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THE BLOODLINE WITH LLS

A PODCAST FOR PATIENTS AND CAREGIVERS

Episode: 'Hope for a Rare Disease: Myelofibrosis'

Description:

"If you have a rare disease, it's not rare to you."

In this episode, Dr. Naveen Pemmaraju of MD Anderson Cancer Center in Houston, TX, sheds light on the latest treatment advancements for myelofibrosis. The pace of scientific discovery for rare diseases is moving at a fast rate, resulting in better outcomes for myelofibrosis patients.

***This episode was recorded on Rare Disease Day, February 29, 2024**

Transcript:

Elissa: Welcome to *The Bloodline with LLS*. I'm Elissa.

Lizette: And I'm Lizette. Thank you so much for joining us on this episode.

Elissa: Today we will be speaking to Dr. Naveen Pemmaraju, an Associate Professor in the Department of Leukemia at the University of Texas, MD Anderson Cancer Center in Houston, Texas. He is the primary investigator on several clinical studies, and his research interests are focused on improving outcomes and developing novel therapies for patients with rare myeloid malignancies, including adolescents, young adults, and older adult patients with myeloproliferative neoplasms, or MPNs, acute myeloid leukemia, or AML, and blastic plasmacytoid dendritic cell neoplasm, or BPDCN.

Dr. Pemmaraju is also active on social media and has developed a community with the hashtag, #mpnsm, that is focused on the discussion of topics of interest to MPN researchers, providers, and patients during medical conferences and throughout the year. Welcome, Dr. Pemmaraju.

Naveen Pemmaraju, MD: Oh, thank you for having me; and thanks for all the wonderful work that the LLS team is doing. Thank you.

Elissa: Thank you. And so, our episode today is on myelofibrosis. Could you explain to our listeners what that is?

Dr. Pemmaraju: Well, what a great place to start and very important; and sometimes these terms are confusing, including for our fellow physicians out there.

So, really, myeloproliferative neoplasm is the family of rare blood cancers. So MPN, myelo meaning from the blood and bone marrow; proliferative, too much of; and then neoplasm, new growth or cancer. It's important to state that these terms, they used to be called MPDs, myeloproliferative disorders. But it was changed to neoplasm to represent that these are blood cancers, not disorders, because of the clonal or cancerous origin of them.

So, within that family of MPN, you have three, let's call them, classical blood cancers. The first one is ET, essential thrombocytosis, too high platelets. The second one is polycythemia vera, PV, too high of not only the red cells, but usually all three. And then there's myelofibrosis. So, from the bone marrow, myelo; fibrosis, scar tissue. So now the cells are being made so much, and then the bone marrow is starting to scar over. And then actually the blood cells are too low, now requiring transfusion. So, myelofibrosis represents one of the three MPNs. And unfortunately for our patients, it's actually usually the most advanced form of these three.

Elissa: Okay, now how common is myelofibrosis, and does it have a good prognosis?

Dr. Pemmaraju: Extremely uncommon, it turns out. So, in the definition of rare diseases, however you define a rare disease, this one meets that criteria. And actually today, I should note February 29 is actually Rare Disease Day because it's the rarest day. It only occurs one out of every four years. So, on this Rare Disease Day, we're

talking about a series of blood cancers that only affects 4 out of 100,000 Americans a year. That's how rare-

Elissa: Wow.

Dr. Pemmaraju: -these MPNs are.

Yes, it's worldwide distribution, males and females both affected, but it's really rare compared to some of the more common cancers such as breast cancer, lung cancer, prostate, for example.

The second issue is, unfortunately, the prognosis is varied. So, if you have lower-risk myelofibrosis, the good news is some of our patients can live decades or even a normal lifespan as long as the blood counts are stable, not requiring transfusions, etc. That's called low risk.

But as you go forward into the intermediate and high risk, the overall survival for our patients can be very limited. And that means, not even years, but less than that in the most advanced stages.

