Greetings and welcome to Diagnosing and Treating Myeloproliferative Neoplasms Telephone and Web Education Program. It is now my pleasure to introduce your Moderator, Lizette Figueroa Rivera.

Ms. Lizette Figueroa Rivera:
Hello everyone. On behalf of The Leukemia & Lymphoma Society (LLS), a warm welcome to all of you. Special thanks to Dr. Jason Gotlib for sharing his time and expertise with us today.

Before we begin, I’d like to introduce The Leukemia & Lymphoma Society’s Executive Director of our Field Patient Access Team, Nicole Bell, who will share a few words. Nicole, please go ahead.

Ms. Nicole Bell:
Thank you, Lizette. I’d like to add my welcome to the patients, caregivers and healthcare professionals attending the program today. The Leukemia & Lymphoma Society exists to find cures and ensure access to treatment for blood cancer patients. Our vision is a world without blood cancer. For more than 60 years LLS has helped pioneer innovations, such as targeted therapies and immunotherapies that have improved survival rates and quality of life of many blood cancer patients. To date we have invested over $1 billion in research to advance therapies and save lives. Until there is a cure, LLS will continue to fund promising research from bench to bedside.

In addition, as this program demonstrates, we are the leading source of free blood cancer information, education and support, and we touch patients in the communities through our 58 chapters across the United States and Canada. LLS also acts as the voice for all blood cancer patients. We advocate for patients and survivors and their families, helping them navigate their cancer treatments and ensuring that they have access to quality, affordable and coordinated care.

We’re fortunate to have our presenter today, Dr. Jason Gotlib, one of the nation’s leading experts in myeloproliferative neoplasms. We appreciate his dedication to supporting our mission and his commitment to caring for patients living with blood cancers. I’d like to thank him for providing us today with important information on MPN.

Thank you all, and now I’ll return the program back to Lizette.
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Ms. Lizette Figueroa Rivera:
Thank you Nicole, and we would like to acknowledge and thank Incyte for support of this program.

Slide 3 - Disclosures
I am now pleased to introduce Dr. Jason Gotlib, Associate Professor of Medicine and Hematology, Stanford University School of Medicine, Stanford Cancer Institute in Stanford, California. On behalf of The Leukemia & Lymphoma Society, thank you for volunteering your time and expertise with us today. Dr. Gotlib, I'm now privileged to turn the program over to you.

Slide 4 - Diagnosing and Treating Myeloproliferative Neoplasms
Dr. Jason Gotlib:
Well, thank you very much, Lizette and Nicole, and I'd like to thank The Leukemia & Lymphoma Society for creating this venue in the form of an interactive webinar with questions and to provide what I hope will be useful information on diagnosing and treating MPNs for patients and their caregivers as well as health professionals.

Slide 5 - Myeloproliferative Neoplasms (MPNs)
Now, let me just start with a general overview of myeloproliferative neoplasms. You can see on this slide that there are actually eight separate diseases within the group of MPNs, but the three diseases that I'm going to focus on today are polycythemia vera, or PV; essential thrombocythemia, or ET; and primary myelofibrosis, or PMF, and these have been referred to as the classic MPNs, or so-called Philadelphia chromosome negative MPNs, or BCR-ABL negative MPNs, because they lack the Philadelphia chromosome which is characteristic of a disease called chronic myelogenous leukemia.

Slide 6 - Myeloproliferative Neoplasms (MPNs) Are a Group of Hematologic Malignancies
MPNs are a group of hematologic malignancies—and again, the ones I’m going to talk about today are PV, ET, and myelofibrosis—and these are acquired disorders; they are not inherited. They basically commonly have molecular or cytogenetic or chromosome abnormalities. They are characterized by overproduction of one or more types of blood cells, such as white blood cells, red blood cells or platelets, or one or more of those together, and they are increased because there is a problem with the bone marrow, meaning that the blood cells are at an increase in number because there’s another stimulus, and I can go into perhaps some of the other reasons for why red blood cells, white bloods cells or platelets may be increased in number.
Dr. Jason Gotlib:
These diseases are characterized by what we refer to as extramedullary hematopoiesis. That is, there are other organs besides the bone marrow that are trying, in some cases, to produce blood cells because the bone marrow becomes ineffective, and the specific example is having a big spleen. These patients often have increased fibrosis or scar tissue in the bone marrow. These patients can have an increased propensity to transform to acute myeloid leukemia, and most notably, these patients have an increased risk of thrombosis or blood clots as well as bleeding.

Slide 7 - Evolution of Myeloproliferative Neoplasms
Now it’s important to understand what the natural history of myeloproliferative neoplasms is. If you take patients with PV or ET, you can see that such patients, in the case of PV, 10% to 20%, or in the case of ET, 5% to 10%, do have a potential to progress to what we refer as post-PV or post-ET myelofibrosis. In turn, patients with PV and ET, once they develop myelofibrosis, can then in turn develop acute myeloid leukemia, and you see the percentages there: on the order of less than 5% for ET developing AML, and about 10% of PV patients are developing AML, and this is not something that happens usually over a few years but is something that occurs over the course of one to two decades.

Then, if you take patients with primary myelofibrosis, about 15% to 20% of such patients over time—again, usually years—can develop into acute myeloid leukemia. So it’s again important to understand that there is primary myelofibrosis but also secondary myelofibrosis arising from PV and ET, and all these MPNs can ultimately develop into acute leukemia, but the frequency is on the low side, anywhere from 5% to 20% and usually takes a few decades, but it can be variable with some patients presenting with high-risk disease developing acute leukemia at a shorter time interval.

Slide 8 - JAK2 V617F Mutation Frequency
Now, one of the characteristic features of MPNs is the development of knowledge that shows that almost all patients have one or more genetic abnormalities that is a basis for these acquired blood diseases, and the most common one that we’re familiar with, of course, is the JAK2 V617F mutation. You see at the bottom of the slide a cartoon, in a manner of speaking, of the JAK2 gene and the location of V617F mutation. This is a mutation that’s found in almost all patients with polycythemia vera, about 95% to 98% of patients, although about 2% of patients will have another mutation in the JAK2 gene referred to as Exon 12 mutation. So, if there is high suspicion that a patient has PV but does not have the JAK2 V617F mutation, then it’s incumbent upon the doctor to see if they have an alternative JAK2 mutation in Exon 12. Then for patients with essential
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Dr. Jason Gotlib:
polycythemia and primary myelofibrosis, about 50% to 60% of such patients will have the JAK2 V617F mutation.

