Hello, everyone. My name is Daniel D'Angelo. I'm Chief of the Division of Leukemia at the Dana-Farber Cancer Institute in Boston, Massachusetts. Welcome to the CME program on systemic mastocytosis, where we hope to educate you on the recognition, diagnosis, and clinical management of this rare disease. This CME activity is supported by an educational grant from Blueprint. This slide also has my disclosures. So let's begin with an overview of systemic mastocytosis. As noted, this is a very rare clonal neoplastic proliferation of mast cells. Mast cells are part of our innate immune system. We all have mast cells, but malignant or clonal mast cells are present in about one out of 10,000 of us. And they're often driven by a mutation in the gene KIT, K-I-T, with a canonical D816V. And this is seen in about 95% of patients with systemic mastocytosis. Bone marrows are characterized by proliferation of atypical mast cells, but they can be present not only within the bone marrow, but other tissues such as skin, most commonly, liver, spleen, GI tract, or lymph nodes.

It's a highly heterogeneous disease that range from indolent with a relatively normal life expectancy to life-threatening diseases such as advanced systemic mastocytosis or mast cell leukemia. The difficulty that most patients experience is time from the beginning of symptoms to when they're actually diagnosed. This is mostly true in patients with more indolent disease where time from onset to diagnosis can range from nine to 10 years. Patients with mediator symptoms, this is where mast cells de-granulate. The mediators can release or the mast cells can release histamine, serum tryptase, prostaglandin, cytokines, and a variety of other factors that leads to the sequela of mast cell activation syndrome. Now, as I mentioned, the KIT D816V is the canonical mutation seen in about 95% of patients. This can be difficult to ascertain. Remember, there's no circulating mast cells normally, so only in a very advanced state are you going to have circulating mast cells in the peripheral blood.

Furthermore, in a tissue biopsy or in a bone marrow examination, there's very few mast cells that are extracted in the bone marrow assay. Therefore, digital droplet PCR is the preferred method for investigating whether or not a patient has a KIT activating mutation. In my consultative practice, the most often reason why a KIT mutation is not identified is because the wrong test is ordered. Next generation sequencing, which is more common with other bone marrow disorders has a much lower sensitivity. An ASLQPCR is a acceptable alternative to digital droplet PCR, but the sensitivity is one to two logs less sensitive. So again, this mutation leads to constitutive ligand independent KIT signaling and therefore uncontrolled proliferation of these atypical mast cells. Interesting, there seems to be also a paraneoplastic process that you can see increased normal mast cells in the background, which we may come back to later.

WHO diagnostic criteria, major criteria we'll review in a second, but many patients, at least with advanced disease, in addition to the canonical KIT mutation, will have other high risk mutations that are listed here in the box in red. SRSF2, ASXL1, and RUNX1, or RUNX1 are the most common.

So the WHO is complicated, and your pathologist is reading the tissue biopsy, but they're not necessarily separating patients between non-advanced and advanced. What the pathologist will often tell you is whether or not the patient makes the criteria based on the WHO 2022 classification for systemic mastocytosis. It's up to the clinician to differentiate between non-advanced and advanced. And the subtypes of non-advanced are listed on the left. Indolent systemic mastocytosis is the most common. Smoldering. These are patients with higher burdens of disease, but they do not have C findings. We'll review those in a second. And then there's a new WHO entity called bone marrow mastocytosis. It's really a subset of indolent, historically would be classified as indolent systemic mastocytosis, but there's no skin lesions. These patients can still have significant symptoms of anaphylaxis and other mast cell degranulation symptoms. On the right of the slide is the subsets of advanced systemic mastocytosis.

These patients have a limited life expectancy. These patients can be very ill at presentation in deference to patients with non-advanced, where patients with non-advanced often present with symptoms of

mast cell degranulation, where patients with advanced systemic mastocytosis often suffer from organ infiltration and therefore organ dysfunction. Patients with pure mastocytosis, these are patients termed aggressive SM, an unfortunate choice of words because aggressive and advanced, these get confused often. The most common subtype of advanced systemic mastocytosis is a category called SMAHN or associated hematologic neoplasm. Now, the AHN can be diverse. It's usually consists of a myeloid neoplasm, not lymphoid. It's often gets confused. As many patients as you get older may have lymphoid proliferations. That does not count. It's only myeloid. So mostly patients with MDS or myeloproliferative neoplasia or MDSMPN overlaps. And these patients have a very limited prognosis. The third category and most rare is mast cell leukemia.

