Waldenstrom’s Macroglobulinemia: Advances in Treatments

Waldenstrom’s macroglobulinemia (WM) is a lymphoma, or cancer of the lymphatic system. The disease begins in a type of white blood cell called a B-lymphocyte, which normally matures into a plasma cell. In WM, there is a malignant change to the B-cell and it continues to proliferate into a clone of identical cells in the bone marrow, lymph nodes and other tissues and organs of the lymphatic system.

The current standard treatments for WM consist of Rituxan (rituximab), Imbruvica (ibrutinib) combinations or monotherapy in the first- and second-line setting. Treatment is mainly focused on the control of symptoms and the prevention of organ damage.

The CureTalks panel talks to Dr. Larry Anderson of UT Southwestern Medical Center and Dr. Rachid C. Baz of Moffitt Cancer Center on the current standards of care for WM, as well as novel agents currently being evaluated. Joining the panel bringing in the patient perspective are advocates Meg Mangin and Peter DeNardis.

Full Transcript:

Priya Menon: Hello and welcome to CureTalks, I’m Priya Menon your host. Today’s Show is part of our Innovative Series where we discuss breakthrough treatments and research. The topic for today’s discussion is Treatment Advances in Waldenstrom’s Macroglobulinemia. Joining us on the panel are Dr. Larry Anderson, from UT Southwestern Medical Center, Dr. Rachid C. Baz from Moffitt Cancer Center, patient experts, Meg Mangin and Peter DeNardis. Welcome to CureTalks, everyone. Doctors between me, Meg, and Pete here we have quite a few questions. So, I’ll start with mine first and then hand it over to the patient’s panel for theirs’s. My first question Dr. Anderson is to you so that we get some basics straight before we get deeper into the discussion. What is Waldenstrom’s Macroglobulinemia and what causes the condition?

Dr. Larry Anderson: Great question. So just I’ll give a little primer answer on this. So, Waldenstrom’s Macroglobulinemia often referred to as WM or sometimes Waldenstrom’s is a rare cancer of the bone marrow and lymphatic system. It’s a subtype of non-Hodgkin’s lymphoma. But instead of starting from a regular B Lymphocyte like most other lymphomas, WM cells come from lymphocyte that is in a partial differentiation state between lymphocyte and a plasma cell. So, WM is sort of like an overlap or a cross between lymphoma and multiple myeloma in which multiple myeloma is the cancer of bone marrow plasma cells. So, WM shares some of the treatments with both of those disorders, and also because these cells are in between a lymphocyte and a plasma cell they’re often called lymphoplasmacytic cells. And another name for WM is lymphoplasmacytic lymphoma, so you’ll hear that term, otherwise known as LPL. There are some versions of lymphoplasmacytic lymphoma that make a different type of protein from Waldenstrom’s. So, they’re not all the same but Waldenstrom’s fits under the lymphoplasmacytic umbrella. The WM cells are, however, are known for making a certain type of protein called Immunoglobulin M or IGM and usually in large amounts and this protein is also known as macroglobulin because it’s five times bigger than an IGG or Immunoglobulin G made by myeloma cells. And so, it’s a lot larger protein or macroglobulin. But all the IGM made by these Waldenstrom cells is of the same exact size. And so, it’s referred to as monoclonal protein or M protein. In the build-up of this protein in the blood and the patient can lead to sludging of the blood known as Hyperviscosity in which the patient could have bleeding problems or visual disturbances. It could cause nerve damage; it can cause stroke-like symptoms and so hyperviscosity is one possible symptom. Many of these patients, however, present with symptoms of crowding of their bone marrow with these Waldenstrom

