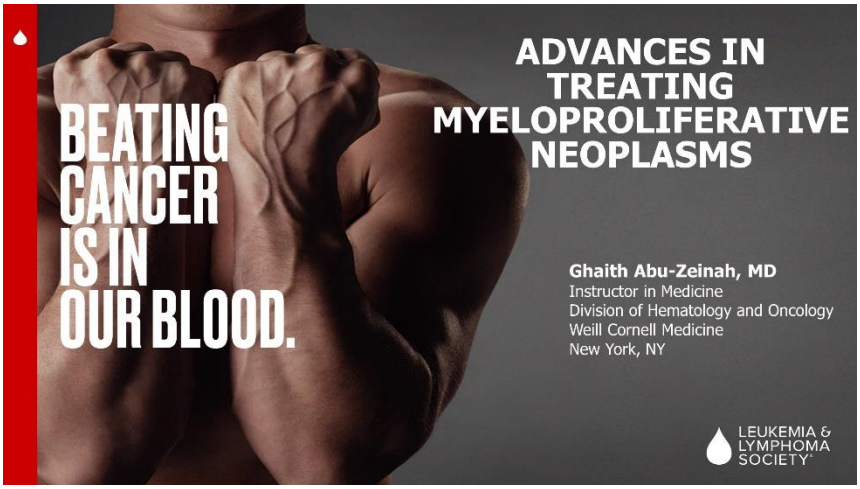


Advances in Treating Myeloproliferative Neoplasms

Operator
Greetings and welcome to Advances in Treating Myeloproliferative Neoplasms, a live telephone and web education program. It is now my pleasure to introduce your moderator, Ms. Lizette Figueroa Rivera. Thank you. You may begin.

Ms. Lizette Figueroa Rivera
Hello, everyone. On behalf of The Leukemia & Lymphoma Society, a warm welcome to all of you. A special thanks to Dr. Ghaith Abu-Zeinah for sharing his time and expertise with us today.

Before we begin, our President and CEO, Louis J. DeGennaro, Ph.D., will make some remarks.

Louis DeGennaro
I am Dr. Louis DeGennaro, President and CEO of the Leukemia and Lymphoma Society. I would like to welcome all of the patients, caregivers, and healthcare professionals attending the program today. At the Leukemia and Lymphoma Society, our vision is a world without blood cancers.

Since we started in 1949, LLS has invested more than $1.2 billion in breakthrough research to advance lifesaving treatments and cures. We have played a pioneering role in funding many of today's most promising advances, including targeted therapies and immunotherapies that have led to increased survival rates and improved the quality of life for many blood cancer patients. Though LLS is known for funding groundbreaking research, we do so much more.

As this program demonstrates, we are the leading source of free blood cancer information, education, and support for patients, survivors, caregivers, families, and healthcare professionals. We also support blood cancer patients and their local communities through our chapters across the country, and we advocate at the state and federal level for policies to ensure that patients have access to quality, affordable, and coordinated care. We are committed to working tirelessly toward our mission every single day.

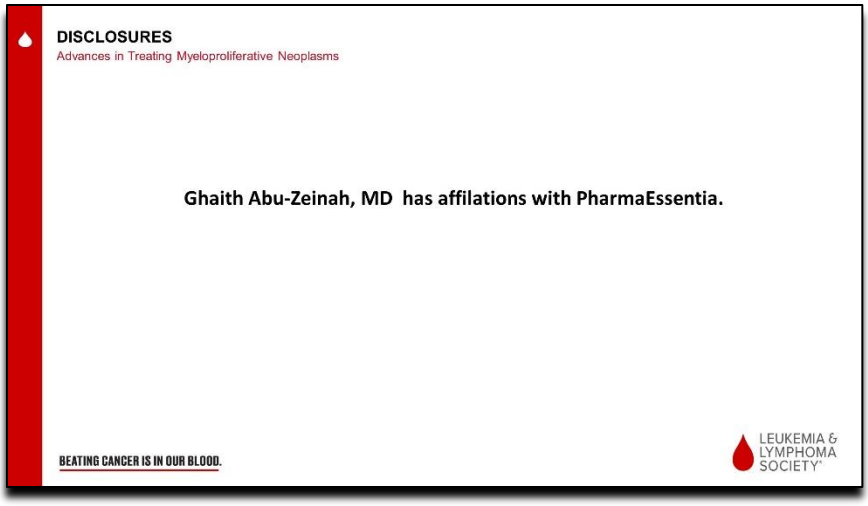
Today you will have the opportunity to learn from esteemed key opinion leaders. They each have volunteered their time, and we appreciate their dedication to supporting our mission, their commitment to caring for patients living with blood cancers. Thank you for joining us.

Ms. Lizette Figueroa Rivera
Thanks to Dr. Lou for his remarks and thank you for joining us today. As you continue to face your blood cancer diagnosis during a pandemic, The Leukemia & Lymphoma Society hears from blood

cancer patients and caregivers each day about the profound effects of the pandemic on their cancer care and daily lives.

While it has been an incredibly trying time, there are bright spots ahead as we all celebrate FDA authorization for two COVID-19 vaccines and look forward to more safe, effective vaccines on the horizon. LLS has information about COVID-19 as well as information about the vaccines on our COVID webpage, LLS.org/coronavirus, or you may contact one of our Information Specialists. We will continue to update our vaccine information as further studies are released.

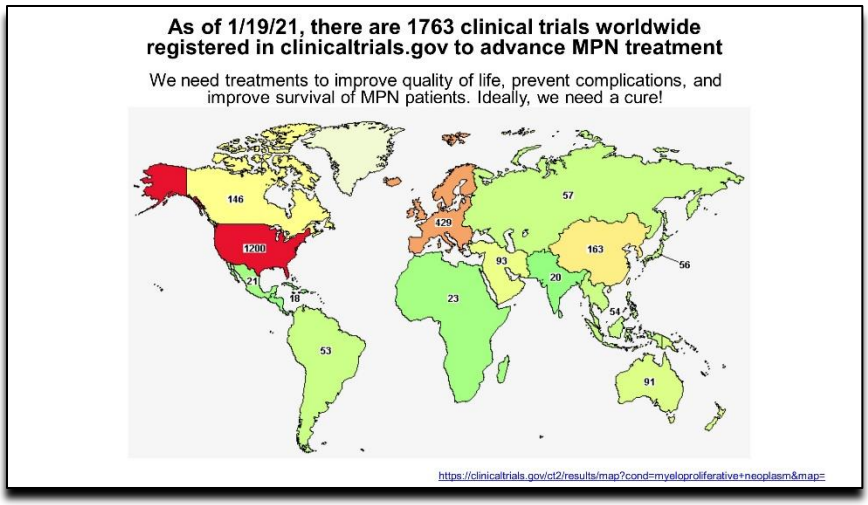
For this program, we would like to acknowledge and thank Bristol Myers Squibb and Incyte for their support. I am now pleased to introduce Ghaith Abu-Zeinah, Instructor of Medicine, Division of Hematology and Oncology, at Weill Cornell Medicine in New York, New York. On behalf of The Leukemia & Lymphoma Society, thank you so much, doctor, for volunteering your time and expertise. I am now privileged to turn the program over to you.



Disclosures

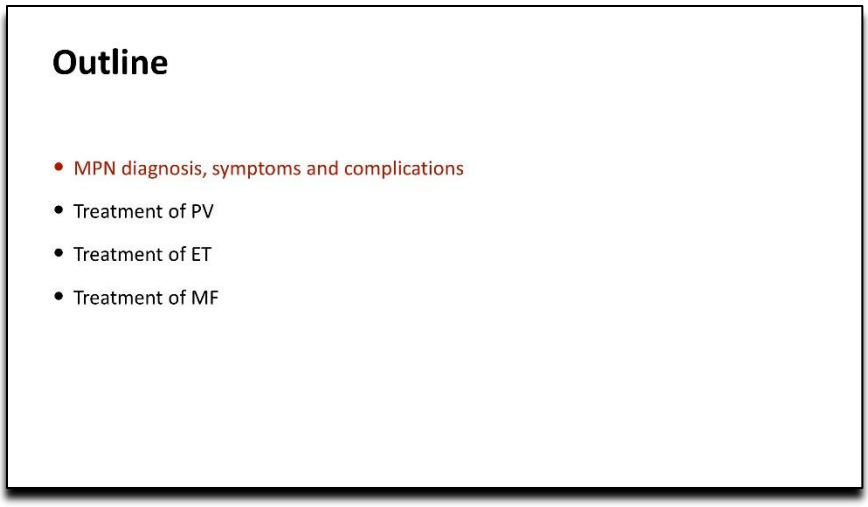
Ghaith Abu-Zeinah, MD
Thank you, Lizette, for this kind introduction, and thank you to The Leukemia & Lymphoma Society for everything you do and also for inviting me here today.

Good morning, afternoon, and evening to all of our audience across the world, and glad you are here joining us today to discuss the important topic on advances in treatment of myeloproliferative neoplasms.



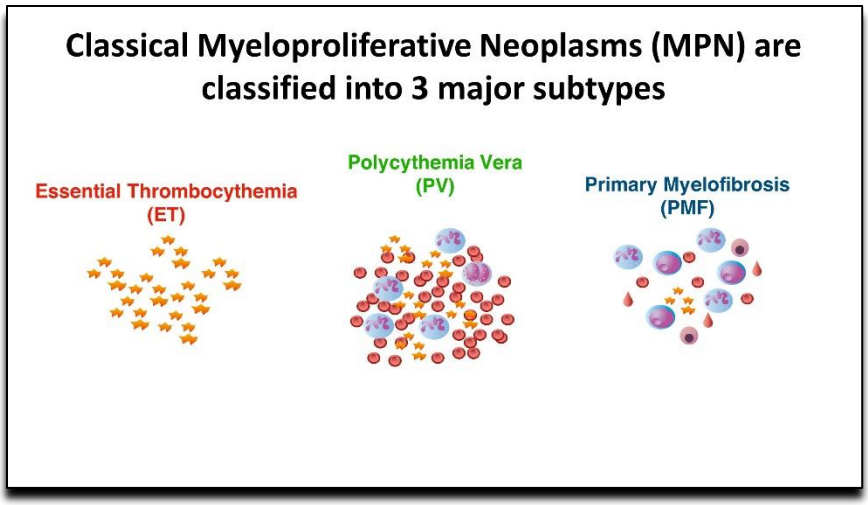
As of 1/19/21, there are 1763 clinical trials worldwide registered in clinicaltrials.gov to advance MPN treatment

So, I thought I would start the talk off by showing a map of all of the clinical trials across the world that are actually focused on finding better treatments for MPN patients. As of 2 days ago, there are 1763 clinical trials worldwide that are registered on the clinicaltrials.gov website, with the unified purpose of advancing MPN treatment and finding better treatments to improve the quality of life, prevent complications, and improve the survival of MPN patients. We hope that, ideally, we can find a treatment that can cure all of these diseases.



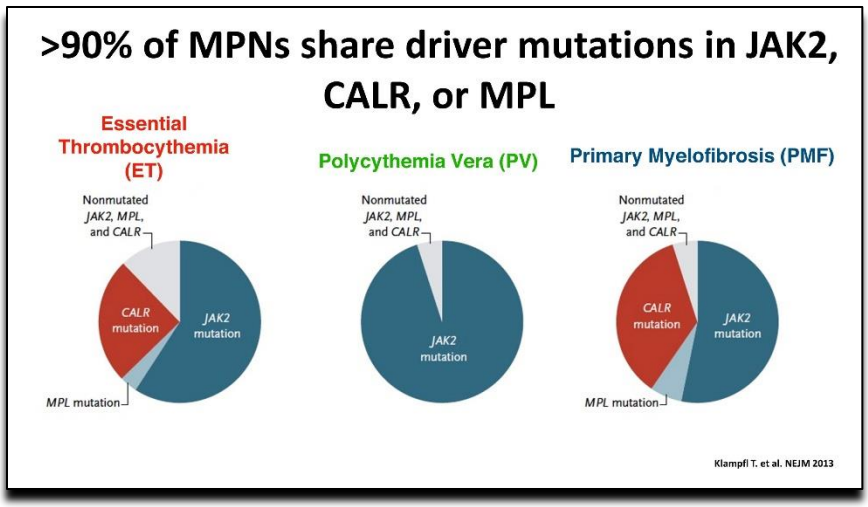
Outline

So, here is my outline. I think before we get into treatment, it's very important that we talk about the diagnosis, the symptoms, and the complications, and how important it is about the treatment of each subtype.