And mast cell leukemia, or the definition of mast cell leukemia is a little bit different from how we classify patients with acute myeloid leukemia, where acute myeloid leukemia, for example, will have 20% blast in the blood bone marrow aspirate or core biopsy. Whereas in mast cell leukemia, it's 20% mast cells in either the bone marrow aspirate or peripheral blood, not core biopsy because patients with systemic mastocytosis often have 20, 30, 40% mast cells in the core biopsy. Mast cell leukemia is really referring to the bone marrow aspirate or peripheral blood. And these patients have a very limited life expectancy. So this is how we differentiate as clinicians between non-advanced and advanced, and furthermore, separate the non-advanced between indolent and smoldering. So let me take you through this. These are the B findings and C findings. And again, just to reiterate, the pathologist is not going to go through this with you.

The pathologist is going to say whether or not a patient has systemic mastocytosis or not, based on the WHO criteria. These are clinical findings. So B findings, B for burden of disease, that's how I like to think of it. And patients with B findings have lots of mast cells. So bone marrow biopsy, more than 30%, or a serum tryptase more than 200. Evidence of dysplasia. Organomegaly without organ dysfunction, important point. So hepatomegaly or splenomegaly, but normal liver function tests. And a high KIT VAF, this is a newer addition in the WHO 2022 that was not present in earlier additions.

So these patients have high burden of disease. Still no evidence of organ dysfunction, just organ involvement. Patients with C findings, and so the presence of one or more C findings will put you into that category of advanced systemic mastocytosis and C for requiring cytoreduction. That's where the name came from. And it really is a hallmark of organ dysfunction, if you will. So if there's too many mast cells in the bone marrow, for example, patients have cytopenias, neutropenia, anemia, thrombocytopenia. Patients who have too many mast cells in the liver can develop a hepatopathy with liver dysfunction or portal hypertension.

Patients who have too many mast cells in the spleen, but it's not splenomegaly, that's a B finding. It's splenomegaly with hypersplenism defined as a low platelet count of less than a hundred thousand, or GI symptoms or GI infiltration, I should say, leading to malabsorption and hypoalbuminemia. The third bullet here, skeletal involvement with large osteolytic lesions is a rare C findings. It's a very seldom seen, but it is important to note. So these are the four C findings that differentiate advanced from non-advanced. So now, how does one suspect a diagnosis of systemic mastocytosis?

As I alluded to, it can take many years for patients to come to a definitive diagnosis, and that's most common in patients with indolent or non-advanced disease. And these are some of the spectrum of symptoms that can be seen involving the skin with the classic rash of urticaria pigmentosa. This is not the only rash that is seen in patients with systemic mastocytosis or cutaneous involvement, but it's the most common. Really means pigmented hives. So if you rub the lesions, they can cause a histamine release, and it looks like hives. Of course, if you do that to your patient, the patient will not be very happy. What patients do experience in addition to the spots, as they're often called, or the lesions, which can be numerous and will grow with time, is they can develop flushing, itching or pruritus.

But patients can also have, due to the mast cell, involvement of other organs such as the heart, the cardiovascular system, leading to episodes of hypotension, syncope, POTS, posterior orthostatic tachycardia syndrome. Multiple patients will have cardiovascular symptoms or musculoskeletal such as bone pain, osteoporosis, unexplained osteoporosis specifically in a man. You need to think about whether or not a patient has systemic mastocytosis. And furthermore, once a diagnosis of SM has been made, it's important to follow bone DEXA scans. Many patients will present with abdominal pain, and get misdiagnosed of having irritable bowel syndrome. They may even have a gastroenterologist perform an endoscopy either upper or lower, but the GI tract in a patient with systemic mastocytosis often appears normal, and so it's important that the gastroenterologist be aware of the potential diagnosis and perform random biopsies. And then it further precludes the gastroenterologist to warn the pathologist that he or she is concerned about mast cell involvement, so that mast cells can be stained for appropriately.