Slide 9 - The New England Journal of Medicine
It’s always been a mystery to investigators in this field up until a few years ago, while for those patients that have ET or myelofibrosis that don’t have the JAK2 mutation, what is another mutational cause of the disease? Investigators from two groups, both from Europe—the groups led by Robert Kralovics and also Tony Green—in December 2013 published a finding that in patients that have ET and myelofibrosis but are non-mutated for JAK2, that the overall majority of these patients will have mutations, another gene referred to calreticulin, or abbreviated as CALR, C-A-L-R.

Slide 10 - Mutational Landscape of BCR-ABL1-Negative Myeloproliferative Neoplasms (MPN)
If you look at this pie chart on the next slide, you can see again that almost all patients had the JAK2 V617F mutations in PV, but again there is large white space in that pie for ET and MF and that pie has been filled in by the CALR mutation in red there. Again, about 80% of patients that are non-mutated for JAK2 will end up having a CALR mutation, and if you take all patients with ET and myelofibrosis, about 25% to 30% of such patients will have a CALR mutation.

Now you see additionally there is a little stripe of green in the pie chart for ET and myelofibrosis and that refers to a MPL mutation, M-P-L. This is found in about 5% to 10% of patients with ET and myelofibrosis.

Then finally, there are about 5% to 10% of patients with ET and myelofibrosis that don’t have a JAK2 mutation, don’t have a CALR mutation and don’t have a MPL mutation, and these patients are referred to as being so-called triple-negative, and there are ongoing studies to determine what could be the mutational cause for these individuals who develop ET or myelofibrosis.

Slide 11 - Red Blood Cell
Now, in the next slide, what I’ve done here is provide another schematic or cartoon of the inside of a red blood cell to try to provide some more useful information about what’s going on to make these red blood cells divide. You can see there, there’s a gray stripe on the top of the inside of the cell that’s called a membrane or plasma membrane of the cell, and there’s a receptor called the EPO Receptor; that’s shown in green. The EPO Receptor binds a red blood cell hormone called erythropoietin, or EPO, and in normal physiology the normal erythropoietin binds to the EPO Receptor and then stimulates or
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Dr. Jason Gotlib:
causes the JAK proteins to bind to the receptor. That in turn recruits these proteins called STATs and the STATs then go to the inside of the cell’s nucleus and bind to DNA and cause the red blood cells to survive longer and to divide and proliferate, making more red blood cells. This is referred to as the JAK-STAT pathway.

Now, what goes on in PV for example, one has a mutation, the JAK2 V617F mutation that causes JAK to be turned on all the time, so you have this messenger, the JAK2 proteins, that basically cause signaling to be turned on all the time within the red blood cell, causing the red blood cell to divide and make more of themselves, and that’s why we have an increased hemoglobin or hematocrit because too many red blood cells are being made because the JAK proteins are turned on all the time. In turn, you don’t even need EPO to bind to the receptor because the internal signaling is turned on all the time from the mutated JAK2 protein.

Slide 12 - Megakaryocytes/Platelets
Now in this next slide, like we focused on the prior slide with red blood cells, the focus is on the cells that give rise to platelets, the so-called megakaryocytes that are made within the bone marrow. In these patients with, for example ET, where there are too many platelets, in myelofibrosis where there can be increased platelets as well, we have other potential causes of why the cells are made in too many numbers. First of all, I mentioned that in about 5% to 10% of patients there is a mutation in MPL, and MPL here is actually the receptor for thrombopoietin or TPO, and that again is shown in green. So you can see here that in addition to the JAK proteins being mutated in ET and myelofibrosis, that you could also have mutation of the TPO receptor or MPL, and that’s again shown in green. So it can either be through the JAK proteins or mutated receptor shown in green, that again being the end result of increased JAK-STAT signaling.

Now, I mentioned that the third major mutation that occurs in ET or myelofibrosis is an immune protein called CALR, and you can see that in the right part of the screen where you see those little yellow bars showing the CALR protein. It’s stymied investigators why should CALR—which is in another part of the cell separate from that JAK-STAT signaling access—how can that actually cause increased JAK-STAT signaling, which in fact has been found in patients with mutated calreticulin? Well, in fact, because CALR is mutated, it actually causes a mutated protein to move to the inside of the cell, as I’ve shown there, and it actually binds to the JAK proteins and the thrombopoietin receptor and actually turns on that signaling pathway. So, in a sense you have CALR, which is in another part of the cell normally, but when it becomes mutated it travels from that part
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Dr. Jason Gotlib:
of the cell, binds to the JAK-STAT signaling access and turns it on, and therefore you have increased JAK-STAT signaling and you can have, for example, increased numbers of platelets.

This is very interesting biology and now I think we have the answer as to why JAK2 mutations cause increased red blood cells or increased platelets, why MPL mutations cause increased platelets and why CALR mutations cause increased platelets and lead to the presentation of a patient with ET or myelofibrosis.

Slide 13 - Mutations in genes outside of the JAK-STAT pathway in MPN patients
I mentioned three proteins or genes that are mutated and cause activation of the JAK-STAT pathway and those are shown in red on this next slide. For example, again, JAK2 V617F, the JAK2 Exon 12 mutation in PV, MPL, CALR and there’s another protein called LNK which actually is also mutated and binds to JAK2 and can cause increased activation of the JAK-STAT pathway. But in fact, we have found that there are multiple other genes that have been found to be mutated in these diseases and are actually located outside of the JAK-STAT pathway, and they can be mutations that lead to increased initiation of the disease or actually cause progression of the disease where it produces more advanced forms of either ET or myelofibrosis, or in some cases even PV.

So, you have these proteins that are mutated that are, in a manner of speaking, part of the iceberg that’s visible, but there have been now other proteins that have been found mutated that we never were aware of before and we now understand that they contribute to disease initiation or progression.

Slide 14 - Average number of acquired mutations in: PV, ET, PMF
Moving to the next slide, it’s important to realize that PV, ET and myelofibrosis are not single-gene related diseases; that again there are multiple mutations that have been found in these acquired disorders. So, for example, I’ve shown here that the average number of mutations that a patient with PV has are 6.5; similarly, the average number of mutations that a patient with ET has are 6.5; and myelofibrosis tends to be more genetically complex and that might be one reason why these are more challenging disorders to treat, and the average number of mutations in these patients is actually 13.

