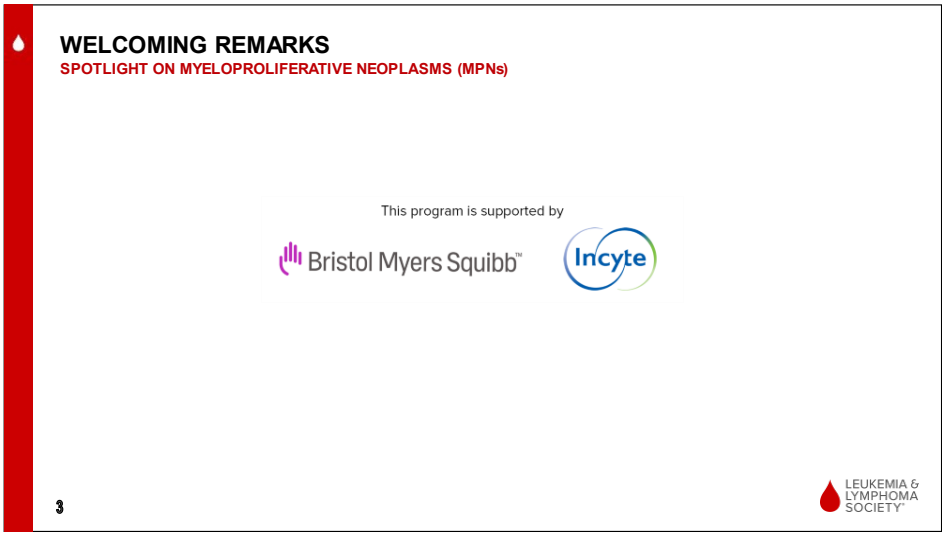
WELCOME AND INTRODUCTION

Lizette Figueroa-Rivera, MA

Hello everyone. On behalf of The Leukemia & Lymphoma Society (LLS), a warm welcome to all of you. Special thanks to Dr. Aaron Gerds for volunteering his time and expertise with us today. We have over 450 people participating in today's program from across the United States, as well as Canada.



We would like to acknowledge and thank Bristol Myers Squibb and Incyte for their support of today's program.

Following the presentation, we will take questions from the audience. We are also taping and transcribing this program for future posting on our website.

The Leukemia & Lymphoma Society funds leading edge research for every type of blood cancer, including myeloproliferative neoplasms (MPNs), as well as other blood cancers. As the largest nonprofit funder of cutting-edge blood cancer research to advance cures, LLS has invested more than $1.5 billion in cancer research since we started in 1949, leading to breakthroughs in immunotherapy, genomics, and personalized medicine that are improving and saving lives of patients. LLS is also collaborating with the MPN Research Foundation to develop therapies for MPNs.

Thank you for joining us for this important update on MPNs, and in the future, please continue to inform of us of what you need, and please continue to let us be here for you.

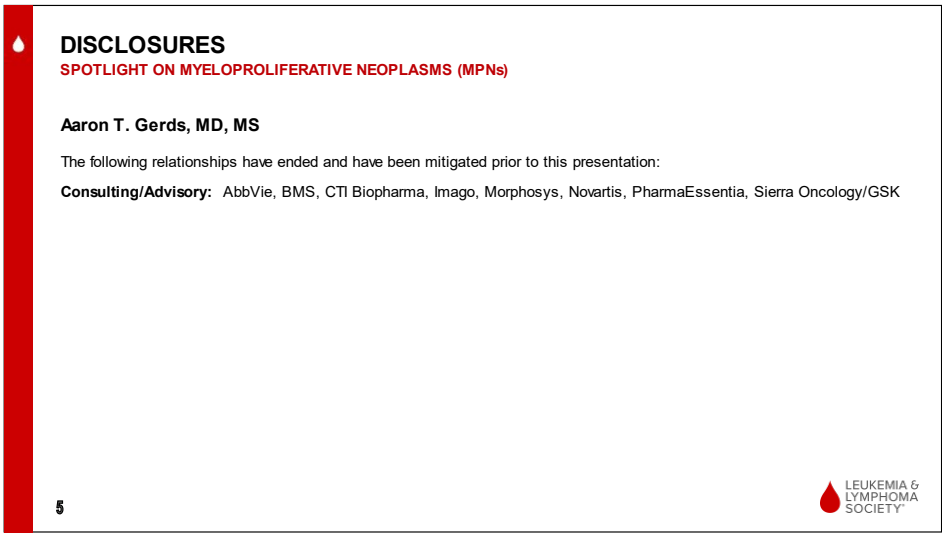
PRESENTATION

Lizette Figueroa-Rivera, MA

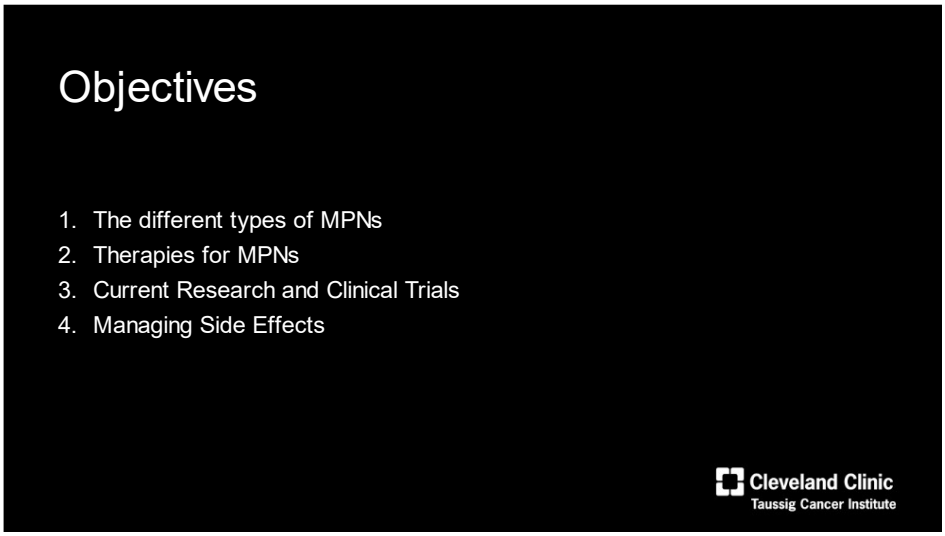
I'm now pleased to introduce Dr. Aaron T. Gerds, Associate Professor of Medicine, Hematology & Medical Oncology and Deputy Director for Clinical Research at the Cleveland Clinic Taussig Cancer Institute. He also serves as Medical Director at the Case Comprehensive Cancer Center Clinical Research Office in Cleveland, Ohio. Dr. Gerds, I'm now privileged to turn the program over to you.

Andrew T. Gerds, MD, MS

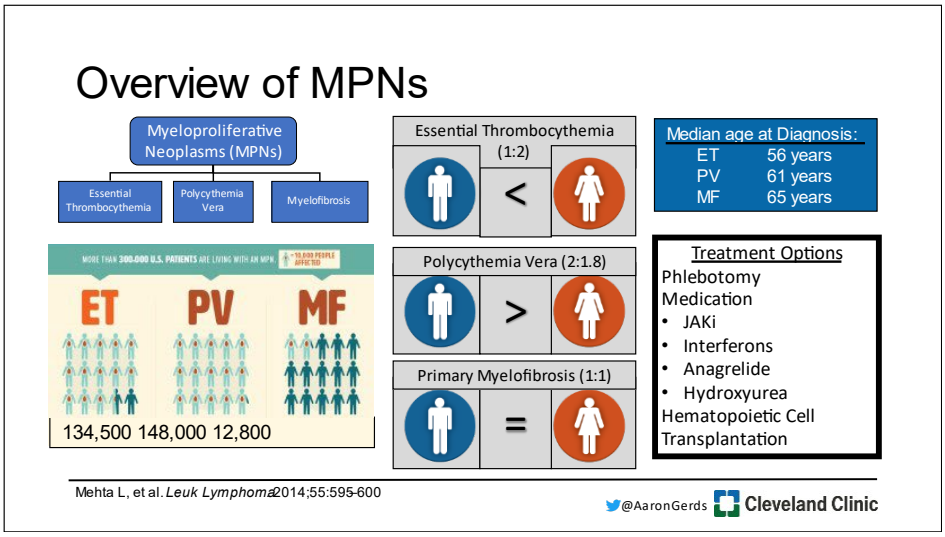
Well thank you so much. It's absolutely an honor to be with you, invited to speak with all of you on the phone and via the Web here today. We have quite a bit of material to cover, so I'm going to just jump right in.



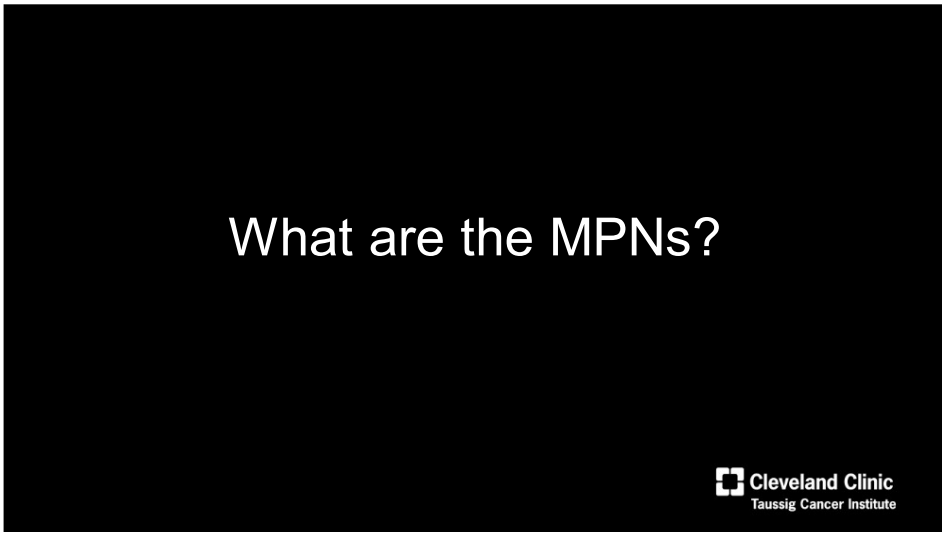
First, we have my disclosures, so I'm going to let those sit there in all their conflicted glory for a second so you can take a look.



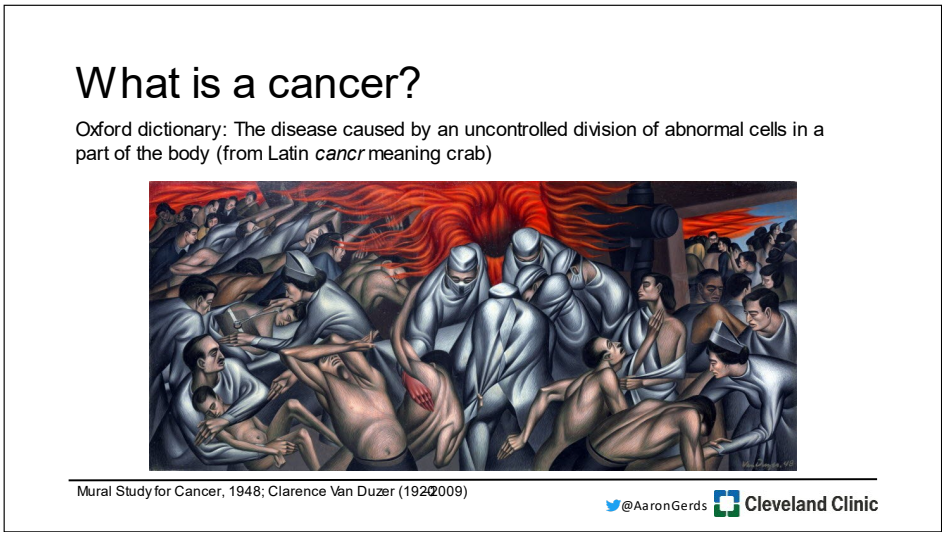
All right, and today we are going to cover four main topics. We're going to talk about the different types of MPNs, different therapies for MPNs, some current clinical research and clinical trials, as well as managing side effects.



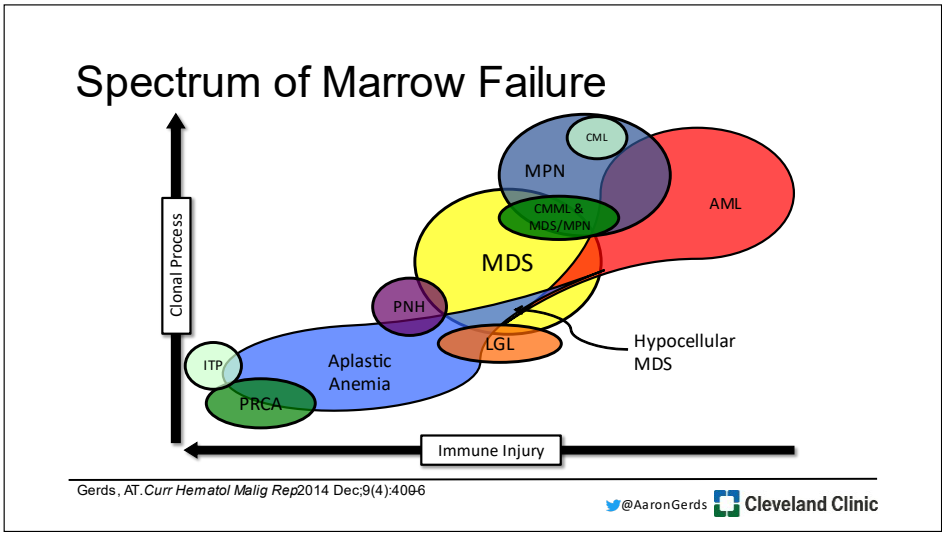
So, first of all, a little quick overview: one slide snapshot of MPNs. In the United States, MPNs affect roughly 300,000 people; and you can see the differences here between ET (essential thrombocythemia), PV (polycythemia vera), and myelofibrosis (MF). In terms of who they affect, you know, it seems that essential thrombocythemia is more commonly found in women, where polycythemia vera is more commonly found in men, where primarily myelofibrosis is kind of equal between both men and women. The average age is in the 50s to 60s at the time of diagnosis, and there are a number of different treatments that we use to treat MPNs.



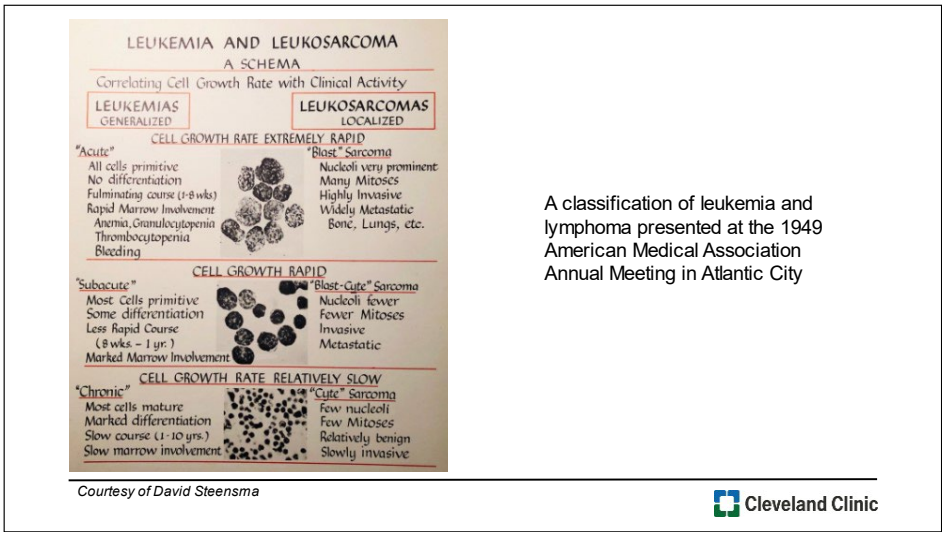
So, what are the MPNs?