Neuropsychiatric involvement such as brain fog, memory loss, anxiety and depression can be seen, and then the usual systemic constitutional symptoms of fatigue, sweating, and swelling. And so the triggers that can cause mast cell activation are often just environment. Sometimes they're not even known. They're idiopathic. There can be very specific food substances, emotional, physical, or medications such as contrast eyes, surgeries, vaccinations.

Oftentimes anesthetics, there's a wide range of medicines that can cause this. So it's important to know what are the triggers, and if they are known, that there's avoidance and/or ability to try and ascertain what they are. So working with your allergist can be very helpful. So this is the diagnostic odyssey that many patients will go through. And as I've already alluded to several times, those patients with indolent disease can have the longest migration, so to speak, through the healthcare system before a diagnosis can be made. And common misdiagnoses are listed here. I've already mentioned with the GI involvement, irritable bowel, inflammatory bowel disease, often misdiagnosed, I can't tell you how many times. Chronic urticaria, allergies, idiopathic mast cell activation syndrome. It's important. I mean, these patients are often seen by dermatology because of the skin rash or allergy because of the anaphylaxis or rashes, or GI because of abdominal pain, and then come into my office in order to obtain a bone marrow examination for definitive diagnosis.

There are rare patients where the mast cells are confined to the GI tract and are simply not present in significant quantity in the marrow, but that's a rare entity. And the range of severity of patients from indolent to advanced diseases is partly allocated here in this particular slide where patients with indolent SM and smoldering SM as well seem to have relatively normal life expectancies. It's really the quality of life that will force a patient into the healthcare, and they're having lots of symptoms. If you end up in the hospital because of an anaphylactic period, once in a while, that's one thing, but if it's recurrent, every time you take your kid to the park and you're sitting on the grass, and all of a sudden you break out in hives, it can be rather disturbing. Or if you're having even more severe symptoms such as cardiovascular neuropsychiatric issues, like I mentioned, these are really symptoms that can interfere with your quality of life.

The patients with aggressive or SM-AHN, these patients will often present to the hematologist because of abnormal blood counts or organomegaly. These patients can be quite sick, and as I've mentioned, require cytoreduction, and they often have a limited overall survival. So when should you suspect a patient with systemic mastocytosis? These are some, just an illustrative case. So this is a 40-year-old male truck driver who has some back and leg pain, has a history of a T3 compression fracture, significant osteoporosis, osteopenia in both the spine and hip, as documented by a DEXA scan, goes to see his internist. I doubt that the internist would have, at the first thing, measured a serum tryptase level, but a tryptase level was obtained. And then on exam, has had these mole-like lesions called urticaria

pigmentosa for decades and some GI complaints. This is the classic constitution of a patient with systemic mastocytosis. No male patient should really have significant osteoporosis like this, and it's often missed.

The patients will just venture in the healthcare system. So red flags, unexplained osteoporosis, anybody with an elevated serum tryptase, Urticaria pigmentosa are the pigmented lesions, again, often seen by dermatology, recurrent anaphylaxis, chronic diarrhea may venture through a gastroenterologist, brain fog, neurologic symptoms, and a Darier sign would be a physical exam finding that will help nail it.

So let's move on to diagnosing systemic mastocytosis. This is the WHO 2022 classification. There's major and minor. They're listed here for edification. This is what the pathologist is going to do for you. Again, as we spoke before, it's up to the clinician to differentiate non-advanced from advanced. So briefly, the major criteria is multifocal dense infiltrates. So it's not having mast cells. We all have mast cells, and mast cells can go up or down depending on whether we have allergies or chronic inflammation. So it's aggregates of mast cells, and they're defined as 15 mast cells or more in the bone marrow biopsy or other organs. Again, this often gets misdiagnosed in the GI tract specifically because a patient's having chronic diarrhea, you're going to see increased mast cells, but that does not constitute mastocytosis or at least the major criteria unless you see aggregate. So that's the major.

