(PLEASE NOTE: Transcribed automatically by Vimeo, mistakes are possible/likely. Our apologies.)

TRANSCRIPT - GR 07 08 22 ***"Evolving Therapy of MPNs 2022"*** – Ruben Mesa, MD from the UT Health San Antonio

- 00:15:47Today we have a special guest, we have Dr Reuben Mesa he is the Executive Director of the maze cancer Center at ut house San Antonio MD Anderson Cancer Center.
- 00:15:57For almost 30 years the maze Cancer Center has provided world-class cancer care advancing cancer research and educating the next generation of cancer care scientists.
- 00:16:06and care providers the maze cancer Center in particular is advancing the science of cancer, specifically with latinx patients enrolling a majority into active clinical trials.
- 00:16:16Dr a messa was appointed the director of the cancer Center in 2017 and was fundamental on establishing the Center as a partner side of the md Anderson partner cancer network.
- 00:16:26Since his appointment that maze cancer Center has undergone a period of great progress with the development of comprehensive.
- 00:16:33A comprehensive patient centered cancer service line renewal of the nci cancer Center support grant and designation.
- 00:16:40Active development of a cancer focused hospital to open in 2024 and significant growth and faculty extramural peer review funding robust Community engagement and cancer research career enhancement programs.
- 00:16:54After earning degrees in nuclear engineering and physiology with minors and radiation biophysics and bio engineering from the University of Illinois at urbana champaign.
- 00:17:04Dr Messer received his medical degree from the Mayo graduate school up at Mayo in Rochester Minnesota.
- 00:17:12he completed his residency in internal medicine and then his fellowship and hematology medical oncology at Mayo as well.
- 00:17:18Prior to this transformational work at the maze cancer Center but he's gonna read it, I was going to spare this looks like my Secretary send like the version my mom last night I did I did I even.
- 00:17:33feel free to just you gotta get ready yeah I didn't want to shorten too much of it so it's not a fangio but he's done a lot of great work before being at the cancer Center.
- 00:17:45at how in Texas, he did a lot of transformational work as well at the Mayo clinic in Arizona.
- 00:17:52So I was going to end it by saying, and also Dr Mexican fly as a somewhat of a joke Superman because this is quite impressive resume.
- 00:18:02But his specialty is in Milo proliferative neo plazas and we're very happy to have him with us today and i'm happy that he spared me the the another page of introduction.
- 00:18:13There you go figure.
- 00:18:18yeah i'll check with my assistant about that that's the kind of keep mom happy version but.
- 00:18:25I mean hematologist who's really focused his career i'm trying to make a difference, with the development of new drugs, as well as had a lot of interest in listening to patients.
- 00:18:35Developing patient reported outcomes as ways to kind of measure the true impact of therapies that we're using and incorporated those in in drug development so excited to be here.
- 00:18:47Also honored that I think in the south, Texas spirit you order those Brussels tacos it'll get clearly I pulled up their little website they've got a nice little a little.
- 00:18:58map there of Texas, and the brazos river down there in South Texas so I'm sure that was intentional, so I am deeply honored.