Classical Myeloproliferative Neoplasms (MPN) are classified into 3 major subtypes

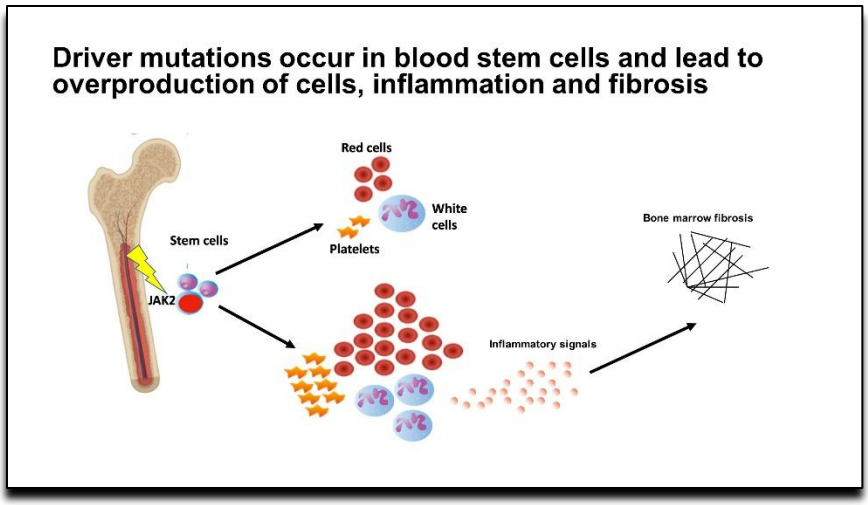
So, the classical MPNs are classified into three major subtypes. The first on the left: essential thrombocythemia or ET, polycythemia vera or PV, and primary myelofibrosis or PMF. ET is characterized by an elevation in the platelet count, and usually, that is the only abnormality we see in blood. PV is characterized by an elevation in all blood counts with particular focus on the red cell count elevation that is characteristic of PV. In primary myelofibrosis, patients can have elevated blood counts or low blood counts. But there are particular features of this disease, primarily the fibrosis that occurs in the bone marrow, that ultimately leads to a lot of the blood cells sort of leaving the bone marrow and circulating in an immature form and going to places like the spleen, causing big spleens and a lot of symptoms.



90% of MPNs share driver mutations in JAK2, CALR, or MPL

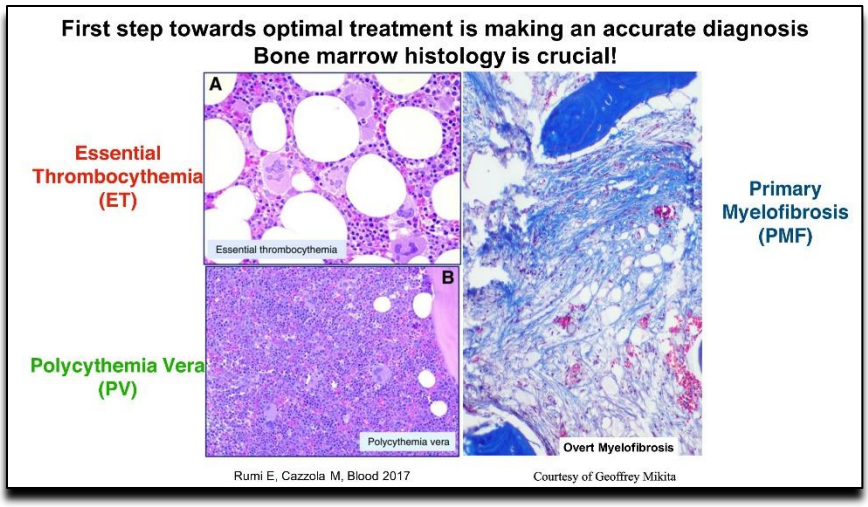
So, next I would like to highlight that the majority of MPNs—more than 90% of them—share driver mutations and *JAK2*/CALR or MPL. PV patients—more than 98% of them—have *JAK2* mutations. But in ET and primary myelofibrosis, although the *JAK2* is more common, we can find mutations in CALR and also MPL.

There are a subset of patients who don't have mutations in any of these three. It is important to highlight these mutations in order for us to be able to understand the biology of these MPNs a little bit better.



Driver mutations occur in blood stem cells and lead to overproduction of cells, inflammation and fibrosis

And I hope that this schematic can clarify that a little bit. What the schematic is showing, but really all MPN patients have both normal stem cells and MPN stem cells that have a mutation. But the MPN stem cells are generally in competition with the normal cells and are capable of overproduction of blood cells. Not only do they overproduce blood cells, but it is also problematic because these abnormal mutated cells are capable of releasing inflammatory signals that can promote or further progress bone marrow fibrosis and also lead to a lot of symptoms that patients suffer from.

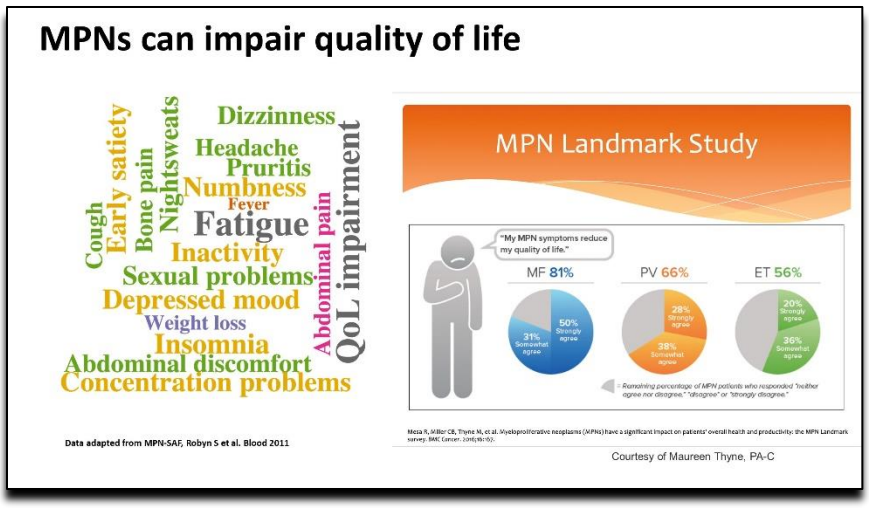


First step towards optimal treatment is making an accurate diagnosis Bone marrow histology is crucial!

I put this slide in because I think it is very important is a requirement. It is a required criteria for the diagnosis of an MPN, and the initial evaluation of bone marrow biopsy should be done because the subtype of MPN matters when deciding on treatment. So, when in the bone marrow findings under the microscope between these three subtypes, patients who have ET typically have what we call a normal cellular marrow. And that refers to the amount of blood cells that there are in the marrow in proportion to the amount of fat cells shown in white.

Patients with polycythemia vera, on the other hand, typically have a hypercellular marrow, as you can see in panel B. But this is one of the main findings—one of several—and the second one that I wanted to highlight is if you see those large they actually differ between these different subtypes. So, in the ET

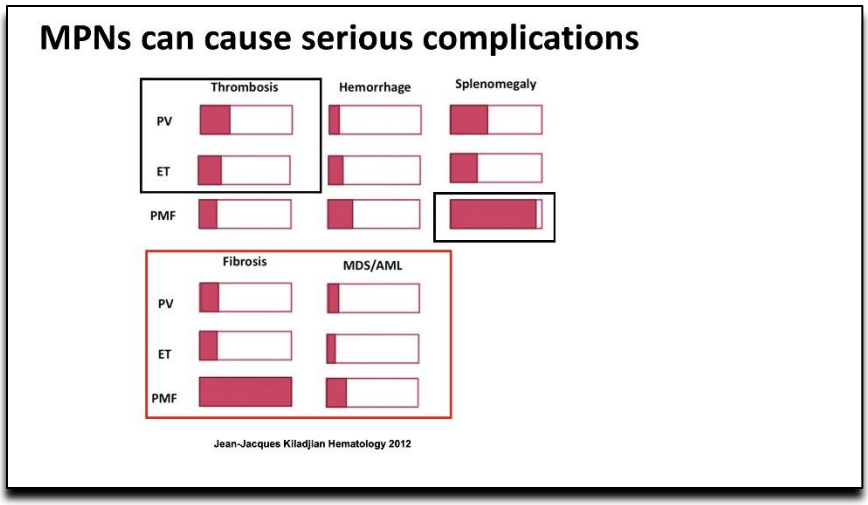
marrow, you can see them. They are a little bit clustered; they look somewhat abnormal. They're there present in the polycythemia vera patients as well, and they also have specific characteristic features than myelofibrosis highlight is the presence of fibrosis itself in the marrow, which is very uncommon in patients with ET and also less common in patients with PV but is a predominant feature of patients who have myelofibrosis. Actually shows a fibrotic marrow. This is called the trichrome stain in blue, and it shows these coarse collagen fibers in the marrow that ultimately displace the blood cells and impairs blood cell production in patients with myelofibrosis.



MPNs can impair quality of life

Now, all of this put together, the elevated blood count, the inflammatory signals, the fibrosis in the marrow—all of this leads to significant symptoms that patients experience. And in an effort led by Dr. Robyn Scherber, Dr. Ruben Mesa, and others that have led to the development of the MPN symptom assessment score. These symptoms shown here in the word cloud are some of the common side effects, many of them as constitutional symptoms, such as fatigue, but also symptoms of depressed mood, weight loss, insomnia, and even concentration problems that ultimately together lead to an impairment in the quality of life of patients.

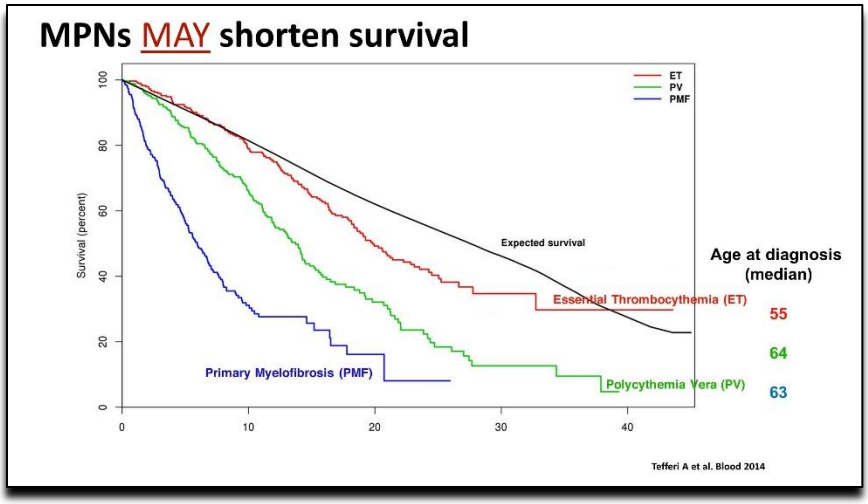
In another landmark study led by some of the same investigators there was a survey that was actually sent out to patients, asking if you do have symptoms how bad are these symptoms and how often do you experience them, and does it actually affect your quality of life and in the myelofibrosis patients, their symptoms affected their quality of life. In PV patients, it was a little bit less, but still the majority, 66%, and it was also the majority of patients, 56%, who had ET felt that their symptoms impaired their quality of life.



MPNs can cause serious complications

Moving on, shown here is actually a summary of some of the main complications of MPN subtypes that we worry about. And for the longest time, thrombosis has been the primary concern in patients with polycythemia vera or ET. It is one of the more common and morbid complications of this condition that we want to really try to avoid. It is less so in myelofibrosis but still possible, and when we look at some of the other symptoms or some of the other complications splenomegaly, seems to be a predominant feature of myelofibrosis. And it is an issue that can cause a lot of symptoms to patients.

But I think we also should focus on not only sort of the immediate short-term concerns but also long-term. We are dealing with chronic diseases, and we want to think about the future and how to prevent some of these future complications. And so, that brings me to talking about fibrosis and also leukemia, which can both potentially develop in patients with really any subtype of MPN. But I will say that it is very uncommon and quite rare for patients with ET or PV to get to those advanced stages of myelofibrosis and transformation to acute leukemia, but it is certainly a complication we have to keep on our radar.