And then there's four minor here. Atypical mast cell morphology, these are the spindle-shaped cells, normal mast cells around or ovoid, aberrant mast cell markers. So it's atypical to have CD25 and CD2 expression. CD30 is often not done. Usually, CD25 is the one that's easily done in the laboratory, but aberrant CD25, two or 30 on the surface that would differentiate an atypical mast cell from a normal mast cell. A KIT activating mutation, KIT D816V is the most common. There are a handful of others, and then an elevated serum tryptase above 20. Not valid in patients with myeloid neoplasm, and it needs to be corrected, not listed here, corrected for those patients with hereditary alpha tryptasemia where you have an extra copy or two of the gene that makes tryptase. And this is the workup that we usually will do. The usual initial evaluation, many times already done for you, history and physical, full body skin exam, noting rash.

I seldom do a Darier sign in the lab, I'm sorry, in the office, just because patients are not so happy when they develop hives. It's important to do a good spleen and liver exam, and you'll be following patients this way. And then of course, neuropsychiatric evaluation. Their neurologic exam may be normal, but it's really neuropsychology that's the issue. In terms of common lab testing, serum tryptase, the usual chemistries with CBC and a metabolic profile. And again, back to the KIT D816V really needs to be ascertained with the digital droplet PCR. NGS is just simply not sufficient to pick that up. It is, however, sufficient to pick up some of the other mutations, SRSF2, ASXL1, RUNX1 being the most important. Every patient who meets some of these criteria, that is, with an elevated tryptase or organoma [inaudible 00:21:06] really should go to a bone marrow examination. And here in the bone marrow, you're going to ask your pathologist to look for the mast cells, stain for KIT, KIT, which is the CD117, and then look for aberrant staining of the mast cells with CD25, two, or 30.

And it's important to note that if you have greater than 20% mast cells in the bone marrow aspirate, that constitutes mast cell leukemia. In our institute, we do flow cytometry for mast cells. Not every place will do this. You need to do at least half a million events, so you need to have a large volume. And this is a very easy way of looking for aberrant expression of mast cells, but not every lab will do it. Cytogenetics FISH are important just to look at the AHN. It doesn't really help you with the diagnosis of SM. Serum tryptase here is a critical marker. The normal level is less than 11. It's interesting how this was developed. Most patients, you, me, who don't have chronic allergies, our tryptase should be in the 5-6 range. And then there is about 6% of patients in the population where their tryptase is in the 13, 18 range.

And those individuals will have an extra copy or two of the tryptase gene. That's called HAT. We'll talk about that later. And so if you put the two together and you average it out, this is where the 11 and a half has come. But the rule of thumb is under 11 normal, over 20 abnormal, and that 11 to 20 range is kind of in the gray zone. Remember, advanced or smoldering patients will have a tryptase level of greater than 200. And then the fourth bullet here is this hereditary alpha tryptasemia. So what is that? So you should inherit two copies of the tryptase gene from mom, two copies from dad. The typical is one alpha, one beta from each parent, but there are some unusual genotypes where you have one alpha and two betas on the chromosome. So you have four genes altogether, but three beta, one alpha.

And there are patients who have just all beta, they've lost their alpha. There's no difference between the alpha and the beta gene, but there is about 6% of Caucasians that will inherit an extra copy or two, so five or six genes in total. And as a result, we'll have an increased serum tryptase level, as I alluded to before. And this can be checked. There are reference labs that will do this for you. It's usually a send out. We don't do it in my institution, but it's important. And then there's a formula to correct for the tryptase level. And again, organomegaly is not uncommon. It can be seen in both patients with smoldering or advanced disease, good physical exam skills, and of course, radiographic imaging that's done here, demonstrating a nice example of splenomegaly in this particular patient.

So with respect to the GI symptoms, as I've alluded to, these patients are often misdiagnosed with having irritable bowel syndrome or inflammatory bowel. Symptoms can be abdominal pain, periodic. It's not a constant abdominal pain often after meals, diarrhea, nausea, rarely vomiting. If the tryptase level is high and the mast cell component's high, due to the high level of tryptase and histamines, you can have peptic ulcer disease. That's not usually a manifestation of mast cell involvement, but it's the sequela of all the cytokines, GI bleeding as a result of the peptic ulcer disease. And the etiology is also listed on the right hand. The first two are the ones that really grab your attention with the altered gut motility due to the mast cell mediators leading to this.