- 00:19:06But my area focus our MPs and for those kind of new in residency, these are the miler proliferative neologisms a group of chronic leukemias.
- 00:19:16And why we're talking about them as we've learned quite a bit about them over the past few years and we've learned more about the biology and we've learned and developed therapies really based on matt understanding of biology.
- 00:19:29So here my disclosures I've been involved what could say I'm highly conflicted or I like to say that I'm equally conflicted that I pretty much have have played with everyone and have a good sense of the different things that have been tested.
- 00:19:44Now, with diseases like this, the amount of proliferative nia pleasant our colonial nia Plaza classrooms that go way back.
- 00:19:53And originally used to be called the model proliferative disorder is before we recognized, they were colonial.
- 00:19:59There, a type of malignancy which kind of comes with its own connotations, but how they affect people can really be quite heterogeneous.
- 00:20:08And they really fall in one of these categories of what I like to call chronic cancers that again people can have for a long time, some of them can have further their natural lifespan.
- 00:20:19You know people hear the word cancer and it's one of the most emotional words that you can listen to.
- 00:20:24You know, and everyone jumps when they hear that word and they think pancreas cancer, you know they think brain tumor or gbm and they can be like that, but more there are more chronic leukemias smoldering multiple myeloma low grade lymphomas.
- 00:20:45Even individuals now, sometimes with limited metastatic breast cancer ovarian cancer can live years over 10 years.
- 00:20:54Stable phase myeloma so increasingly we're having this group of chronic leukemias so it's important as we have these diseases, to have a sense before we really talk about therapy.
- 00:21:05To really have a bit of an understanding of what exactly are we trying to accomplish when we're treating a disease are we trying to improve overall survival.
- 00:21:16Are we really trying to avoid progression, are we trying to improve symptoms of symptoms are present, is there a risk patients can face that we're trying to mitigate.
- 00:21:29With these diseases there's three central thrombocytopenia policy female Vera and myelofibrosis and, to some degree, there severity is is in that order et npv patients.
- 00:21:44can live as long as age match controls, but there are exceptions model fibrosis can be a more 30 life threatening disease.
- 00:21:55The first third diseases that all of you, wearing hats as Internet or other specialist made run across does it can ever risk of vascular events.
- 00:22:03So, for example, if you take on selected individuals that have portal vein thrombosis a third of them may have an MPs or an occult mpm if you look at the jack to mutation.
- 00:22:16They can have side opinions, particularly as they progress an email thrombocytopenia much less frequently leukemia or neutropenia.
- 00:22:27They can have a split Omega and other Dr hall asked me to spend the entire hour talking about the spleen I'm going to limited that just to say that the spleen can be.
- 00:22:38A significant barrier, it can sometimes be dramatically enlarged up to 10 kilograms so the normal speed is 100 to 300 grams.
- 00:22:49And we believe that it grows through filtration of early immature Milo itself in the blood and they find a kind of vestigial home that they used to have in the spleen when we were developing as a fetus and that can cause all sorts of morbidity.
- 00:23:07They can have difficult symptoms, or we have earned are linked to the biology of the disease related to cytokines related to migration of white blood cells, they can really be quite profound.

- 00:23:19And they can progress for most patients that I visit with if their disease did not progress, they would live out their normal lifespan so its progression that leads them to move from a disease that can be a burden to being fatal.
- 00:23:34Now, as we think about therapy, we have now mcc and guidelines for these diseases, as we do for other cancers and hematologic cancers.
- 00:23:46And I led the inaugural group that pulled these together and we thought it was important for a variety of reasons, one they were being treated quite heterogeneous live in the United States.
- 00:23:55And to they were a little different than many of our other cancers in terms of what our goals were how we would be monitoring them with therapies, we had etc.
- 00:24:07So let's first begin with a central thrombocytopenia.
- 00:24:10And as we think about therapy for et all patients.
- 00:24:16We tend to think about decreasing the risk of blood cuts are bleeding in fact historically that had really been the focus of our therapy were initially we treated all patients with an aspirin.
- 00:24:31We have pulled back on that a little bit there are three main driver mutations these patients can have that are mutually exclusive, and maybe you've ordered.
- 00:24:41Through your lab a selective test for jack to that labs then if you're negative for jack to may then check for the cow ridiculous mutation.
- 00:24:53Or the mpl mutation because they're mutually exclusive, and there may be some biological differences between being Calvin tickling mutated or the others.
- 00:25:03So count our mutated patients, we may we may skip an aspirin if they're low risk if they're higher risk we are assessing for cardiovascular risk.
- 00:25:13We want to control their limits their blood pressure if they have diabetes, whatever their higher risk age over 60 ever had a prior blood clotting event, we want to control their blood counts, we want to bring their plate account under 400,000.
- 00:25:31Now these patients are at risk of both clotting and bleeding so people sometimes ask well the cladding thing makes sense, but the bleeding thing doesn't you know why would having an increase in pay that increase your bleeding.
- 00:25:45The reason for that is that how we clot is both based on platelets but also on the clotting factors that in the end, developed fiber the fiber and holds the platelets together.
- 00:26:00All of the body's mechanisms for making fiber and the whole coagulation cascade that usually gives nine hematologist Angela.
- 00:26:10are not creating an any greater amount, if you have too many platelets so if your brain it's our million and a half.
- 00:26:16You have a relative in balance so that can manifest as an acquired bond willa brands, but it can really lead to a net of bleeding.
- 00:26:26or there was worst case scenario for for for someone like for Ferris have who's on call this weekend is you get called to the patient who has a clot and it's bleeding at the same time.
- 00:26:36and trying to trying to navigate that and manage that which usually is a is a tight rope with a free service and other things, trying to manage these folks.
- 00:26:46Now, historically, we use primarily two sets of drugs long acting interference or we'll get to in a moment or hydroxyurea that could control accounts.
- 00:26:58And they have their pluses and minuses hydroxyurea it's easy it's cheap it's a pill interferon perhaps a greater impact on the underlying stem cell clone.
- 00:27:09Drug this been used in a variety of different indications may decrease the level of the abnormal aaliyah burden and maybe have more impact on progression free survival.
- 00:27:20Now, this constitutes roughly about 150 to 200,000 patients in the US, where the T.
- 00:27:27So I like to tell folks you know it's not a common disease, but nor is it rare you know it's not one of these really.