So, for example, if we were able to screen all the genes in the human genome and look for mutations, there would be 6.5 mutations found in PV and ET, and 13 in myelofibrosis. It’s important to stress again that these are not inherited mutations; these are acquired in the blood cells over time, which lead to the development of these three disorders.
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Slide 15 - Diagnosis of MPN
Dr. Jason Gotlib:
Okay, now having talked a little bit about the biology of the disease and the mutations that cause them, let’s move forward and segue to the diagnosis of myeloproliferative neoplasms. It’s important to note that the diagnosis of these disorders is not just based on a gene mutation, in part because as I’ve shown you can have the JAK2 V617F mutation in PV, ET or myelofibrosis, so finding a JAK2 mutation is not sufficient to identify whether someone has PV versus ET or myelofibrosis. It’s important to realize that the diagnosis of an MPN requires patient history-taking, physical examination, a review of the blood counts, review of the chemistries and liver function tests, certainly a bone marrow biopsy in almost all cases, and yes, the additional molecular testing. So, for example, if I have a patient who presents in my clinic with a high red blood cell count, we can’t immediately make the determination that that patient has polycythemia vera. That patient, for example, can have a high red blood cell count because they have another disorder. For example, people that have chronic lung disease, maybe due to smoking or emphysema or obstructive sleep apnea, those are patients that can present with an elevated red blood cell count, so we have to find other reasons for that elevated red blood cell count to make sure that we can decide whether they have PV or not. There are patients that have a high platelet count, for example, which can be a sign of PV, ET or myelofibrosis, but on exam if we find a very big spleen or these are patients that present with a blood clot, we may start thinking about whether they have, for example, myelofibrosis or essential polycythemia, because patients with myelofibrosis can have a big spleen and patients with MPNs certainly have a higher frequency of blood clots.

Bone marrow biopsy is very important because we’re looking to see whether these patients have fibrosis, for example, in the case of myelofibrosis; whether patients have increased early leukemia cells, what we call blasts; whether the cellularity of the bone marrow is increased because these are very cellular, very productive marrows in terms of making too many blood cells; and whether patients have chromosome or genetic abnormalities, which again, go along with the idea that these are acquired disorders that are due to one or more genetic mutations or chromosome abnormalities.

Now, we are providing molecular testing in an extended way with what we call next generation sequencing because there are certain mutations in addition to JAK2 that when we identify them, appear to be related with higher-risk or poor-risk disease and this might help us stratify patients into relatively better risk or worse risk and whether that may modify the decisions we make regarding treatment options.
Dr. Jason Gotlib:
So again, the take-home message is that we require all these items—interviewing, exam, review of the blood counts, bone marrow biopsy and molecular testing—to parse out what type of MPN someone has and whether they have an MPN in the first place.

Slide 16 – Essential Thrombocytemia
Shown here on the next slide is just an example of a blood smear and bone marrow biopsy features of a patient with essential thrombocytemia. For example, in the upper left-hand corner, I've shown a blood smear, and if you look right in the center of that smear you can see a purple cell that's on the large side and you can see a lot of other small purple cells, and those are platelets. But what we see in patients with ET is that we see often too many of them, and believe me, these are way too many platelets in the peripheral blood. We should see half of this number. Sometimes you see platelets that are very large like the large purple cell right in the middle.

In the lower left-hand corner, one has a picture of a bone marrow aspirate and you see those clumps of purple and those are actually megakaryocytes, the cells that give rise to platelets that ultimately circulate in the peripheral blood. Again, based on our experience of looking at bone marrow aspirates, the fluid portion of the bone marrow, there are too many platelet precursor cells, megakaryocytes, here. There should be at least half of these or less, consistent with a normal marrow. So this is way too many megakaryocytes.

Then on the lower right, again we have a core bone marrow biopsy showing these pink cells that are clustered together. Again, these are megakaryocytes, and based on our experience of looking at bone marrows, there are too many megakaryocytes here and this is again consistent with a patient with ET.

Slide 17 - Myelofibrosis
Moving to the next slide, these are some features that we’ll look for in myelofibrosis. In the upper left-hand corner, this is actually a patient of mine that I’ve seen in the past, and you can see that the abdomen is markedly distended, and you can see some lines that I’ve drawn on the patient’s abdomen. The patient’s spleen is markedly enlarged here. It goes down to the pelvis, some 30 centimeters, and in a normal individual one should not be able to actually feel the spleen because it’s tucked behind the rib cage. So this is a markedly enlarged spleen and this is what we refer to as extramedullary hematopoiesis, big spleen. The spleen is big because the spleen is trying to make blood cells because the bone marrow has essentially failed, and the cells that are made from the bone marrow are often abnormal and the spleen acts like a filter to try to
Dr. Jason Gotlib: remove them. So the spleen becomes big because it’s trying to make blood, albeit very ineffective, and it’s a filter of blood and gets very big like a sponge soaking up all these abnormal blood cells.

In the lower portion of the slide we see different aspects of the peripheral blood. On the left panel you can see a very large cell in purple and blue. That’s a very large abnormal platelet. You can see another very small purple cell there; that’s actually a normal-sized platelet. In the middle panel, you can see red blood cells and you can see some that look like tear drops. Those are so-called tear-drop red blood cells, and if you imagine some of these red blood cells trying to squeeze out of the fibrosis in the bone marrow, they become tear-dropped in appearance, so this is one of the features that we look for in myelofibrosis. Finally, in the right panel, you can see a large cell that’s blue and purple and that’s actually a circulating blast or very immature cell we refer to as a leukemia cell, and when we see more and more of those, we get concerned about the patient progressing toward acute leukemia.

Slide 18 - Myelofibrosis
Shown here on the next slide are some examples of a core biopsy from a patient with myelofibrosis, and you can see, for example, on the right-hand side you see a green-looking core biopsy and a red-looking core biopsy, and in fact, these are different stains that have been used to evaluate the amount of fibrosis or scar tissue in the bone marrow. These are heavily scarred examples of bone marrow biopsies where you can’t even see the cells because they’ve been obliterated by all the scar tissue. This is what we refer to as MF3 grade fibrosis.

We use a scale of 0 to 3, 0 being no fibrosis, 1 being mild, 2 being moderate fibrosis and 3 being severe fibrosis where the scar tissue is weaving throughout the bone marrow and obliterating the bone marrow space, making it hard for the bone marrow to produce any blood cells. So that’s again an example of a high grade fibrosis.