But you can see where patients can be misdiagnosed as having irritable bowel syndrome. If they have this intermittent belly pain with nausea or diarrhea or both that comes and goes, it's not constant. It can really defy a specific and definitive diagnosis. These are just some examples from a patient of mine with impressive mast cell involvement. But as you see on the left, the standard H&E stain, although there's the impression of having some cells between the villi, this is a small intestinal biopsy, they're hard-pressed even at a higher magnification to see whether or not these are mast cells. But you can see in the middle with the, what I call brown stains for tryptase stain, you can see that in fact, most of the cells in the villi are mast cells, including clusters or aggregates of cells. And this is a colon biopsy between the CRIPS.

Again, a little bit reversed. So on the right side, you see the H&E slide. And I'm not a pathologist, but if I were to look at that, there's some eosinophilic cells, there's some small cells, you could have very broad diagnosis, could this be lymphocytic colitis? Could it be eosinophilic colitis? But then you see the immunohistochemical stains when you stain for tryptase, that in fact, most of these cells between the crypts are actually mast cells, including many aggregates of mast cells. And here the diagnosis is systemic mastocytosis with GI involvement. Again, another example here showing the liver involvement where you see immunohistochemistry stain that, when I spoke to the pathologist, they said, well, there's no evidence of mastocytosis. This is a patient of mine with an alcohol use disorder who had mild hepatomegaly and splenomegaly with significant hepatopathy with abnormal liver tests. And in the liver H&E, so I got a liver biopsy, and I knew the patient had systemic mastocytosis based on a bone marrow exam.

So I got a liver biopsy to differentiate, was this metabolic associated liver disease? Was it alcohol use disorder with liver involvement or was it mast cell involvement, which is what I was worried about. And

the pathologist said there's no evidence of mastocytosis. So I begged and pleaded. You really need to do the immunohistochemistry stains. And as you can see on the right slide, significant involvement of mastocytosis. So again, an illustrative, you need to talk to your pathologist. And this is that theme that I've been trying to have with that clinical pathologic diagnostic criteria. So again, multifocal mast cell aggregates in the bone marrow or other tissue is the hallmark with aberrant mast cell expression of CD25 or CD30 can be diagnosed by flow as well. And then of course, the canonical KIT mutation best obtained with a digital droplet PCR. Again, the number one reason why this is missed is because the PCR sent is a non-sensitive assay and it just won't pick up because of the rarity of the mast cells in the aspirin.

So let's move on to some clinical cases. Again, this is another patient, an elderly patient of mine who presented to the hematologist, of course. Why? Because there was a leukocytosis with an elevated white count at 27,000. Patient was anemic, thrombocytopenic, and then I measured a tryptase level was almost 200. He had organomegaly on exam. I've showed you the CT scan before, and here you can see the CT scan showing both hepatosplenomegaly with some ascites, bone marrow examination was performed showing mast cell aggregates and mast cell involvement of 40%. Again, that's not mast cell leukemia, that's just systemic mastocytosis because there was only one or 2% mast cells in the bone marrow aspirate. In addition to the canonical kit mutation, the D816V, there were other mutations, especially this high risk SRS TET2 and a CUX1 mutation. So what is the diagnosis here? This patient has SMAHN, and here is a example of the patient's bone marrow showing very hypercellular marrow, low power and high power H&E on the upper photomicrographs.

And then the lower photomicrographs are showing the histochemical stains, the mast cell tryptase on the left and CD25 on the right. So on the left, their mast cells, on the right, it shows the invariant. You should only see CD25 and malignant mast cells really helping with the diagnosis. So this patient meets the criteria of advanced systemic mastocytosis. 75 to 80% of patients with advanced SM will have SMAHN with an associated hematologic neoplasm. Again, just to reiterate, this is a myeloid AHN. If you have concurrent lymphoid that does not meet the criteria, often forgotten. This patient was charted on avapritinib. This is an FDA-approved agent for systemic mastocytosis. Patient achieves a complete remission, does remarkably well. Later in the course, although his mastocytosis is in remission, his AHN progresses to AML and he gets AML-directed therapy. Published in the Explorer and Pathfinder, you can see in the red box data from avapritinib.

