda, Karen sent in this question: As CLL NCCN guidelines are rapidly changing, do you have an opinion regarding the appropriate sequencing of treatments?

Dr. William Wierda: I have an opinion about what my recommendation is for sequencing. I will start by saying there isn't any data that shows that there is an appropriate sequencing. That's more based on patients and what the patients and the physicians identify as the priorities and how we want to manage the disease. There haven't been any trials that have shown that if you start with a BTK inhibitor for example, over a BCL-2 inhibitor-based therapy, there will be a difference in survival.

So, I would start by prefacing it with it's more of a preference and strategy. My preference and strategy is to start with time-limited therapy, a BCL-2 inhibitor-based therapy. I like the concept of having patients in remission, in a deep remission and off treatment for extended periods of time rather than being on a maintenance. You can always go back and retreat if the disease comes back after a long period of remission with venetoclax-based therapy, for example, and then, if you have a remission that's not as long as what you consider optimal, then you can always switch to the maintenance.

But if you commit to starting with a maintenance, you're pretty much committing to long-term maintenance therapy.

The median progression-free survival with ibrutinib, for example, is nine years. And so, if we start with a BTK inhibitor, pretty much patients will be on treatment for the remainder of their life if we start with a BTK inhibitor.

You might get a brief period of remission if you switch over ultimately to a BCL-2 inhibitor as opposed to starting with a BCL-2 inhibitor and leaving that an option to retreat later on. In those individuals, they will have extended periods of time off treatment. So, that's my preference is having patients in remission and off treatment.

Jamie Forward: Okay, great. Dr. Ferrajoli, this one's for you. Tim writes: Does vitamin D3 really help prolong the watch and wait period?

Dr. Alessandra Ferrajoli: No. But we do want patients with CLL to have normal vitamin D levels so, they should check their levels of vitamin D and use supplements as needed.

Jamie Forward: Okay, and a related follow-up question to that is: Is watch and wait still the safest option to follow if you're not having symptoms? What does the research show?

Dr. Alessandra Ferrajoli: Yes. The research shows again that in early intervention in a patient that has a regular prognostic factor it's not advantageous. And this was tested even with the new medications such as ibrutinib and was tested by the German cooperative study group and published last year in JCO. We can make a little sidenote and say that if patients have particularly high-risk factors, then maybe looking at the participation to an early intervention in a clinical trial is something that can be considered. But outside of a clinical trial for a very high-risk patient, we have again shown that there is no benefit in early intervention.

We also need to remember that there is a number of patients, about 20 percent or so that have the so-called smoldering CLL where intervention will not be needed ever. So, we don't want to take away this opportunity of not needing any intervention by coming up with a new rule that everyone needs to be treated.

Jamie Forward: Okay, great answer. So, we've received several questions about fatigue. So, Leo writes: How can I stop from being tired all the time?

Dr. Alessandra Ferrajoli: So, I'll take this one too. I'll volunteer myself. So, the first

thing we recommend is exercise. Moderate exercise done three times a week, appropriate for your level of fitness has shown that there is improvement in the level of fatigue because fatigue is most likely related to cytokine, cytokine levels that increase in our blood.

However, fatigue, a severe fatigue is a fatigue that affects your daily activities, can be a reason for starting treatment. And, in general, we do see an improvement in the fatigue level after treatment is started. Interestingly, that's not necessarily related to how deep your response is, so it may not be necessary to achieve a complete remission to obtain resolution of your fatigue. But just any intervention that we modify the CLL in the majority of the cases is also from a part of your fatigue.

Of course, you need also to make sure that your fatigue is not due to other causes such as thyroid dysfunction or having other components like an anemia or another concomitant condition.

Jamie Forward: Sure, and, of course, you started this with exercise which sounds counterintuitive but if you're thinking about it, what is the sort of base level? Is it a 20-minute walk? What would you suggest?

Dr. Alessandra Ferrajoli: A little more. We have done this study, and actually a resistance exercise is particularly useful. So, using like elastic bands, using some weight, doing some resistance exercise is useful as well, and then, of course, doing some cardio work that can be walking at a brisk pace for 20 minutes is recommended.

Jamie Forward: Okay, that's a good place to start. So, Dr. Wierda, is there any progress with immune reconstitution? Is it being worked on?

Dr. William Wierda: There haven’t been any strategies yet that have been identified for immune restoration or reconstitution.