Okay, so we’ve talked about how to diagnose MPNs. We’ve talked about some of the molecular features and what perhaps the bone marrows can look like in these patients. Let’s talk about some of the clinical issues that PV and ET and myelofibrosis patients face.

Slide 19 - Burdens of PV and ET
This is a slide that basically is a Venn diagram of some of the overlapping issues that PV and ET patients face. So, number one would be symptoms. These are patients that often can have multiple symptoms related to their high red blood cells, to their high
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Dr. Jason Gotlib:
platelet counts, or just the disease in itself. They can include itching, fatigue. There’s a
term that we use called erythromelalgia which refers to burning hot feet or toes or
fingers. That relates to the fact that when the red blood cells are very high or the
platelets are very high, it can cause sludging of the blood within the small vessels and
can cause painful, burning hot sensation in the fingers and toes and the feet.

We also, of course, have patients deal with issues of vascular risk. These are patients
who can have an increased frequency of blood clots or bleeding, and the blood clots
can be in the arteries or veins. Clots in the veins are referred to as a deep venous
thrombosis in the leg, or if it occurs in the lungs it’s referred to as a pulmonary
embolism, and they cause significant morbidity and can even cause death.

We also have the issue of transformation. That is transformation to acute myeloid
leukemia or AML. Again, I refer to the frequency of transformation to AML in one of the
initial slides of this presentation. Again, on the order of about 5% to 15% to 20% in
patients with PV, ET and, respectively, myelofibrosis.

Then in those patients who require treatment for their disease, of course there’s the
omnipresent issue of treatment-related side effects related to the therapies that we use,
and this is no small issue because patients are trying to deal with their disease and
trying to deal with their side effects at the same time.

Slide 20 - Burdens of Myelofibrosis
Now the burdens of myelofibrosis are perhaps even more extensive than those of PV
and ET, depending on the stage of the disease. So, in contrast to patients with PV
whose red blood cell counts are too high, patients with myelofibrosis often develop
progressive anemia and with that worsening fatigue and shortness of breath, or
decreased exercise tolerance. Patients also have issues of weight loss because of their
big spleen, night sweats or itching or bone pain, and certainly fatigue, and in uncommon
circumstances they’ll also develop fevers. Patients will also have issues with a large
spleen, and again, that can lead to decreased appetite and weight loss and abdominal
discomfort, and we’ve talked about the fibrosis in the bone marrow which leads to
lowering blood counts, which makes it very hard for the patient to have normal
production of red blood cells and platelets. So, these are a constellation of clinical
issues, laboratory issues, which with the disease worsening can make a major impact
on quality of life for patients with myelofibrosis.
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Slide 21 - Prevalence of Symptoms in 96 MF Patients
Dr. Jason Gotlib:
This is a chart showing the prevalence of symptoms in 96 patients with myelofibrosis, and you can see that the frequency of symptoms ranges anywhere from about 20% all the way to basically all patients at 100%. So again, you have, uncommonly, individuals who may have fever and headaches, weight loss. We often see abdominal pain and night sweats. It might be sometimes difficult to talk about it, but we also have issues of depression and issues with libido or sexual problems. Patients oftentimes talk about issues with concentrating or so-called brain fog. Of course major issues are early satiety—that means early fullness when you eat—because of that big spleen, fatigue with inactivity and impairment of quality of life. So, patients and their caregivers, we often stress to them it’s important to relay these issues so we can try to address them in clinic, because PV and ET, but particularly MF, have major issues with the quality of life. We always focus on labs, we focus on exams, but it’s important that we as caregivers and physicians focus on symptoms that patients are telling us about so we can try to steer the road in the right way.

Slide 22 - Goals of MPN Therapy
Okay, so regarding treatment options, what are they? What are the goals of MPN therapy? Well, we would love to be able to cure all patients with MPNs. These are chronic diseases and certainly the hope of physicians and the LLS and the other patient care groups is to make sure that we can try to achieve cure someday. Short of cure, our goals are focused on eliminating or at least reducing symptoms, as I’ve just talked about; decreasing the large spleen size, because again, that impacts the ability to take in food and causes abdominal pain and weight loss. A major focus is trying to reduce future blood clots or bleeding events which are increased in these patients. We’re always trying to find ways to improve blood counts; that is red blood cell count that is decreased and contributing to shortness of breath and fatigue, or a reduced platelet count that can be contributing to bleeding or bruising. We want to see whether we can somehow modify the natural history of the disease. That is, can we impact the molecular or cytogenetic abnormalities that we’re seeing in patients, because it’s our feeling that these are findings related to the disease, that if we can make them disappear it may portend well for having long and meaningful responses for patients, although that data is not clearly the case for certain types of therapies, and I’ll get into that; for example, interferon. Of course we know that acute myeloid leukemia is very challenging to treat, so if there are any treatments that we can provide or alternatively avoid that we feel are associated with increased risk of AML, it really is incumbent upon us to try to reduce the evolution to AML, because again, AML often has a very challenging and poor prognosis.
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Slide 23 - Risk-Adapted Therapy for PV and ET  
Dr. Jason Gotlib:  
So how do we go about thinking about treatment for patients, specifically for PV and ET? Well, the first thing that I do in clinic when I have PV and ET patients is risk stratify them. So for example, patients with PV and ET, we put them into lower-risk and high-risk groups, and risk refers to the issue of a future risk of a blood clot. Patients with PV that are low-risk are those that are less than age 60 and have no history of thrombosis. High-risk patients with PV are those that are above age 60 or have had a history of a blood clot or thrombosis. For low-risk patients with PV, we will just use low-dose aspirin and phlebotomy. The phlebotomy goal is less than 42 for women—that is the hematocrit—and less than 45 for men.

For high-risk patients with PV, again, those above age of 60 or history of a blood clot, we will use low-dose aspirin and phlebotomy but we’ll also add what we call a cytoreductive drug. That is a medication to try to reduce the blood panels to reduce their risk of a future blood clot, and that can be a drug such as hydroxyurea or pegylated interferon-alpha.

For patients with ET we use a similar type of strategy. Again, for low-risk patients, we just use low-dose aspirin. We don’t need to use phlebotomy because the red blood cell count is not elevated in these individuals. For high-risk patients, we’ll use aspirin, and again either usually hydroxyurea or pegylated interferon-alpha.