So, heterogeneous, varied disease, anywhere from decades or longer to only a few years; and we can use risk stratification models to tell. And then, of course, we can tell does this person need a clinical trial, JAK inhibitor, stem cell transplant, etc.?

Elissa: Now what is making myelofibrosis different than the other MPNs?

Dr. Pemmaraju: That's an essential question. It turns out that all of these are a spectrum of disorders. The body doesn't read a textbook. So, a person can start out as ET or PV and then transform into myelofibrosis; or you can just present with myelofibrosis directly. And then, unfortunately, all three of these can go to acute myeloid leukemia.

You're asking an important question because on the surface, these three have a lot in common. They're all mediated, essentially, by the same three molecular mutations –

JAK2, CALR, MPL. They all present in similar ways, but the difference is that the ET and PV are usually too high of cells, platelets and red cells, respectively. Myelofibrosis oftentimes is less cells. So, the bone marrow is starting to shut down.

In that shutdown, instead of having too many cells, you end up having too few. So, you need blood transfusions. Then the spleen and the liver can get enlarged to help out the bone marrow that's starting to fail. People can feel sick. They can actually look sick, weight loss; and ultimately if you get super sick from the myelofibrosis, you can be so ill that you need a wheelchair or you can't get out of bed.

Whereas ET and PV, almost all of our patients, particularly in the early stages, are chronic phase. They're able to work. They're able to go about their lives. So, two completely different aspects of the disease.

Lizette: Wow. Now, we know that there's both primary myelofibrosis and secondary myelofibrosis.

Dr. Pemmaraju: Right.

Lizette: What's the difference between those two?

Dr. Pemmaraju: So that's exactly the next question. Myelofibrosis can either present first time by itself. Let's call that de novo, from scratch, brand new or it can arise out of the other two as a precursor. So ET, PV, I have patients who've had those for 20 to 30 years. Hanging out. It's stable. They're going about their lives, jobs. But then one day the blood counts start to go low. The spleen starts to enlarge. We do a repeat bone marrow biopsy; and oh, man, it's now transformed to MF-2, myelofibrosis. So, that's called secondary if it comes out of ET or PV and then primary if it comes out by itself.

Elissa: Are we knowing if ET or PV might turn into myelofibrosis when they're first getting diagnosed? Is that a possibility?

Dr. Pemmaraju: Yeah, what a great question. Exactly what we're trying to follow in the clinic. Unfortunately, as of now, we don't have a definitive way to predict and know in terms of timing. But we have risk factors; we have things that we all look out for as providers and patients and family.

I would divide them into several buckets. So, this is the patient who has ET or PV, more of a chronic phase, active outpatient. But now something is changing, and now you're suspecting myelofibrosis. So, this is exactly why we need to have these discussions.

One category is that if the peripheral blast count is starting to go high. So, blasts are immature cells or leukemia cells. It can be okay for someone to have X number of these. So, let's say 1 to 4%, just a small number. But if it starts going high, especially into the double digits, then you know something may be going on. This can be present on a CBC, and so that may be a trigger to look for a bone marrow biopsy; and, oh, we're transforming to myelofibrosis.

A second bucket is, as I was mentioning, the other two backup organs, the reserves, the spleen and the liver. When we were inside our mother's womb, those were the primary places where the bone marrow or the hematopoietic tissue was. And then as soon as you're born, they revert to a secondary role and actually the bone marrow that takes over. And so that explains why people with end-stage myelofibrosis have big spleens and big livers, because they come into effect to help out the failing bone marrow as a reserve system. So that's called organomegaly or extramedullary hematopoiesis. So, I don't think a lot of people know that. That's what explains that.

The third bucket is if the blood counts start to change. Too high of a white blood cell count, too low. Too low of a platelet count. Starting to need blood transfusions when before if you were PV, you'll just be taking off the blood. It's completely opposite end of the spectrum. So, if that happens, a change in the blood counts or transfusion needs, that could prompt you to do a bone marrow [biopsy].