Well, you know, I usually begin by saying that MPNs are a cancer. You know, there are mutations that occur that cause abnormal growth of cells in the bone marrow; and that, by definition, is a cancer. And so, I think calling this a disease or a disorder is, one, inaccurate, but two, doesn't do justice to the disease. Although, you know, it is not often an aggressive disease with survivals being measured in months for most people, it is still a type of cancer; and I think we should call it as such.

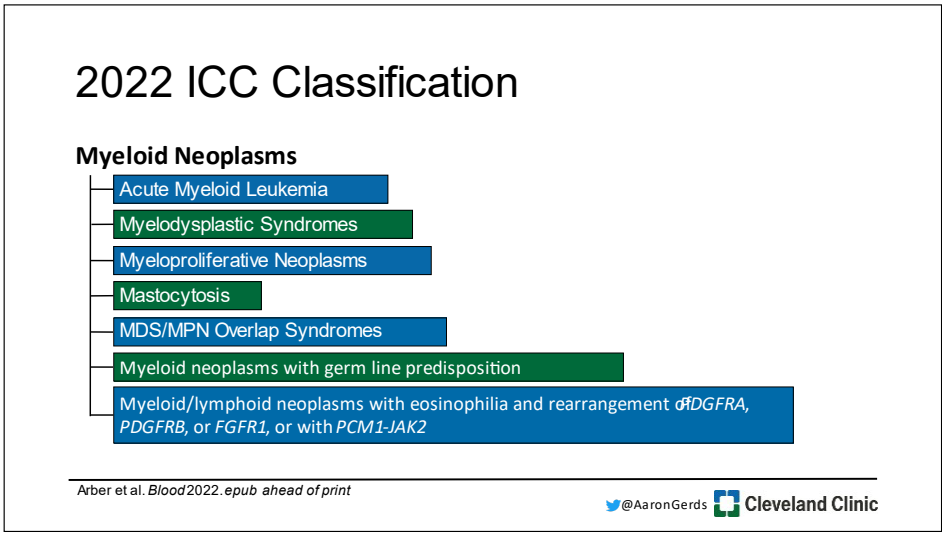


It is on the spectrum of disease with many other types of blood cancers and blood disorders, along with myelodysplastic syndromes (MDS), acute myeloid leukemia (AML), aplastic anemia, where really there's an intersection of immune injury in the bone marrow as well as clonal process. And the clonal process meaning a large group of cells that acquire a mutation and grow abnormally. And so, it's nestled in here with all these diseases, and this is what reality looks like when you're trying to take care of patients with bone marrow failure syndromes and blood cancers.

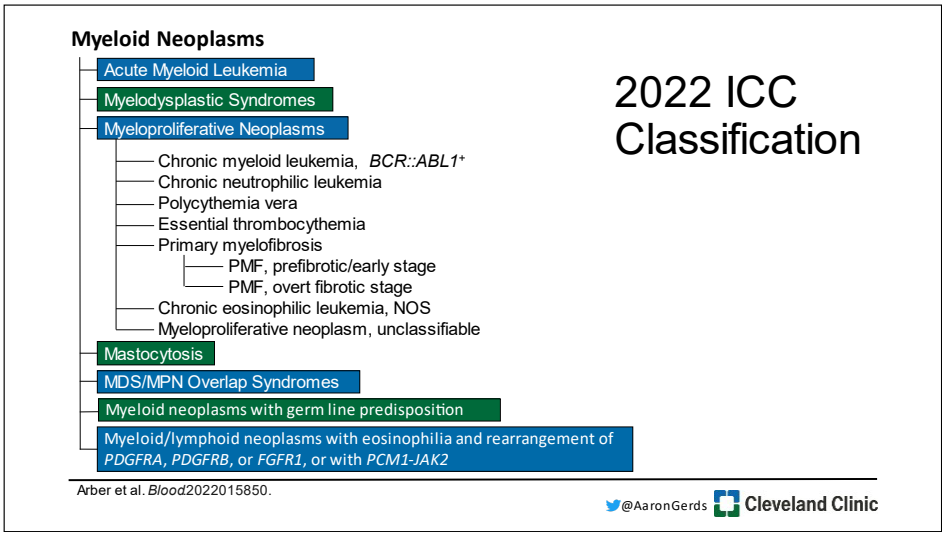


A classification of leukemia and lymphoma presented at the 1949 American Medical Association Annual Meeting in Atlantic City

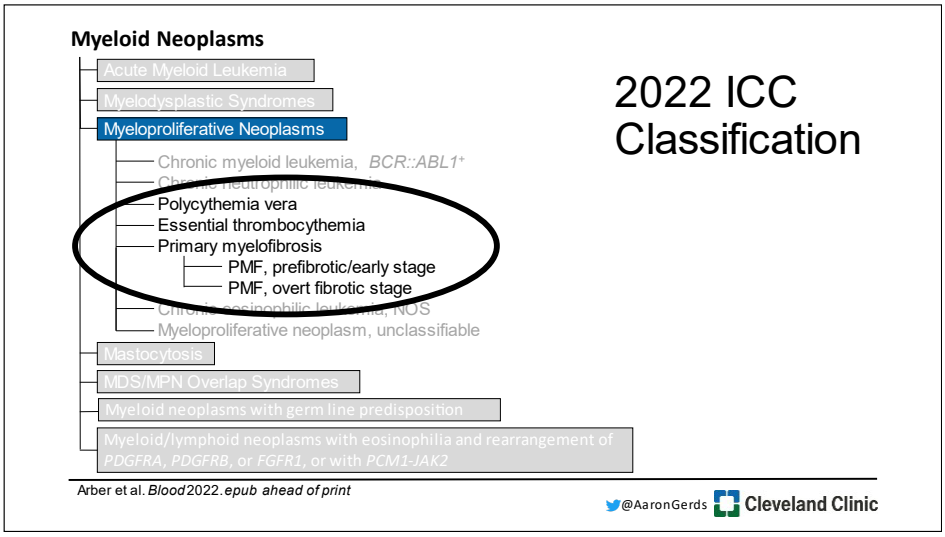
But we're organizers as human beings, and we like to put things in discrete bins so we can describe things and talk to each other about them and better understand them. And some of the earliest classifications of leukemias are shown here, where it was just acute, subacute, and chronic; and that was the best we did back in 1949.



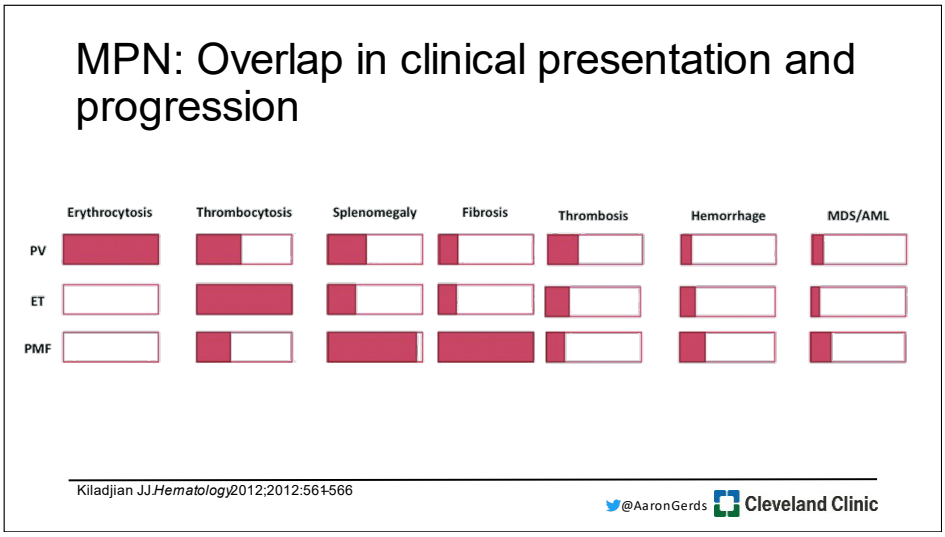
And of course, now we're much more sophisticated with lots of different classifications. And these are the classification systems for myeloid neoplasms of which MPNs are one of them.



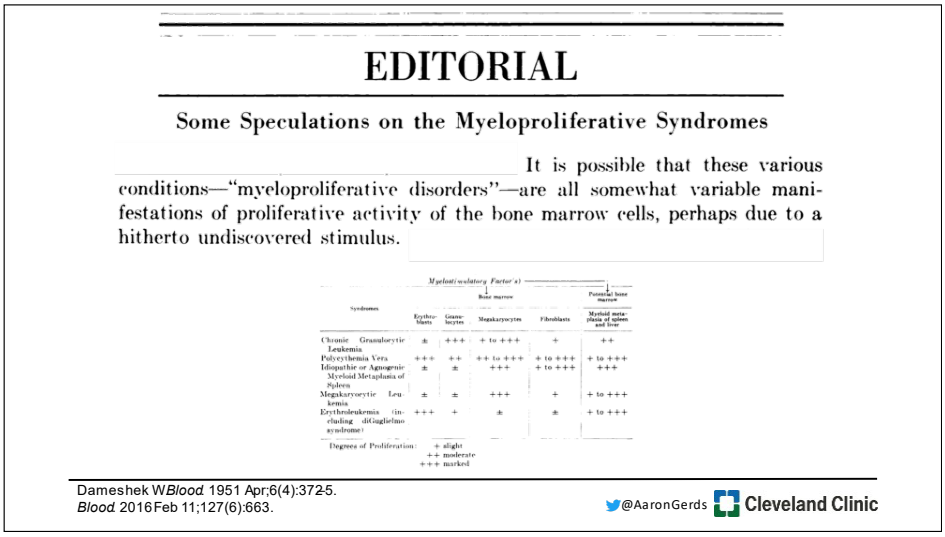
And if we open up the myeloproliferative neoplasm section, we'll see there are other diseases in there, not just ET, PV, and myelofibrosis, but diseases like CML (chronic myeloid leukemia), some rarer things like chronic eosinophilic leukemia, or even the obscure myeloproliferative neoplasm unclassifiable.



But for today's talk, we are going to speak solely about PV, ET, and myelofibrosis.

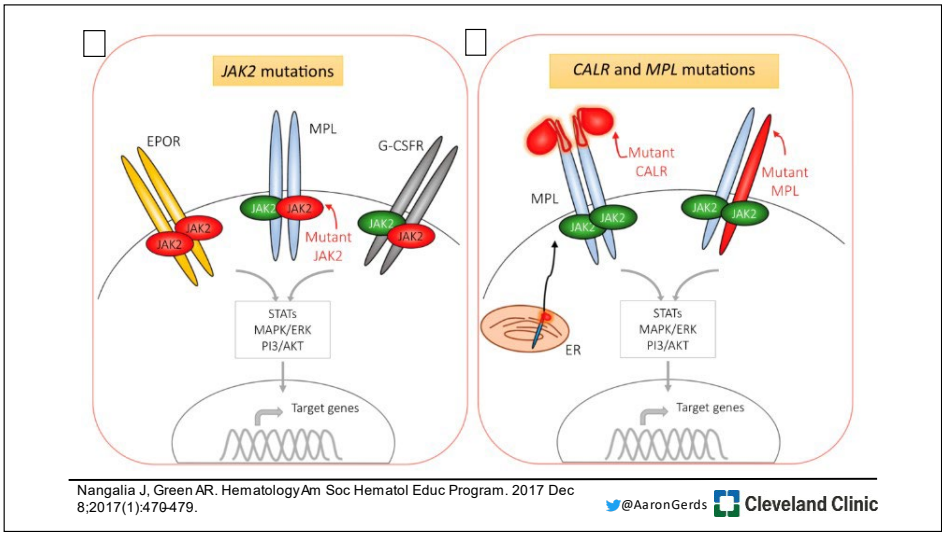


And we talk about these things in the same vein often because they have so much clinical overlap. You know, these outpatients with MPNs are predisposed for having elevated blood counts and large spleens, scar tissue in the bone marrow, are at risk for blood clots and bleeding, as well as progression to a more aggressive form of disease.



And this is nothing new. In fact, Dr. Dameshek, who was the first Editor and Chief of the *Blood* journal, as well as a past President of ASH (American Society of Hematology), first identified in 1951 that these diseases are all very closely related and that there might be some sort of key factor connecting all of them together.

But it wasn't until the end of 2004, beginning of 2005, when four groups independently identified recurrent JAK2 (Janus Kinase 2) mutations in patients with MPNs, and we now know that this JAK2 V617F mutation is present in 97% of PV patients and over half of patients with ET and myelofibrosis. So, it was a long time before we took the clinical observations onto the genomic level.



Nangalia J, Green AR. Hematology Am Soc Hematol Educ Program. 2017 Dec 8;2017(1):470-479.
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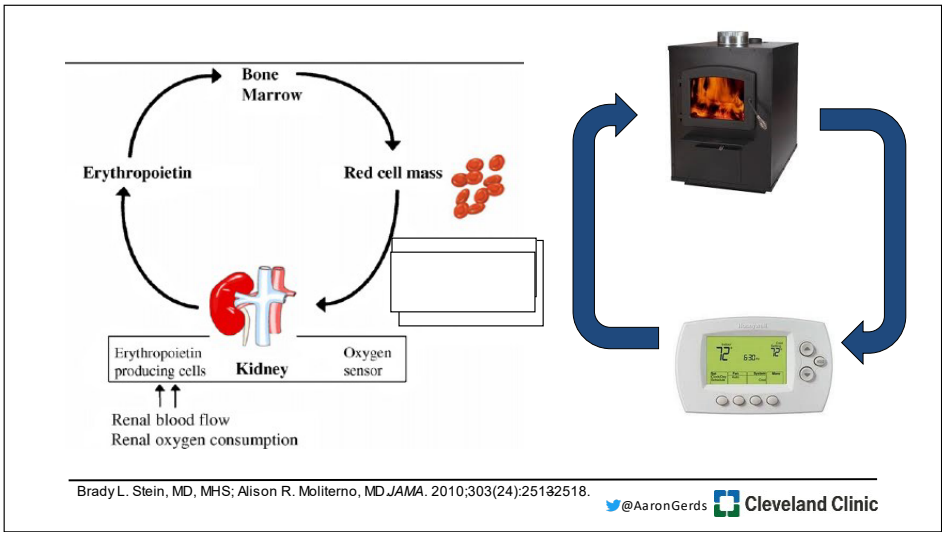
And we now know that not only are there JAK2 mutations, but there are calreticulin (CALR) and MPL (myeloproliferative leukemia/thrombopoietin receptor) mutations that drive disease. But it doesn't matter if it's a JAK2 mutation or a calreticulin mutation or an MPL mutation. The downstream effect is always the same. Constitutive activation of that pathway where the target genes are always on, and these downstream effects all lead to the proliferation and growth of these cells inside the bone marrow and all the cytokines and other consequences we see of these diseases.