Slide 24 - Risk-Adapted Therapy for PV and ET  
Now, there is a new drug called ruxolitinib, or Jakafi®, that was approved in 2014 for patients with PV who have had an inadequate response or have not tolerated hydroxyurea. So if you are a PV patient, have been on hydroxyurea and have not reached adequate goals of therapy or don’t tolerate it, this JAK inhibitor ruxolitinib is an alternative option for these individuals.

Slide 25 - PV: Thrombosis Risk and Hct  
I mentioned in the prior slide that risk is all about the risk of trying to avoid future blood clots, and you can see here in this graph that as the hematocrit, which is on the lower axis, the X axis, goes up from 40 to 44 to 49 to 54 to 59, you can see that an elevated red blood cell count or hematocrit is associated with an increased risk of thrombosis or blood clots, and that is what we’re trying to mitigate or avoid.

Slide 26 - Cardiovascular Events and Intensity of Treatment in Polycythemia Vera  
For many years, we in hematology again have used phlebotomy thresholds of less than 42 for women and less than 45 for men to keep that threshold, meaning that if it’s above
Dr. Jason Gotlib:
45 for men or above 42 for women, we have patients undergo phlebotomy, but that practice was not necessarily based on very rigorous data until this publication that came out in the *New England Journal of Medicine* in 2013.

**Slide 27 - Optimal Hct Target <45% in the Treatment of PV: Cyto-PV Study**
In this trial there were groups of patients with PV that were randomized to two groups: one was a low hematocrit group, that is their hematocrit was maintained below 45, and then a high hematocrit group where the hematocrit was maintained in the range of 45 to 50.

**Slide 28 - Cardiovascular Mortality or Major Thrombosis Was Significantly Lower in Patients with PV and Hct Level of <45%**
Essentially, the outcome of the study was that in patients whose hematocrit was maintained below 45, the rate of death or cardiovascular events or major clots was four-fold lower in those patients. Alternatively, in those patients whose hematocrit was maintained at a higher level, 45 to 50, the risk of death from cardiovascular disease or clots or death was four-fold higher. This basically confirmed our practice that for men, and by inference women, keeping the hematocrit below 45 is very important because it reduced the risk of blood clots and death, so this is now standard of care for patients with PV in terms of phlebotomy thresholds.

**Slide 29 - Indications for Cytoreduction in PV and ET**
Now, we will also use hydroxyurea or interferon for other reasons and I go through them here. So, in addition to using it for high-risk patients as I’ve outlined, we will use it if there are patients who have poor tolerance of or the need for frequent phlebotomy; for patients that have spleens that are getting larger and larger; for patients whose platelet counts are rising very high, for example above 1.5 million; or the white count is going very high, in part because if the platelets go very, very high we get concerned not only about clotting but perhaps even more so about bleeding risk and having platelets that high gets very dangerous. Hydroxyurea or interferon-alpha is considered first-line therapy at any age for PV or ET. Hydroxyurea, we feel, should be used with some caution in young patients, in part because although there are some data, it’s never been proven that hydroxyurea increased the risk of leukemia in patients with PV or ET who may already have an increased risk of leukemia, so we generally favor the use of interferon in younger patients, although hydroxyurea could be used. Again, no proven data that hydroxyurea increases the risk of leukemia in individuals, but because younger patients have many years ahead of them and we can’t definitively rule out a contribution of hydroxyurea for selected individuals in terms of increasing their risk of leukemia, we generally favor the use of interferon for younger individuals.
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Dr. Jason Gotlib:
There are some drugs that seem to be associated with an increased risk of leukemia in patients with PV and ET and I’ve listed them there—pipobroman, busulfan and a radioactive agent called $^{32}$P. Generally, we will only refer to these agents or use them when we have gone through the other therapies and for patients that are at least 70 to 80 years old because they can increase the risk of leukemia, so we tend to avoid them in younger individuals.

Slide 30 - Pegylated interferon-α-2a in PV and ET: Hematologic and Molecular Response Rates
Another agent that has garnered interest is pegylated interferon-alpha and it has been used in PV and ET. Generally, the data show with this agent that hematologic response rates, that is a complete hematologic response, can be achieved in 75% to 80% of patients, and notably, about 60% of patients can have some reduction of the JAK2 mutation with longer-term therapy, of which about 15% of patients can achieve a complete molecular remission of the JAK2 mutation. So that seems very appealing and I think that we in the field of hematology are very interested in this agent because we’ve seen these molecular remissions, but we still don’t have any long-term data to know how those molecular remissions translate into modification of the natural history of the disease. That is, does achieving a molecular remission or a complete molecular remission actually reduce the risk of evolving to acute leukemia? Does it reduce the risk of evolving into myelofibrosis if you have PV or ET? We just don’t know. We think that achieving molecular remission is a good thing but we need longer term data to sort that out. But this is an agent with increasing interest and certainly, this is an agent that I have used in individuals with PV and ET that need cytoreduction, and particularly those who are younger in age.

Slide 31 - RESPONSE Trial in PV: Ruxolitinib vs. Best Available Therapy
There are data from the so-called RESPONSE trial in PV. This is a trial looking at ruxolitinib, the JAK inhibitor, versus best available therapy, which included drugs like hydroxyurea, to see which agent does better, ruxolitinib or the group of agents used under best available therapy. These were, again, individuals that had been previously treated with drugs like hydroxyurea. The bottom line of this trial is that ruxolitinib achieved the primary endpoints of a greater than 35% reduction of spleen volume or control of the hematocrit much better than best available therapy. You can see the data there for the fact that ruxolitinib achieved a composite endpoint in 21% of patients versus only 1% of patients in the best available therapy arm. Panel B here shows that the responses are durable.
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Slide 32 - RESPONSE Trial: Symptom Assessments
Dr. Jason Gotlib:
If you look here on the RESPONSE trial, you can see that ruxolitinib was significantly better than best available therapy in reducing the symptom scores of patients, and you see in Panel B the dark blue bar showing the significant reduction of symptoms across a spectrum of various symptoms, including tiredness, itching, concentration and dizziness and abdominal discomfort and early satiety. So not only is ruxolitinib able to achieve better phlebotomy control and spleen reduction, but most importantly, symptom control compared to best available therapy.