And then, of course, another aspect of this is patient directed. Increasing progressive fatigue, drenching night sweats, nightly that have no explanation, fevers that are not in the setting of infection, we call that constellation B symptoms or constitutional symptoms. And that could be a trigger to say, "Hey, something's changing in the body."

But no matter what, you have to do a bone marrow biopsy because that's where you can make the definitive diagnosis, restage of the disease. So that's why we try to advocate, do a bone marrow biopsy if you can, right, if you can at the beginning, so that later on if you're suspecting myelofibrosis, you have something to compare.

Elissa: Now, we know that many blood cancers have genetic mutations associated with them, and you mentioned a little bit earlier some myelofibrosis mutations like JAK2. Could you go a little bit more into those?

Dr. Pemmaraju: Ooh, I love the way you're asking. This is exactly what we do in the clinic. So, whether you're a new patient or you've been with me for 20 years, it changes over time as technology improves and our understanding improves.

The basics that I want everyone to know is that 90%, of patients with MPNs will have one of the following three mutations. JAK2, followed by CALR, followed by MPL. Let's talk about those.

So, I mentioned earlier in the program that MPDs, disorders, changed the name to neoplasm or cancer. That wasn't random or arbitrary. It was because of what we're talking about here.

In 2005, that year changed everything. I had just started at Johns Hopkins Hospital. This is almost 20 years ago. I remember that day forever. It changed us from disorder to cancer because it was found that the most common recurrent mutation is JAK2V617F. This is amazing. It happens in male or female all around the world. It is about 50 to 60% of patients with ET or myelofibrosis and almost virtually 100% of

patients with PV. So, that one mutation alone, which was added to every pathology panel, every bone marrow, made it definitive. "Ah-ha, you have an MPN."

But it didn't stop there. In 2013, our colleague, Dr. Jyoti Nangalia in the UK presented at ASH; and I remember that moment like it was yesterday. Boom, the second most common mutation, CALR was elucidated. That's only, what, 10 or 11 years ago. And so that was added to every panel. That explains 20 to 30% each of ET or MF. And then a third mutation was found along the way called MPL. That's the rarest of the three, maybe about 5 to 7% of ET and MF. But taken together, that's 90%.

Now there is 10% who will be negative for the big three drivers. We call those patients triple negative. You've heard that term in other cancers, maybe breast cancer, for example. Among those triple-negative patients, if you look deeper, some of us have access to that, as I do here at MD Anderson. Then that would be further mutations, ASX01 and other mutations. So, almost everybody will have some driver mutation if you look deep enough.

But the reason why that matters to the patients, the caregivers, and us is that that helps to diagnose the MPNs, particularly the challenging cases and differentiate it from other things. Two, it can help you to risk-stratify or prognosticate. Meaning that if you have triple negative, for example, those patients are higher risk or worse prognosis than the others. And then, we're now in the era of targeted therapies that can help you to decide on what treatment and maybe what clinical trial.

Lizette: That's great to hear.

Now, I know you spoke about some B symptoms. Going back, what are the common signs and symptoms of myelofibrosis? So, what would bring someone into the doctor prior to diagnosis?

Dr. Pemmaraju: Hmm, that's an important thing to think about because it's actually the most important first thing to know about the disease because, again, I like to

contrast our rare MPNs that we're talking about with the more common things that most folks have heard of. Most folks have heard of breast cancer, prostate and lung cancer, colon cancer. But almost nobody has ever heard of this.

So, I think it reminds us of a very patient-centric thing to say, which is if something isn't right in your body, you know better than anyone. Get it checked out. And getting it checked out is important because oftentimes you won't know what's wrong with you unless you ask somebody.

So, what I mean by that is a lot of times our patients tell us it's nonspecific stuff. By far and away, the most common presentation is fatigue. Okay, everybody has fatigue as you get older, as you have life stress, job, family. Okay, that's fine. But the fatigue is a progressive one. It's not explained by other things, and of course it can be subtle. You may think it's normal aging. You may think it's stress. So that's tough, right? Fatigue can present at anything.