cells, they crowd out the normal cells and cause anemia or low immune system, therefore increasing the risk of infections. And only about a quarter of the patients with WM will present with enlarged lymph nodes and spleen, which is different than most other lymphomas. WM is only diagnosed in about 1,500 patients per year in the U.S., typically between the ages of 60 and 70 with an average of about 65, and less than 1% of patients are under 40. Although we certainly see it and it's often slow-growing. And we do have many treatment options. And so, these patients often have quite a long survival. But right now, it's not a curable disorder with the current therapies, even though we can control it for many years. And the next question is, what causes Waldenstrom's. Now, we don't really know. There's no specific cause known for Waldenstrom's. However, it does often arise after patients have a precursor condition known as IGM MGus or monoclonal gammopathy of undetermined significance. Possible risk factors include male sex, Caucasian race, increased age, family history of Waldenstrom's, presence of chronic hepatitis C or HIV infections, and possibly exposure to certain chemicals. Waldenstrom's is twice as common in men as women and more common in Caucasians than other races. There is a familial predisposition Waldenstrom's in that about twenty to twenty-five percent of patients with Waldenstrom's will have a primary relative, a first degree relative with some sort of B cell cancer either Waldenstrom's or lymphoma or myeloma, but there's not really a genetic mutation that we can test for to see if their families at risk at this point.

Priya Menon: Okay. Dr. Baz, I would like you to add to the general understanding what is the current frontline treatment for WM?

Dr. Rachid C. Baz: Yeah, I think the main thing is that there isn't one specific treatment that's going to fit all the patients. And I think a lot of the choices for frontline therapy will depend on the patient's characteristics, what is the indication to treat and whether there is an indication to treat in the first place. So, a lot of patients who are asymptomatic may be observed without receiving treatment. For those who do need therapy then the only approved agent currently in order two only approved agents in the US are Ibrutinib and Zanubrutinib. However, that's not the only therapy for Waldenstrom and sometimes especially in older patients we may elect to think about other therapies as a first-line and reserve those agents for subsequent lines of therapies. And there are some specific features on the presentation, whether it's Mag neuropathy only or whether it is mild anemia, how high the IGM level is that can help guide the treatment discussion. But some of the agents that have activity include CD20 antibody called Rituximab some of the agents having activity, include alkylating agents. We talked about the BTK inhibitor, Ibrutinib, and Zanubrutinib and then there are proteasome inhibitors that have activity at times. So, there is a number of different therapies that one can consider. I don't think there is one standard approach for everybody in the first-line setting, but a lot of it will depend on what's going on with the patient.

Priya Menon: Thank you. Thank you so much for that summary. Meg, you are a WM patient, so would be great if you could share your Waldenstrom's treatment journey with us.

Meg Mangin: Okay, I was diagnosed in 2016 and my first treatment was Imbruvica or Ibrutinib. I was in a clinical trial, the trial for naive patients. It was working very well for the first three months, but then, unfortunately, I got some liver enzymes elevated and they just wouldn't go down. So, I had to stop the Ibrutinib and when I stopped it, I got a massive increase in IGM, probably tripled what I had to begin with, and I ended up having plasmapheresis to get that down. So, I could start on Bendamustine and Rituximab that I had for four cycles, and it worked very well and then I did go on maintenance for two years with Rituximab and that ended in 2019 in August, and I have been in remission since then. Numbers are good.

Priya Menon: That's awesome. That's great. Peter, what about you? You were diagnosed at the age of 43.

Peter DeNardis: One of those abnormal young people that get Waldenstrom's. So at least I broke the 40-year barrier when I was diagnosed, but I was heavily symptomatic at the time and was treated with probably things that are not used so much for the frontline. At that time, I was treated with Fludarabine, Cytoxan, and Rituxan. I got a good five or six years of remission out of that. And my IGM was very high when I was initially diagnosed. It was run the 6,000 level and I had all the classic symptoms, but then I had a relapse. And it was an unusual relapse with multiple things that were occurring at the time and so I was