Brady L. Stein, MD, MHS; Alison R. Moliterno, MD *JAMA*. 2010;303(24):25132518.
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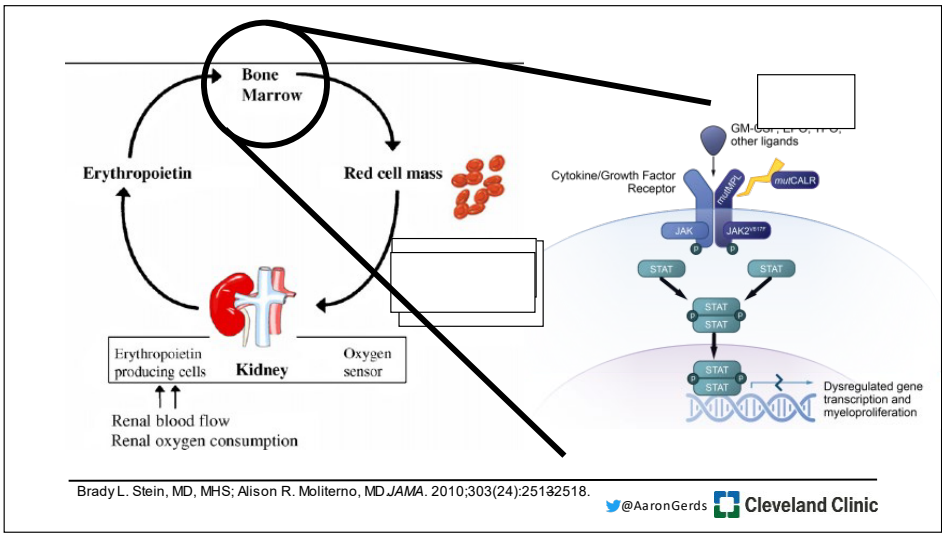
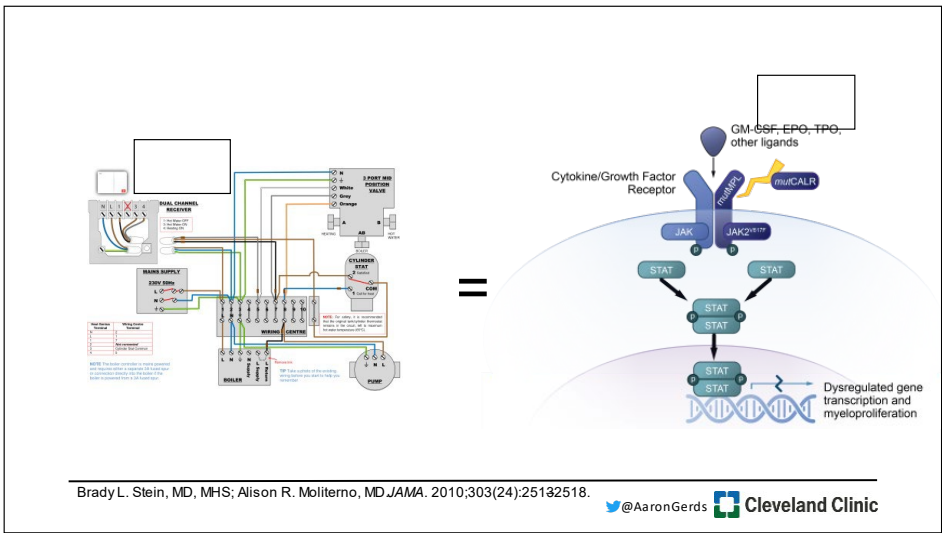
To explain this a little bit further, I often use the analogy of a furnace and a thermostat. For those of us in the northern climates, we are now turning on our thermostats and our furnaces and experiencing this firsthand. But the way I like to describe it is that we have systems in our body that keep things in balance, and one of these systems is shown here where the kidney senses the amount of red blood cells carrying oxygen in our body. That's what red blood cells do mostly, right? They carry oxygen, and there's little oxygen sensors inside the kidney. And when there's less oxygen coming to the kidney, the kidney thinks, well, gee, there must not be enough blood, so I'm going to send a signal, erythropoietin, to the bone marrow and tell the bone marrow to make more red blood cells.

And that is just like a thermostat. The kidney's a thermostat, and the bone marrow's a furnace. So, when your house needs more heat, the thermostat turns on, tells the furnace to make more heat. The furnace makes more heat, and then the thermostat turns off. Same thing with the kidney and the bone marrow. That relationship is the same with the messenger being between being erythropoietin.

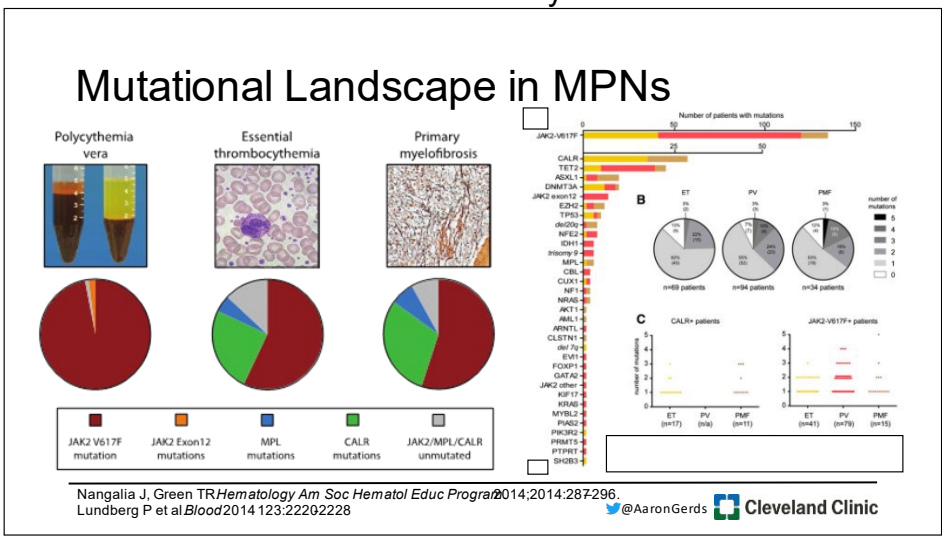


So, if we focus in on the bone marrow, inside the bone marrow is this JAK/STAT (JAK-signal transducer and activator of transcription) pathway. And when mutations occur in JAK2, MPL, or calreticulin, the furnace is on. It's on all the time, right? So, the bone marrow's making all these, in particular, PV, making red blood cells all the time. Or in ET and myelofibrosis, making other cells as well all the time and ignoring the thermostat.



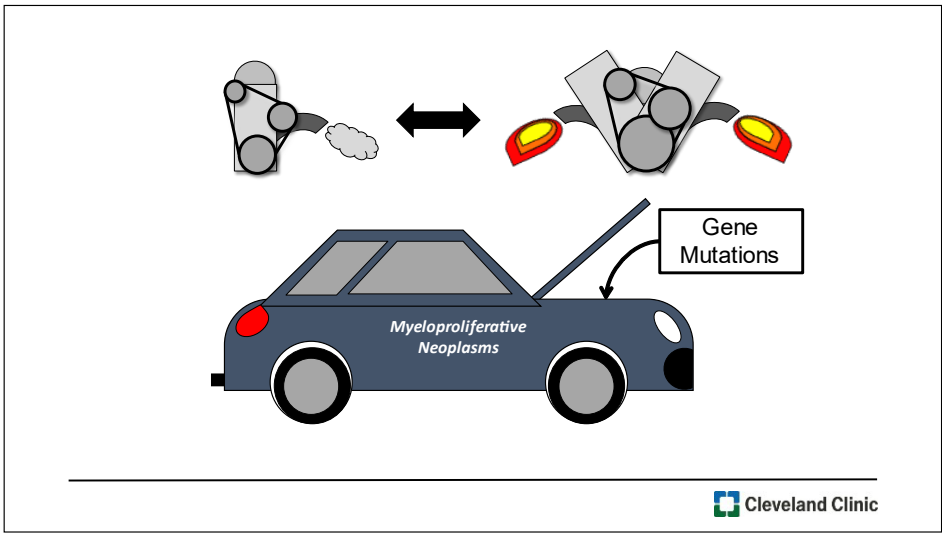
So, we go back to that analogy. It's really the JAK2 pathway is the wiring in the furnace, and when the wiring in the furnace is off or broken or not functioning, the furnace is on all the time, independent of what the thermostat or the body is asking for. So, it works just again like a thermostat in a furnace.

And so, this is the key piece of the biology behind MPNs, and this discovery has changed the way we think about these diseases and the way we treat these diseases.



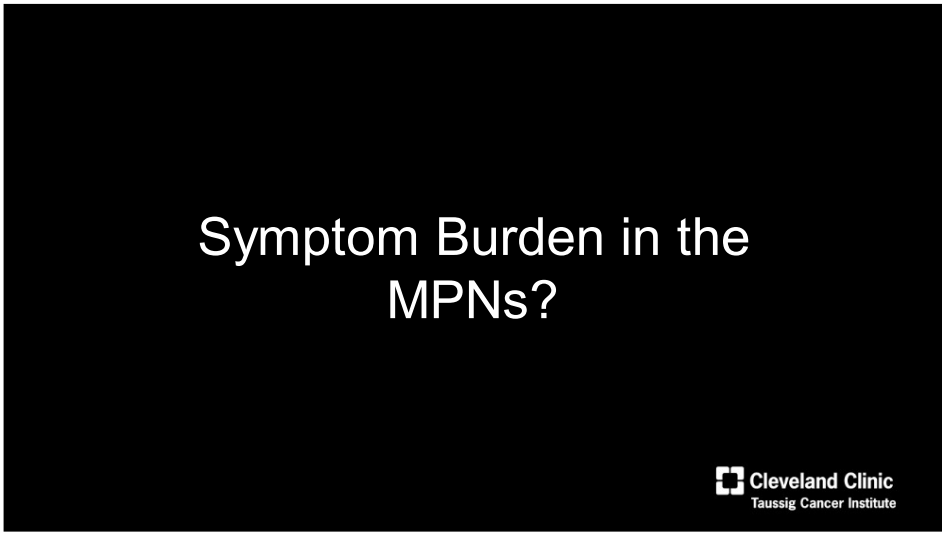
And again, here on the left-hand side of the slide are the proportions of patients with PV, ET, and myelofibrosis who have JAK2 mutations as well as calreticulin and MPL mutations. So, you know, in ET and PV, calreticulin mutations make up about a third of patients, and MPL is about 5, 10% and then there's a chunk of" others".

But these, of course, are not the only mutations that we see in these diseases. We see lots of other mutations, and that's that figure on the right. Kind of a sliding plot there of different bars showing that lots of patients have other mutations in their disease.

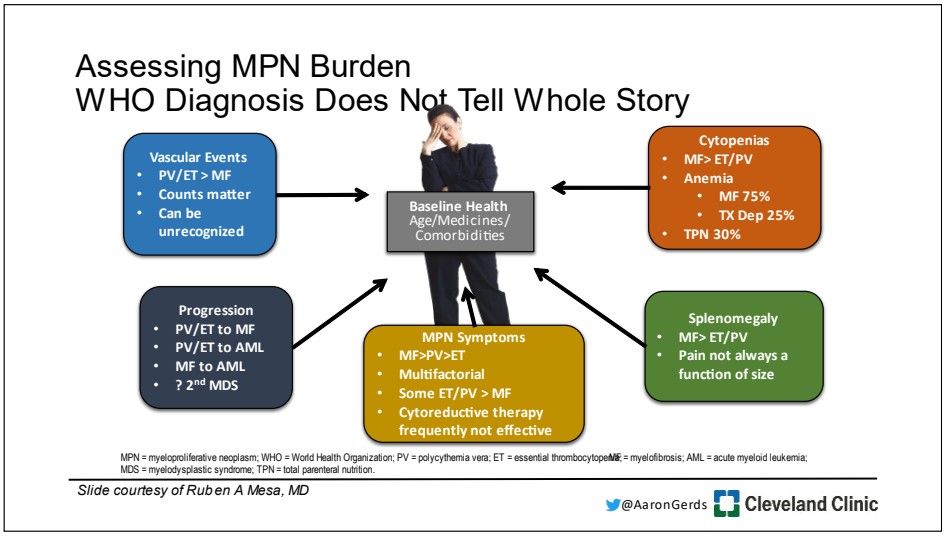


And we know that's really important in disease, too, because it makes the car go. So, we think about some mutations being, well, not that bad. You know, kind of if we think about in an engine in a car, if it's like a four-cylinder engine, maybe a two- or three-cylinder engine in a car, the car's not going to go very fast. But boy, if there are some really heavy, if you drop a V8 engine in that car, that car's going

to go super-fast. So, there are some mutations that we know are V8 engines and predict for much more aggressive disease course over time.
So, this is why doctors taking care of patients with MPNs focus on the mutations so much, because one, it helps us in diagnosis when we find JAK2, calreticulin, or MPL mutations; but also, these second and third mutations that, if they're present, can predict for disease course. So, getting genomics on a person's MPN cells are a key piece of information we like to get.

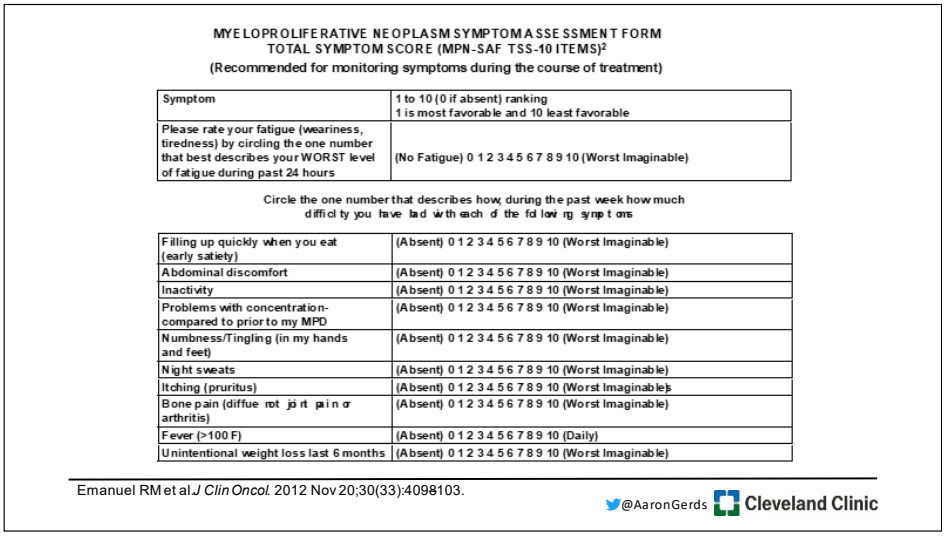


All right, we're going to pivot a little bit to symptom burden in MPNs or the consequences or side effects of MPNs.



And this is a really big kind of discussion because so many things factor into how an individual feels. Of course, there are vascular events that can cause symptoms and side effects. Of course, there's the risk of progression. There's kind of the classic MPN symptoms we think about, like fever, night sweats, fatigue, those types of things. Patients with MPNs can experience cytopenias or low blood counts, and anemia can make people feel worse, or thrombocytopenia can lead to bleeding events. And of course, in PV, ET, and myelofibrosis, we think about enlarged spleen, which can cause pain

and early satiety, or filling up right away when you eat. So, it's really a big, complex picture of how an individual feels with these diseases.