Number two, is the drenching night sweats that we mentioned, and then number three is unexplained fevers. You know, when you have fevers, you take a Tylenol®. You think it's an infection or fever, or some other viral infection. But if it's not, you want to get checked out.

The other issue is that of the big spleen and the big liver. We have patients who present with that, and they don't know what's going on. And so, if you have organomegaly, so organs that are growing that you don't have an expectation of that, that's something to get checked out.

So, what's interesting about this discussion is that in a rare disease, even the presentation is a bit esoteric, nonspecific. You can't really hang your hat on anything. And then the other issue is you can mistake it in your busy day-to-day life for normal aging, normal stress.

So, I think the concept that we should be mentioning to people is trust your body, trust yourself. Oftentimes your loved ones, your family may notice before you do. "Hey, your skin is looking more pale. Hey, you're getting more tired. You're not getting out of bed." And almost all of us will be reluctant. "Ah, it's okay. I'm going to keep trucking along." So, maybe this is a good public service announcement that if something isn't right in your body, get it checked out.

Elissa: That is excellent advice.

Now, let's talk about treatments. What are the current treatments for myelofibrosis, and are there different treatments for primary versus secondary myelofibrosis?

Dr. Pemmaraju: Four main JAK inhibitors now exist. The only real class of drugs we have approved; and LLS, you guys have been instrumental in getting the word out about these, has really changed. It's a revolution in our field.

So, I mentioned 2005 is the time that it was elucidated that the JAK2 mutation was very common. Interestingly, these JAK inhibitors that have been around over the last 10+ years work in all of our patients, regardless of their mutation, because it doesn't hit the JAK2 mutation. It hits the JAK2 pathway. So, let me explain what that is.

Inside of these myeloproliferative cells, that light switch that's on all the time that's telling these cells incorrectly to be immortal, to keep growing and dividing, that's called the JAK/STAT pathway. That pathway turns out to be essential for these cells to keep growing and dividing. So, in the normal noncancer cell, there's a little bit of a rhythm and a cadence. Grow/die, grow/die. Oh, there's an inflammation or infection, let's have more cells. Inflammation, infection is gone. Let's go back down. That's the normal, right?

But in the cancer cell, it's always growing, always dividing. That pathway turns out to be very essential to these cells. So, the first-in-class drug was called ruxolitinib. Many of our viewers have heard of that or they're on it. That changed everything because

now you have a JAK inhibitor. It's a pill that you take twice a day, different doses based on your platelets. It's been around for more than 10 years.

My goodness, it's one of the only class of drugs, that I give to patients, and they feel better. Let me repeat that. They feel better because what it's doing is decreasing the cytokine storm, the big spleen, and the big liver to calm back down. The bone marrow to wake back up, and so the JAK inhibitor effect usually takes place instantly within the first week into the first three months.

Never seen anything like it before or since. When you get a JAK inhibitor and you're really sick from myelofibrosis, intermediate to high risk, it makes you feel better, it gives you some energy back, and then you're able to take it. We've had patients who have been on these drugs for many, many years.

The second drug in the class is called fedratinib, so everyone should know about that. Also shown to decrease the spleen, improve the symptoms.

The third drug is known as pacritinib, an interesting drug that just got approved in the last two years specifically for myelofibrosis, less than platelets 50, which is an important subgroup of our patients out there.

And then most recently, can you believe it just within the last six months, is momelotinib, the fourth JAK inhibitor which also has a signal that it may improve your anemia. So, the red blood cell count that might be too low.

So there you go. That's four drugs I mention, all representing the JAK inhibitor class. Outside of that, we've used other medicines before and since – hydroxyurea, interferon. Those have been around for a while. And then, of course, we have a host of clinical trial drugs that are in combination with the JAK inhibitors or by themselves.

Elissa: Now, what about cellular therapies like stem cell transplant or CAR T-cell therapy?