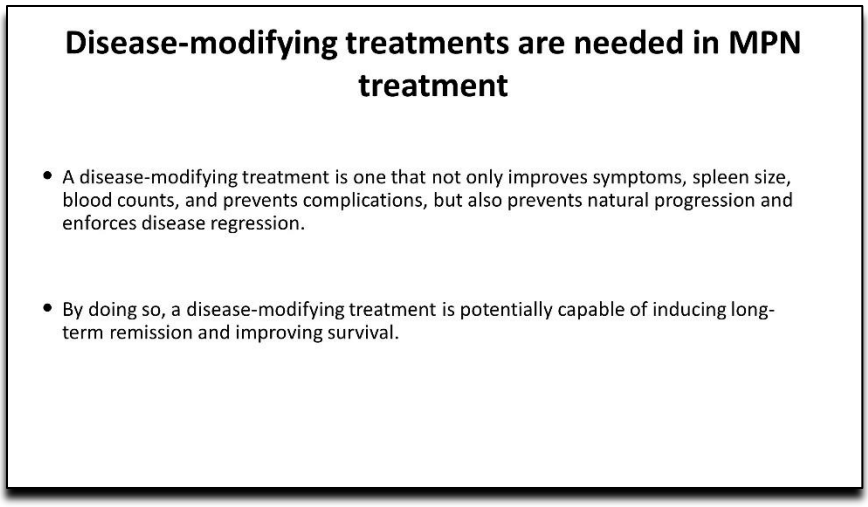


MPNs MAY shorten survival

So, all of this put together—the symptoms, the complications of MPNs—what does that translate into on the long term? And I thought this was an important study to show, and I don't want us to over-interpret what the survival curves are suggesting. But in sort of a study that is now outdated for many reasons it seemed to suggest that patients who had an MPN did not live as long as a patient who didn't have an

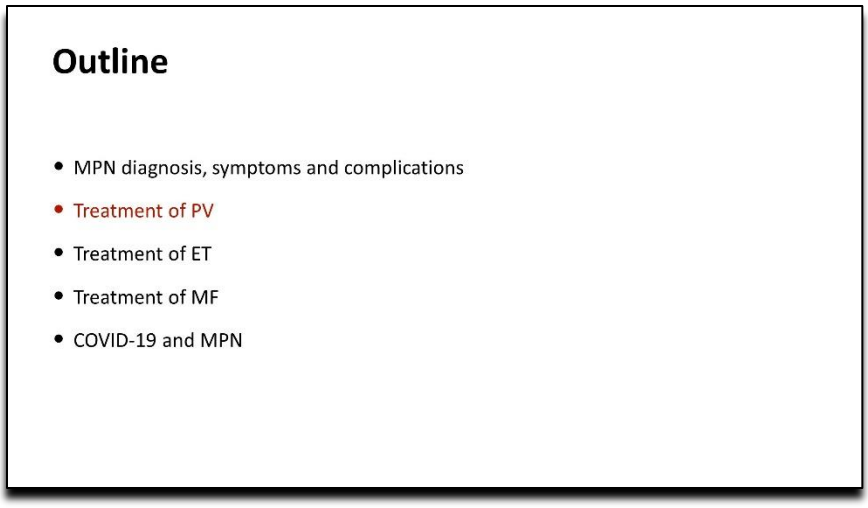
MPN. So, the expected survival of this black solid line is where patients should be on the survival curve over time, but carrying a diagnosis of ET, PV, or myelofibrosis shortened that survival to varying degrees. And I highlight that one of the reasons this is outdated is we really have to look at what was the median age of diagnosis of the MPN in these patients. And we could see that patients who are a little bit older—we're diagnosing these diseases a lot earlier now, which is providing room for earlier intervention. And the study also obviously includes all patients, including those who were treated and those who weren't treated and what have you.

So, the bottom line is just the general idea of this is to say that we need a lot of work to try to get to the point to how patients live long and healthy lives, and we need research to do that. And we need really new and advanced therapies to try to get us to that point.



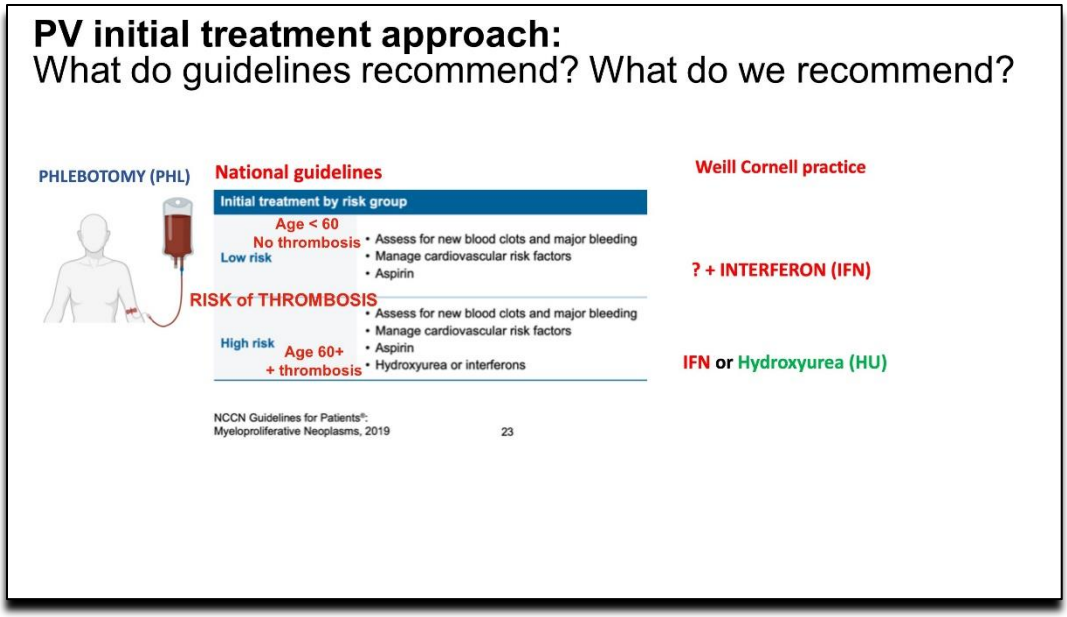
Disease-modifying treatments are needed in MPN treatment

So, how do we do that? I think that the short answer to that is identifying and developing disease-modifying treatments. And what I think of when I hear disease-modifying treatment is a treatment that not only improves your symptoms, your spleen size, and your blood counts, but it can also prevent the complications and prevent the natural progression of the disease and maybe even enforces disease regression. By doing so, a disease-modifying treatment is potentially capable of inducing a long-term remission and therefore translating into an improved survival and, ideally, a cure.



Outline

Moving on to specific treatments.



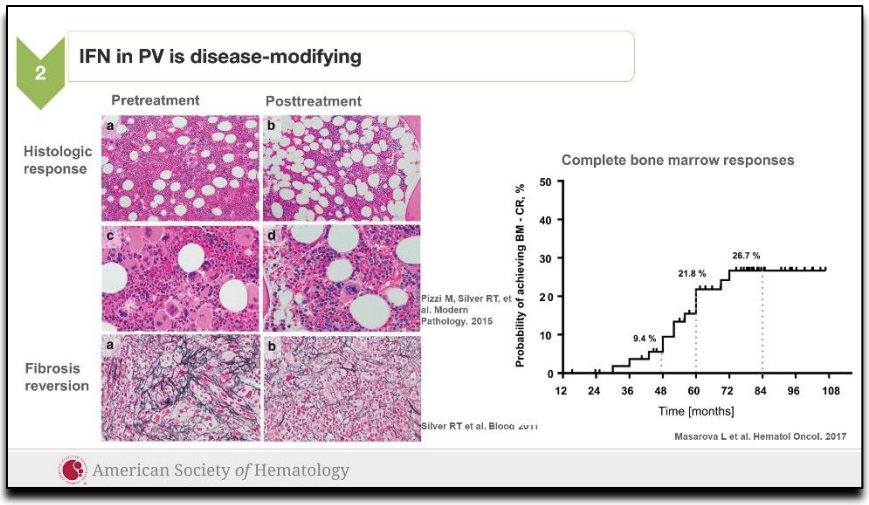
PV initial treatment approach: What do guidelines recommend? What do we recommend?

Let's talk first about polycythemia vera. And the treatment approach for polycythemia vera for really the past century has been to focus on reducing the risk of thrombosis or blood clots, and that has been originally and initially done. And still till this day we do this by a process called phlebotomy, which is bloodletting—essentially taking out extra blood and normalizing the blood count. And people use different thresholds of red cell count, hematocrits, or even hemoglobin.

But the idea is that by lowering the blood counts you will reduce the viscosity of blood and the chances that the blood will clot. But it seemed that that alone was not enough in a subset of patients to prevent clotting, and particularly it gave rise to this risk classification system of low versus high risk, which is based on the risk of thrombosis where the low-risk patients are those who are younger than 60 and never had a blood clot and the other patients who are thought to be at lower risk for good reason. Older patients and those who have had a clot are considered high risk, and those are the patients who phlebotomy alone is not protective enough from developing a blood clot. And so for high-risk patients, both the national and international guidelines have recommended the use of cytoreductive treatments. So, these are cell-reducing treatments. They could be chemotherapy. It could be interferon. This keeps the blood count in a range that is considered safe from a blood clot happening.

Now, there is some truth to a lot of this, and there is definitely evidence to back it up. But our practice is different in the sense that when we think about a lower-risk patient again, this is risk geared toward clotting. And if I may remind you, one of the things we have to also think about is what are the long-term risks: the risk of developing fibrosis, leukemia, things like that. We also asked ourselves the question of, if we are going to observe a low-risk patient just do phlebotomy and not treat, then we are running the risk of our low-risk patients becoming high risk by developing a blood clot.

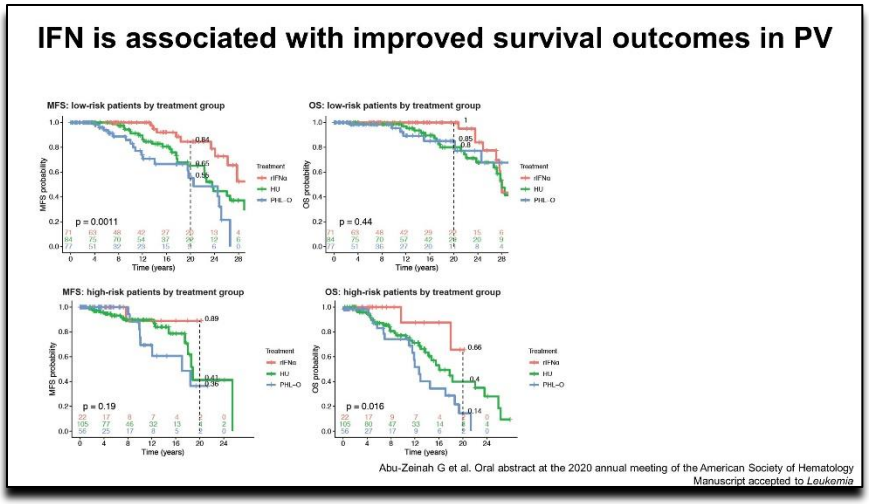
So, why wait for a lower-risk patient to become high risk in order to recommend the treatment that could truly be disease-modifying, control symptoms, make patients feel better, and potentially live longer? So, for a very long time, Dr. Richard Silver at our center has pioneered the use of interferon-alpha in treating polycythemia vera patients really since the 1980s, and that has been offered to young patients—not necessarily those who are considered high risk.



IFN in PV is disease-modifying

So, why is that? Well, we have now a lot of data that suggests, and I think the MPN community in general will agree and attest to this, that interferon is a disease-modifying treatment. And what I am showing here is a few examples of bone marrow biopsies before and after treatment with interferon. So, comparing the pretreatment marrow on the left to the posttreatment in the first panel, what you can see is that the cellularity of the marrow has actually improved. There's less cells to affect. There's more fat in the marrow. There's less cellularity. So, that is a feature of the PV marrow that has already improved with treatment.

Look at the second panel. These megakaryocytes—those big angry-looking cells. They are less angry on the right, and there's less of them, so that is another good feature. But even more importantly if you look at the fibrosis in some PV or patients who have myelofibrosis, there have been several patients who had reversion of their fibrosis. Or you can see sort of thick coarse reticular fibers on the left that get significantly reduced after treatment. So, others have shown also similarly encouraging findings where several patients treated with interferon after 5 or 6 years have achieved a complete response in their bone marrow—really, as high as 27%.



IFN is associated with improved survival outcomes in PV

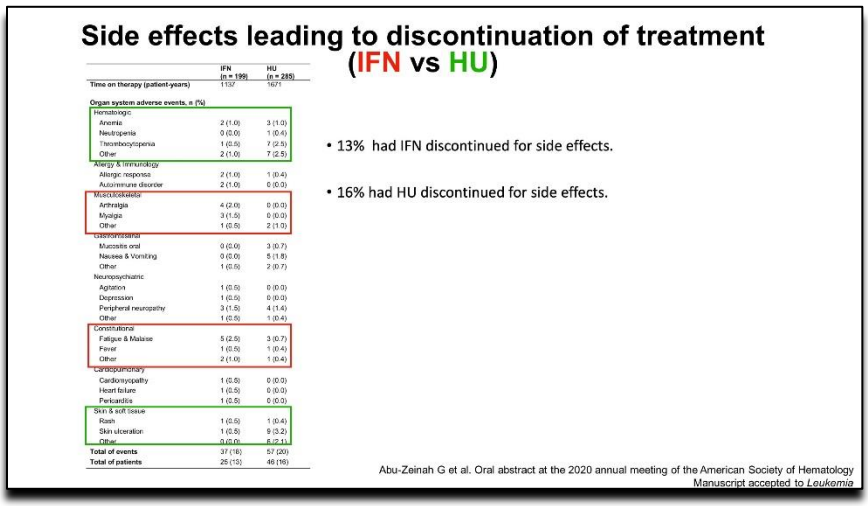
So, we actually just conducted or completed a study that was accepted to *Leukemia* and is currently in press. That's the name of the journal. And what our study was based upon is the question of, well, Dr. Silver and others at our institution have been using interferon to treat PV for the past 30 years. Can we

look back and see if patients who were treated with interferon did better than those who treated with what was considered standard of care, such as phlebotomy alone or hydroxyurea (Hydrea®)? And it turns out in the low-risk patients—this is the panel I'm showing here on the left—is a myelofibrosis-free survival curve showing that interferon continues to be superior and better than hydroxyurea or phlebotomy alone.