The one strategy that we have used for several years now is for patients who have low antibody levels and have infections. If their IgG level is less than 500, they are candidates for replacement IgG with IVIG. Those are

infusions given once a month. They're usually most helpful during the winter months when we're at greatest risk for viral infections etcetera. We have a group at Anderson that we're working with, laboratory colleagues doing corelative studies to understand what are the mechanisms of immune dysfunction in patients with CLL?

And the next step will be to identify strategies to correct those features that are abnormal as strategies to have immune restoration.

It's been interesting to me; we have very effective treatments these days to get most of our patients undetectable with regard to CLL good deep remissions. Despite the fact that they're in a good deep remission, we typically don't see immune restoration back to normal; for sure not right away, and sometimes it takes years for immune restoration to occur, so patients are at persistent risks for infections and second cancers. So, this is a great area of interest for me and something that I'm spending a lot of time thinking about and working on.

Jamie Forward: Okay, great. So, Dr. Ferrajoli, this one comes from Shawn: What research is ongoing regarding hereditary propensity of CLL, and what progress has been made?

Dr. Alessandra Ferrajoli: So, I would say that this is a situation that is being increasingly recognized.

Over the years, there have been several papers that have shown that up to 10 percent of the patients with CLL are going to have a first or second-degree relative that either has CLL or has the precursor to CLL, the monoclonal B lymphocytosis or has another chronic lymphoproliferative disorder that is within the family of the B-cell chronic lymphoproliferative disorder like an indolent lymphoma. So, we are recognizing this more and more, and we are getting now into the genetic aspect of this. We just reported and the paper is going to come up any day on HemaSphere.

A group of patients with CLL that has familial CLL as a mutation in a gene that is called POT1. This gene has to do with a telomeres. Telomeres are structures that have to do

with really aging and predisposition to other cancers.

And indeed the patient that have POT1 mutation, they not only have familial CLL, but they have an increased rate for other cancers. So, yes, the research is going on. We at MD Anderson pay attention to this. We ask all our patients about their history of CLL, and we work with our hereditary leukemia clinic where we do referrals to our colleagues that focus on hereditary leukemia so that they can be done a full genetic assessment for the risk.

I would say that this is important not only for the patient, but it is very important for the family because making the family aware an increased risk for CLL and with it, sometimes an increasing risk for other cancer can really be helpful in performing the right level of screening.

And also making sure that when our, for example, the children of a patient with CLL have their routine health maintenance appointment with their doctor, a blood count is included in the assessment.

Jamie Forward: Okay. Great advice. So, the next one comes from Carol: My husband does respond to BTK inhibitors but has gotten AFib with Imbruvica and acalabrutinib. Are the newer BTKs better? Dr. Wierda?

Dr. William Wierda: Sure. So, pirtobrutinib in the randomized trial, for example, the BRUIN CLL-313 randomized trial where patients were assigned a treatment as their first treatment with pirtobrutinib versus chemoimmunotherapy, bendamustine plus rituximab, on that trial, the incidents of atrial fibrillation was the same in both of those arms. So, if you talk about BTK inhibitors, in my opinion, the risk is lowest with pirtobrutinib.

Probably next high is, and an increased risk for atrial fibrillation, although lower than ibrutinib, are the second generation BTK inhibitors, acalabrutinib and zanubrutinib. And, of course, ibrutinib is the one that has really been associated with highest risk for atrial fibrillation and cardiac events. So, pirtobrutinib would be the preferred BTK inhibitor to avoid any risks or as much risk for atrial fibrillation as possible.

Dr. Alessandra Ferrajoli: Just to comment, it also needs to be kept in mind that the expected risk for atrial fibrillation for a patient with CLL, just based on age and other conditions is not zero. There is a low risk that is common to the population with similar characteristics in terms of sex, in terms of age, in terms of presence of hypertension.

So, that has been demonstrated. But yeah, I agree with Dr. Wierda. It seems that the more selective the agents are within the BTK mechanism, the lower the risk is for atrial fibrillation.

Jamie Forward: Okay, great. So, we're going to take one last question. So, this one is from Larry: What is your view on the efficacy of consolidation therapy?

Dr. William Wierda: I'll take it, and maybe, Alessandra, you can add if you would like. I am interested in that strategy. Consolidation in my mind today for patients with CLL would be a strategy that we would add treatment to something that they're already on that's been effective at achieving disease control but not necessary a deep remission. We've done a couple of trials with that strategy.