Dr. Pemmaraju: I'm glad you mentioned that. Stem cell transplant is essential to say, as it is the only curative approach for myelofibrosis. I'm going to repeat that because it's such a shocking statement. As of this recording, 2024, stem cell transplant is the only known curative therapy. Now, what we mean by that is these JAK inhibitors, amazing sea change revolution, as I mentioned earlier. But almost nobody is able to be cured by them, and they must be taken daily, twice a day.

But, what the transplant does is it's like a control/alt/delete on your computer to the immune system in the body. You get strong chemo before; you jumpstart the immune system in the body; repopulate it with a donor, somebody else's cells; and then you try to get rid of the disease that way. It's an amazing thing.

The problem, guys, is three-fold. One, is not everybody can go to the transplant. You've got to be fit enough to do it. We've pushed the age. My group and others are routinely transplanting folks in their 70s; but, again, there's an age limit and a fitness limit. Two, is not all centers have the capability of doing it, so it's a limited availability. And then three, is you can have problems after the transplant, including life-threatening problems – infections, graft-versus-host disease (GVHD), so it's not for everybody. So, it turns out that the minority of my patients are able to be offered and actually go, so we need different cellular therapies that can be more widely available.

You mentioned one, CAR T-cells. Everyone's heard of those in lymphoma and leukemias. They've been amazing for some patients. Not yet ready for primetime or available in our MPNs, so we're all working on that.

What about other immune therapies – ipilimumab, nivo(lumab) – you've heard of those. Vaccines. So, all those are in clinical trials in our patients.

I'd also like to highlight that we and others are working on the first bispecific agent. That is, for example, targeting CALR. I mentioned that the era of molecular targeting is there. So, I just opened up a study with the first ever mutant CALR by CD3-directed bispecific antibody. We have that open and enrolling. So, it just gives you this sense

that all of these things in the last three years are going in the direction you guys said, which is do we have novel therapies, immune-directed therapies, something outside of transplant and CAR T that can stimulate the body's own immune system. So, we have those in Phase I and II clinical trials now.

Elissa: Wow. Now, can you explain a little bit so our listeners understand what bispecific antibodies are?

Dr. Pemmaraju: Oh, yeah, great point. And, we should let people know you can look these up, if not on the LLS website, on clinicaltrials.gov, these publicly available sites.

I'm glad you asked that. So, when we're talking about the immune system, really what we're talking about is stimulating the body's own T cells to recognize and rise up to try to attack the cancer. And the best known explanation of that has been in melanoma where my colleague here at MD Anderson, Dr. Jim Allison, was awarded the Nobel Prize for what we're talking about just recently. So, that is the class of drugs in melanoma – nivolumab, ipilimumab – all these that try to engage the CTLA-4 and PD-L1 and PD-1 access to combat the cancer.

It worked like gangbusters in melanoma. That's great. Probably in kidney cancer and some of these others. But in our blood cancers, we've been slower to find those breakthroughs.

The first breakthrough came in lymphoma for these CAR T cells and immune therapies, and now we're trying them in others. So, the bispecific antibody is not as complex or involved as a CAR T. But what it tries to do is it tries to bring your T cells, called CD3 cells, which can be infection and cancer-fighting cells to the actual target that you're trying to do.

So, trying to bring these things together, the CD3 T cell to the mutant CALR cells, right? And so, in doing that, you try to spare healthy and normal cells. That's important. And you try to do tumor-directed therapy.

Elissa: So, if we're describing it, like if we were imagining an image, we're really looking at kind of a cell with two arms, right? So, one grabbing the T cell and the other can grab onto the target, right-

Dr. Pemmaraju: There you go, bispecific. That's it.

Elissa: -and bring the T cell?

Dr. Pemmaraju: Oh, I like the way you explained that. That's really cool.

Now, in so doing, as we've seen with CAR T and some of the other immunotherapies, we're still susceptible and need to watch out for too much immune system stimulation. That's called CRS, so cytokine release storm. And so, that's one thing. So oftentimes, patients would be admitted maybe for the first cycle, observation. Make sure they're doing okay. And then it'll shift to outpatient. You can give these things as IV or sub-Q (sub-cutaneous).