And just to give you an example: At 20 years, the risk of developing myelofibrosis in PV or I should say the myelofibrosis-free survival of interferon-treated patients was 84% compared to 65% for the hydroxyurea-treated patients and 55% for the phlebotomy-only treated patients. The overall survival, as you can see, is actually quite encouraging compared to the figure I originally showed you about survival in PV. The numbers here are significantly better. And may I remind you that this is in the low-risk group of patients, so they are younger than 60.

The patients who are on interferon survival at 20 years is 100%. It is a little bit lower for Hydrea® and phlebotomy, but for lack of enough number of patients or years to follow up that statistically doesn't come out to be significant. But it seems that interferon not only prevents progression to fibrosis but may also prolong the survival of lower-risk patients with PV.

The panel at the bottom shows the high-risk patients. And again, on the left is myelofibrosis-free survival. On the right is overall survival. And in red, the interferon curve again is significantly better than the hydroxyurea or phlebotomy-only survival, and I would like to draw your attention to this now. We don't treat high-risk patients anymore with phlebotomy. There was a time where it may not have been standard of care for patients to get on cytoreductive agents, but you can see that the survival is drastically different in this group and yet another reason to recommend interferon over other therapies.

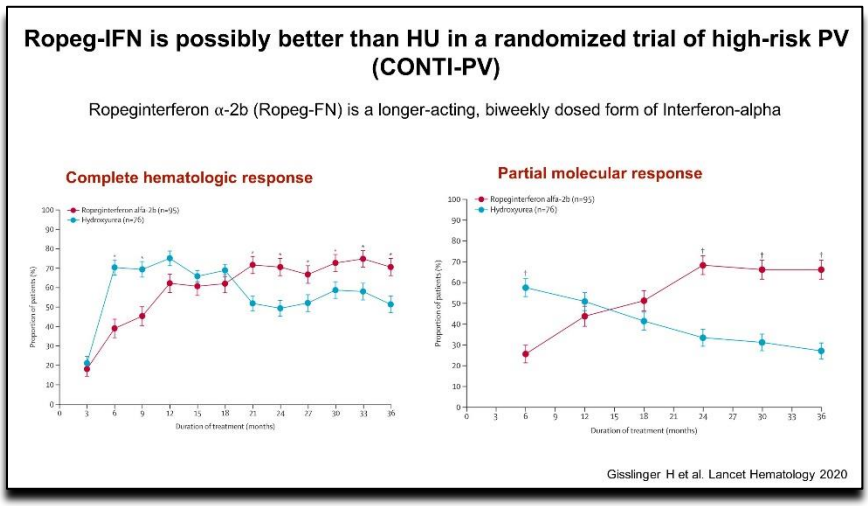


Side effects leading to discontinuation of treatment (IFN vs HU)

And I thought I would show this slide just to highlight side effects, because I think one of the major concern's patients have—and I think the reputation that interferon has received several years ago—was the side effects that come with it. It is very important to emphasize that when you use the right dose of interferon, it is very well tolerated, and the side effects aren't any more frequent than the ones you would see with hydroxyurea.

So, what this slide highlights is what is the frequency of side effects that led to discontinuation of treatment? So, there problematic enough that the patients say, I can't do it anymore. I want to come off the treatment, this drug." So, that is about 13% for interferon and 16% for Hydrea®, so comparable and potentially even lower with the interferon patients.

The table gives you a little more detail about sort of the distribution of what kind of symptoms patients really have trouble dealing with, and musculoskeletal and constitutional symptoms kind of stand out for the interferon group. Whereas the hematologic and the skin problems that come with Hydrea® also stand out.

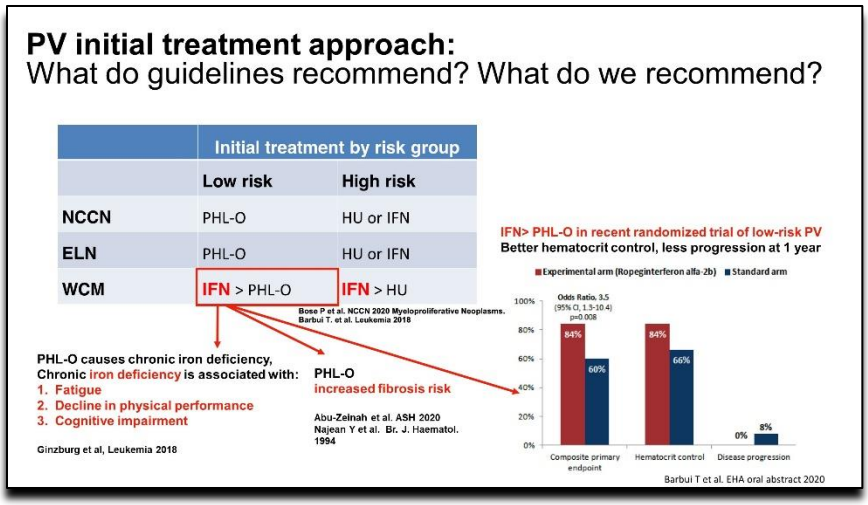


Ropeg-IFN is possibly better than HU in a randomized trial of high-risk PV (CONTI-PV)

So, what's new? Interferon has been around for a long time, but it's been around in different versions and formulations. Most recently, ropeginterferon has been developed, which is an even longer-acting interferon. And the reason we are excited about this is actually it is the first randomized clinical trial to compare an interferon to hydroxyurea over a duration of at least 5 years so far. I would say 3 to 5 years.

So, this ropeginterferon, which is longer acting, it is dosed every other week and can potentially be dosed even less frequently than pegylated interferon (Plegridy®), seems to work very effectively in controlling the blood counts for patients with PV. So, the figure showing here, the complete hematologic response rate the fraction of patients who have had a complete response in their blood count comparing interferon or ropeginterferon in red to the hydroxyurea patients, where it does seem that interferon takes some time, and it lags behind. But really eventually it's the drug that leads to a durable long-term response or remission, whereas in the hydroxyurea in several patients that response can be lost.

But it is important to also highlight the partial molecular response. And the idea behind this is what is the reduction in the *JAK2* percentage in the blood? And again, interferon was superior here, is really vastly superior and much better than hydroxyurea. So, this is more evidence to suggest the disease-modifying activity of interferon over other drugs.



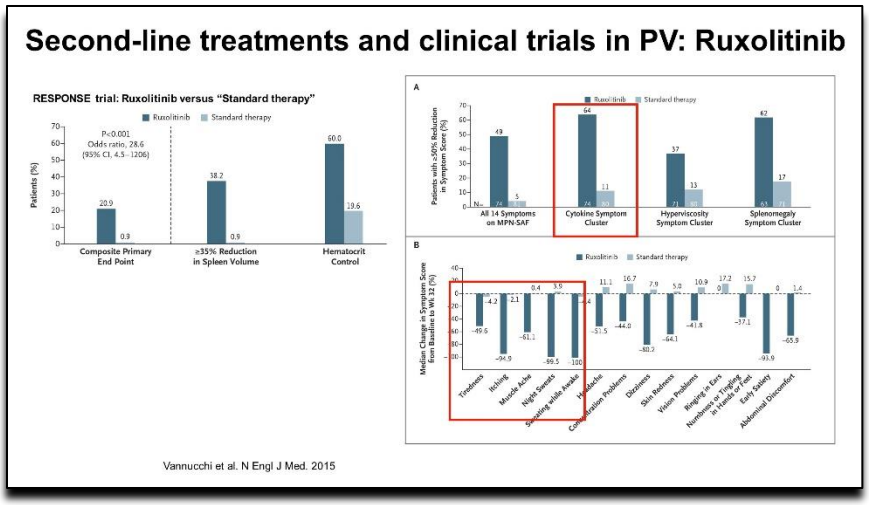
PV initial treatment approach: What do guidelines recommend? What do we recommend?

So again, showing what the guidelines currently recommend and what some practices might still be doing and what we continue to advocate for is really the incorporation of interferon into those guidelines. And these guidelines are not set-in stone. They are definitely subject to change, and we may see a positive change in the near future.

So, I thought by showing this slide also that I would highlight a few cons or negatives about doing phlebotomy alone particularly focusing on the lower-risk group of patients. And the first one of those is really that phlebotomy alone causes chronic iron deficiency, which by itself is a problem for patients from a symptom standpoint. Chronic iron deficiency can be associated with fatigue, a decline in physical performance, and cognitive impairment. So, these symptoms are things that you want to avoid. And the other thing to think about is the inconvenience of coming in for phlebotomy often or frequently really affects the lifestyle of many of our young patients who are being committed to this treatment.

The second component is that not only did our study show a myelofibrosis-free survival benefit for interferon, but there was also a signal that phlebotomy-only when you compare it, for instance to hydroxyurea, was associated with an increased risk of developing myelofibrosis. And this sort of confirms some of the original observations made, back in 1994 by Najean and others that phlebotomy alone may actually accelerate myelofibrosis rate. And the third, as a piece of evidence, I think comes back to high-level evidence from the randomized controlled trial now that ropeg is available, a study was conducted in Italy comparing ropeginterferon to phlebotomy only in low-risk PV patients.

What the study has shown is that after really only 1 year of treatment with ropeginterferon, there was a better control of the blood counts. And there was really no disease progression seen in patients treated with ropeg compared to the standard arm, which was phlebotomy only, so that 84% of patients were doing very well; 60% of those on standard arm were doing well. So, that was significantly different and a reason to again encourage the use of interferon early on.

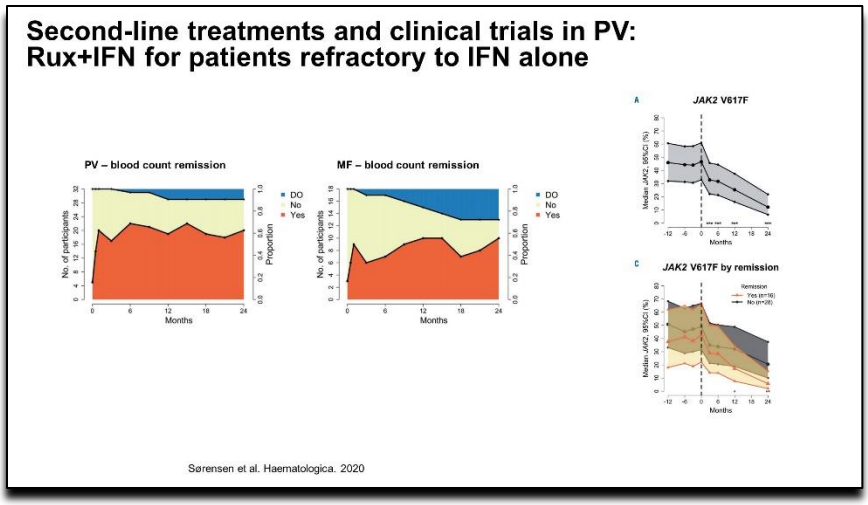


Second-line treatments and clinical trials in PV: Ruxolitinib

So, moving away a little bit from interferon just because we do recognize that interferon isn't a curative treatment and there are patients who don't tolerate it, have side effects, or do not necessarily respond to it. So, we have to think about second-line options, and ruxolitinib (Jakafi™) really stands out as the only FDA-approved drug which was actually approved for polycythemia vera around 2014, a few years after its approval for myelofibrosis. And the study that led to its approval is called the RESPONSE Trial, which compares ruxolitinib to standard therapy. And you can see the composite endpoint was met in a higher proportion of patients on ruxolitinib compared to standard therapy.

Standard therapy was a little bit loosely defined and that includes really other treatments that, can include hydroxyurea, interferon, potentially other drugs, or even phlebotomy alone. But it was effective in achieving the endpoint of hematocrit control and also spleen-lowering reduction. But what I would like to highlight, I think, is how effective ruxolitinib actually is at controlling symptoms. And if you look at all symptoms on the NPNS score, 49% of patients had significant improvement in symptoms compared to only five on standard therapy and the specific symptom clusters. So, I wanted to highlight the cytokine symptom cluster, which includes symptoms of feeling tired, itching, having muscle aches, and night sweats, and ruxolitinib was very, very effective at controlling those symptoms.