MYELOPROLIFERATIVE NEOPLASM SYMPTOM ASSESSMENT FORM
TOTAL SYMPTOM SCORE (MPN-SAF TSS-10 ITEMS)[2]
(Recommended for monitoring symptoms during the course of treatment)

Symptom	1 to 10 (0 if absent) ranking 1 is most favorable and 10 least favorable
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

Circle the one number that describes how, during the past week how much difficulty you have had with each of the following symptoms

Filling up quickly when you eat (early satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with concentration-compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Numbness/Tingling (in my hands and feet)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (>100 F)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)
Unintentional weight loss last 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

Emanuel RM et al. *J Clin Oncol.* 2012 Nov 20;30(33):4098-103.
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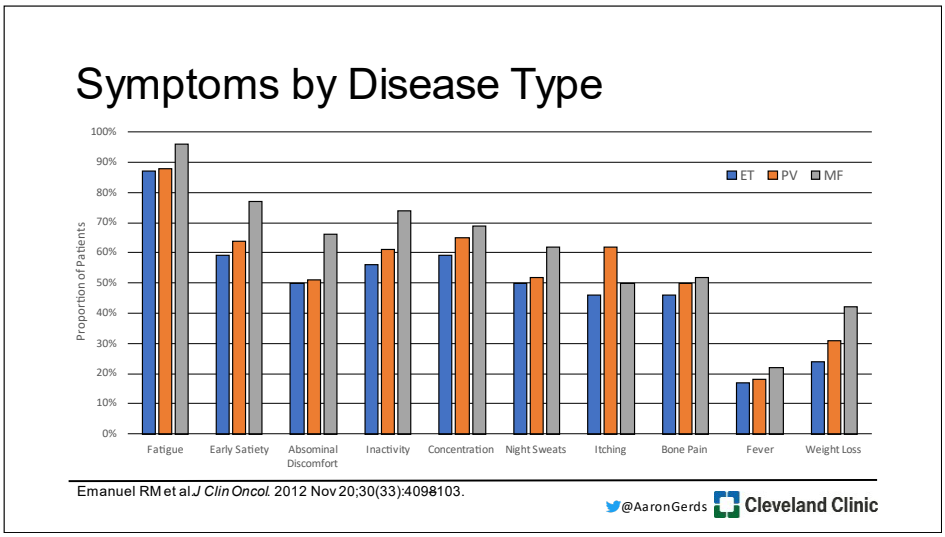
But to kind of better catalog, if you will, an individual's symptom burden, we often use this MPN 10 which is a list of ten symptoms that we see quite frequently in patients with MPNs. This is not an exhaustive list, but these things are common and things we like to measure and monitor as patients go on treatments or off treatments just to see and document how well the treatment may be working and how the patient may be feeling over time.



Emanuel RM et al. *J Clin Oncol.* 2012 Nov 20;30(33):4098-103.
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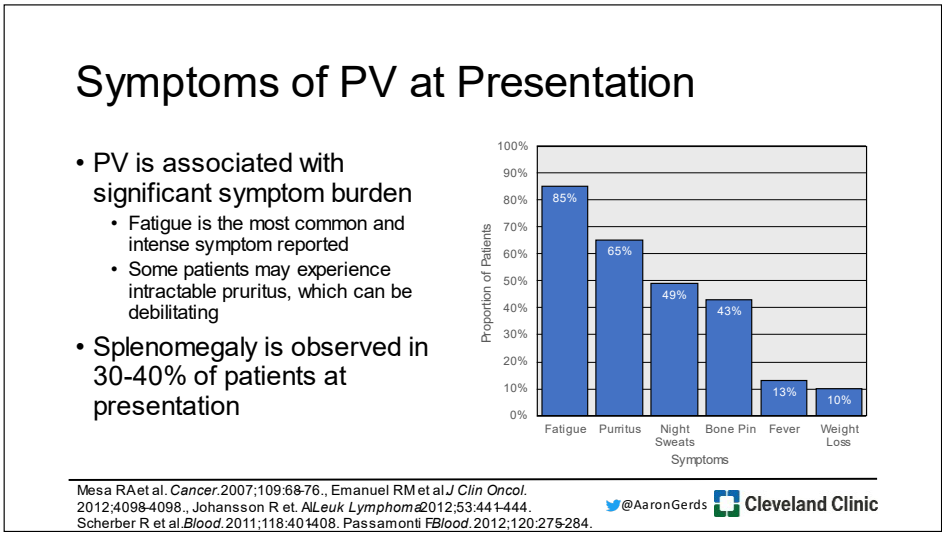
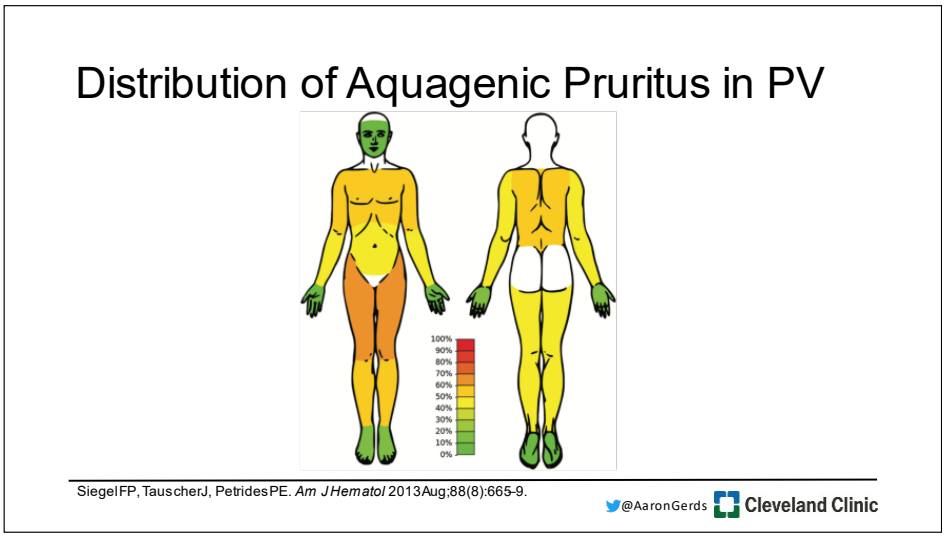
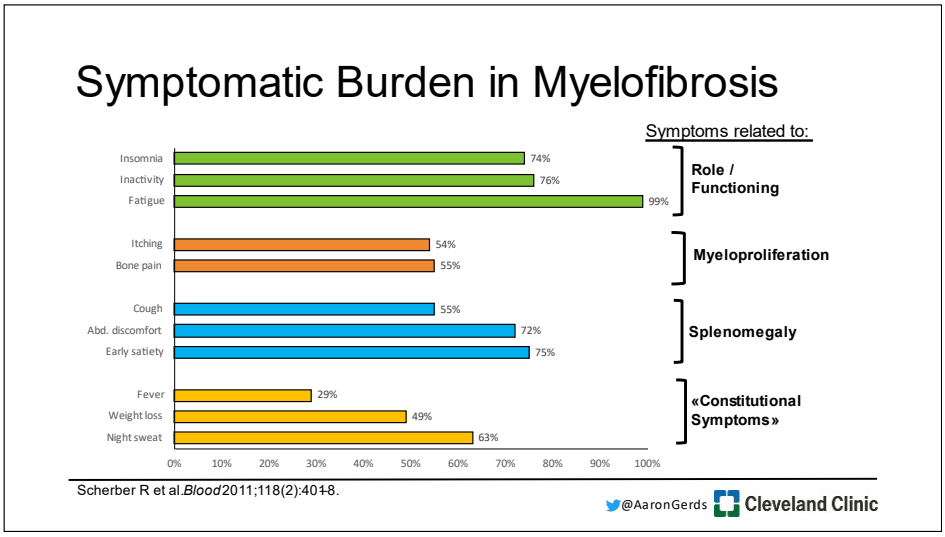
And again, we've chosen these symptoms because they are quite prevalent and common in patients with ET, PV, and myelofibrosis. And you can see here those bars are pretty close to being the same. Now definitely the MF bars are the tallest, the gray bars here, meaning that the larger proportion of patients are experiencing symptoms; but there are sizeable bars in all these symptom domains for ET and PV. So, certainly patients with ET and PV do have significant symptoms that need to be monitored and addressed as they come up.



Example here is PV, so many patients can have fatigue, itchy skin, night sweats, bone pain, fever, and weight loss with polycythemia vera. And in fact, many patients do have enlarged spleens as well. And so, all these things need to be thought about when you first see a patient with polycythemia vera. So, this is, again, what your doctors are thinking about as they see patients.



One of the more famous symptoms, and I kind of like this for the picture of the map in polycythemia vera is this aquagenic pruritus or itchiness of the skin when you get out of water, particularly hot water. So, out of a hot shower, out of a bath, and get really intense itchy skin.



But of course, we also think about, again, symptom burden in myelofibrosis because that's what a lot of JAK2 therapies are directed at, our symptom burden. And we often think about symptoms not only in individual symptoms themselves, but kind of grouping the symptoms together into role functioning: from insomnia, inactivity, and fatigue; to myeloproliferation, which is itching and bone pain; splenomegaly, or enlarged spleen, can lead to cough, abdominal discomfort, and early satiety; and then constitutional symptoms: fever, weight loss, and night sweats. So, these are how we kind of group the symptoms together to look to see how treatments might affect groups of symptoms as, again, patients start treatments or stop treatments and go along their treatment course.

Cause and effect

Symptom	Cause
Organomegaly	Elevated red cell mass, extramedullary hematopoiesis, elevated cytokine levels
Pruritus/bone pain	Presumed 2/2 mast cell degranulation – histamine, prostaglandins, etc…(unproven)
Erythromelalgia or ocular migraine	Thrombocytosis
Fever	Elevated cytokine levels
Weight loss	Splenomegaly (early satiety), elevated cytokine levels
Hyperuricemia, gout, renal stones	Increased cell turnover
Fatigue	????, IL-6/IL-8, Multifactorial

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When we start to try to tackle these things, we want to think about, well, what's causing the symptoms. You know, for when the spleen and liver get enlarged, that can be due to increased red cell mass or blood-forming elements inside of those organs or elevated cytokine levels. We think a lot of the itchiness and bone pain is related to histamines; so, that's often why antihistamines are prescribed to patients having itchy skin or bone pain.

Erythromelalgia (a rare skin condition that can affect the feet, hands, arms, and legs with symptoms of burning pain, heat, redness, swelling) or ocular (relating to the eyes) migraine are thought to be due to platelets and microvascular disturbances, so often for those we use aspirin.

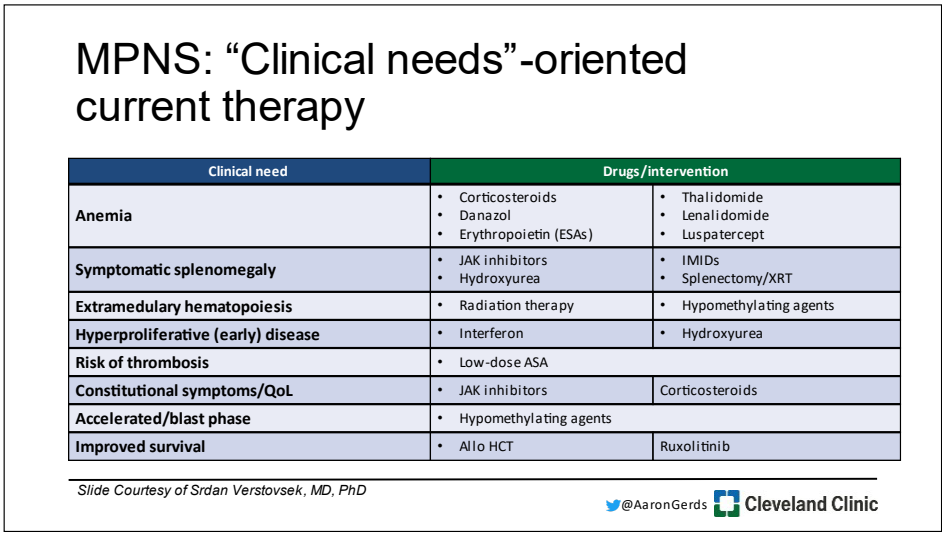
Weight loss can be due to enlarged spleen pressing on the stomach, effectively a gastric bypass surgery, as well as elevated cytokine levels.

Hyperuricemia and gout and renal stones can happen as well because if cells are turning over so much and from those cells being recycled in your body, the byproduct is uric acid, which then can crystallize into the joints causing gout or into the kidneys causing kidney stones. And so, we may want to address that with something like allopurinol, which can block the production of uric acid.

And then fatigue though is a tough nut to crack. It's always multifactorial. There are so many reasons to be tired. Outside of MPNs as well, we think about things like sleep apnea or blood pressure medications or poor sleep hygiene. All these things can lead to fatigue, in addition to MPNs and MPN treatments.

We do know that within the MPN realm, elevation of certain cytokines are associated with worsening fatigue, like IL-6 (interleukin-6) and IL-8 (interleukin-8), although this is still kind of more of a research question about lowering those cytokine levels individually and impacting fatigue.

All right, so with that, thinking about the symptoms, we can start to pivot towards treatment of MPNs. I've already touched on this a little bit.



MPNS: "Clinical needs"-oriented current therapy

Clinical need	Drugs/intervention	
Anemia	• Corticosteroids • Danazol • Erythropoietin (ESAs)	• Thalidomide • Lenalidomide • Luspatercept
Symptomatic splenomegaly	• JAK inhibitors • Hydroxyurea	• IMIDs • Splenectomy/XRT
Extramedulary hematopoiesis	• Radiation therapy	• Hypomethylating agents
Hyperproliferative (early) disease	• Interferon	• Hydroxyurea
Risk of thrombosis	• Low-dose ASA	
Constitutional symptoms/QoL	• JAK inhibitors	Corticosteroids
Accelerated/blast phase	• Hypomethylating agents	
Improved survival	• Allo HCT	Ruxolitinib

Slide Courtesy of Srdan Verstovsek, MD, PhD

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With this "clinical needs"-oriented therapy, where we think about for any individual in front of us, what are the symptoms that they're having? What is the most pressing issue? You know, an individual may have a number of issues. They have may low blood counts and fatigue and enlarged spleen. But when a patient comes to your office that day, you kind of say, "Well what's the most pressing issue? And let's tackle that one first." Right. So, a person who comes in and, you know, anemia is the major issue, we think about medicines that can improve anemia, like steroids, danazol, erythropoiesis-stimulating agents, even the IMiDs (immunomodulatory drugs), or luspatercept (Reblozyl®).

If a person comes in and they have a big spleen, you know, and that's really affecting their quality of life and their ability to function, you know, we'll want to tackle that directly with things like JAK inhibitors. Extramedullary hematopoiesis, which again is blood-forming elements outside of the bone marrow, whether it's in the liver, the lungs, the retroperitoneum, or the spleen, there are different ways we can attack that, either with interferons, hydroxyurea (Hydrea®, or even to some degree JAK inhibitors or radiation therapy. Of course, in ET and PV, we're talking about thrombosis (blood clots) risk often; and we would want to minimize that with aspirin.

Constitutional symptoms, being night sweats, fevers, and weight loss, we can address those with steroids and JAK inhibitors as well. In patients that the disease is kind of heading towards that spectrum of acute leukemia, we want to use chemotherapies really to kind of slow and stop that progress.

And then, of course, in patients where we really think we want to affect the overall survival, we can affect the overall survival. We recommend transplantation, which to date is the only treatment that we know has curative potential, meaning people can live a long time without treatment, without the need for treatment.

Okay, so that's kind of a general overview on the treatment of MPNs. Now I'm going to focus a little bit on each of the individual diseases themselves.

Risk-Stratification in PV

Risk Group	Factors	Treatment
Low	Age < 60 yrs No thrombosis Hx	Phlebotomy CV risk modification ASA
High	Age ≥ 60 yrs - *and/or* - Thrombosis history	Cytoreduction (± phlebotomy) CV risk modification ASA

Crisà E et al.*Ann Hematol* 2010 Jul;89(7):691-9.