Slide 33 - Core Issues with Available Drugs for PV
So if one looks at the core issues related to the available drugs for PV, with hydroxyurea, usually there’s good tolerance, but about 15% of patients may not show good tolerance, and generally this drug is considered cosmetic; it doesn’t change the natural history of the disease. Pegylated interferon-alpha, the issues regarding tolerability are that there are issues regarding tolerability and there are about 20% of patients that over time will drop out because of side effects, but as I mentioned before, there may be potential for disease modification with those molecular remissions, but we haven’t proven that yet.

Then finally, ruxolitinib, which is now approved for patients who are resistant or intolerant to hydroxyurea. Generally it’s very well tolerated, but at this point in time without the benefit of long-term data, we don’t have specific data that it actually can modify the long-term outcomes of patients with PV.

Slide 34 - Myelofibrosis Prognostic Scoring Systems
Okay, now moving forward, I just wanted to indicate that in the case of myelofibrosis we do have scoring systems available to us that help us gauge the prognosis of patients. They go by names such as the IPSS or DIPSS Plus, and it includes either five or eight clinical or laboratory features that help us gauge the prognosis of patients. They include age; hemoglobin less than 10; white count above 25,000; the presence of symptoms; the presence of early leukemia cells or blasts in the blood; the need for red blood cell transfusions; a low platelet count, less than 100,000; and the presence of unfavorable cytogenetics or that is chromosome abnormalities.

Slide 35 - DIPSS Plus
We use and add up the number of risk factors for patients and we can actually draw a prognostic curve showing the average survival for such patients. So, for example, if someone has low-risk disease, meaning none of those risk factors, the average survival is in the order of 15.4 years. If someone has in the order of four to six risk factors, then
Dr. Jason Gotlib: 
you can see that the survival goes dramatically down to in the order of about 1.3 years. 
Whenever we’re in clinic we use these prognostic risk factors to gauge potential survival 
of patients, and we also use this to stratify potential treatment options for patients with 
lower-risk disease versus higher-risk disease where we may be more inclined to use 
high-intensity options such as bone marrow transplant.

Slide 36 - Conventional Medications for MF
What about medications for myelofibrosis? Well, historically there have been very few 
medications that have been useful. We’ve used various medications for anemia or for 
big spleens or for symptoms, but frankly, many of these have been quite ineffective with 
very low response rates.

Slide 37 - Myelofibrosis (MF) in 2016
So in 2016, only the JAK inhibitor ruxolitinib is FDA approved for myelofibrosis. This 
was approved now some five years ago. No medicine has been proven to cure or 
definitively alter the natural history of the disease, and only allogeneic stem cell 
transplant can cure myelofibrosis, but it can carry significant risk and the use must be 
selective and it may be it’s certainly not available to most individuals because of age or 
donor availability or performance status, that is the health of the individual.

Slide 38 - JAK2 inhibitors tested in clinical trials in patients with myelofibrosis
This is somewhat of a busy slide, but it just goes to show that there have been many 
JAK inhibitors that have been evaluated in clinical trials. The only one, again, approved 
is ruxolitinib. Pacritinib is a JAK inhibitor that has been in Phase 3 trials, but more 
recently placed on clinical hold by the FDA (U.S. Food and Drug Administration) 
because of concerns of issues of increased mortality and cardiac issues and stroke. 
We will have to see where that program unfolds, whether it will be resumed. Momelotinib is a JAK inhibitor that is actually in two Phase 3 trials, and we will 
determine over the next year to year and a half whether this drug has traction and will 
be approved by the FDA. There are others that are ongoing in investigation or have 
halted. You can see there are at least four drugs that have been halted, mostly 
because of neurologic side effects. Although they seem promising at first, the toxicity 
warrented them to be discontinued from further evaluation.

Slide 39 - COMFORT-I and COMFORT-II
There are two major trials, the COMFORT trials, that evaluated ruxolitinib in patients 
with intermediate to high-risk myelofibrosis, and it’s worth going over the fact that there 
are some myths and truths about this drug, and I wanted to go through them briefly 
here.
Slide 40 - Ruxolitinib in Myelofibrosis: True/False
Dr. Jason Gotlib:
First of all, true or false: the reduction of symptoms in spleen size and improved quality of life are major benefits of the drug. That is true.

Another issue is some people think they only work for JAK2 V617F-positive patients. That is false. These drugs will work in patients that have the calreticulin mutation or the MPL mutation, or are triple negative.

Number three: major molecular remission of JAK2 and normalization of fibrosis occurs in most patients. That is actually false. Although there are a proportion of patients that can have lowering of their JAK2 mutation burden or decreases in fibrosis over time, this is not certainly an observation that we see in most patients. Perhaps in the order of about 10% to 15% of patients will we see some reduction of the JAK2 burden or reduction of fibrosis.

Finally, higher doses of the drug are most effective for achieving and maintaining key benefits. That is actually false, and in fact using a very high dose may lead to substantial anemia or lowering of the platelet count. Generally speaking, we physicians generally take a start low road and go high as tolerated with this drug, meaning that we tend to use lower doses to begin with and incrementally increase a dose as tolerated and to try to achieve better increasing benefits with the spleen and symptoms as tolerated. However, the dosing of the drug needs to be geared toward the individual patient and there’s not one dosing regimen that fits all. There are issues of anemia and low platelet counts and that’s why generally we recommend that we start low and move high as tolerated, and there are other options such as red blood cell booster shots like Procrit® or red blood cell transfusions that can be used to try to help the anemia of such patients.

Slide 41 - Splenomegaly in MF Patient Pre-Therapy
This is just an example of a patient with a big spleen before ruxolitinib.

Slide 42 - Splenomegaly after 2 Months of Therapy
You can see it’s very large, filling the whole abdomen, and with ongoing therapy you can see a substantial reduction of the spleen size and this is what we commonly see with patients after several weeks or just a few months on therapy.
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Slide 43 – Duration of Spleen Response (COMFORT-II Trial)
Dr. Jason Gotlib:
People often want to know what the duration of spleen response is and these are recent data out of the COMFORT-II trial where ruxolitinib was compared versus best available therapy, and the bottom line is that about 50% of patients will still maintain significant reduction in spleen size after three and five years of follow-up.

The message here is that the durability of the response is long, and again, there may be selected individuals where the responses are not as long, but these are the cumulative data from the trial and they are very encouraging with durable responses in reduction of spleen size.