So, that kind of led us and others to consider actually adding ruxolitinib to interferon in patients who don't achieve an optimum response with interferon. But we would like to keep them on interferon because of its sort of long-term benefits, so why not combine interferon with ruxolitinib to try to control symptoms better and control blood counts better and maybe their effect would be synergistic?

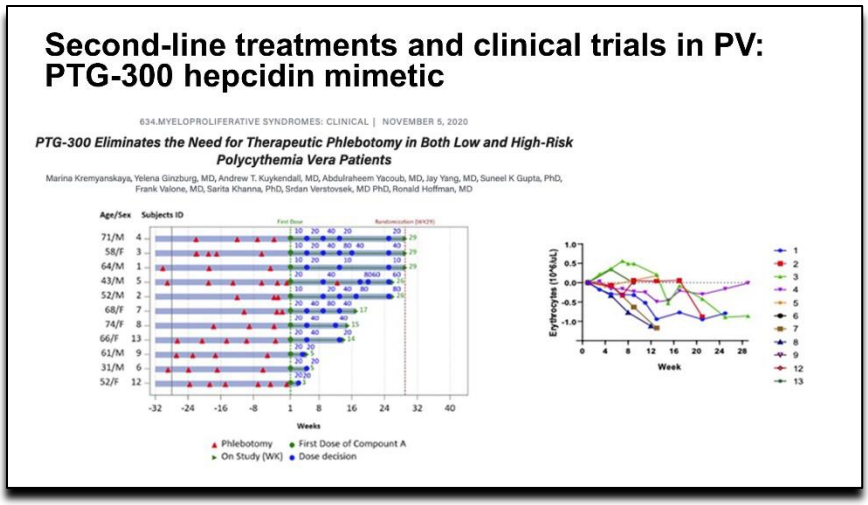


Second-line treatments and clinical trials in PV: Rux+IFN for patients refractory to IFN alone

So, this is sort of leading into my next slide, which actually is not a made-up regimen. It has been studied. There has been a clinical trial that looked at it. Actually, the Danish have published this quite recently: the combination of ruxolitinib and interferon together to use in patients who are refractory to interferon alone. And the results of this study are quite nice.

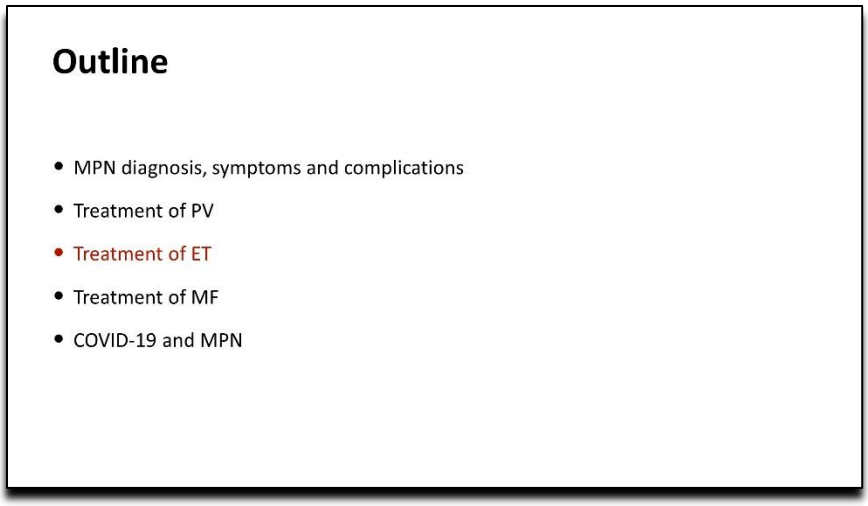
If you look at PV patients and you look at blood count remission, almost immediately—a few weeks after you start patients or add ruxolitinib onto their interferon regimen—you get a high proportion of patients responding with a complete blood count remission. So, this is shown here in orange. So, quite high—ultimately around 60% of patients—I would say about 20% do not have a blood count remission. And there is a subset of patients who early dropped out of the study. The study similarly also showed good complete response rates or remission rates in the myelofibrosis group of patients who have counts that need to be better controlled.

And then focusing on what happens to the *JAK2* mutation, the median between 40 and 50 before this combination treatment drops down dramatically to 10% after the combination is given at around 2 years here. So again, is it possible that there is some synergy between the two drugs? Because we don't see such dramatic responses in this group of patients with interferon alone, clearly because they are interferon refractory. We also don't see that kind of response with ruxolitinib alone. So, the combination is, I think, a new approach to treatment that could be considered on a case-by-case basis.



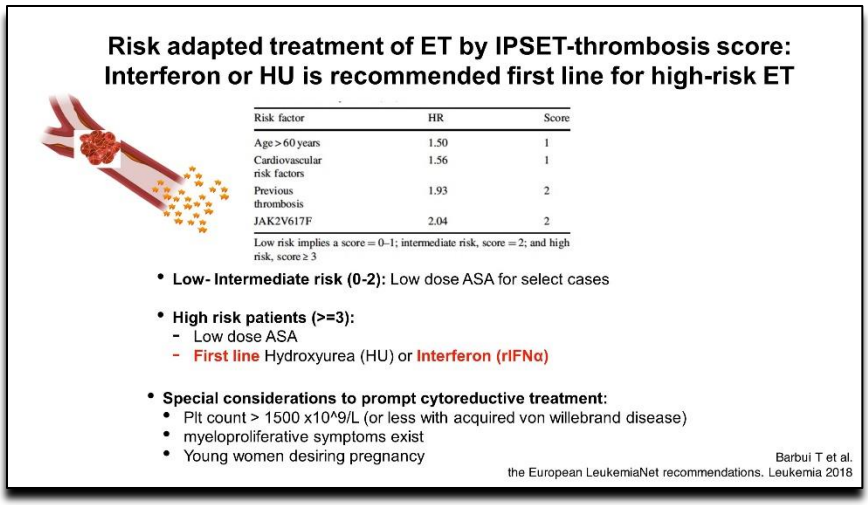
Second-line treatments and clinical trials in PV: PTG-300 hepcidin mimetic

What else is new? So, if we need another agent to control blood counts and we are trying to stay away from phlebotomy for obvious reasons and to prevent chronic iron deficiency, there actually is a novel approach. And this is a new drug called PTG-300, which is a hepcidin mimetic. What that means biologically is that it tries to shut the door, of iron getting into red cells. And you are trying to really deprive the red cells from iron while maintaining the total body iron and not making patients iron deficient overall. And so this drug in the preliminary data presented at ASH has shown some promise. Just by looking here at the patients who are getting treated before treatment required several phlebotomies, as indicated by these red triangles. And then after this new treatment was administered the frequency of phlebotomies has significantly gone down—almost to zero in many of them. And that also reflects in a reduction in the red blood cell count seen over time.



Outline

There're obviously are more clinical trials in PV, but we have to talk about all three subtypes. And ET really comes next,



Risk adapted treatment of ET by IPSET-thrombosis score: Interferon or HU is recommended first line for high-risk ET

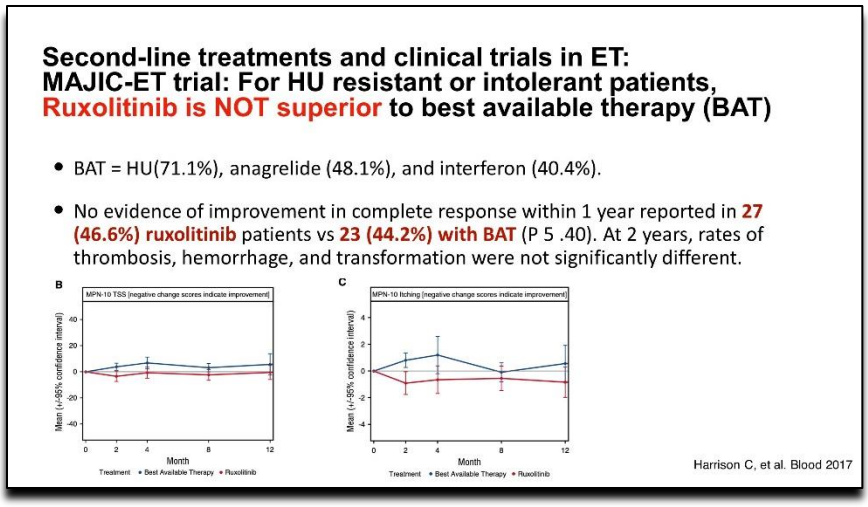
And with ET, I really tried to summarize the treatment algorithm here in one slide by saying that similar to PV treatment, it is risk adapted based on the risk of thrombosis, of getting blood clots. And how that is determined is really by a scoring system that includes age, having any cardiovascular risk factors. So,

things like hypertension, diabetes, high cholesterol, and then presence of a prior thrombosis or having the *JAK2* mutation. These are all risk factors.

Remember, PT patients can also have calreticulin or MPL, which seem to have a lower risk of developing clots than *JAK2*. So, if you add up the score and you come up with a risk category, patients who are low to intermediate risk are recommended to be only on aspirin—not everybody, actually. Patients who are considered high risk would be on aspirin in addition to a cytoreductive agent to lower the count. The guidelines would say hydroxyurea or interferon. We would say preferentially interferon if the patient is a candidate.

But there are special considerations to this stratification system. And what are those considerations? Well, if platelet counts are very, very elevated and people have different thresholds, I say, “Is it 1 million or above?” Others would say 1.5 million and above. Some are comfortable with platelets up to 2 million. But the bottom line is the higher the platelet count, the more we are concerned about the development of not only blood clots but also a condition called acquired von Willebrand disease, which is associated with bleeding. And so, that is something we can check for, and your hematologist can check for that. If that is present, it would be an indicator to say it's time to start cytoreductive treatment.

Of course, patients having symptoms is another reason to treat. And a special category is actually young women who desire pregnancy. And there are studies to show that the use of interferon during pregnancy is not only safe, but it is actually effective and much better than not treating with interferon in terms of the pregnancy outcomes both for the health of the mother and the health of the baby. So, we do have to consider case by case.



Second-line treatments and clinical trials in ET: MAJIC-ET trial: For HU resistant or intolerant patients, Ruxolitinib is NOT superior to best available therapy (BAT)

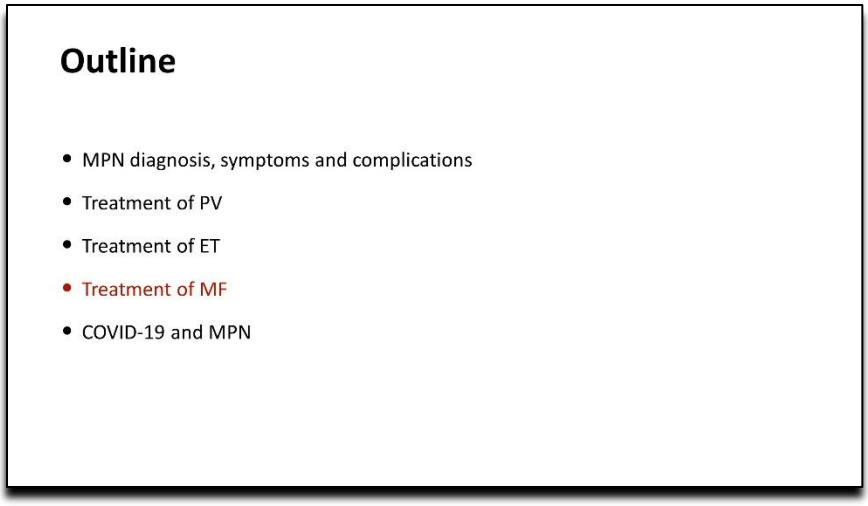
Second-line treatments for ET. So, if interferon or hydroxyurea aren't effective enough at controlling platelet counts in some cases, even an anagrelide has been used. Ruxolitinib has also been explored as a potential treatment in a randomized controlled trial, so this was randomized to ruxolitinib or best available therapy, which is highlighted here, and to be honest doesn't make a whole lot of sense because best available therapy still includes Hydrea® patients. If you are calling them Hydrea® resistant or intolerant, that they are not going to do well by staying on hydroxyurea. So, this is sort of a flawed study, but the bottom line is the study actually did not show superiority.

So, ruxolitinib does seem to be better than other options, so it's almost a toss-up. But I think that what may be important to highlight in this study is there may have been a trend toward symptom benefit with giving ruxolitinib because as you had seen with the PV data, it seems to be a good treatment to control some of the cytokine-associated symptoms. And particularly in this study they actually found

that ruxolitinib was effective at controlling itching, which is a symptom that some patients with ET do have.