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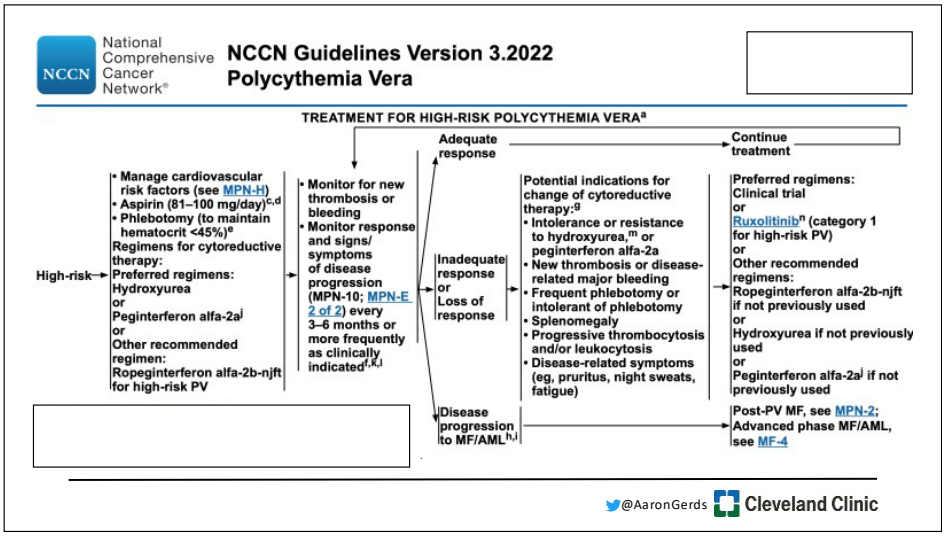
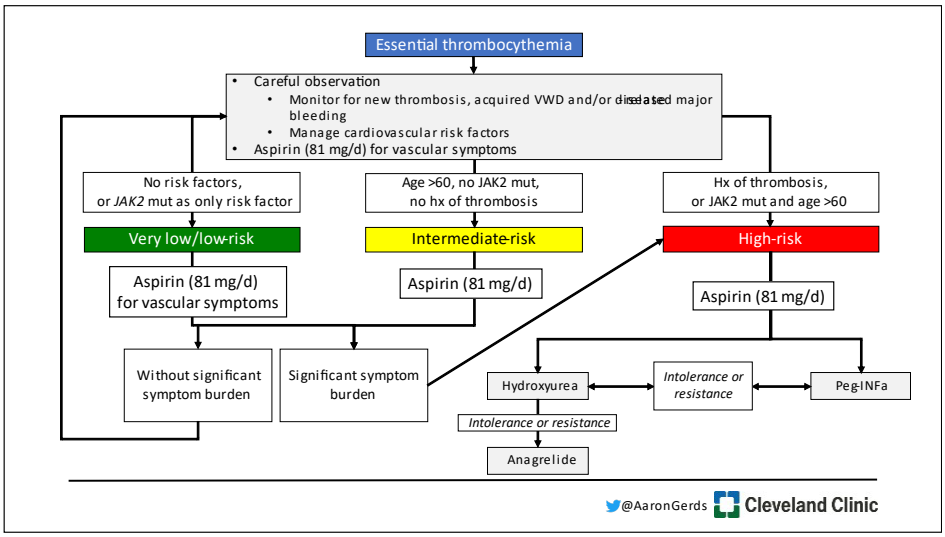
So, for polycythemia vera, kind of the main construct here is thinking about risk. We use age and history of blood clots to parse patients out into low- and high-risk categories. So, patients in the low-risk category who are young and never had a blood clot, we used phlebotomies to control their hematocrit, keep it under 45%, and also use daily aspirin. In patients who are high risk, we often include cytoreduction, whether that is a hydroxyurea, interferons, or other treatments to try to control the counts beyond phlebotomy.



And that's outlined here in a snapshot of the NCCN (National Comprehensive Cancer Network) guidelines. So, the NCCN guidelines are a network of cancer centers who all have delegates that come together to develop guidelines to help all doctors and care providers taking care of patients here in the United States. And it kind of sets the tone for what the kind of country-wide therapy should be for patients with MPNs. In particular, this is a snapshot again from high-risk polycythemia where we're monitoring for signs and symptoms of advancing disease; but you can see in that first column there, we're really focused on giving a medication to control the counts, whether again hydroxyurea, interferon, and now of course now with ropeginterferon (ropeg, Besremi®), that is on the list.

And then if it works, great, we stick with it as you're moving from left to right across this algorithm; but if things change, we want to adapt our therapies to the changing situation with any given individual. So, that's where maybe ruxolitinib (Jakafi™) comes into play or if the disease progresses, we may think about treating this more like an acute leukemia as opposed to a chronic leukemia as a polycythemia vera.

So, the treatment for essential thrombocythemia, likewise, is risk stratified.

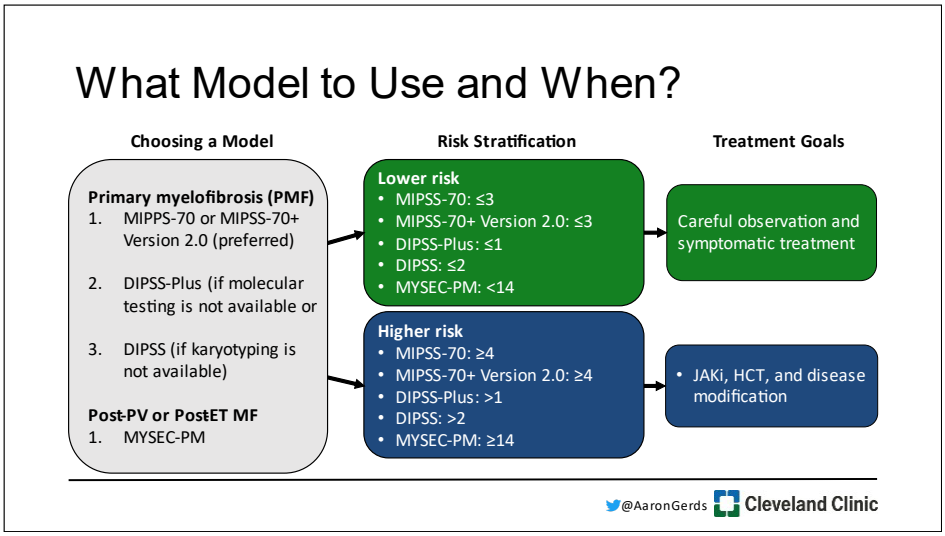


We stratify patients when we think about kind of clot risk, and so we use this thing called the revised IPSET-thrombosis score (international prognostic score for thrombosis in ET) to identify patients who are at low risk for blood clots, those who are at intermediate risk for blood clots, and those who are high risk for blood clots. And we adapt treatment to each of those situations.

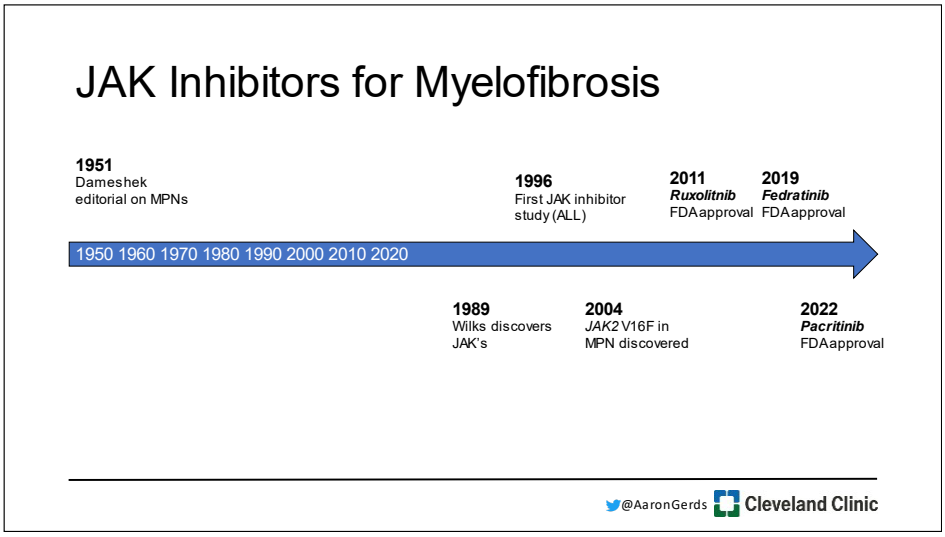
So, if patients have very-low, low, or intermediate risk essential thrombocythemia and are asymptomatic, we recommend just simple observation because, to date, the data suggests that if we intervene to try to control this count with a medication, we're not actually making anyone live better or anyone live longer. So, careful observation is the key there in asymptomatic patients with lower-risk disease.

In patients with high-risk disease, the data does suggest that, by intervening on these counts, we can perhaps lower thrombosis risk or blood clot risk. And so, that's why you see for the high-risk patients, it's recommended to control the counts with either hydroxyurea or interferons or potentially anagrelide (Agrylin®) in the second-line setting. The key here being is there's no magic platelet count number. You may not see a platelet count number here at all. And in fact, if you read the entire hundreds of pages of the NCCN guidelines, you will not see a single reference to platelet counts in terms of a goal of treatment because there is none. There's no study that's ever identified a platelet count number that's associated with thrombosis risk reliably, nor a goal for reduction reliably. So that is still an unknown question in essential thrombocythemia.

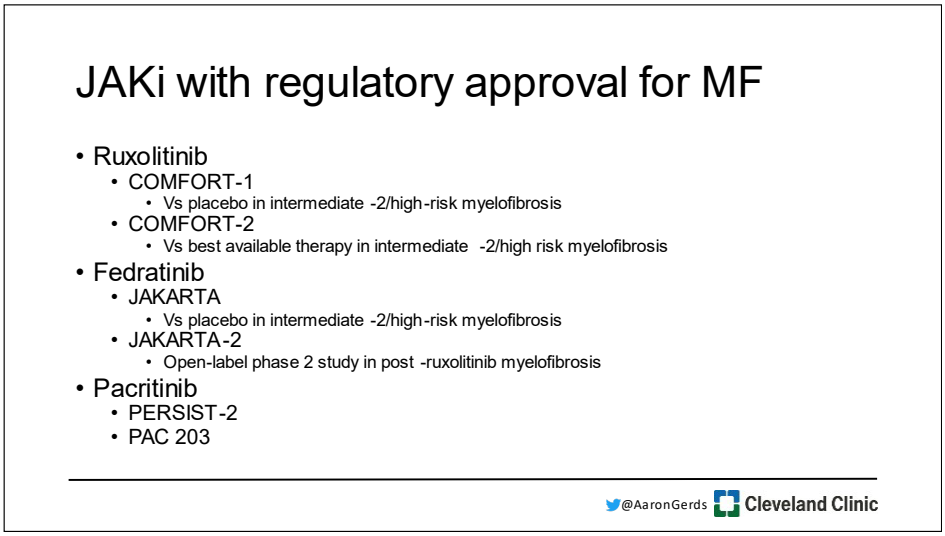
So, for myelofibrosis, we again, like PV and ET, we think about risk as a big split for how we ought to treat disease.



So, there are patients with low-risk disease and patients with high-risk disease, and we use the available information we have to risk-stratify patients, patients' disease. Whether we have genomic information or not, or cytogenetic information or not, or whether the disease is primary myelofibrosis or myelofibrosis out of ET or PV. But at the end of the day, there's two kind of major bins: patients with lower-risk disease where you expect the disease to not do much over a long period of time; and higher-risk disease where it could become more aggressive sooner. And for patients with lower-risk disease, careful observation and focusing on the symptoms is the main treatment goal. Where patients with higher-risk disease, we think about JAK inhibitors and transplantation as well as disease modification.



So, I said JAK inhibitors here a few times, and I think it's worth thinking about the development of JAK inhibitors over the span of time since Dr. Dameshek in 1951 postulated that there might be a key unifying factor amongst the MPNs. But again, as I mentioned, it wasn't until 2004 when JAK2 V617F was discovered. But even before then, JAK inhibitors were being developed to treat acute lymphoid leukemia, kind of a distant relative to MPNs for treatment. And then, but after the JAK2 V617F discovery, there was a real big push to develop JAK inhibitors in MPNs. And then in 2011, we had the approval of ruxolitinib. In 2019, we had the approval of fedratinib (Inrebic®), and in 2022 we had the approval of pacritinib (Vonjo™).

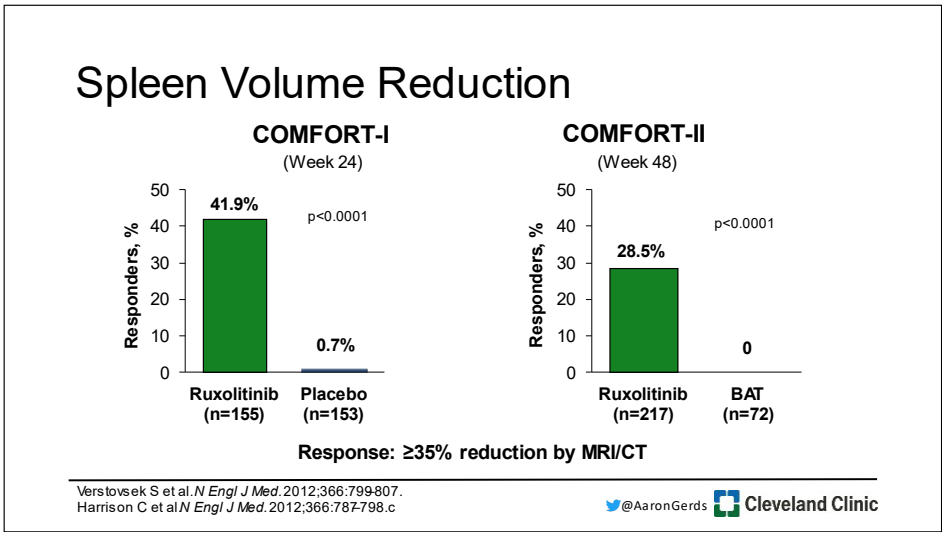


So, ruxolitinib, or the brand name for that drug is Jakafi®, as marketed here in the United States, was based on the results from the COMFORT-1 and COMFORT-2 studies. These were patients with myelofibrosis with high-risk or intermediate-risk myelofibrosis who required treatment and had big spleens and lots of symptoms.

Fedratinib, and the brand name here in the United States, is Inrebic®, so fedratinib was approved based on the JAKARTA and JAKARTA-2 studies. So, JAKARTA was, again, in patients who have

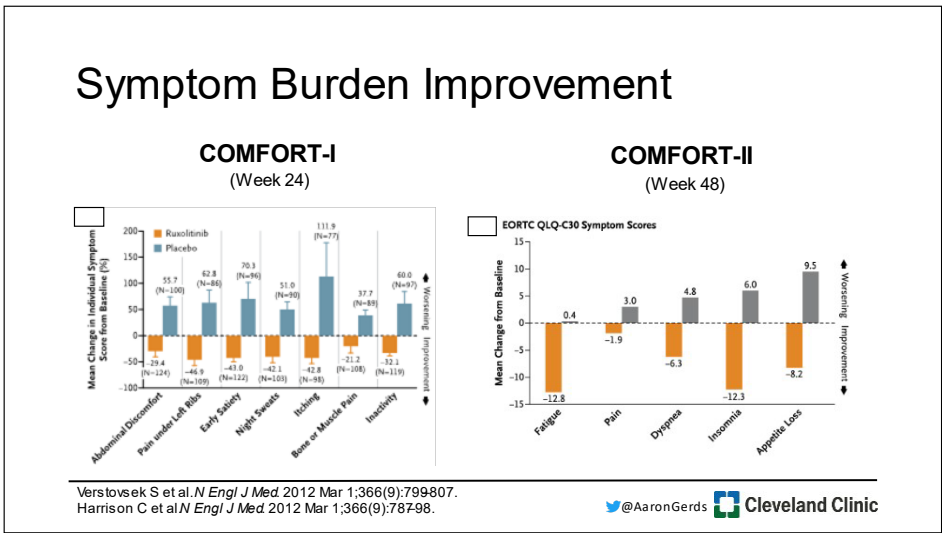
never had a JAK inhibitor before. And JAKARTA-2 was in patients who had already had ruxolitinib, so kind of a second line, if you will.