And that would be a scenario where patients go a BTK inhibitor, their disease is controlled, they get into a remission but not a deep remission. And Philip Thompson initiated a trial several years ago where we added venetoclax in that setting as a way to deepen the remission where patients got combined BTK inhibitor plus venetoclax for one to two years, and 70 percent of patients became MRD-undetectable and came off treatment on that study and Dr. Ferrajoli has taken over that study and has updated it more recently. So, I'm a proponent of that strategy.

We can do that with the addition of venetoclax to a BTK inhibitor and the question is are there other strategies that maybe as are more effective than that like the bispecific antibodies or CAR T-cell therapy.

Dr. Alessandra Ferrajoli: Yeah, I agree. I agree with Dr. Wierda. I mean, we were able to test the addition of venetoclax to a number of

patients with ongoing treatment with ibrutinib, acalabrutinib, and zanubrutinib and so a significant benefit. Right now, the challenge is that as we move more to time-limited therapy, we tend to use multiple agents together upfront so the strategy for the consolidation need to switch more to either cellular therapy or bispecific or maybe other agents that are still in the earlier phase of development.

Jamie Forward: Okay, great. Well, thanks to all of you that submitted your questions. So, let's hear some closing thoughts from our guests. So, Dr. Ferrajoli, what would you like to share about the future of CLL research and treatment. Are you encouraged?

Dr. Alessandra Ferrajoli: I'm very encouraged. I think we have really reached what we call the functional cure where the majority of the patients with CLL are able to have a life expectancy, are able to have long life, and live a life that is full and that is an active life, and is almost always outpatient as long as we use all those very powerful treatments that we have. We need to use them wisely. We need to continue to do clinical trials to learn even better how to use it, but yes, the armamentarium for the treatment of this disease is really changing the history of the disease and has been very rewarding as a physician to be working in this field.

So, I see a very bright future. And then, of course, as the expectation for life increases, as we live longer, I do feel that health maintenance, cancer screening, immunization are becoming more and more important to be the other component that allows us to live long, healthy lives.

Jamie Forward: Well, that's very encouraging. Thank you. So, Dr. Wierda, what would you like to leave our audience with as we wrap up?

Dr. William Wierda: I completely agree with Dr. Ferrajoli. I think some of the things to keep in mind and to highlight are recent analyses have shown, in terms of overall survival, that patients who are treated including those with ibrutinib as their first treatment, have a life expectancy that is similar to that of age-matched, non-CLL individuals in the population. So, the survival now is exceptionally good even if patients

need treatment. I think working on optimizing that treatment, and for me optimizing that treatment is curing the disease.

And I think that will be possible with our combinations. We're still working on the combinations, but we've done very well with identifying very effective combinations with our more recent strategies. It's hard to think about how we can improve further on those. So, most of our patients are getting in complete remission, MRD-undetectable state, and we'll see what percentage of those patients are cured.

And as I mentioned a little while ago, we're still struggling with immune dysfunction in these individuals even they're MRD-undetectable, and so for me, the focus and the goal and the interest and all of the activity, much of the activity, I should say, is directed around understanding the immune dysregulation, the immune dysfunction and developing strategies for immune restoration. That will help us reduce the risk for infection and second cancers.

And probably will help with us improving the effectiveness of our immune-based treatments, CAR T-cell therapy and the bispecifics. So, we still have work to do. We're aggressively working on curative strategies. We're aggressively working on strategies to improve the quality of life, reducing infection and as Dr. Ferrajoli mentioned, I think we're in a situation where many of the patients experience a functional cure even if they're needing a maintenance-type treatment. So, things are good. We need more funding to do our research.

We're in an interesting era in our politics, and I think we need to be steadfast in our support of research and focus on making improvements for our patients. That's what's most important for us.

Jamie Forward: Well, that's a nice way to close, Dr. Wierda. So, I want to thank our experts for taking the time to join us today, and, of course, our audience for tuning in and submitting such thoughtful questions.

Don’t forget to fill out the survey that will follow today's

town hall. It will help us provide information that's important to you. I'm Jamie Forward. Thank you for joining us.

Dr. William Wierda: Thank you, Jamie.

Dr. Alessandra Ferrajoli: Bye everyone. Thank you, Jamie. Bye everyone who attended.

Jamie Forward: Thank you so much.