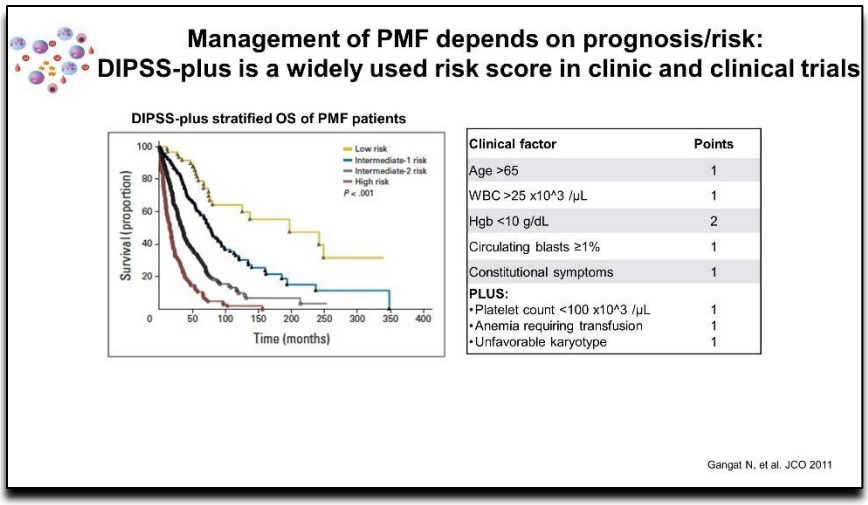
Second-line treatments and clinical trials in ET: Ropeg-IFN

So, what other second-line treatments there are for ET, ropeginterferon, is being explored? There is actually a clinical trial looking at that compared to anagrelide, which is an international study, and there are participating sites in the US, including our center, but we don't have any data yet on this.



Outline

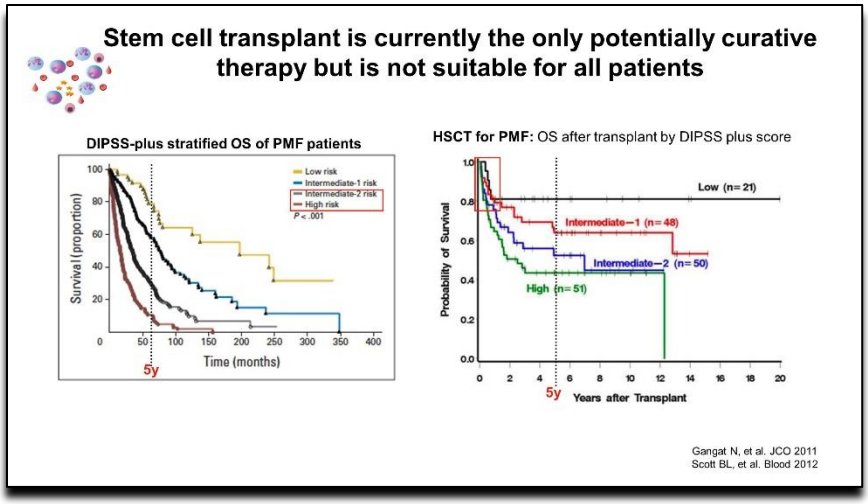
So, moving to myelofibrosis.



Management of PMF depends on prognosis/risk: DIPSS-plus is a widely used risk score in clinic and clinical trials

And I think with myelofibrosis again, I will start off by showing our clinical risk stratification system, which is used by many oncologists. And also, stem cell transplant physicians to decide on how to treat patients with myelofibrosis. And so it is called the DIPSS score, and DIPPS Plus is sort of the second version of that. And the table on the right shows you what goes into that scoring system.

So, you look at age, white count, hemoglobin, circulating blast, presence of symptoms plus some of these variables here, and then you come up with a score that puts a patient in one of these four categories: low risk, intermediate, and high risk.



Stem cell transplant is currently the only potentially curative therapy but is not suitable for all patients

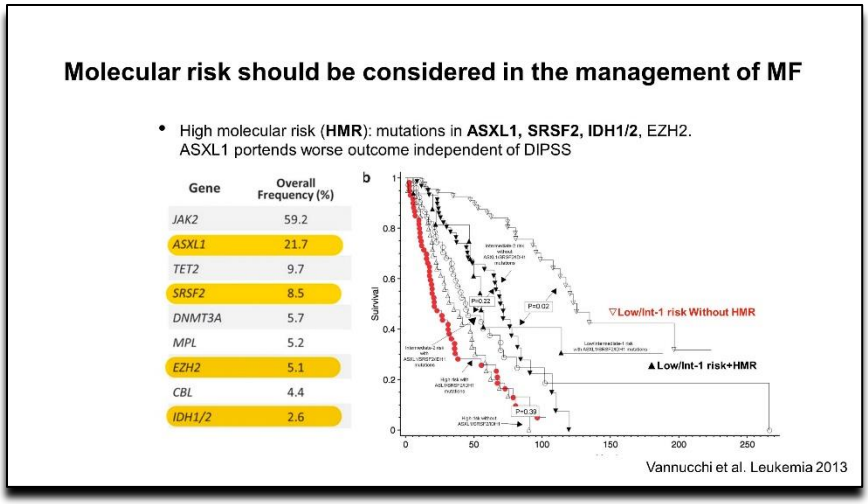
And where that becomes important is actually when we start talking about stem cell transplant for the treatment of myelofibrosis. And that I think is a major deviation from what we have been talking about the past half an hour about disease-modifying treatments and novel drugs.

Stem cell transplant is a procedure. It is considered cellular therapy. And the reason transplant is a good option for some patients is it does have the potential to cure those diseases. It does have the potential to cure myelofibrosis, but we do have to recognize that transplant is not a benign procedure. Just like any drug or treatment has side effects, transplant does have significant side effects and

potential complications that we always have to weigh what are those risks with the benefits of the transplant. And in order to make that comparison, I decided to actually show the survival curve of myelofibrosis patients who do undergo transplant and do a little comparison between these two figures to get an idea of why we offer transplant only for patients who are intermediate or high risk—or I wouldn't say only, but in most cases.

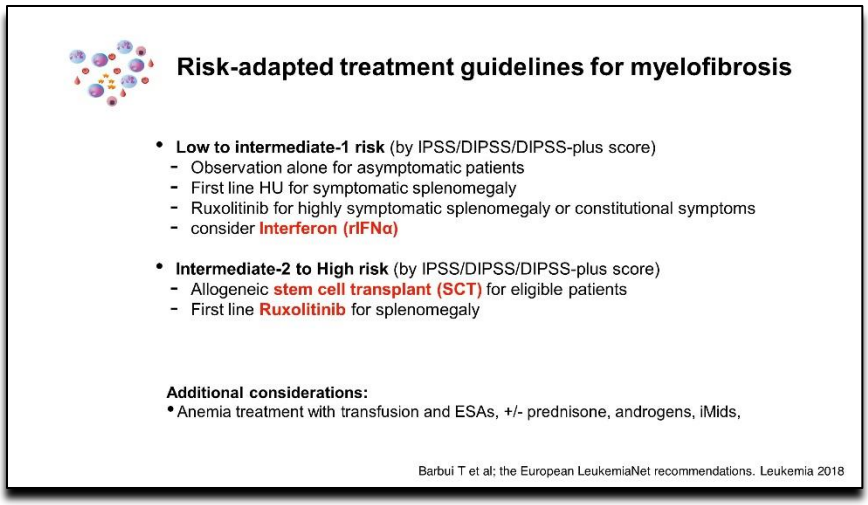
And so, highlighted on the right panel figure is the patients who underwent transplant. And in the first year regardless of what risk patients had there was the about a 20% mortality in this study. So, that could be attributed to many factors, but it does suggest that when you go into transplant one of the things we have to think about is trying to get through the first year or two. After getting through the first year or two, things do seem to flatten out at least in some of those myelofibrosis subtypes, but we do have to consider justifying a transplant for somebody who is low risk or intermediate risk if they have a similar survival without a transplant. Why would you put them through it? Whereas if you look at the intermediate to and high-risk patients, when you look at the survival at 5 years, it appears to be better with transplant—therefore justifying performing a transplant.

Now again, the challenge here that this is group data. It is not individualized data. It is very important that patients discuss all of the factors with their hematologist–oncologist and also their transplant physician.



Molecular risk should be considered in the management of MF

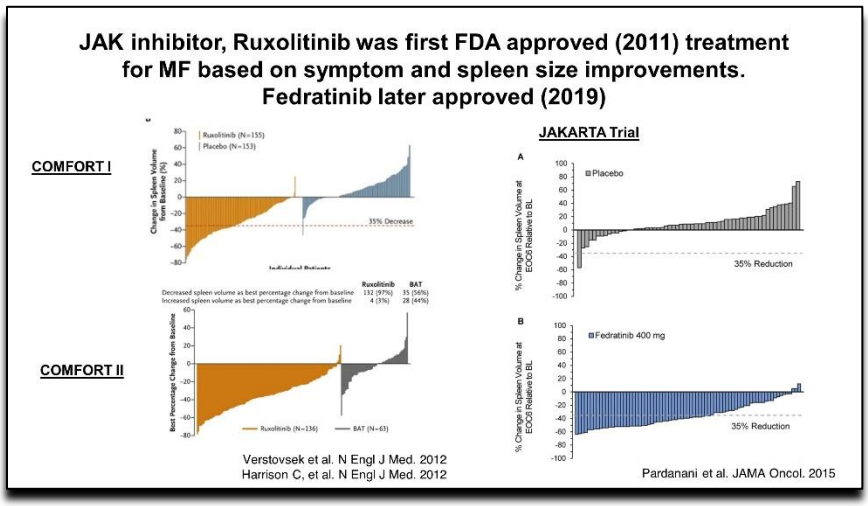
Because one example of another factor that may play in, is the presence of what we call the molecular risk. The presence of high-risk mutations can influence where patients are categorized in this risk-stratification system. So, as patients do have mutations and other genes, such as ASXL-1, SRSF2, and others, the evidence so far and what we have learned is that some of these mutations carry a worse prognosis that if a low-risk patient has, for instance, a ASXL1 mutation, they might be at high enough risk for us to talk about transplant. So, that is something to keep in mind.



Risk-adapted treatment guidelines for myelofibrosis

So again, what are the guidelines recommending? This is the European guidelines that essentially suggest that if you are low or intermediate risk, observation alone might be sufficient. Now again, this is one of those scenarios where we disagree with. And we think that if there is something to offer there, we should offer. And interferon actually has a place in the low to intermediate risk for patients with myelofibrosis.

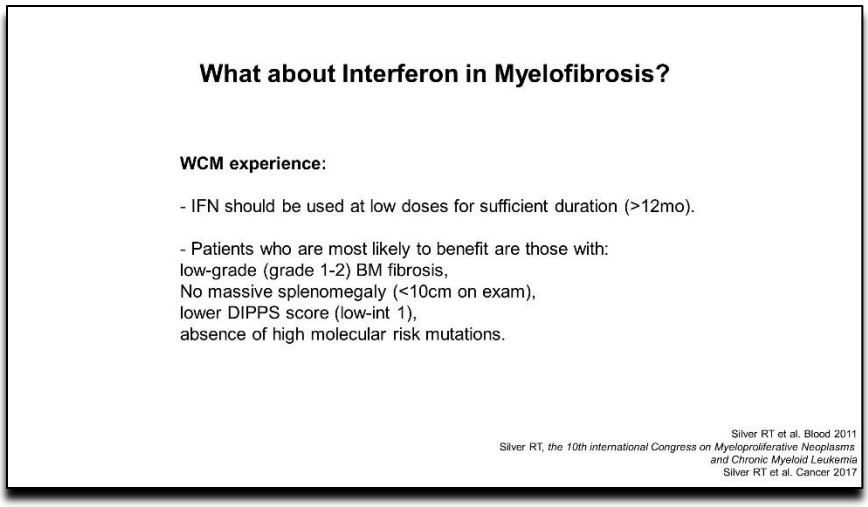
But there are other options, too, for low-risk patients. Going to the intermediate-2 and higher-risk patients as I emphasized, stem cell transplant should be considered. But also, ruxolitinib is the first-line agent approved by the FDA. There are additional treatments that are symptom targeted, including transfusions and injections of erythroid-stimulating agents, short courses of prednisone (Deltasone, predniSONE Intensol, and Rayos), androgen, and IMiDs, such as lenalidomide (Revlimid®), may help treat the anemia and the symptoms that come with it.