Pacritinib and the marketing name here in the United States is Vonjo®. That approval was based on PERSIST-2 and the PAC 203 studies. So, PERSIST-2 was a trial looking at patients who did have prior ruxolitinib treatment, but had platelet counts less than 100,000. PAC 203 took a number of different patients who had ruxolitinib before, whether their platelet counts were low or high.

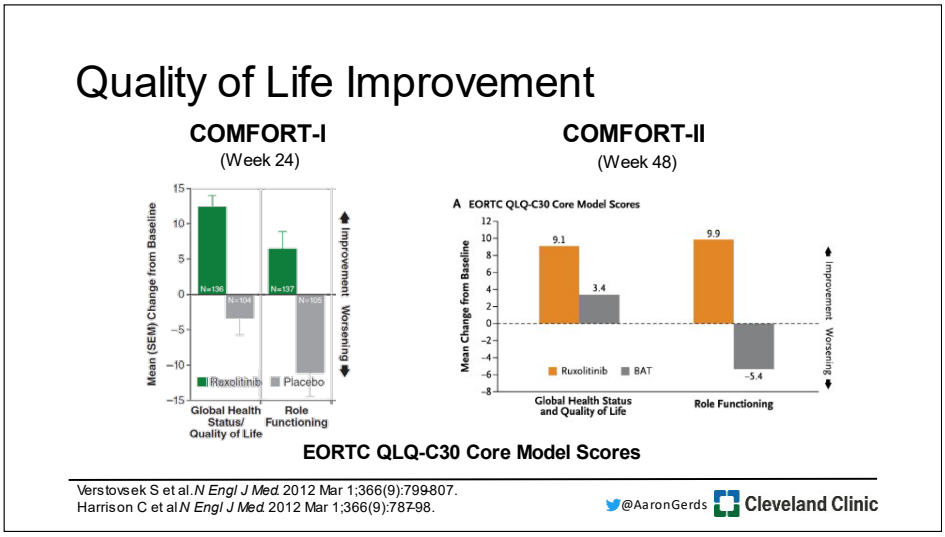


At the end of the day, what can JAK inhibitors do? Well, they can shrink spleens to a large degree. And this is data from the COMFORT-1 and COMFORT-2 studies. So, you can see here ruxolitinib on the left-hand side of each of these figures had significant spleen volume reductions versus placebo or best available therapy, also known as BAT, on the right-hand figure.

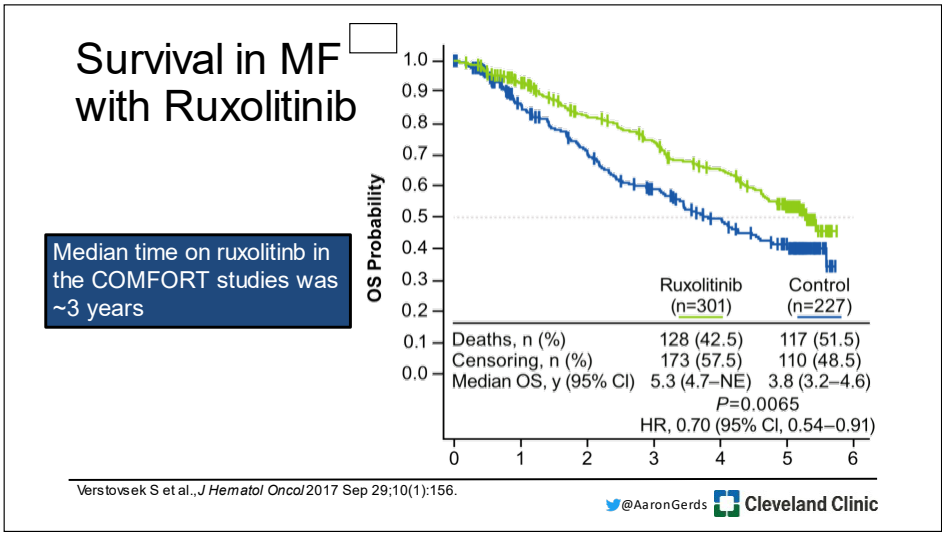
So, these are all the number of patients that had at least a 35% reduction in the volume of their spleens, so real big spleen improvement for these folks on the study, as well as improvements in symptom burden.



So, we can see here symptom burden going up and down on this figure. So, if the bars go up, that means symptoms are worse. If bars go down, symptoms got better. You can see the orange bars all go down, representing the improvement in symptom burden with ruxolitinib; and the gray bars go up, meaning symptom worsening with either placebo or best available therapy.



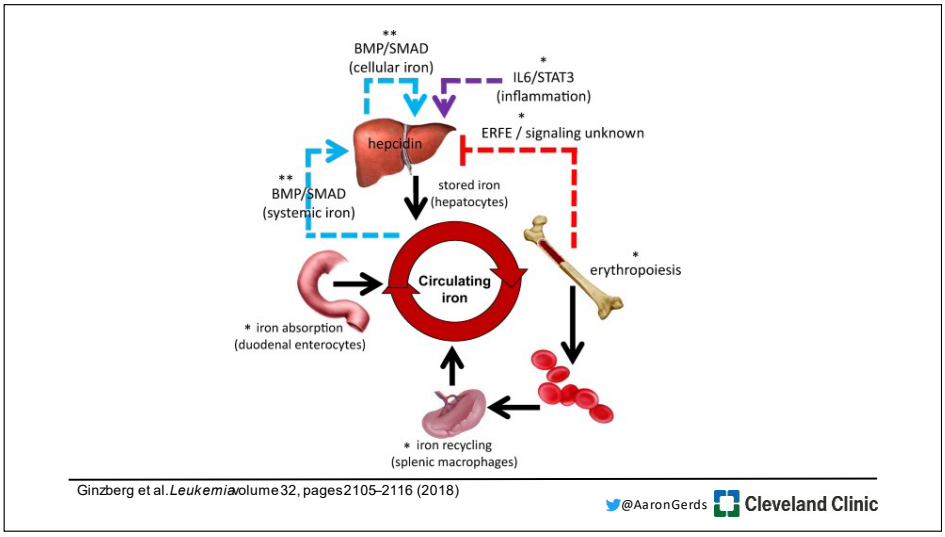
And this, of course, translates into an improvement in quality of life. This graph is the other way where bars go up, it's better. If bars go down, it's worse. But you can see patients treated with ruxolitinib in both these studies had an improvement in quality of life versus the placebo or best available therapy.



And last, we can see that ruxolitinib may actually improve survival. Now this is certainly an area of debate within the MPN community of how it does that and why it does that and how big this effect may really be. But patients in the pooled analysis from the COMFORT studies, the ones that were randomized to ruxolitinib, lived longer than those who were randomized to best available therapy or placebo. Now, there were lots of patients who got the placebo or best available therapy and ultimately crossed over to get ruxolitinib. So, you can't really measure the survival benefit, but clearly patients

are not only living better, but living longer in the presence of ruxolitinib. But you know, ruxolitinib and the JAK inhibitors are not perfect by any stretch of the imagination.

And, if we look at these figures where on the horizontal axis, time goes in years from zero, one, two, three, four, five, six; and the percent of people alive are on the vertical axis here, you can see these, there's no plateau in these curves. Ruxolitinib is not curative. It's not like treating chronic myeloid leukemia where we give people imatinib (Gleevec®), and they're functionally cured. So, we need to do better because these drugs are not perfect. They're a big help, they've revolutionized the care of MPNs, but they are not perfect and not curative.

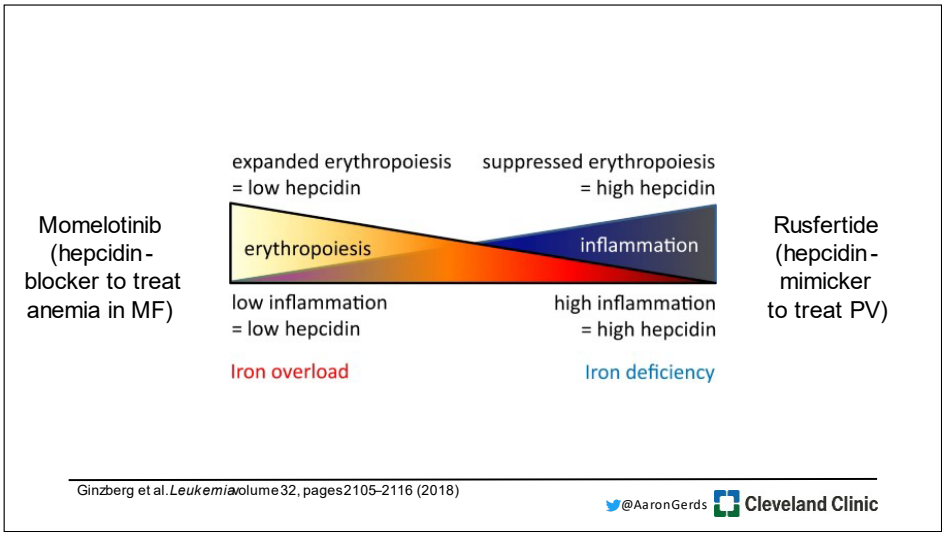


And one of the major issues that we run into is anemia, and not only patients with myelofibrosis at the time of diagnosis have anemia, but, you know, using JAK inhibitors can worsen that anemia in a lot of patients. So, there's been a big focus on trying to attack anemia in a number of different ways. So you can see here in this figure there's a bone with bone marrow in it, and the bone marrow produces red cells. So, we can give erythropoiesis-stimulating agents to force the bone marrow to make more red blood cells. Luspatercept, a different drug, also does a very similar thing.

There's increased interest in this thing called hepcidin. And so, hepcidin is actually part of this iron cycle, and that's what this whole figure is showing: how we absorb iron, how we shuttle iron from say our spleen and liver into our bloodstream and then to the bone marrow and around again, this iron cycle.

And by manipulating the iron cycle, we can perhaps improve anemia in patients with myelofibrosis and, conversely, control hematocrits in polycythemia vera. So, right now it's a really neat time in MPN treatments because we're not only, we're manipulating this hepcidin molecule to treat both PV, with too many red cells, and myelofibrosis, which has too few red cells, just in opposite directions.

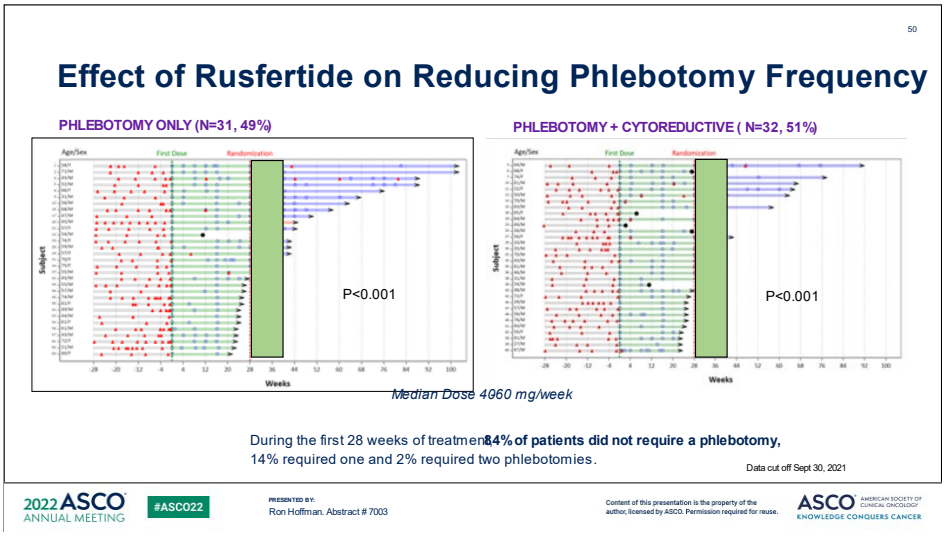
And the reason that, myself, I get so excited about this and many hematologists do is hepcidin is a very nerdy thing to hematologists. When it was first discovered, how iron would shuttled around, and how it affects the production of red blood cells. You know, the hematologists get pretty excited over that. So, it's like going to a *Star Trek* convention and talking about the USS Enterprise. It's something that's kind of key in how we understand red cells are produced. So, the fact that we're harnessing that information to treat MPNs in both directions, improving anemia as well as controlling red cell counts, is really kind of an exciting concept.



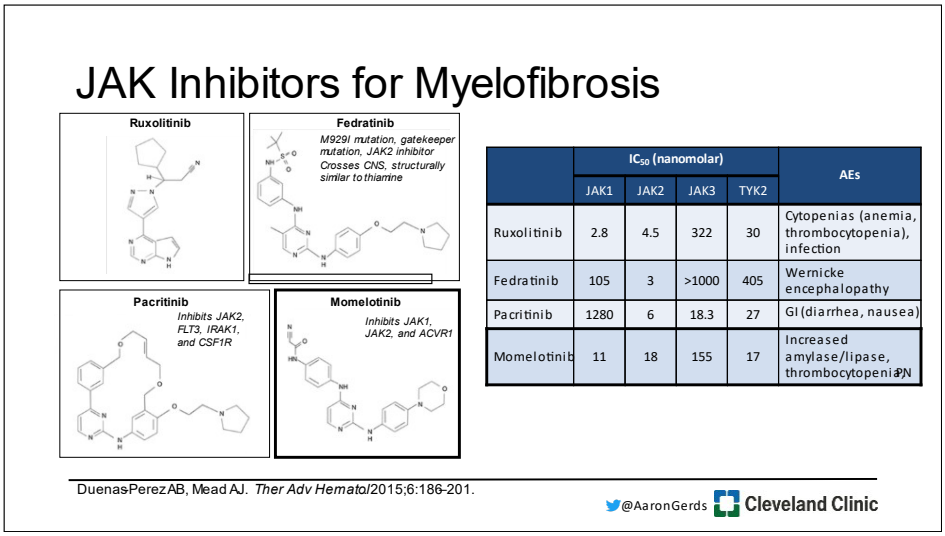
And that's shown here a little bit too.

So, momelotinib, and to some degree pacritinib is too, are JAK inhibitors that can maybe improve erythropoiesis by altering this hepcidin thing and addressing iron overload and all these types of things. Where on the other end of the spectrum, we're using this drug called rusfertide in large trials. It's a drug that mimics hepcidin, so it basically tricks the bone marrow into thinking it's iron deficient.

So, on the left-hand side, we're forcing the bone marrow to deal with this iron overload, reduce inflammation in the bone marrow to improve anemia by regulating hepcidin. And on the other end of this figure, we're actually tricking the bone marrow into thinking it's iron efficient so it doesn't make red cells through the rusfertide, which is just a really cool concept.