Lizette: You just said that stem cell transplantation may be curative. But since myelofibrosis is more so of a chronic disease, usually quality of life and management of the disease is the goal for treatment, right?

Dr. Pemmaraju: This is exactly right. So, with all the excitement we're talking about, the vast majority of our patients in the clinic are, older, frail. They're unfit for a lot of these stem cell and other therapies. And so, the goal ends up being how do we make sometimes an intermediate to high-risk disease that can turn acute into a more manageable chronic disease? And so quality of life is actually one of the most important things patients tell us.

So, not just quantity of life, but quality of life. The disease, the MPNs, the myelofibrosis can make our patients feel sick – flu-like symptoms, fatigue. It's a cytokine storm, cytokine upregulated state. These cytokines are protein messengers that if they're firing abnormally, tell your body to be at war and to be in an unrest state.

And so that's why someone can look okay on the "outside," quote/unquote, but as always, one never really knows what somebody's battling, right guys, on the inside? So, it's an internal cytokine war, and that can make you not want to feel like getting out of bed. It can make you be at a party, and you're there in person, but inside you're not feeling well.

And so, the aim of these medicines should be to not worsen that, right. But the problem with chemo, is that sometimes you do, do that. You're trying to get some other goal, so we're trying to develop therapies with our colleagues and sponsors that can improve symptoms; and it can minimize the side effects.

So, I'll give you an example of that. With the JAK inhibitor class, what's been great about those drugs is not only it shrinking spleen and trying to decrease the blood counts appropriately, but it's also trying to have people improve their fatigue, bone pain, and night sweats. So, basically, that's that balance. The disease itself can make you feel bad. You want to try to make medicines onboard that don't contribute to that, and that's a challenge.

Lizette: Sure. And I know that there's common side effects of all of the treatments that you've mentioned too. So, continuing talking about quality of life and management, what are the typical ways that you manage these side effects from all of these meds?

Dr. Pemmaraju: Super important question, so let's make it very specific. Let's talk about these four JAK inhibitors because it takes hundreds of hours to research, and I'd like to distill it here.

So, for the ruxolitinib, the first in class and the longest running JAK inhibitor, there's a few things that have popped up. Generally, very well-tolerated drug, but one you'll see is increased incidence of nonmelanoma skin cancers. So, that's basal cell and squamous cell. Extraordinarily common, but there is a signal that these drugs can exacerbate, increase that frequency. So, almost all my patients see a dermatologist, which is fine. I call it onco-dermatology. And so, it's just something that if you have some skin spots, it's very common in MPN patients, regardless of the therapy, to have that. So that's one thing to know about.

Second thing is, with ruxolitinib, some folks can have an increased risk of opportunistic infections, sometimes very rare and serious infections. The most common one is herpes zoster, or shingles. We've all mostly heard of that, so there are vaccines you can take to prevent it, medicines you can be on. So, you need to be on the lookout for that.

And then finally, a new signal that we're starting to understand is that of weight gain with the ruxo(litinib). It's an interesting weight gain. I see it more in my patients with polycythemia vera where the drug is approved in the advanced setting.

For the fedratinib agent, the second approved drug, there is an FDA black box warning, an important warning that one needs to know about, which is that of encephalopathy. It was thought to be called Wernicke's encephalopathy, but now a more general encephalopathy. What's that?

So, encephalopathy is the medical term for like kind of confused thinking or unbalance, and it can be due to a lot of different things – GI, malnourishment, neurological.

Thiamine seems to be the important thing. That's vitamin B1. So, if you're going to give that drug, you just have to know to check the thiamin level, replace it, watch out for that while you're treating these patients, and then the GI signal – nausea, vomiting, diarrhea.

The third drug is pacritinib, another great drug as we mentioned, all these JAK inhibitors; but it's specifically approved in platelets less than 50, so you do have to watch out for bleeding events. So, if you're on blood thinners, you need to be very careful watching that, especially in the setting of low platelets and also GI side effects as well.