treated again, but it was more to treat, not only rising IGM numbers, but also a mass right below my spinal column that we had ended up being lymphoplasmacytic lymphoma cells. And so, I'm one of those soft tissue tumor kind of people that have Waldenstrom's, and that's another unusual occurrence. So, we consulted with some experts, and my local hematologist had the right plan, which we did the high dose Cytoxan and some Rituxan, some dexamethasone, and also radiation to the location of that tumor. And then, so that was maybe 10 years ago. But in 2016-2017 I started to have some pain and so they thought it was a classic, what they called a schwannoma. It had all the earmarks that it was benign and everything else. So, when they went into surgically removed it, they said, oh, yeah, let's test that. It's lymphoma cells again and sure enough, it was the LPL. So, we just treat It with that surgery and where it's located. It's not a good spot to try and, yank it out of there, any further. So, we did some local radiation again, and since then I've been on Ibrutinib for the past two years, low dose to possibly keep that in check and we're just keeping an eye on it by PET scans and so far. I can't complain since 2010, my IGM has been virtually non-existent, all my Immunoglobulins are pretty much wiped out. So, I am an unusual case, but I've seen just about everything so far. So hopefully that's enough. And I'd like to keep it that way. In the meantime, I have been working with the IWMF volunteering because it's been a great resource for me. So, I wanted to return the favor.

Priya Menon: Thank you. Thank you for sharing that. I'm going to circle back to Dr. Anderson and talk about the novel drug CLR 131. Dr. Baz, I would like you also to chip in on this. So Dr. Anderson, can you give us all some background on this drug and the result of the clinical trials? And why do you see this as being very important?

Dr. Larry Anderson: Yeah, great question. So CLR 131, it's investigational cancer therapy. It's known as a phospholipid drug conjugate or PDC. This really takes advantage of this selective uptake and retention of phospholipid ethers or PLEs by cancer cells compared to normal cells. And they have these higher concentrations of lipid rafts on the surface of cancer cells compared to normal cells that allow the uptake of drugs that are conjugated to those phospholipid ethers. And CLR 131 in is an example of this it's designed to provide targeted delivery of radiation from iodine 131 to malignant cancer cells and therefore, minimizes radiation exposure to normal tissues. The reason it's exciting in Waldenstrom's is that there is some data presented at the American Society of Clinical Oncology meeting or ASCO meeting this year, in 2021 by Dr. Ailawadhi et al., and they showed that out of the first six patients with Waldenstrom's treated, with this compound, 100 percent of them had a response and they responded to the treatment. And so that's very exciting. And it's really, this ability of this first-in-class drug to work in Waldenstrom's, that appears to be independent of others whether they're sensitive to chemotherapy or immunotherapy. And it doesn't seem to matter if the patients have a different genotype or gene mutation status of their genes, which we call MYD88 and CXCR4, which do make a difference with other therapies like the BTK Inhibitors. So that sets it apart. Some of the preliminary findings that were presented were that out of these patients that responded 83% of them were previously, treated with Rituximab combinations and 100% were refractory or had sub-optimal response to ibrutinib. So, if patients do start to relapse after BTK Inhibitors then these trials would be a good option. And basically, they've also shown data that Waldenstrom's cells have an even higher concentration of these lipid rafts compared to other b-cell malignancies, which makes it particularly better and Waldenstrom's potentially. And what they saw was that there were really no, well there were side effects patients, most patients had low blood counts, either low white blood cells are red blood cells, but generally manageable and as blood cancer doctors were used to taking care of those side effects with most therapies, but fortunately, they did not see deaths from this, they did not see heart, liver, kidney, eye, neurologic toxicities that we worry about. So those were not seen and based on the results of this we're now doing a phase 2 kind of global pivotal phase 2 study, a registration study that's seeking to enroll about 50 more Waldenstrom's patients with relapsed disease.

Priya Menon: Dr. Baz, what about anything if you can talk a little bit about the mode of administration of this drug and those scheduled optimum dosing as well as probably the durability. What is the response? How durable of responses?