JAK inhibitor, Ruxolitinib was first FDA approved (2011) treatment for MF based on symptom and spleen size improvements. Fedratinib later approved (2019)

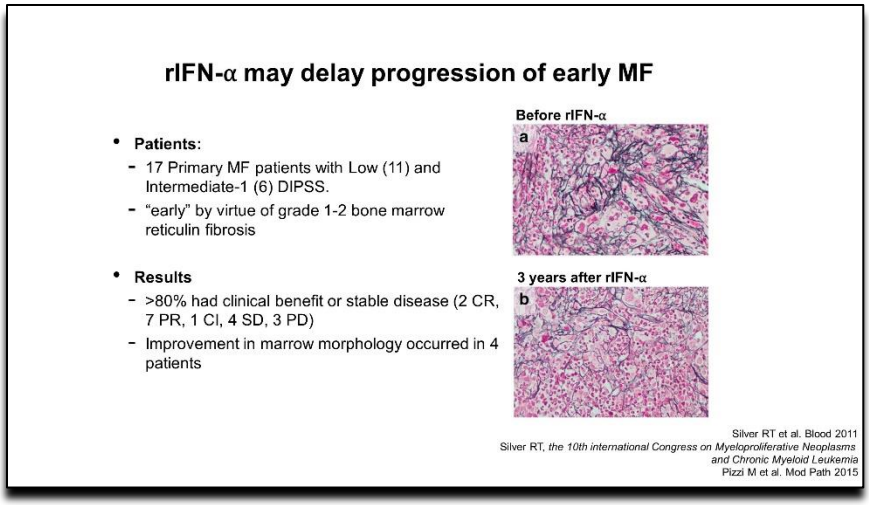
So, I'm going to maybe skip over this slide, but I just wanted to highlight that really, we only have two FDA-approved drugs for myelofibrosis. Ruxolitinib was the first one in 2011. Only recently we got fedratinib (Inrebic®), which is very similar to ruxolitinib, and their approval was really based on the response and the spleen sizes. These waterfall plots, which you will become familiar with, just show how significant of a reduction in the spleen size you can get with giving ruxolitinib when you compare

that to placebo or best available therapy. Clearly ruxolitinib is much better, and that is also the case with fedratinib. So, we have to recognize that both of these drugs got approved by the FDA for their effectiveness in reducing spleen size and improving symptoms and not necessarily for improving fibrosis, improving survival, or any sort of long-term outcome.



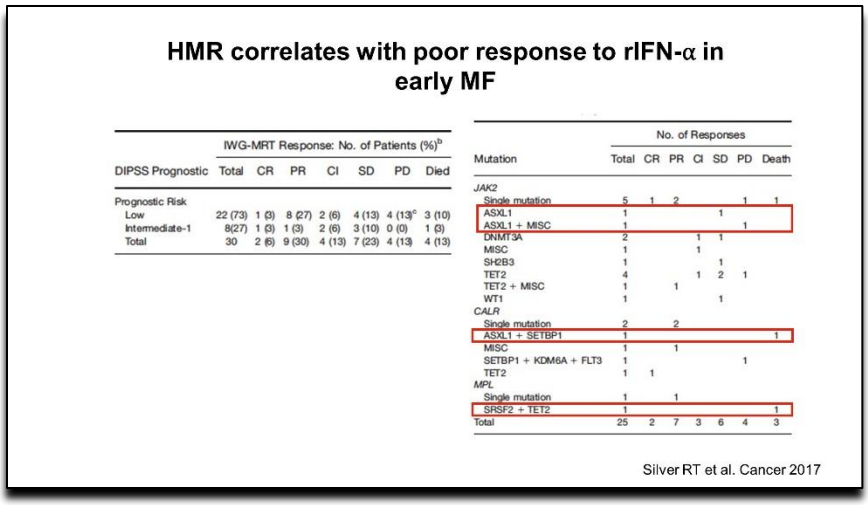
What about Interferon in Myelofibrosis?

So, what is Cornell's experience with interferon? Interferon in myelofibrosis is actually our experience has been pretty good with that. For patients who have low-grade fibrosis, sort of the earlier stages who don't have any of the high molecular-risk mutations, and generally fall in the low score in the DIPPS scale.



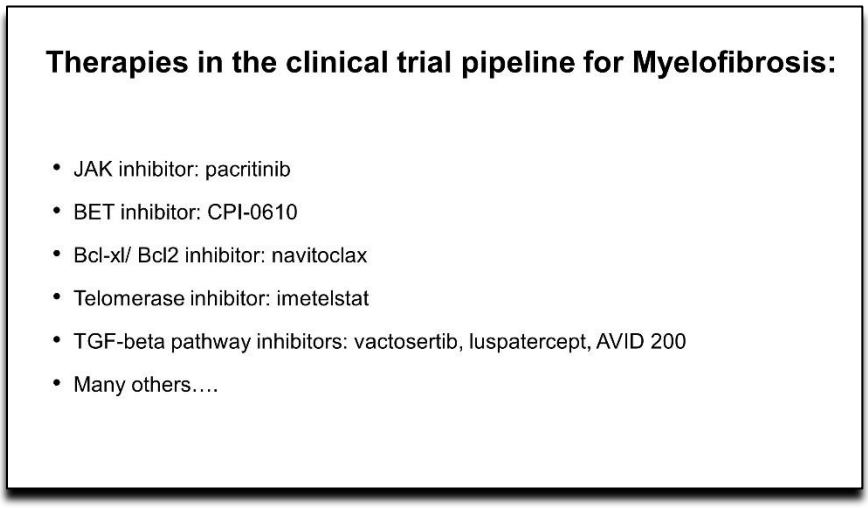
rIFN-α may delay progression of early MF

And this is actually some data from the study published by Dr. Silver. There's two studies. And one in 2011, one in 2017, that looked at the pretty good responses in some of the patients on interferon.



HMR correlates with poor response to rIFN-α in early MF

And this actually table summarizing again the responses but highlighting that some of these the patients who didn't respond too well may have had actually high-risk mutations. And therefore, we may want to think twice before using interferon in some of them.

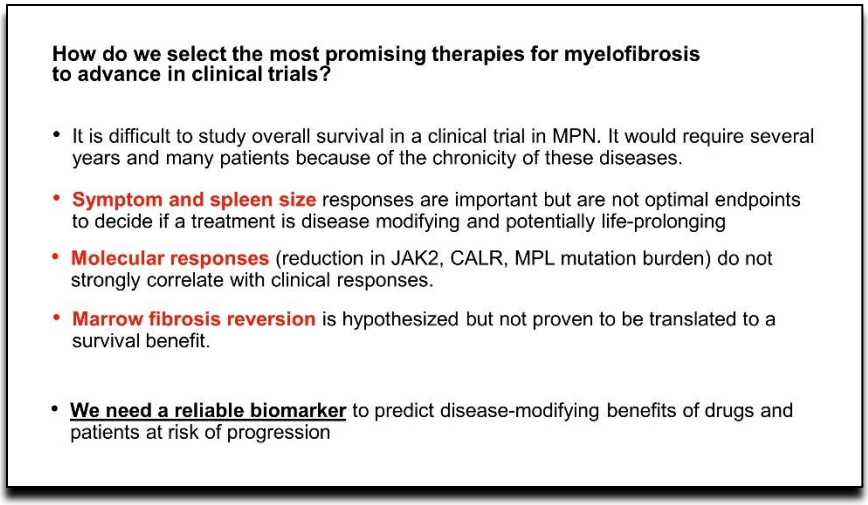


Therapies in the clinical trial pipeline for Myelofibrosis

So, there are a lot of therapies in the pipeline for myelofibrosis. It is definitely an area of unmet need, as you have seen from survival curves. It is still area that we want to focus on. And often what ends up happening is a lot of the drugs that we get for myelofibrosis can get later on studied in PV and ET. But in the pipeline for myelofibrosis, these are some of the drugs that I put up here. Some are in phase 2 or phase 3 studies, and some of them have actually been presented at the annual meeting of the American Society of Hematology.

And I wanted to highlight some of them. Because what we are excited about is some of these drugs, such as CPI-0610 or navitoclax, for instance, have reported not only benefits in spleen size and symptoms but also about a 30% to 40% reversion in bone marrow fibrosis. So again, thinking about the biology and everything we talked about that may suggest that there is disease-modifying activity. Now we don't know that yet. We need more time for follow-up, and we need more data. And we need more science to prove that. But there are a lot of therapies in the pipeline—there are many others. We do encourage you to speak with your hematologist about some of these clinical trials. And obviously seek an expert opinion, too, at centers where there are clinical trials running to discuss individualized

treatment for you and where you could belong or where you could participate in one of these clinical trials.



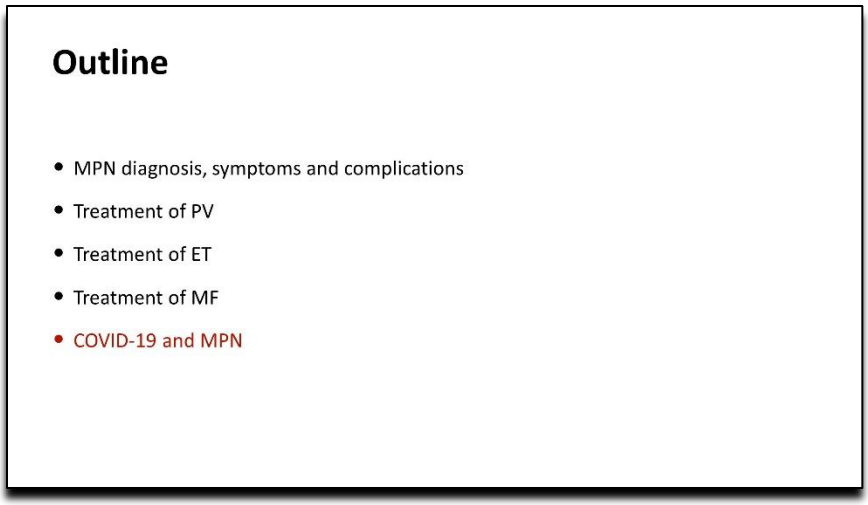
How do we select the most promising therapies for myelofibrosis to advance in clinical trials?

So, this is sort of a conclusion slide from the treatment standpoint. I think I wanted to highlight some of the issues we have so far and how we can moving forward how we can improve our ability to select and identify these disease-modifying treatments to help patients better. So, how do we select the most promising therapies?

Well, we do recognize that ideally, we want a therapy to improve survival and cure the disease, but it is very difficult to study that in MPNs because they are chronic diseases and patients live many, many years. That is a great thing, but it does affect our ability to study that in a randomized control trial. It takes a very long time and a very large number of patients to get the answer, so we want answers sooner. So, looking at symptom and spleen size has been sort of a shortcut to do that. But we have never proven, and we don't believe that those improvements although they improve quality of life, we don't know that they prolong survival. And that is what we need to get to the bottom of.

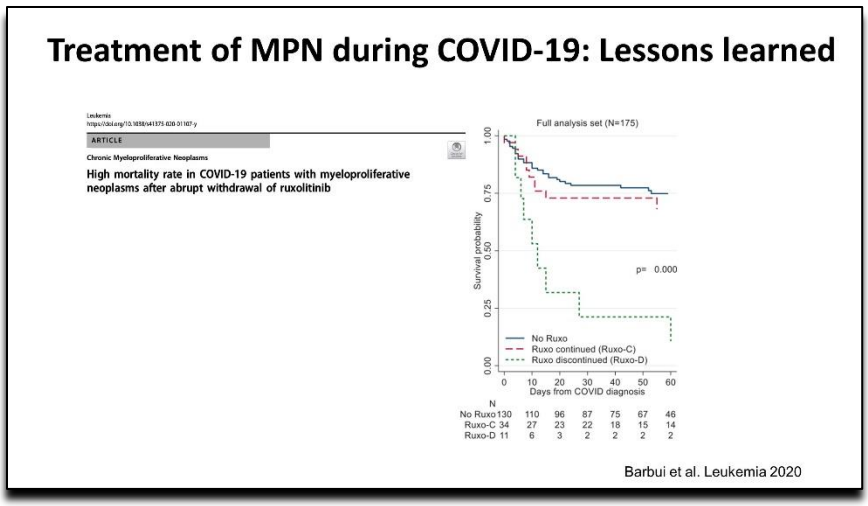
Molecular responses sort of touch on the biology a little bit by saying, well, if the *JAK2* and the other mutations are coming down, then maybe the MPN is getting better. But they have not been shown to strongly correlate with clinical responses. You know, we have patients who do very, very well clinically but have a high *JAK2* percentage or vice versa. So, it's not the only factor.

Marrow fibrosis reversion seems to be a promising endpoint to say, well, if the marrow fibrosis in patients who have it does get better over time, then maybe that translates to better long-term outcomes. So, what we really need is a reliable biomarker to predict the disease-modifying benefits of drugs and patients who are at risk of progression, and that has sort of been the thesis of my research in the lab for the past 3 or 4 years. And we do hope that what we have done—both us and our patients who have contributed to some of this research—we do hope that we bring something new that can potentially help accelerate identifying some disease-modifying drugs to help patients with MPNs.