And on that note, rusfertide, in polycythemia vera, is doing an amazing job of eliminating the need for phlebotomy. This figure here, at time zero, the vertical line between the gray and the green bars represents the time at which patients start this medication called rusfertide. On the left you see lots of red dots. On the right of that line, you see very few red dots. That's the number of phlebotomies that these patients were getting. Each bar is a patient, and you can see these patients getting tons and tons of phlebotomies; starting on rusfertide, and then fewer and fewer and fewer phlebotomies are needed, which is really, really kind of neat.



And I mentioned momelotinib, which is a drug that can affect hepcidin as well be a JAK inhibitor and treat spleen symptoms.

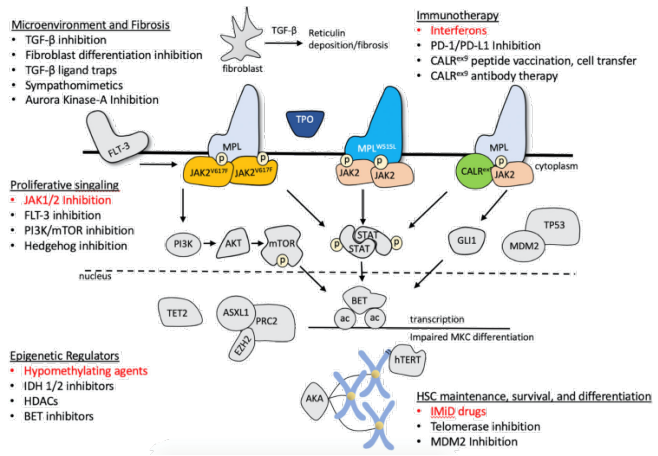
MOMENTUM: Top-line Results

Wk 24 Endpoint	Test	MMB	DAN	p-value
TSS response rate (primary), %	Superiority	24.6	9.2	0.0095
TI rate, %	Non-inferiority	30.8	20.0	0.0064 (one-sided)
SRR ≥25%, %	Superiority	40.0	6.2	<0.0001
TSS change from BL*	Superiority	-9.36	-3.13	0.0014
SRR ≥35%, %	Superiority	23.1	3.1	0.0006
Zero transfusion rate, %	Superiority	35.4	16.9	0.0012

*Least-squares mean from mixed model for repeated measures.

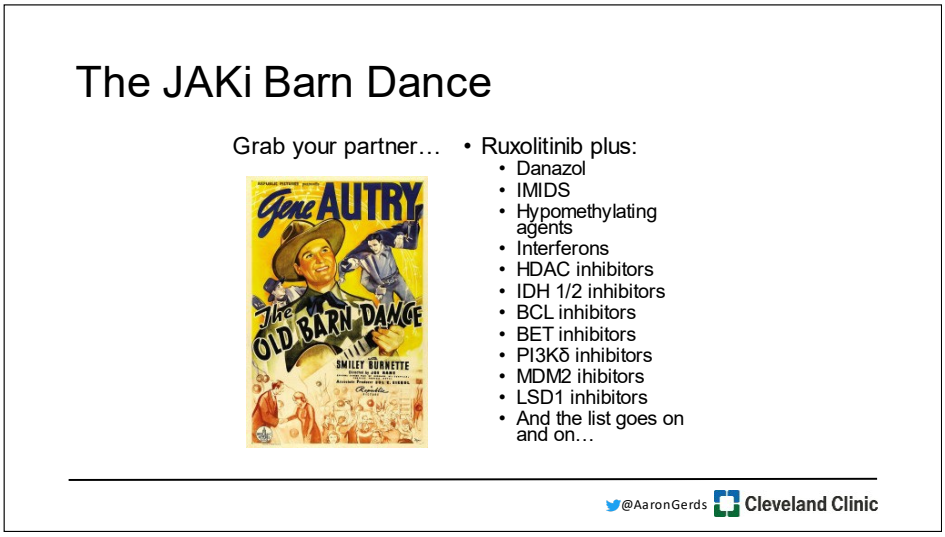
Mesa R, et al. *Journal of Clinical Oncology* 2022 40:16_suppl 7002–7002
Verstovsek S et al. *HemaSphere* 2022;6:S3;96-97; abstract S195.
@AaronGerds Cleveland Clinic

And we see that patients treated with momelotinib can have improvements of their anemia. And so, in this table, it's the TI (transfusion independence) rate, the second row down, where patients treated with momelotinib, 30% of patients remained transfusion-independent versus danazol, which is another drug we use to treat anemia, like 20% of patients. So, we're targeting this hepcidin thing from both ends to treat two different MPNs with two different consequences. It's really truly an amazing story that's emerging in the MPN world right now.

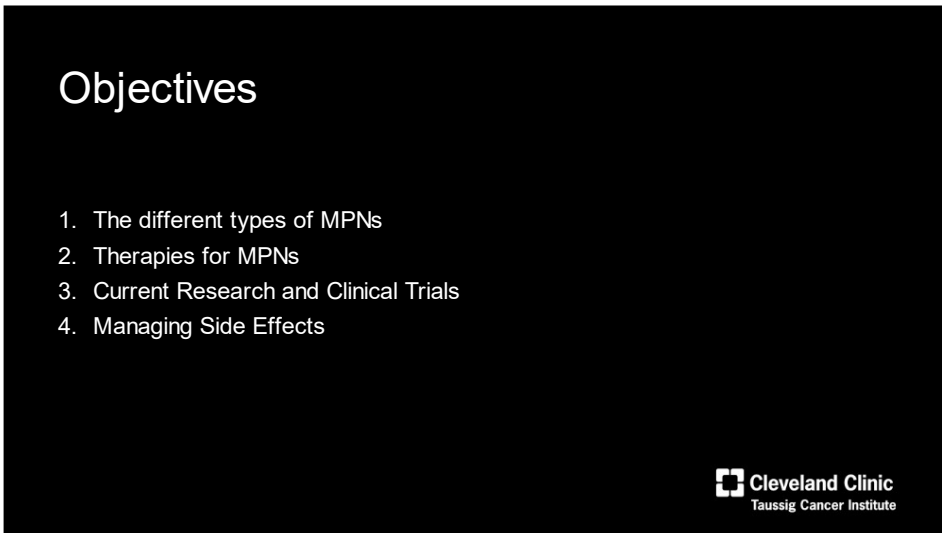


Schieber M, Crispino JD, Stein B. *Blood Cancer J.* 2019 Sep 11;9(9):74.
@AaronGerds Cleveland Clinic

But of course, there's so much more to MPNs and particularly myelofibrosis and all the different pathways that are just regulated and activated in these diseases. And there are studies ongoing that are targeting all of these different pathways or they're talking about epigenetic regulators, proliferative signals, microenvironment in the myelofibrosis, you know, the actual fibrosis being put down. Of course, we're trying to harvest the power of the immune system through immunotherapies and even vaccine trials, as well as the maintenance of these hematopoietic stem cells that are deranged in these diseases.



So, really kind of the next frontier, if you will, or the next stage in development and treatment for MPNs is going to be this combination therapy where we're using something like ruxolitinib as a backbone, and then trying to do better by adding a second drug in there. Whether we're talking about BET (bromo- and extra-terminal domain) inhibitors, PI3 kinase delta inhibitors, or LSD1 inhibitors, and so on and so forth, where we're taking the success we've had with JAK inhibitors and ruxolitinib and trying to go even further by adding in a second agent. And honestly, that is going to be the next big wave.

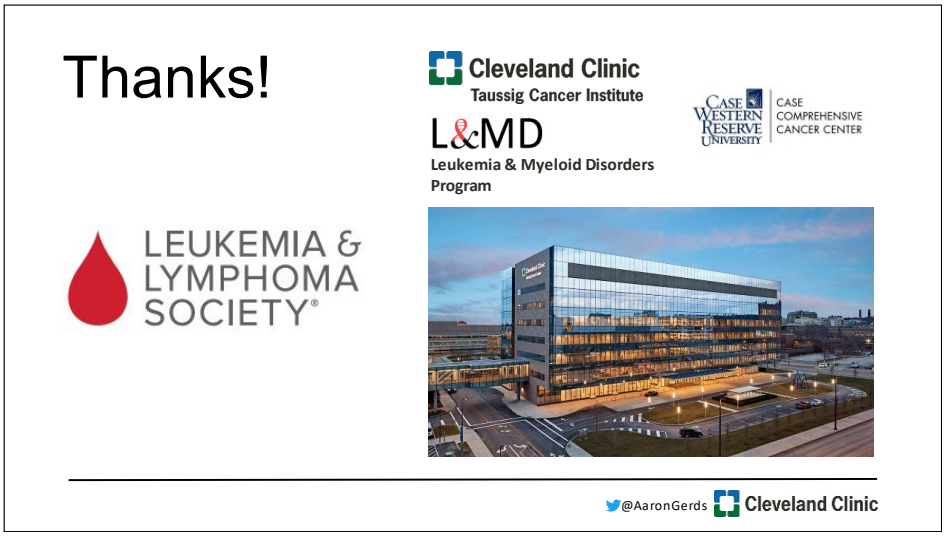


All right, so in this short period of time, we were able to cover some kind of key types, the different types of MPNs – PV, ET, and myelofibrosis – and kind of how they fit together. And the reason that we think about all these so closely is that they are so closely related.

Talked a little bit about the treatment for MPNs. Again, for most patients, it's symptom based. We think about, first and foremost, the symptoms that a patient may be having as a result of their disease. And with PV and ET, we're also thinking about blood clot risk and the potential for that complication to happen and how can we best mitigate that.

And then with current research and clinical trials, I would say the two biggest stories right now in MPN treatment development is this concept of attacking PV and myelofibrosis, the anemia and the too many red cells through hepcidin, this kind of common iron regulatory pathway. And then the other big story is combination therapies. Using JAK inhibitors, like ruxolitinib, plus another therapy to get deeper responses, to get more responses, to get durable responses.

And then prior to that, we did talk about some of the symptoms that occur with MPNs and how we try to think about why they happen and ways to address those.

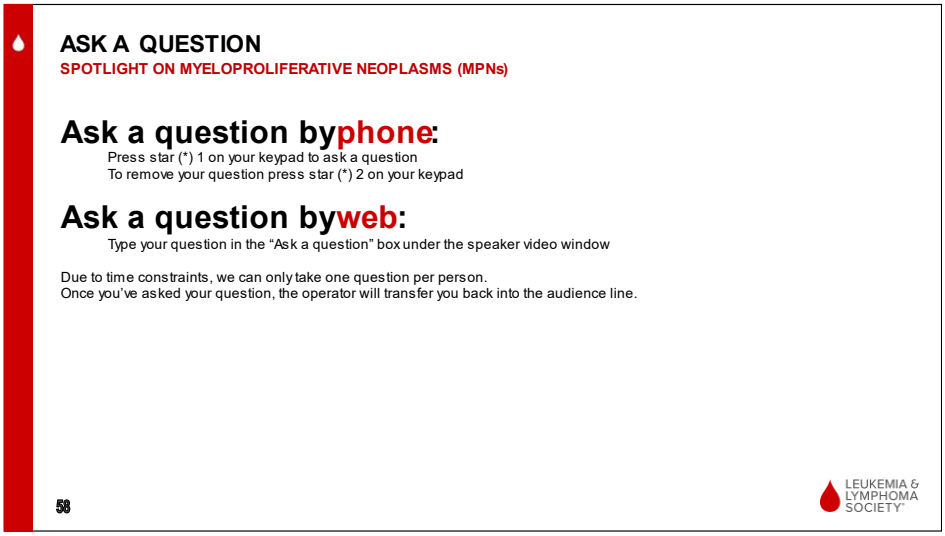


So, with that, I'd like to thank you for your attention, and we can move on to the discussion section.

QUESTION-AND-ANSWER SESSION

Lizette Figueroa-Rivera, MA

Well thank you so much, Dr. Gerds, for volunteering your time with us today to update us on treatment advances for the MPNs.



And like you said, it is now time for the Question-and-Answer portion of our program. For everyone's benefit, please keep your questions general without many personal details so Dr. Gerds can provide answers that are general in nature.

Thank you. The first question, doctor, comes from Cynthia. Cynthia is asking, "What is flow cytometry, and how does it apply to MPNs?"

Andrew T. Gerds, MD, MS

Yes, so, flow cytometry is a technique where we look at individual cells. So, to think about it simply, it's a tube, a microscopic tube where cells go through one by one. And we can look at different proteins and markers, if you will, on the surface of the cell. And that can help identify what cells are there.

So, in MPNs, we can use flow cytometry to see how often we use it to see how many blasts are in either the blood or bone marrow, and to me that is the most useful part of flow cytometry within the diagnosis of MPNs. Outside that, you know, it's not used that often; but it's really a diagnostic tool.

Lizette Figueroa-Rivera, MA

Thank you. And we'll take the next question from our telephone audience please.

Operator

Thank you. And our next question comes from Serena calling from California. Please state your question.

Serena from California

Yes, hi doctor. I wanted to know if you could repeat, I think it's a treatment or a drug, to help with anemia that you mentioned and that doctors may have access to? Not the ones in the study, the hepcidin, thank you.

Andrew T. Gerds, MD, MS

My pleasure. Thank you for that question. You know, it's an important question because anemia is so common in myelofibrosis. You know, half of patients will have it at the time of diagnosis; and all will develop it over the course of their disease.

And so, really, we think about three treatments that are commercially available at this time to treat directly the anemia in myelofibrosis. One is our erythropoiesis-stimulating agents. These are synthetic versions of the erythropoietin hormone that our bodies would normally make that push the system and overdrive the system more to produce more red blood cells. There are a number of these like darbepoetin (e.g., Aranesp®), as an example, or erythropoietin (Procrit® or E[ogen®), as well as a few others from various manufacturers.

There's another drug called danazol, which is a pill. It is kind of like an anabolic steroid, in that class of medications. But that can also increase red cell production. There have been a couple of Phase II trials that have been done. Of course, the control arm for the MOMENTUM study as well that we mentioned earlier.

The third drug that is available to improve anemia that we often use is something called luspatercept. It's approved for treating anemia and related disease called myelodysplastic syndromes, but there was a large Phase II trial that did show efficacy and an ongoing Phase III trial. So, that drug works similarly to the erythropoiesis-stimulating agents and pushes red cells out of the marrow at increased numbers.

Sometimes we use these drugs called IMiDs, like thalidomide (Thalomid®), lenalidomide (Revlimid®), to improve red cell production as well, but I would say overall they're less commonly used.

Lizette Figueroa-Rivera, MA

Thank you. And doctor, our next question from Moshi is, "Other than symptom burden, does an enlarged spleen have to be shrunken for medical reasons, or is it okay to live with it?"

Andrew T. Gerds, MD, MS

Yeah, if the spleen isn't causing any symptoms, there's no good reason to shrink it. Generally, most people who have a spleen that is felt at roughly 10 centimeters below the rib cage will have symptoms. But if a patient comes to me and is asymptomatic, but has an enlarged spleen, I don't necessarily need to start treatment at that time, depending on other factors, of course. But just having a big spleen does not mean you need to shrink it. If it doesn't cause any problems, we kind of let it be.

Lizette Figueroa-Rivera, MA

Thank you. And we'll take the next question from our telephone audience, please.

Operator

Our next question is from Marie calling from Pennsylvania. Marie, please state your question. Your line is now live.

Marie from Pennsylvania

Okay, when you have a bone marrow biopsy and the results are zero blasts, exactly what does that mean in relationship to fibrosis?