Dr. Rachid C. Baz: Yeah. I think, Larry covered the mechanism of action very nicely. This is a phospholipid drug conjugate. So, the active iodine is delivered to the cancer cell by virtue of the fact that the cancer cell

expresses more of those lifted rafts can internalize the phospholipid conjugate and radiation is an effective treatment for lymphoma Waldenstrom in particular and so that would be one way of tumor cell killing. What I find particularly neat about CLR 131, it's a finite treatment duration if you think about BTK inhibitors, for example, patients have to keep taking the medicines for very long periods of time which usually means that the drugs are effective for long periods of time. But as has been the experience of one of the panelists, once you stop ibrutinib there is a lot of times that you are going to flare in the IGM levels, and it can be a little bit hard to manage. So, Ibrutinib and BTK Inhibitors work very well for as long as the patient, takes them generally, the acquisition of resistance to BTK inhibitor is, it happens in Waldenstrom may be less likely that it happens in other conditions like CLL, but it itself becomes a challenge this time will be the tolerance, the tolerability of those agents is long-term. So, the neat thing about CLR 131 is that it's given in two cycles, each cycle is comprised of two infusions. The Cycles are about a 56-day type of duration and that's it. And after that, the patients are on observation and the data that Dr. Ailawadhi presented at ASCO suggested the responses are durable. Now it's hard to assess when you're talking only about the experience of six patients. But a lot of the responses are still holding, there is a patient that was almost three years out and still is benefiting from treatment. So, I think this is all very encouraging and I think really this is the neatest part of therapy in my mind is that you have a treatment free interval which from talking to a lot of patients is what patients probably value the most.

Priya Menon: Absolutely. I just want to ask one more question before I let Megan and Peter ask theirs. Dr. Baz, can you briefly touch upon some of the other new drugs and treatments that have been researched for studies of WM.

Dr. Rachid C. Baz: Yeah, I mean, so we mentioned BTK Inhibitors, we also mentioned some proteasome inhibitor, an alkylating agent, CD20 antibodies, but there is more actually treatments that can be considered but that treatment study is not approved for the conditions, but we could use off label including BCL inhibitor, like Venetoclax would be used off-label that has nice data and Ibrutinib for an intolerant or resistant patient about, Venetoclax efficacy, that is clinical trial data with PI3-kinase inhibitor in combination with CD20 antibodies. So, I think there's a lot of reasons to be optimistic overall, I think given the number of agents we have to treat Waldenstrom I think the therapeutic armamentarium we have is going to keep growing over time and that's great because we understand biology better, but there's some of the existing agent still going to be helpful even years down the line some of the older stuff and maybe less cool stuff, so to speak.

Priya Menon: Okay, thank you Dr. Baz. I'll not let Meg start with hers. Meg, all yours.

Meg Mangin: Okay. Dr. Anderson, you mentioned before that there's a familial aspect to Waldenstrom's. My sister also has Waldenstrom's, but her course has been very different. What I like to know is, what do I tell my adult children? How should they be tested or if they should be tested or what they should be looking for.

Dr. Larry Anderson: And so, unfortunately, there's not a specific test that can say when or what age should they start looking or what testing to be done? I would just say especially if you had a family member especially with 2 members with Waldenstrom's, they would probably want to get with their yearly checkup just a blood count and a chemistry panel and if they have anemia or elevated protein, then they would want further work up to look for a monoclonal protein or evidence of Waldenstrom's.

Meg Mangin: Okay. Thank you. Dr. Baz, have you been working with Pirtobrutinib? Have you seen any success with that new BTK inhibitor?

Dr. Rachid C. Baz: I have not. There are a number of BTK Inhibitors that are already in development and actually obviously the three that are currently FDA approved so to speak, you think about Acalabrutinib, Zanubrutinib, and Ibrutinib. For the Waldenstrom indication mostly we are thinking Ibrutinib, Zanubrutinib but the main mechanism of resistance seems to be a C481S mutation and BTK Gene and there is a novel BTK Inhibitors that, hopefully, will be able to overcome that resistance in the future. Although this will be determined there is a loxo compound. And there is also Vecabrutinib that we've worked with at Moffett. But I

think it's an interesting field out there in terms of further BTK inhibition and trying to overcome resistance and intolerance to the first generation so to speak.