And then lastly, the momelotinib, the newest agent, the newest drug available trying to improve the anemia and decrease the spleen size. Maybe 9 to 10% of patients have been associated with peripheral neuropathy, so numbness and tingling in the nerves and then, again, this GI signal.

So, those are some of the broad side effects. Obviously, let's let people know this is not personal advice. You have to always talk to your own physician and provider team, look at the package label, do the research, see what the clinical trial showed, see what the real data shows. But generally, these four drugs, these JAK inhibitors have been well-tolerated, and they're oral drugs that people can take at home.

Elissa: Okay, now you briefly brought up your excitement about some clinical trials earlier. Are there any emerging therapies or are those on the horizon in trials that you're particularly excited about?

Dr. Pemmaraju: Yes, well this is a perfect time to do this program because we're just a few months after the ASH (American Society of Hematology) meeting in December at which I presented.

So, I think there's three major categories to share all the excitement and hope with our viewers. Category 1, is that of combination drugs. So, these are brand new pathways, most of which are not FDA approved, are not approved in the myelofibrosis space; and we're combining those drugs with the JAK inhibitor. And so, there were three major trials presented.

The first one was the one I presented myself, which is called navitoclax. It's the TRANSFORM-I study in which we combined the not-yet-approved Bcl-xL inhibitor oral drug with the ruxolitinib. This is in frontline patients, myelofibrosis, never seen a JAK inhibitor. Large study, 252 patients randomized.

So, rux-navitoclax versus ruxolitinib plus placebo, and what we found is an amazing result. The primary endpoint was met. It doubled the spleen size reduction. So, 60+ percent versus only 30+ percent, and that's spleen volume reduction at 24 weeks. So, people had double the benefit if they're on the combination.

The symptom score was not found to be statistically significant between the two, and so even though both groups had reduction and improvement of the symptoms, there wasn't a statistical significance for that secondary endpoint. Obviously, one of the factors could be that when you add two drugs over one, per our earlier discussion, it's difficult to show that statistical difference.

So, that's very exciting. That's continuing to be maturing, watching out for all the other endpoints. So, we'll try to see what that shows over the next few years.

The second one was presented by Raajit Rampal from Sloan Kettering. Briefly, that was the pelabresib molecule which is a bromodomain (BrD) or BET inhibitor. Again, not yet FDA approved for any indication. Similar results. Large study. Ruxolitinib plus pelabresib versus ruxolitinib alone. The combination, again, doubled the spleen volume reduction. Similar numbers, 60+% versus 30+%. Well-tolerated drug, and so that one again, we're awaiting to see the maturity of the data.

Those both, interestingly, were international Phase III randomized studies marking the first time we've ever done that in our field for combination therapy upfront; and they were largely conducted during the pandemic.

The third one is a little bit earlier on called selinexor. That was presented in the ASH world by our colleague Srinivas Tantravahi from Utah. But early on, just a few patients

treated only in the Phase I experience. But in a weekly dosing with this drug, they found that majority of the patients had spleen volume reduction, symptom benefit. There is a GI signal with that drug, so they lowered the dose; and so that one's going into Phase III testing as we speak. So that's a very exciting option as well.

So, that's three drugs that I just mentioned to you that are being combined with JAK inhibitor.

The second category, if that wasn't exciting enough for folks, is that of completely novel agents. So, these are agents who, unfortunately, the JAK inhibitor wasn't working; and now you're in the second line and beyond, host of drugs that many folks have heard of – imetelstat, the telomerase inhibitor, etc. But the concept there is a drug that may work by itself, so without the help of the JAK inhibitor because that's already deemed to not be working. And so, there were lots of updates there.

And then finally, as you guys were mentioning, immune therapy but also anemia-improving drug. So, this is where you have the luspatercept agent and some of these JAK inhibitors such as pacritinib or momelotinib which they themselves aim to improve the anemia, whereas the earlier JAK inhibitors may have actually made them worse.