Andrew T. Gerds, MD, MS

Yes, thank you for that question. Yeah, there's a lot of gobbledygook in those bone marrow biopsy reports, and so it's sometimes hard to cut through the clutter. So, blasts are very, very immature cells in the bone marrow. They can grow up to be lots of different things. They're not quite stem cells, but they're pretty close. And so, normally a bone marrow should have 0-2% blast in it. If the blasts get too high, that's akin to accelerated or blast phase disease. And if they're over 20%, that's acute leukemia. So, that's why we're interested in counting the number of blasts in the bone marrow.

It has nothing to do with the fibrosis. So, fibrosis is seen on something called a reticulin stain and is scored by a pathologist, and pathologists use four scores or grades and they assign it to the amount of scar tissue they see. It'll be MF-0, MF-1, MF-2, or MF-3 in increasing amounts of scar tissue there. So, they're actually two very separate things that are measured inside of bone marrow on a biopsy.

Lizette Figueroa-Rivera, MA

Thank you. And our next question comes from Jesse. Jesse's asking, "What factors determine use of interferon versus hydroxyurea? Is hydroxyurea cheaper, and does hydroxyurea have fewer side effects?"

Andrew T. Gerds, MD, MS

That is a fantastic set of questions and something that, you know, we usually debate at the big hematology meetings and struggle within everyday practice.

So, there are advantages of each medication. I would say hydroxyurea (Hydrea®) is, it's' a pill. It's easy to prescribe. It is cheap. It's easy to take. Interferon, it's a shot; and if we're talking about pegylated interferon (Pegasys®), it's a shot once a week. If it's ropeginterferon (e.g., Besremi®), it's a shot every two weeks. So, for some patients, it's actually more convenient because you do your once-a-week shot and you forget it. You don't have to take a pill every day.

Interferons are more expensive, and ropeg is even more expensive, certainly, than hydroxyurea. So, on the health insurance side of things, it can sometimes be very difficult to get these medications covered and may take weeks of insurance authorization, even though ropeg has an indication from the FDA to treat polycythemia vera and they are endorsed by the NCCN guidelines. This is certainly a challenge.

In terms of side effects, you know, I think they're pretty comparable. If we look at both the clinical trial that was done here in the United States, the MPN-RC 112 study that compared hydroxyurea versus pegylated interferon, the number of patients that discontinued due to side effects was similar between the two groups.

And then likewise, you know, in the PROUD-PV trial where hydroxyurea was pitted against ropeginterferon, you know, side effects rates were quite similar between the two medications. One was not wildly more toxic than the other. They have very different drugs, so they have very different side effect profiles. You may want to match side effect profiles to an individual that way.

And then lastly, we think there may be some additional benefit with interferons in terms of reducing allele burden and leading to molecular responses and even molecular remissions and what that might mean long-term for a patient receiving those treatments. Although we have to say that the data is still being generated for that; those are not kind of conclusions that are without debate, but certainly we are looking at that with a lot of interest.

Lizette Figueroa-Rivera, MA

Thank you, and we'll take the next question from the telephone audience please.

Operator

Our next question is from Cordell in Florida. Cordell, please state your question. Your line is now live.

Cordell from Florida

Well, my question is, what could be done? My hemoglobin is very low, and my oncologist wanted me to have a bone marrow transplant; and what could be done for me to have my bone marrow transplant because one cardiologist said maybe I don't need it, so I was asking you if it's possible for, I'm a very old lady, and for 72 years old, if I'm too old to have a bone marrow transplant and what could I do to see if my hemoglobin will come up because when I went to the hospital, when I was sick and in the hospital, my hemoglobin dropped to 6.2.

Andrew T. Gerds, MD, MS

Yeah, that's a pretty low hemoglobin, for sure. So, a great series of questions, and I'll try to address them. So, we talked a little bit earlier about the different treatments for anemia, mainly erythropoiesis-stimulating agents, danazol, luspatercept, and maybe the IMiDs.

Now transplant would certainly fix anemia because the idea of transplant is we replace your bone marrow that's dysfunctioning with a new bone marrow and immune system. So, that would certainly do the trick.

In terms of determining who should get transplanted or not, we really look at two things. There are two major factors. One is how aggressive we think the disease is. How aggressive is the myelofibrosis? What do we expect from that over time? The other is the health of the patient, the health of the person who would get the transplant, right? Because if the person who's going to get the transplant has lots of kidney and heart and liver disease, they may be at high risk for a complication; and the transplant may actually shorten their life. So, we look at both of those things together to say, "Yeah, a person could be a good transplant candidate. It's worth thinking about or, no, we shouldn't really push that too much because I might actually make the person worse."

And that's done on a case-by-case, individual-by-individual basis. There are tools like the Comorbidity Index and the different risk models we have for myelofibrosis that can help us make those inferences and kind of quantify what we think about risk. And all that's really important in the context of meeting with a transplanter and having those discussions.

Certainly, there's no upper age limit for having a transplant. We used to joke where I did my fellowship: it was two years minus the age of our oldest faculty member. But, you know, honestly, when patients do get up into their middle to late 70s, it becomes very difficult to do transplant with a lot of success. Now there are patients in their 70s who do get transplanted and do very well, but it certainly becomes much more difficult at that point.

So, again, I advise anyone with high-risk disease to meet with a transplanter because, again, to this day, this is the only thing that could potentially cure this disease and reverse all those problems and complications. So, I think it's at least worth the conversation.

Lizette Figueroa-Rivera, MA

Thank you and thank you for the question. Dr. Gerds, we have some folks asking about more information about what you said about platelets. You mentioned that platelet volume is not a predictor of thrombosis. Does the same apply when the doctor notices a sudden increase in the platelet level during one of the follow-up visits with a patient, or is that a sign of disease progression?

Andrew T. Gerds, MD, MS

Yes, so the platelets can go up and down for lots of different reasons. Immunologic kind of things that can happen that can make them go, you know, like infections, can make the platelets go up or down. Other medications can do that. But in someone who has say essential thrombocythemia, an increase in the platelet doesn't necessarily mean disease progression either. In fact, year over year, time over time, patients, particularly those with calreticulin mutations, we do see steady increases in platelet counts often. But it's not indicative of disease progression necessarily.

So, again, try to take things in the whole picture, where we're looking not only at just the numbers, which are just numbers, but more importantly within the patient, right? So, we treat patients not numbers, and we want to focus on are you having symptoms? What are your risks for complication and really addressing those things as opposed to just a sheer platelet count number.

Lizette Figueroa-Rivera, MA

Thank you. And Julie's asking, "How can patients more successfully distinguish side effects due to the cancer, the treatment, or just aging?"

Andrew T. Gerds, MD, MS

That's something we certainly struggle with. It's impossible almost. You know, I can use the example of night sweats. Right, so we know that disease causes night sweats. You know, that's a common symptom we see with MPNs. And in women who are going through menopause, that's a common side effect of menopause, right? And which is it? You know, you try to kind of guess via timing of when these things occur and kind of the quality of the different night sweats. But at the end of the day, it's really hard to tell. And so, you kind of have an educated discussion, you know, an informed discussion with your patient. That's what we do. We sit down with our patients and say, "You know, it could be this. It could be that, and these are the different things that we can do," and you kind of come up with a shared plan.

And then true, the treatments can cause side effects too, like fatigue or itchy skin. You know, oddly enough, interferons can treat symptom burden, like itchy skin and make it much better for some patients. But actually, one of the side effects of interferons is itchy skin, and so it can be kind of a challenge in someone who develops those symptoms on treatment. What is it? Is it the disease? Is it the medication or is it something completely unrelated?

And so, sometimes it's about trying to find subtle qualities amongst those symptoms or the timing of when they appear, the association with other factors, and sometimes it's a process of elimination. So, we think it's a side effect. We stop the medication temporarily. If it is a side effect, it should get better, right? If it doesn't, well, it's probably due to something else and we can restart the medication and move on to the next type of thing. So, it is a very difficult thing to kind of sort through.

Lizette Figueroa-Rivera, MA

Thank you. And Ron is asking, "Are there any lifestyle, kind of like dietary, modifications that might help prevent or reduce any of these MPN symptoms?"

Andrew T. Gerds, MD, MS

Yeah, a fantastic question and one I get all the time. So, to the best of our knowledge, there is not anything specific to lifestyle that can improve disease. Now there is some data suggesting that exercise, particularly yoga, can help with symptom burden; but it was just a pilot study, so it wasn't a very large study.

You know, what I often recommend is the commonsense stuff, you know, three square meals a day, well balanced, you know, fruits, vegetables, fiber, the whole nine yards, regular exercise. Because we know those things, universally, can help keep a person at their healthiest.

And as people age and as the disease changes and we need to change our treatment, the healthier you are at your baseline, the better we can apply treatments. So, kind of taking care of yourself, getting a good, well-balanced diet, exercise, doing your primary care stuff and kind of regular checkups with them, are all real important pieces to keeping you as healthy as you can in case we need to use treatments to treat your myelofibrosis or PV or ET down the road. And that way we can have the full armamentarium of things available for us to do.

Lizette Figueroa-Rivera, MA

Thank you, and we'll take the next question over the telephone audience please.

Operator

Our next question is from Debbie in Illinois. Debbie, please state your question. Your line is now live.

Debbie from Illinois

One question. You were talking about that combination therapy. My husband just went into the MF-3 this past week. He's 48. Is that combination therapy good for the MF-3 or is that something that would have been better in the earlier stages?

Andrew T. Gerds, MD, MS

Yeah, I think that's a good question. You know, I think the way the trials are being designed, combination therapy is being done across the spectrum of disease. Generally, there are patients who have not had any JAK inhibitors before, those who have had JAK inhibitors before, patients that have caught earlier disease and later disease. So really, we're using combination therapies in all aspect of disease to try to get improved outcomes beyond what we already have with JAK inhibitors.

Lizette Figueroa-Rivera, MA

Thank you. And Dale is asking, "Is there any research going on in regards to chronic neutrophilic leukemia?"

Andrew T. Gerds, MD, MS

Yes, good question. So, chronic neutrophilic leukemia is kind of this smaller entity within the MPNs, one we don't often talk about a lot of times in these big meetings because it is so uncommon. I mean even at a big place here like Cleveland Clinic, we'll see just a few patients per year with this diagnosis, so not a very common disease.

Now there is some really neat research that's come out in the past looking at the different mutations within these cells and how different treatments might be better than others for this. So, the one story is about the CSF3R (colony-stimulating factor 3 receptor) mutation and the different type of mutation and whether or not we may be able to use drugs like dasatinib (Sprycel®) or ruxolitinib (Jafaki®) to treat these. So, there is ongoing work really kind of focusing on taking the mutational information from that disease and trying to apply the best treatments to it.

But by virtue of being somewhat of a rare disease, you know, unfortunately, it doesn't get the attention because they're just, there are fewer patients in order to have enrollment trials and try to learn more. But, you know, they are included in a lot of larger trials as subsets, which I think is very important. So, stuff is coming along but doesn't always make the top line as maybe some of the other diseases do.

Lizette Figueroa-Rivera, MA

Thank you, and we'll take the next question from our telephone audience please.

Operator

Our next question is from Savannah in Florida. Savannah, please state your question. Your line is now live.

Savannah from Florida

Good afternoon. My question is regarding cord blood and stem cells and how those can be used as treatment for ET?

Andrew T. Gerds, MD, MS

Fantastic, well thank you for the question. So certainly, cord blood or cord blood transplantation can be used to treat myeloid cancers like acute leukemia. We don't often use it for myelofibrosis or MPNs because of the risk of graft failure where it just doesn't stick and grow. It remains to be seen if cord blood expansion will change that, but we generally don't use cord blood.

For stem cells, so that again refers to stem cell transplantation where, it's like a bone marrow transplant, but the cells are collected through the peripheral blood as opposed to directly from the bone marrow. And that's actually the preferred graft source for doing a transplant is stem cells, again to minimize the risk of graft rejection. So, they are used quite a bit and particularly for high-risk myelofibrosis in patients who do need transplantation.

Now for essential thrombocythemia, you know, patients live for so long and do so well that we don't want to risk the complications often that occur with transplantation because it will most likely shorten people's lives and worsen their quality of life as compared to what the ET would do over time. In transplant, there's this concept of five years. If we think an individual, that their disease will take their life within five years, then transplant actually can be of great benefit. If we think that person's going to live longer than five years with their disease, then transplant is actually worse than nontransplant therapies. And so, that's how we really kind of think about when to apply transplant.

Lizette Figueroa-Rivera, MA

Thank you. And Myla is asking, "Can I take vitamin K2 with ET?"

Andrew T. Gerds, MD, MS

Yeah, there's no reason that you couldn't take vitamin K. Certainly if you have a vitamin K deficiency, it would help to reduce your risk of bleeding. But specifically, there's no worry about taking vitamin K with ET directly.

Lizette Figueroa-Rivera, MA

Thank you. And Michelle is asking, "Why are some people high risk and others low risk? What makes the difference, and why do some people never get that bad with their MPN?"

Andrew T. Gerds, MD, MS

Well, that's a great question, and I wish I had the answer to that, in honesty. Now, we use different factors that we see that know predict for more aggressive disease course. Some of these are clinical, like anemia and thrombocytopenia, predict for more aggressive disease. Some of these are genomic. We know that mutations in certain genes like ASXL1 (additional sex combs like 1) or p53 predict for more aggressive disease. And all these different models use different combinations of these different factors because we want to understand, again, who may do well for a long time without even treatment or who may have a more aggressive disease course, so we can apply the right treatments? And I think every time we learn more information about which of these risk factors are more prominent and more powerful than others, we refine these ways of thinking about disease risk. So, we're slowly chiseling away at that question of fully understanding why some people do really well and why others do not.

As we're peeling back the layers of the onion of these different risk factors, you know, it used to be just kind of simply age and anemia, and that's what we used, which is not very precise. And now we're, again, including chromosome abnormalities and genomics into understanding disease risk which is a much fuller picture. And in the future, we could use all ‘omics,’ proteomics, as well as and to try to even better fine-tune in to disease risk as it goes along. And then later you can envision a future where applying like say machine learning or even AI (artificial intelligence) to better understand the relationships between the risk factors within an individual to predict outcomes. So, you know, I think we're just on the cusp of understanding the answer to that question.

CLOSING REMARKS

Lizette Figueroa-Rivera, MA

Well thank you for that question, Michelle, which was the last question today; and thank you all for your questions. Again, thank you, Dr. Gerds, for your continued dedication to patients and providing us with this update on MPNs, giving us even more hope for the future in treating MPNs as more emerging therapies are approved.

And if we weren't able to get to your question today, please call Leukemia & Lymphoma Society Information Specialists at 1-800-955-4572. Information Specialists are available to speak with you from 9 AM to 9 PM Eastern Time or email them at LLS.org/ContactUs.

We also have another offering to patients as well as caregivers. You may schedule a free personalized nutrition consult with our dietitians at LLS.org/Consult.

Now LLS provides a variety of education and support resources, including online chats which are free live forums that are moderated by oncology social workers. We also offer free education videos and podcasts and financial assistance to help individuals with blood cancer.

For more information on financial assistance, please go to LLS.org/Finances. And to order free materials, go to LLS.org/Booklets.

Please note that continuing education credit is not being offered for this program.

Again, we'd like to acknowledge and thank Bristol Myers Squibb and Incyte for their additional support for this program, and thank you, Dr. Gerds, for sharing your knowledge with us today. And to all the patients, caregivers, and professionals participating in today's program, on behalf of The Leukemia & Lymphoma Society, thank you so much for sharing your time with us. Goodbye and we wish you well.