Meg Mangin: Thank you. Dr. Anderson, when should Waldenstrom patients have stem cells harvested and preserved for future use?

Dr. Larry Anderson: Great question. Stem cell transplant in Waldenstrom's is more controversial lately because we have so many great other great options besides transplant. We used to do a lot more, we still do it, but we're usually reserving, the transplant for kind of third, fourth, or fifth line or beyond. But we still especially for patients younger and who want to preserve that option for a stem cell transplant later will often recommend considering collecting and storing their stem cells, whether it's after first-line or second-line therapy. Mainly we want to do that before they've had too much bone marrow, toxic therapy. So, one of the ones that would be good to cause bone marrow damage over time would be a lot of Bendamustine. So, if we do have a patient getting Bendamustine we will want to consider collecting and storing their stem cells from their peripheral blood after 4 or at most 6 cycles, probably not wait until after 8 because then they are going to decrease the yields of those stem cells. But even if we collect and store, we may not use them until after another one, two or three more lines of therapy because of the stem cell transplant, although it can be quite effective. And as a good option is going to cause a lot more side effects than the BTK Inhibitors, the proteasome Inhibitors, Bendamustine and then we also have allogeneic stem cell transplant is also a potential option for these patients, and that's actually the only potential therapy we have that could potentially cure Waldenstrom's because of that, donor immune system. But it has a lot of other toxicities with the donor immune system attacking the patient. And so, we generally reserve that for patients who failed, most things and there is younger. So, it's not that commonly used.

Meg Mangin: Thank you.

Dr. Rachid C. Baz: I would completely agree. I would add to this that there may be some subpopulation of Waldenstrom's patients, who may be really should be considered for a transplant. Especially those who have, for example coexistent, amyloidosis which may be one of the co indications of patients, who mainly have light chain deposition disease. Well, basically there is really, a need to achieve a complete response haematologically. A lot of the existing Waldenstrom's drug therapy can do quite well, but complete responses in Waldenstrom's remain uncommon and I think because of that transplant can get us there and that could be a valuable tool. So, for the right patient, absolutely the data is limited because of the fact that Waldenstrom is not a very common condition, and a lot of the data ends up being case series and smaller publications.

Meg Mangin: Thank you. Dr. Baz, when is Car T therapy appropriate for Waldenstrom's patient?

Dr. Rachid C. Baz: Well, I mean currently Car T is not approved for Waldenstrom specifically. Also, there may be an approval when you look at transform lymphomas, they could be appropriate for Car T therapy and CD19 car and obviously, Waldenstrom's can sometimes transform to aggressive lymphoma. And there is I think a publication where one such patient received a CarT and transformed Waldenstrom and head down quite well. And I think so as a technical aspect, currently, it would be part of a clinical trial. Also, because of the relatively uncommon nature of Waldenstrom, I think I'm not aware of any trial specifically looking at Waldenstrom for Car T. However, some of those trials are looking at many different types of lymphomas, and often indignant Non-Hodgkins Lymphoma would be lumped into one clinical trial. And there may be a Waldenstrom subset that could be treated potentially, but I think the likelihood is that Car T would likely be a very effective therapy for Waldenstrom. What we need to consider is one is that a lot of patients could do quite well, often without needing Car T, two is that a lot of patients with Waldenstrom's could be of older age and Car T in terms of risk benefits, may not be the best option for them. But once you think patients, have had two lines of therapy have become intolerant or refractory to BTK inhibitor thinking about a clinical trial or a Car T clinical trial specifically. I think will be certainly reasonable in the appropriate context.

Meg Mangin: Okay. Thank you.