This is a highly potent selective KIT inhibitor with an overall response rate of about 75%. And in fact, almost 30 to 40% of patients will achieve a CR or CRI or CRH. I'm sorry. This is complete remission or complete remission without hemologic full recovery. KIT D816V or loss or reduction of KIT is seen in 30% of patients. And the median duration of response was about a year and a half or so, 14 months. So again, long course, here's another treatment sequence with a different patient.

46-year-old woman who presented with chronic diarrhea and weight loss, abdominal distension. Actually, she was headed into hospice and had an indwelling catheter for DPN, which was the only way that she was able to successfully receive nutrition. I saw her. Tyiptase was 774, quite impressive. And a bone marrow showed more than 30% mast cells. She had hepato and splenomegaly, as well as esophageal varices from the portal hypertension. She was initially started a midostaurin. Remember, this was a 2006 presentation. So midostaurin was approved, and she did remarkably well on the Midostaurin. Had what I would term as a partial remission with reduction, but not clearance of her mast cells. But she was able to be weaned off TPN. Catheter was removed. She went back to work. She did develop progression on the midostaurin after several years, almost a decade, and then needed next line of therapy. And so of course, what options after Midostaurin failure or progression are available?

Avapritinib is now approved. Bezuclastinib is being studied in phase one, two clinical trials. And so these are the options for patients who have been historically treated with midostaurin, Don't underestimate the burden of disease and symptoms. These are another case of indolent systemic mastocytosis. And as I alluded to, these patients have a relatively normal life expectancy. It's the symptom burden that grabs you. So this is an extension of the case I presented. Patient has spine compression fractures and significant osteoporosis osteopenia. Remember, this is a male. Also has some GERD, some GI symptoms such as abdominal pain, cramping, and diarrhea.

It's had several anaphylactic reactions interesting to stinging insects, hornets in this case, and required several doses of epinephrine. So there's no allergist worth their dime. When you hear this history, is not going to think systemic mastocytosis. That is most patients with anaphylaxis or severe allergies to stinging insects, either fire ants, bees, hornets, wasps. You got to think about systemic mastocytosis. Patient also has some brain fog and depression, difficulty concentrating at work, some short-term memory impairment. This is often due to mast cell degranulation, and then he has a significant rash on his skin that has been increasing over time. So the constellation of these symptoms really raises the error, so to speak, of a diagnosis of systemic mastocytosis. The anaphylaxis is what grabs you, the unexplained osteoporosis in a male patient, and then, of course, the GI and neurocognitive impairment. So in terms of the management, the beginning management is to control the mediators.

H1, H2 antihistamines are the beginning. Chromalin is a poorly absorbed mast cell stabilizer, which is spectacular for patients with GI involvement. Really tries to control that. Needs to be administered several times during the day, preferably before meals. Always, always send a patient home from your clinic with an EpiPen. I think that would be relative malpractice when I see a patient who has a history like this patient, but any patient with systemic mastocytosis, I always make them, even if they do not have a history of anaphylaxis, I make them leave the office with an EpiPen prescription. I always check bone health with DEXA scans, bisphosphonates or denosumab when appropriate, calcium, vitamin D. And then this patient has significant symptoms. If they're not well-controlled with anti-mediator improvement, then cytoreduction would be either a KIT-targeted therapy would be appropriate.

So some pearls and practice takeaways. Always check a tryptase when you're thinking about it. Any tryptase greater than 20 warrants full evaluation. Tryptase less than 11's normal. What do you do in the gray zone? Those are patients you need to think about hereditary alpha-tryptasemia. They still may have systemic mastocytosis, just less common. You have to talk to the pathologist. There has to be that relationship with the referring docs. It's not just referring to gastroenterology. It's not just referring or doing the bone marrow and sending it off. You need to have that communication with the pathologist and with the gastroenterologist, and what you're thinking about because it's the pathologist that does the special stains, if you will, and he or she may not be aware of what you're thinking. They're looking for increased mast cells highlighted by tryptase and CD117 stains. Once that gets diagnosed or seen, then you can look for aberrant mast cells with CD25, CD30 or CD2.