So, anemia in myelofibrosis as a separate entity for drug development, basic science understanding, it's a whole new world. I'm very excited about all that for us.

Elissa: Wow, that is so neat to hear about all those different options coming for myelofibrosis patients; and hopefully, they will continue to be successful.

Now, our final question today. On our patient podcast homepage, we have a quote that says, "After diagnosis comes hope." What would you say to patients and their loved ones to give them hope after a diagnosis of myelofibrosis?

Dr. Pemmaraju: I think that's the whole ball game. What a beautiful question. I think hope to me means that in the setting of fear, vulnerability, and the unknowns,

that in that arises a plan and a pathway which understands that the future is still up to us.

And what I mean by that is I just told you about developments. I'm so excited about some of these things. Some of these things didn't even exist in a lab three years ago. We had a global pandemic which could have definitely shut down all these things, but what I found is that our research efforts actually accelerated even more importance, even more collaboration, even more connection, a lot of which was enabled by platforms such as this in the digital world. So, actually, in a very scary situation, we were able to come together even more.

I think hope also means that in rare diseases, the acceleration and the pace of scientific discovery is mind-boggling. Again, the stuff I'm talking to you about, we didn't have them in clinical trials three to five years, so things are moving so rapidly. You can get a poor prognosis, bad news one day, and then six months later there could be a breakthrough that could directly affect you.

And then finally, that hope, I can tell you, means to me that there are people who care about you and your family and your disease. And what I mean by that on this Rare Disease Day is that if you have a rare disease, it's not rare to you. It's not rare to your mother, to your spouse, to your partner, or to your family. It's a disease, so it doesn't matter to you if it's 250,000 people a year or 5.

And so maybe 10, 15, 20 years ago, maybe before the Internet, it would have been difficult if not impossible to connect with a researcher in Australia or South Africa or India. And now with online, digital platforms like this with LLS, we not only have the ability to connect, but likely there's someone in a lab somewhere on a clinical group such as myself working on an ultra-rare disease that you can then directly link and say, "Hey, can I see you as a patient? Can I get into this hospital? Can I get onto this clinical trial?"

The democratization of information, the availability has equalized the disconnect with the rare diseases. And, my friends, I tell you, that's hope incarnate. That is what hope is, just the ability to take bad news and say, "What's next?" And I'm proud to be a part of that, and you guys at LLS are a part of that too.

Elissa: I love that so much because, you're right, we talk to other patients and their loved ones that have rare diseases, and it's not rare to them. And so we really appreciate you sharing all of this that I hope gives hope to patients and their families.

So, thank you so very much, Dr. Pemmaraju, for joining us today. We really appreciate it.

Dr. Pemmaraju: Thank you, Elissa, Lizette, all of you guys at LLS. What you're doing is noble work for our patients, their families, and their caregivers. So, thank you for all that you guys are doing. Happy to come on anytime.

Elissa: Thank you.

Lizette: Thank you.

Elissa: And thank you to everyone listening today. *The Bloodline with LLS* is one part of the mission of The Leukemia & Lymphoma Society to improve the quality of lives of patients and their families.

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complete a brief survey that can be found in the show notes or at TheBloodline.org. This is your opportunity to provide feedback and suggested topics that will help so many people.

We would also like to know about you and how we can serve you better. This survey is completely anonymous, and no identifying information will be taken. However, if you would like to contact the LLS staff, please email TheBloodline@LLS.org.

We hope this podcast helped you today. Stay tuned for more information on the resources that LLS has for you or your loved ones who have been affected by cancer.

Have you or a loved one been affected by a blood cancer? LLS has many resources available to you – financial support, peer-to-peer connection, nutritional support, and more. We encourage patients and caregivers to contact our Information Specialists at 1-800-955-4572 or go to LLS.org/PatientSupport. You can find more information on myelofibrosis or the other MPNs at LLS.org/MPN. All of these links will be found in the show notes or at TheBloodline.org.

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