Dr. Larry Anderson: And I completely agree. I just want to also point out that what we don't know with Waldenstrom's especially in patients that have nerve involvement might also have more side effects, from Car T-cell therapy with some of these showing neurotoxicity and some of them showing other nerve damage. And so, it might be something to really study in trials before moving forward with patients with a lot of nerve issues from their Waldenstrom's.

Meg Mangin: Thank you. Dr. Anderson, are bispecific antibodies being developed to treat Waldenstrom's?

Dr. Larry Anderson: So, it's really in the same discussion as the Car T cells. We don't have necessarily specific trials that I know of for Waldenstrom's, but a lot of bispecific antibody trials include low-grade lymphomas that will allow Waldenstrom's patients and similar patients on there. Most of these targets CD19, which is expressed on Waldenstrom's or AKA lymphoplasmacytic lymphoma, just like other B-cell lymphomas and should work well. There's not necessarily a trial though, dedicated just to Waldenstrom's that I know of though.

Meg Mangin: Okay. Thank you.

Priya Menon: Thank you, Meg. I'll pass it on to Pete now. Pete, you can ask your questions.

Peter DeNardis: Okay, I'll see for it. Dr. Anderson, given the promise of all the newer agents, all the new nibs that are out there, do you foresee a time when the classic cytotoxic chemotherapy agents but no longer utilized for things like Bendamustine Cytoxan, are they going by the wayside?

Dr. Larry Anderson: Great question. I mean, we do have a lot of less toxic therapies now, but I think they still have a role. So, patients that need a really rapid response that is having hyperviscosity in the hospital, and they need something right this minute to get their Waldenstrom's under control right after their plasma exchange is done, a lot of times we'll go ahead and start them on Bendamustine. There is some possible role there for the BTK Inhibitors so that they can also have a fairly rapid response. But then you usually have to wait a week or two for insurance approval. You have to figure out what the co-pay is, figure out if you need co-pay assistance, and so if a patient sitting there waiting with a viscosity, you can't really wait on those things. So, it I don't think it will completely rule out the need for an alkylator therapy just yet. But yeah, might get there.

Peter DeNardis: Okay.

Dr. Rachid C. Baz: I'll add to that. You know the really neat thing about alkylator therapy actually is the fact that a patient could have a treatment-free interval. And I think this is something that is very important. And then the last point is, obviously, something that Larry ___ do is the cost of therapy, BTK Inhibitors is very expensive, alkylating agent has been around for a while relatively cheaper. And so, when you think about a finite treatment course say six cycles or whatever versus long-term in Ibrutinib and like, I mean, certainly that can have a very different financial impact. And there are patients, obviously, finally who despite all of the availability of those agents in the United States, co-pays are very high, and we talk about financial toxicity, with those agents.

Peter DeNardis: Thank you.

Dr. Larry Anderson: I agree. And I think another point is, just like you mentioned even if I thought that the BTK inhibitor was a very appropriate therapy for someone, and they got it for no co-pay. A lot of patients, don't want to be in therapy for the rest of their life. And so, they just don't want to say, okay what can I do with the least amount of time on treatments? But then other patients may come in and they may live two or three hours away, may not have good transportation. And so, all of the infusions that we have that we may be recommending they may not be able to come in that frequently or not want to do an IV therapy. And so, then it's good to have both options basically.

Peter DeNardis: Okay, so actually you answered one of the questions I was going to ask. Sort of indirectly I was going to ask what factors should a newly diagnosed patient look at when they're trying to decide what treatment to undergo? And sometimes when I have talked to my hematologist when I'm having a relapse, he said, well, which one do you want? How do I know? So, are there a number of factors?

Dr. Larry Anderson: Yeah, it's a whole list of things like I said, how far do they live? Do they have transportation? How fit our functional is the patient? Do they have the bulky disease and needs to get under control right this minute? Do they have a preference? All of these things come into play. What is their co-pay assistant? Do they have prescription coverage? All these things can have a big impact on their treatment.