Outline

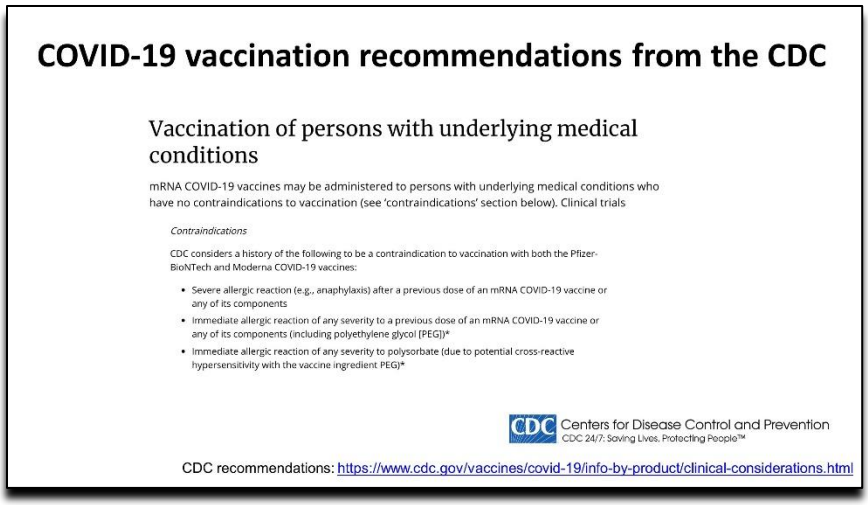
So lastly, before I wrap up, just COVID and MPN. I really have only two slides because I think there might be a lot of questions about this.



Treatment of MPN during COVID-19: Lessons learned

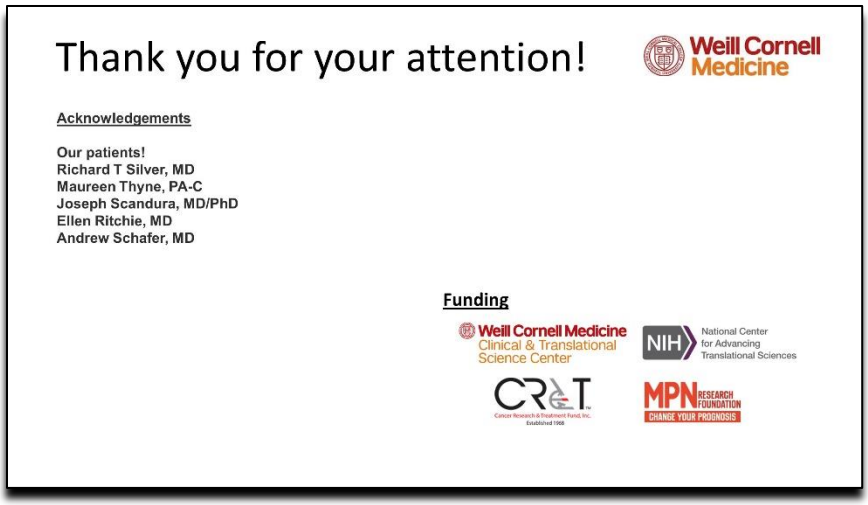
The two sides I wanted to show: This is new published data from Italy looking at patients with MPNs and COVID. And trying to figure out how patients did first of all when they got COVID, and, who recovered and what are the factors that were involved in helping the recovery of patients.

What turned out actually was this study ended up highlighting is very important aspect of MPN treatment is patients who are on ruxolitinib before getting COVID should remain on ruxolitinib. And it should not be stopped. And the patients who, were ruxolitinib was actually stopped during the course of their hospitalization for COVID, unfortunately, did not do very well. So, this is what these survival curves are showing. And this is something important to bring up for any MPN patient with COVID is to make sure that ruxolitinib is continued or at least have to be discussed with the patient's hematologist.



COVID-19 vaccination recommendations from the CDC

The second slide is about vaccination. So, the short answer is there's nothing against vaccination for patients with cancer or immune-compromised conditions or even MPNs, with the exception of the list here of contraindications that the CDC has on its website. So, you can access that. But really, these contraindications are eventually limited to having history of an allergic reaction—severe allergic reaction—potentially to the vaccine. But other than that, discuss this with your physician. And it's generally encouraged that patients do get vaccinated.



Thank you for your attention!

Okay, so with that I will thank you all for your attention. And I wanted to acknowledge all our patients who have participated in advancing this field, whether through research or patient advocacy and other means, and also thank my friends and colleagues and mentors listed here. And with that I will look forward to your questions.

Question & Answer Session

Ms. Lizette Figueroa Rivera
Well, thank you so much, Dr. Abu-Zeinah, for your very informative presentation. It is now time for the question-and-answer portion of our program. We will take the first question from our web audience. George is asking, "It seems that you prefer interferon to Hydrea® in treating PV patients for less side effects. Is this a trend for doctors who specialize in MPNs?"

Ghaith Abu-Zeinah, MD
Yeah, that is a good question. It may have become the trend now, and I anticipate it will be the trend now that we have the data from the randomized controlled trial, which is really the highest level of evidence. It had not been the trend for a very long time, when Dr. Silver sort of privately told me back when he was using interferon—a lot of people had doubts about what he had recommended. And so it had not been the trend. He had used it. There are many pioneers in Europe who had used interferon way back then, but it took a really long time for a lot of this data to mature for everybody to kind of buy in, if you will. So, it probably is becoming the trend right now, but it had not been the trend over the past, 10, 20 years.

Ms. Lizette Figueroa Rivera
Thank you. And we will take the next question from our telephone audience, please.

Operator
Thank you. Our phone question comes from Faith calling in from New York. Please go ahead with your question.

Faith
Yes. I am in remission from AML, and I thank The Leukemia & Lymphoma Society because I had an experimental clinical drug as well as daunorubicin (Cerubidine®) and cytarabine (Tarabine PFS®, Cytosar-U®, Cytosar®), and I have some genetic mutation that is more favorable. And I was wondering if I just am in remission about 4 months, 5 months, if they recommend me doing anything right now? I did go see the bone marrow transplant physician, but I'm in 80% instead of 20% because I have a genetic mutation that is more favorable. And I am just, like, wondering if there's anything that I should be doing?

Ghaith Abu-Zeinah, MD
First of all, congratulations for being in remission. That's great news. You know, AML is certainly a different disease, different treatment than MPNs, and it's certainly is one that requires expertise.

So, I think it's one of those discussions to have with your hematologist and oncologist about what you should be doing to prevent relapse or prevent recurrence. Because the goal of treatment—I mean it is important that we focus on what the goals are—but we should also not only think about treatment but think about prevention. And when we think about prevention is preventing relapse, preventing some of the complications that can occur with the treatment of the condition. Sometimes treatments lead to side effects. So, prevention right now is key. Once you are in remission you really have to focus on prevention. And I would encourage you to discuss that with your physician, obviously. And I would be happy to answer questions afterwards.

Ms. Lizette Figueroa Rivera
Thank you. And our next question, doctor, is from Gloria. Gloria asked, "Can PV be inherited if a grandparent or a parent had leukemia?"

Ghaith Abu-Zeinah, MD
So, that's a good and common question that comes up. The data suggest and the evidence suggest that PV and MPNs, in general, are not inherited in a sense or sort of in a Mendelian fashion. So, they are not inherited by passing genes along from parent to son to grandchild or daughter. So, the inheritance is not passed along, but there is a tendency. So, in some hematologic diseases and cancers in general, we often care about and ask about family history because there are certain scenarios where patients could have a tendency to develop a malignancy if they have a family history of it. But it is not really passed on down the line. That's not how MPNs get acquired. We know that they get acquired through a patient's lifetime. That is not the type of disease that patients inherit directly.

Ms. Lizette Figueroa Rivera
Thank you, and our next question comes from Edward. Edward asks, "How can you reduce fatigue and abdomen distension with PV?"

Ghaith Abu-Zeinah, MD
So yeah, I mean, I think this is where of course this is patient specific. So, in many cases, I mean, we need more detail than that. But I will give you sort of a general idea, is patients who have PV and present with big spleens—and that is actually not unheard of—20% to 30% of PV patients can have big symptomatic spleens. We do actually encourage cytoreductive therapy, so we talk about treatments like Hydrea® and interferon, which do actually, on the long run, lead to spleen size reduction.

But of course, if those initial treatments have been tried and the spleen and symptoms remain problematic, then ruxolitinib, or Jakafi®, is the next-in-line treatment, which, as you had seen from the slide, was effective at controlling spleen size and also symptoms both in PV and myelofibrosis patient. So, that could be another consideration. And of course, combination therapies could even be considered for cases that are a little more resistant. And beyond that, really, there is more specifics to it. But it depends really on the patient what diagnosis they have, making sure they have PV and progressed to myelofibrosis and then evaluate the treatment options.

Ms. Lizette Figueroa Rivera
Thank you, and we will take the next question from our telephone audience, please.

Operator
The next question comes from Nathan calling from Connecticut. Please state your question.

Nathan
My question is, "Assuming that ropeg gets approved sometime this year, when should a patient talk to his hematologist about switching from Pegasys® (peginterferon alfa-2a) to ropeg?"

Ghaith Abu-Zeinah, MD
That is actually a great question, too, because it has come up several times in the clinic. And the switch from Pegasys® to ropeg is going to be physician dependent. Or I mean, obviously patient dependent, too. But I think it is going to be a matter of opinion here because we don't have hard evidence to suggest that one is better than the other. We don't have the evidence to say ropeg is more effective at treating PV than the other.

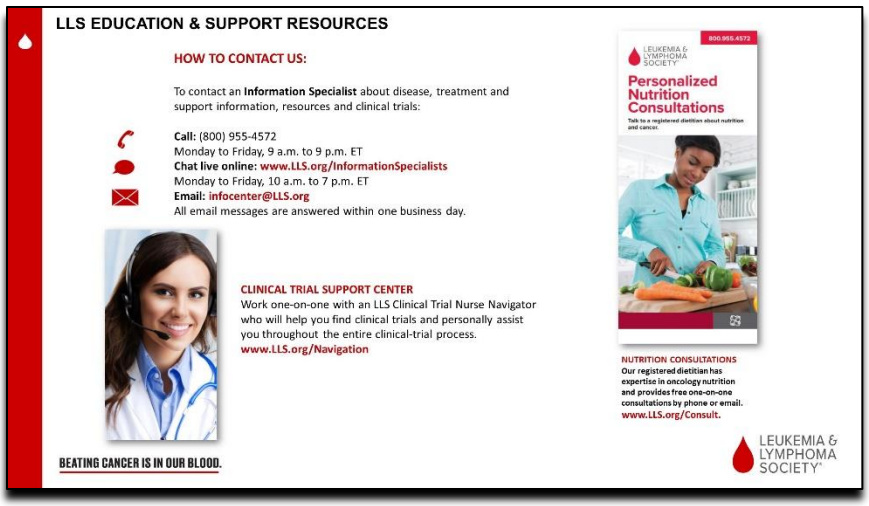
So, talking about physician preference and patient preference: It becomes sort of a comfort level of, if you are doing well on Pegasys® are you willing to come off and try something new, which we can't guarantee and don't know for sure that it will work the same? But we also have to ask ourselves, is the weekly injection actually an inconvenience that we would prefer to switch to ropeg because doing it every other week or once a month is a lot more convenient.

So, I think these discussions you can actually start having now with your hematologist even before the drug gets approved. We don't know for sure it will, but it has been approved by the European Commission. We are hoping it will be here as well, and it can be considered on a case-by-case basis. I don't think the switch has to happen. I do think that individual cases, it might be a good idea to make a switch.

Ms. Lizette Figueroa Rivera
Thank you, and our next question, doctor. Brady is asking, “When considering treatment options, what role does the patient's age play into the decision-making? We actually have had a few questions in regard to young adults with MPNs.”

Ghaith Abu-Zeinah, MD
Yeah, I think, chronological age alone should not be a decisive factor. When we historically think about the use of interferon—the idea of the possible side effects being tolerated differently by older and younger patients—I don't necessarily is a strong factor to decide whether somebody qualifies for instance, a drug like interferon.

So, I think age matters to some degree. It is not so much the chronological age. It’s really how well-performing a patient is. You know, an 82-year-old who is really jogging every day and very active essentially would be a good candidate for a treatment that we would otherwise not give for somebody who is 82 and really bedbound and having a lot of medical issues, unfortunately.



LLS Education & Support Resources

Ms. Lizette Figueroa Rivera

Thank you. And thank you, Brady, for your question, which was our final question today. A special thank you to you, doctor, for sharing your expertise with us and for your continued dedication to our blood cancer patients.

If we weren't able to get to your question today, you can contact an Information Specialist at The Leukemia & Lymphoma Society at 1-800-955-4572 from 9 AM to 9 PM Eastern Time, or you can reach us by email at infocenter@lls.org.

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Again, we would like to acknowledge and thank Bristol Myers Squibb and Incyte for their support of this program.

Thank You

Dr. Abu-Zeinah, thank you for volunteering your time again. And on behalf of The Leukemia & Lymphoma Society, thank you all for joining us today for this program. Please let us know what you need from us during this time and take good care.

Ghaith Abu-Zeinah, MD
Thank you very much.