Slide 44 - Novel Non-JAK2 Inhibitors in Clinical Trials for Patients with Myelofibrosis
This is just a slide that shows that we in hematology are looking at other alternative drugs to treat myelofibrosis, and if they go through different mechanisms—and I’m not going to spend any significant time here right now going through them—but they basically attack different abnormalities within the cells that have gone wrong and these are in active clinical trials as we speak.

Slide 45 - PRM-151 in Myelofibrosis: Durable Efficacy and Safety at 72 Weeks
One of them is a drug called PRM-151 and this has shown some activity with reducing the spleen size and in helping anemia and low platelet counts, and this is felt to be a so-called anti-fibrotic drug which is meant to see whether we can dissolve some of the fibrosis that is in the bone marrow with the intent to try to improve blood counts and shrink the spleen.

Slide 46 - PRM-151: Recombinant Human Pentraxin-2 (PTX-2)
Very early days for the trial, so we will need to see with further time whether this drug actually has substantial activity in patients in meeting its endpoints of improved symptoms, improved spleen size, improving blood counts, and of course reducing fibrosis.

Slide 47 – A Pilot Study of the Telomerase Inhibitor Imetelstat for Myelofibrosis
There is another drug called imetelstat that has another mechanism of action that is in a large Phase 2 trial right now in multiple centers in the US and Europe. This is a so-called telomerase inhibitor that has shown some promising early results in a trial published in the New England Journal of Medicine, and again, we need more tincture of time to see whether its efficacy pans out and whether we can get a better sense of its tolerability profile.
Slide 48 - Double and Triple Combination Therapy Trials in Chronic and Advanced Phases of Myelofibrosis

Dr. Jason Gotlib:
This is a slide that basically shows that many of the drugs that are being used as single agents with different mechanisms of action are also being combined with JAK inhibitors to see if we can get a so-called one-two punch in trying to hit the different lesions within the abnormal cells that are causing myelofibrosis. So, double and triple combinations which include a JAK inhibitor, and again, we will see whether we can produce more efficacy but also improved tolerability.

Slide 49 - Side Effect Management
Whenever we are dealing with patients with myelofibrosis or PV or ET, we’re always trying to balance disease symptoms and treatment and the toxicity of treatments. This can include fatigue or anemia, abdominal discomfort, the presence of infection, new bleeding or bruising, or weight loss. The way we try to manage this is with red blood cell or platelet transfusions, red blood cell booster shots such as Procrit or a drug called danazol, antibiotics for infections, pain medications for an enlarged spleen or other bone or muscle pain, and really trying to keep a focus on getting good food intake, getting your calories in, trying to exercise whenever possible, and if needed, holding, reducing or stopping therapy and re-evaluating where we are with therapy. So it’s always a very precarious balance of trying to make sure that we’re not causing excessive toxicity with the treatments that are intended to be useful for patients.

Slide 50 - The Good Patient (1): Open Communication with Your Treatment Team
Let me just end the talk here with making sure that we focus on the importance of open communication with your treatment team, including your physicians, your nurses and other caregivers. I think it’s very important to ask questions about the disease and treatment side effects; very important to make sure that patients understand and provide information about their current medications and allergies; that they’re compliant with the medications; that patients adhere to scheduled visits and follow-up, particularly when they’re enrolled in clinical trials; that patients inform the team of any new or concerning symptoms so we can act upon it in a very expeditious way; and that you contact the team before taking any new medications or when you’re admitted to the hospital, because many physicians out there really know very little about PV, ET or myelofibrosis. These are really orphan diseases with very low incidence, and so it’s incumbent upon you telling those doctors who don’t know you to contact us so we can help them in your management.
Slide 51 - The Good Patient (2): Open Communication with Your Treatment Team

Dr. Jason Gotlib:
In addition, I think it’s very important that you partner with your family and friends to increase your support structure. It’s important that you as a patient or your caregivers take notes and act as a diarist to make sure that you’re taking in everything that we have to say in often times a very limited clinic appointment time, and that you advocate. It’s very important that as a patient you advocate for yourselves and not just necessarily accept the first opinion, and if you need to get a second or third opinion, and bring up issues during your clinic appointment that you act as an advocate. That’s how you protect yourself and make improvements in your disease course.

Slide 52 - Resources for MPN Education & Finding a Clinical Trial

Finally, there are many resources for MPN patients and caregivers. Certainly starting with your local hematologist, going to an MPN specialist and an academic medical center if need be, online support groups and certainly The Leukemia & Lymphoma Society, which has done a wonderful job in providing education and resources for the MPN patient population.

With that, I’d like to end and I would love to use the rest of the time to answer any questions that the listeners on this webinar have, and thanks so much again for the opportunity to speak to all of you.

Slide 53 - Question & Answer Session

Ms. Lizette Figueroa Rivera:
Thank you so much, Dr. Gotlib, for your very informative presentation. It is time for the question and answer portion of our program. We’ll take the first question from our web audience. Doctor, Jay asks, “Is there a positive number of patients with Stage 1 myelofibrosis not undergoing any treatment other than watchful waiting who never progress or worsen throughout their lifespan, or do the majority eventually progress?”

Dr. Jason Gotlib:
That’s a great question. I would say that a conventional approach to the patient with early risk myelofibrosis, that is low-risk disease per the DIPSS Plus or IPSS scoring system that is perhaps zero or one adverse risk factors, these are patients that typically have very mildly abnormal counts, or perhaps sometimes they have, frankly, near-normal counts; don’t have any major symptoms; don’t have a big spleen, and conventional approach to those individuals is just to watch them, for example, lab monitoring every three to four or four to six months, and if things should change, then there is a re-evaluation of whether treatment is appropriate.
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Dr. Jason Gotlib:
I will say that there are trials now for looking at JAK inhibitors in, for example, Intermediate 1-risk patients, to see whether they can modify the evolution of those patients to high-risk disease. That is, can the use of a JAK inhibitor forestall early-risk myelofibrosis transforming into intermediate- or high-risk myelofibrosis. Now, because such patients may take many years to transform to a higher risk disease, these are patients that, when on trial, need to be followed for many years to get a solid answer to that question, but basically, yes. For low-risk patients we will just do usually watch and wait and we usually don’t intervene. I would say that a large proportion of those patients at some point in time will likely show some progression but it doesn’t mean that they’re going to progress to very high-risk disease, perhaps just Intermediate-2 risk disease, and they have other medical problems that intervene and cause more problems than their myelofibrosis.

Ms. Lizette Figueroa Rivera:
Thank you, Doctor. We’ll take the next question from the telephone audience, please.