Dr. Rachid C. Baz: Yes, I think it's definitely a long discussion between the doctor and the patient that will ultimately come back with a more personalized decision. I don't know that we can really think about a cookie-cutter approach for everybody.

Peter DeNardis: Thank you. This one I guess could be for the three of you, but I'll start with Dr. Baz. Given the new and novel therapeutic agents that are coming out there. Are there any that you see maybe have less of a side effect than others because even with Ibrutinib, there are certain side effects, that patients get hypertension and other issues like that? Is there anything out there that maybe is coming in the pipeline that will have not only will treat WM but won't cause something else that you have to deal with for the rest of your life eventually?

Dr. Rachid C. Baz: Yeah, I mean, I think this is obviously the easy answer is that there is no free lunch so to speak. So, that is not a therapy that's going to be devoid of side effects. But there is always this kind of a risk-benefit discussion on what makes the most sense and obviously, some patients who are at higher risk for say atrial fibrillation you're going to take that into consideration when you're thinking of BTK inhibitor. On the other hand, when you're thinking things of the sort of Venetoclax, it's generally well-tolerated, but some patients will have issues is cytopenia, when you think about Rituximab which has to be a very fairly well-tolerated agent, some patients will have an allergic reaction and still trouble to receive the agents. So, overall, a lot of the therapies that we just talked about are generally considered to be "well-tolerated", and most patients tend to do very well with them. B TK Inhibitors are a prime example of that. There's a small subset of patients who have a credibility issue, but I think, as a whole, I don't know that there is a therapy that's going to be devoid of side effects, but I think a lot of those agents have manageable side effects and I think a good discussion with the treatment team can help kind of navigate those effects.

Peter DeNardis: Thank you. Dr. Anderson, do you want to add anything to that? What are your thoughts?

Dr. Larry Anderson: Yeah, I mean, I completely echo everything he said. I think certainly, I'm excited about bispecific and Car T cells for not just Waldenstrom's but all hematologic malignancies, I think that does have the potential for hopefully getting patients in deeper remissions, and we've seen with some of the other therapies, but it will come at some trade-offs at risk of cytokine release syndrome and neurotoxicity that could potentially be an issue for some of these patients.

Peter DeNardis: Thank you. This one could be for either of you. I'll start with Dr. Anderson and then you can chime in Dr. Bass. When I was first diagnosed back in 2003, I was told that to basically get my affairs in order and I had maybe six or seven years to live and obviously they were wrong, but that's because of the advances in treatment since then. Do you foresee what prognosis if someone came to you now, newly diagnosed? What do you tell them? Like, what outlook should they have?

Dr. Larry Anderson: I guess part of it depends on some of the risk features with that particular patient that we look at things like, the tumor stage and the LDH and the Beta 2 macroglobulin and how aggressive and how rapidly rising other markers, all these things can help us give a better picture of what we expect. But in general, especially in someone that has the typical kind of slower growing Waldenstrom's we can definitely reassure them that we have patients that have had this for over 20 years. The average survival is probably somewhere in the five-to-ten-year range, but there are some data that at five years out 75% of patients are

still in remission or still not having relapse from their Waldenstrom's. And even though we have all these great treatments, a lot of these statistics haven't caught up with them yet. So even if you read a statistic from last year, it doesn't really reflect the FDA-approved drugs that just came out over the past year. We needed a lot more time to see what effect that's going to have on the general population.

Peter DeNardis: Thank you.

Dr. Rachid C. Baz: Yeah, I would add to this that. Yeah, I completely agree. I would add to this that. I don't think we really know what is the expected median survival for patients diagnosed with Waldenstrom's today. We don't know because as Larry pointed out agents that have been approved this year or those that are going to be approved next year or next five years or ten years, are likely going to have an impact on the patient's outcome. So generally, I tell patients to be optimistic. I think statistics are very helpful when you're talking to groups of patients. Not as much when you're talking to one individual. So, in my practice, I've lost more patients with Waldenstrom's to other things in life than to the disease itself. The patients we've lost to Waldenstrom, we've lost generally to transformed disease. And transformed disease tends to be very difficult to manage and treat. But as a general rule, I think patients should be optimistic. I think they should generally do very well with this, and there is despite that diagnosis, there is a lot of reasons for optimism, especially nowadays.