And remember, these are not just normal mast cells. These are spindle-shaped, atypical, looking for paratrabecular aggregates, not just increased numbers. Always prescribe EpiPen even if they haven't had a case of anaphylaxis. I've said this before. I'll say it again. In order to make a diagnosis for the canonical KIT mutation, the D816V, which is seen in greater than 95% of cases, you need to send the digital droplet high-sensitivity assay. There's many reference labs around the country. It's not going to be picked up sufficiently in your routine NGS. And do not miss or dismiss patients with ISM. These symptoms can be going on for decades, and they can be going back and forth from one specialist to another before a diagnosis can be made. So current KIT-targeted therapy or cytoreduction, avapritinib is the only selective KIT inhibitor that's approved. It's approved for both advanced and indolent systemic mastocytosis.

In the United States, it's first-line for advanced SM. There is a restriction for platelet count. You need to have platelets greater than 50,000. That's one black box warning. It's usually not an issue with ISM, but it can be an issue with advanced. Bezuclastinib is in late stage development for both indolent and advanced. The SUMMIT trial and the APEX trial, SUMMIT for patients with indolent systemic mastocytosis and the APEX for advanced. Elenestinib is another selective KIT inhibitor that's being tested in indolent with the HARBOR trial. Mitostorin is an older FDA-approved pantyrosine kinase inhibitor. It's also used in patients with FLT3 AML, but midostaurin was the first FDA-approved agent. Again, it's not a selective KIT inhibitor, and so it does have some limitations. High overall response rate, fewer complete remissions and does have some GI intolerance issues, but it is approved regardless of the platelet count. So it's my go to agent for patients who cannot receive avapritinib, because their platelets are too low, and or may not respond to TPO mimetic agents.

Imatinib actually has a label indication for systemic mastocytosis, but these are only patients who lack the KIT D816B. How many patients have I seen referred to me who have been on imatinib for their systemic mastocytosis because no mutation was documented because the wrong assay was sent. It's amazing how often this happens. Imatinib is a very important drug. It's great as a KIT inhibitor, but it's only for those patients with wild-type KIT or alternative mutations other than the canonical KIT D816V. Again, always send a digital droplet PCR. And this is an example from the PATHFINDER study, which was the phase two of avapritinib. And you can see just in this patient, a picture's worth a thousand words. After only six months of therapy, how this patient who was relatively cachectic with abdominal distension due to organomegaly [inaudible 00:42:09] is responded. And it's important. I mean, we've really changed the natural history of the disease.

So in summary and some key takeaways, systemic mastocytosis is a clonal mast cell neoplasm driven by the canonical KIT D816V and greater than 95% of cases. It still remains an underdiagnosed disorder with average time from presentation of symptoms to actual diagnosis can be about a decade. Always suspect systemic mastocytosis when you have unexplained anaphylaxis specifically to stinging insects or anesthetics. Unexplained osteoporosis, anybody with an elevated serum tryptase or chronic urticaria flushing should have assessment for systemic mastocytosis. The WHO 2022 uses one major and one minor criteria or three minor criteria in order to make the diagnosis. We've reviewed that. Bone marrow biopsy showing atypical mast cells, aggregates of mast cells, and the canonical mutation are important. Even ISM, indolent systemic mastocytosis can have significant morbidity with fatigue, gastrointestinal symptoms, recurrent anaphylaxis, as well as the symptoms I've mentioned before of osteoporosis, neurovascular or cardiovascular symptoms.

There are several FDA-approved KIT targeted therapies available. Midostaurin is a non-selective KIT inhibitor. Avapritinib is a selective KIT inhibitor approved for both indolent and advanced SM. There's several agents in development, bezuclastinib and elenestinib. And remember, you need to have a full diagnostic panel. So a bone marrow should also include a routine NGS panel looking for the high-risk mutation, the SAR mutations, SRSF2, ASXL1, RUX1. These are very important and have high prognostic impact on the outcome. So I hope this has been helpful. We've reviewed systemic mastocytosis, under-recognized entity. Hopefully that some of these symptoms, you'll be able to have more appropriate recognition of the disease when to think about it, how to make the diagnosis, and clinical management of this rare but evolving entity. Thank you for your time.