Operator:
Our phone question comes from Kathy calling from California. Please state your question.

Kathy:
My question is, would an isotope bone scan be any benefit after I’ve been in treatment for the past four years but have been suffering from severe bone pain to a point of being bed-ridden, and right now I’m not in bone pain, and should I still have the radioactive isotope bone scan? Thank you.

Dr. Jason Gotlib:
Hi Kathy. Thank you for that question. I have to say that it’s not been my experience that isotope bone scans have typically been used for patients with myelofibrosis. Usually the bone pain related to myelofibrosis, the basis for that or the mechanism for that is not very well understood. It may be related to the elaboration of these inflammatory chemicals that are produced by the abnormal cells within the bone marrow, and there’s no well-known role for isotope bone scans for diagnosing or treating the bone pain. It could be useful, that is skeletal surveys, plain x-rays, if someone has a discrete lytic or punched-out lesion of the bone, but I have not heard of the use of isotope bone scans for treating bone pain related to myelofibrosis.

I wish we had a better modality to get a handle on it. That’s kind of where the state of the art is right now for myelofibrosis.
Ms. Lizette Figueroa Rivera:

Thank you, Doctor. The next question comes from our web audience. Roger asks, “What are your thoughts about splenectomy and iron chelation for myelofibrosis patients?”

Dr. Jason Gotlib:

Okay. What I would say about splenectomy is that splenectomy certainly has been used in the past for myelofibrosis with very large spleens. The benefits of splenectomy basically depend on the reason why one is doing it. So, for example, if one has pressure or pain related splenomegaly which is intolerable, certainly in the past the benefits have been around 60% to 70% of patients may derive a benefit with splenectomy. If the spleen is being taken out for anemia or thrombocytopenia, the rates of improvement at one year are in the range of 0% to about 25%. However, it’s my sense that now with the availability of JAK inhibitors, which are very good in reducing spleen size, that the use of splenectomy is substantially reduced, and there are real issues with the use of splenectomy in terms of morbidity and mortality. So if one takes all-comers to splenectomy in myelofibrosis, the complication rate with infection or bleeding or clotting is around 30% to 40%, and if one looks at mortality from the procedure, it’s on the order of about 5% to 10%. So we don’t take splenectomy lightly, and again, now with the availability of other agents such as JAK inhibitors, I see the role of splenectomy decreasing in its use over time.

Having said that, there may be some individuals that may have been on a JAK inhibitor, have progressed to splenectomy and need to be considered for it.

Regarding iron chelation, we don’t have standard rules for iron chelation in myelofibrosis or other MPNs. What I would say is that we tend to borrow the rules or guidelines from other diseases such as myelodysplastic syndrome. If there is a patient who has had multiple transfusions—that is more than 20 to 30—or the ferritin is above 2500 and there is an expectation of ongoing need for red blood cell transfusions, iron chelation could be considered, although, again, there is not standard consensus on these issues. Certainly if there’s organ damage felt to be related to iron overload, again, iron chelation could be considered if the patient has years ahead of them needing blood cell transfusions.

Ms. Lizette Figueroa Rivera:

Thank you, Roger, for the question. Our next question comes from our web audience. Erin asks, “Is there any clear, definitive way to know the optimum time for allogeneic stem cell transplant in a post-PV myelofibrosis patient?”
Dr. Jason Gotlib:
That’s a great question and I have to say that this is a question that really arises all the time; what is the best timing for transplant? Well, for this example of post-PV MF, you know, we look at the DIPSS Plus score, number one. So, if someone has Intermediate 2 or high-risk disease, these are patients that we would consider for transplant, number one. Having said that, there is also the issue of the health of that patient. So if the patient has multiple medical problems that might make one less enthused about the idea of a transplant. Number three, there needs to be certainly availability of a suitable donor, either a matched sibling or an unrelated donor, so that will be taken into consideration.

So, there are multiple issues at hand. It’s availability of the donor, the health of that patient, the risk score of the patient, and certainly the age of the patient. If a patient is in their, for example, early 50s or 40s and there’s clearly an increasing pace of the disease, then there’s more urgency in terms of the need for transplant. If the patient is in their 70s, they may not be certainly a candidate for a full transplant, but there are other less intensive forms of transplant, so-called reduced intensity conditioning transplants, that may be considered, but again, with increased age there may be co-morbidities or the expectation of increased complications that may make such a transplant less palatable. So, we need to take all those factors into consideration. There’s not an exact answer about the right time for any particular patient or all patients.

Ms. Lizette Figueroa Rivera:
Thank you, Doctor. We’ll take our last question from Jacqueline. She asks, “If 10% of the ET patients get acute leukemia, is that caused by the medication or the disease?”

Dr. Jason Gotlib:
That’s a great question too, and what I would say is that when you look at patients with ET, about 5% to 10% of patients with ET will ultimately develop acute leukemia, and again, this is something that typically occurs over a large amount of time, at least 10 to 20 years, and I would say that the large majority of those patients get acute leukemia because of the underlying disease. I did make reference to the fact in an earlier slide that there are individuals that get treated with certain types of medications such as the $^{32}$P or busulfan or other types of alkylator agents that can increase the risk of leukemia, and those are drugs that really should be reserved for really a last resort or patients who are of an older age, at least 70 to 80 years old. But in summary, I would say that most of the time it’s related to the underlying inherent risk of the myeloproliferative disorder such as ET.
Ms. Lizette Figueroa Rivera:  
Thank you, Jacqueline, for the question, and thank you all for your questions. Doctor, a special thank you to you for your continued dedication to MPN patients. You and your colleagues’ research successes have really made a positive impact on so many people’s lives. We hope the information from today’s program will assist you and your family in your next steps.

Slide 53 - The Leukemia & Lymphoma Society (LLS) Offers  
If you weren’t able to get your question answered today, please call The Leukemia & Lymphoma Society’s Information Specialists at 1-800-955-4572 from 9:00 AM to 9:00 PM Eastern Time, or reach us by email at infocenter@LLS.org. Information Specialists are available to answer your questions about treatment including clinical trials, or answer other questions you may have about support, including financial assistance for treatment.

Dr. Gotlib, thank you again for volunteering your time with us today and on behalf of The Leukemia & Lymphoma Society, thank you all for joining us for this program. Take good care.

Dr. Jason Gotlib:  
Thank you for the opportunity everyone. Take care. Bye-bye.