Peter DeNardis: Thank you. Something to key off of something you just mentioned about the transformed disease. Now granted, it's a small percentage of WM patients that get the transformation, but let's say if they transform the diffuse large b-cell, usually will not happen but are the treatments not there for diffused large B-cells or is it because WM patients being WM patients, they're harder to treat?

Dr. Larry Anderson: I think it's twofold. One is that WM patients generally are older and transform disease treatment in an older population is harder, but as a general rule when you even look at patients with CLL and transform disease where there is quite a bit more literature, the outcomes are still not good. And transform disease remains very difficult to treat. Now, hopefully, Car T will change some of that, but I still think unfortunately transform disease remains hard to treat.

Peter DeNardis: Okay. Thank you. I think that's my question. Yeah, I don't have another one.

Priya Menon: Thank you, Pete. Thank you, Meg. I think those were some great questions. Dr. Anderson, Dr. Baz, I have one question before we kind of wrap up for today. And this is to address the elephant in the room, Covid-19. So, my question is, is it safe for WM patients, to get the Covid vaccine, given the immunocompromised condition and are there any specific side-effects that you are observing in your patients after getting vaccinated? Dr. Anderson, can you answer this question?

Dr. Larry Anderson: Sure. Yeah. Thank you. Yeah, so Covid vaccines and Waldenstrom's definitely will recommend getting those Covid vaccines and the booster for Waldenstrom's patients. Now certainly we do have information showing that Waldenstrom's patients may have a lot lower response to the vaccines. That means they may not be as protective in Waldenstrom's patients, especially if they're on active therapy with the Anti CD20 antibodies and BTK Inhibitors. Those can significantly decrease the activity of the vaccine. So, it's been tough but certainly, if the patient's been off treatment for a number of years or they are smoldering those patients should respond nicely to the vaccines, and then we do see improvement after that third vaccine, even if they hadn't responded very well with the first two, we can sometimes see a boost. But what I would tell patients is, definitely get the vaccines and then act like you haven't had them just because they may not work as well, but they're better than nothing. And what we don't know is even if we can't see an antibody response because they're on treatment that suppresses antibody-forming cells, they could still have a T-cell response and those T-cells could still be somewhat protective against Covid. And as far as extra side effects, we don't really see an increased risk of side effects in Waldenstrom's patients with the covid-19 vaccines, we would see the usual chills and aches for two or three days and a sore arm, but not really anything else.

Priya Menon: Dr. Baz, you want to add to that?

Dr. Rachid C. Baz: Yeah. Maybe there's nothing much to add here. I completely agree. I mean, I think obviously the vaccine may be less effective in this patient population. However, they're particularly important and a little bit of protection is better than no protection. So, I think Larry said it best, get the vaccine and act like you didn't get them. I think it is perfect. In terms of safety, we also haven't seen any safety issues. We looked at our own patients at Moffatt, not just with Waldenstrom in general, all hematology patients, who received the covid vaccine, and actually, it turns out they had far less side effects than the hospital employee that received the vaccine. So, it may be the hospital employee complaint more. But in general, it was pretty safe for our hematology patients.

Priya Menon: Thank you. Thank you, Dr. Anderson, Dr. Baz, Meg, and Peter, I think this is great discussion. Thank you so very much for all the information that you've shared. We are wrapping today's Curetalks Waldenstrom's with an advice, so, knowledge can be the best medicine of all and when dealing with Waldenstrom's, please do see a specialist. So, with that thank you, everyone. Have a good day.

Thank you.