- 00:27:34You know, a typical H us or Hla are these things that really are quite uncommon you know it's kind of somewhere in the middle.
- 00:27:42Now there are new drugs in development, to try to see if they can have a greater impact on the disease, one of them is an inhibitor of LSD one.
- 00:27:52Which is an enzyme it's involved with really the activation of mega carrier sites in the marrow in these individuals that we believe lead them down this path of harm basically.
- 00:28:08there's a genetic mutation there's something wrong with a stem cells and they're just secondary process mega carriers sites get activated they can release toxic things into the bone marrow micro environment environment they can develop fibrosis and they can develop greater impact.
- 00:28:26This drug is currently under testing it's an interesting drug, these are data from last year's American society of hematology meeting.
- 00:28:33That and people that had failed the prior therapies that we had first it showed that it could lower the plates, which was key those.
- 00:28:41Key then we're trying to do we're trying to lower the plates, in a way that hopefully is both safe, effective and hopefully has a deeper impact on the biology of the disease.
- 00:28:52They looked at it across the three different types of genetic changes and again saw that it was effective in each of those areas so again new drug people that have failed prior agents it's going to be enrolling in a phase three study opening up very soon.
- 00:29:12The next are long acting interferons interferon it's a naturally occurring molecule it's had a range of different impact in both.
- 00:29:24immunology and in the therapy of hepatitis C and is now approved the long acting agent i'll show you in policy female Vera.
- 00:29:33Do two trials done in that setting not yet approved in et I colleagues from md Anderson in Houston and I are leading a global study as a second line for individuals with et and those data are ongoing.
- 00:29:51And what about politics, a female Vera et and polycythemia there are two very much.
- 00:29:58two sides of the same coin they're very similar type of disease there is discussion in our world that if you have the jack to mutation and have et you basically have policy female Vera.
- 00:30:12But 90% of patients with fever, I have the jack to be six and seven F mutation in about half of those with et but the et patients that have the jack to mutation tend to have a higher red blood cell count and tend to have features that are much more like P Vera.
- 00:30:31And there are many things that might constrain the ability to make too many red blood cells, the presence of iron deficiency.
- 00:30:39Or the the features of anemia of chronic disease, so it is not uncommon that will see let's say a 36 year old.
- 00:30:47Woman that has an elevated platelet count the hemoglobin is is generous, they have the jack to mutation.
- 00:30:53But they're frankly iron deficient do in my in laws from menstrual blood loss fairly common scenario where we have a fair amount of confidence that if we gave them iron, it would just you know shoot the hemoglobin up so are they to really different diseases.
- 00:31:08there's a lot of discussion, whether or not that is the case now these individuals like the et patients, how do we manage an aspirin but also phlebotomy.
- 00:31:22Now phlebotomy is an ancient therapy, you know we've used it for almost every disease along the way.
- 00:31:27And this is one of the last holdouts with this and hemochromatosis as being said some of the few things left for us phlebotomy, but what we have learned is that one, it is very effective in decreasing the risk of blood clots.

- 00:31:42You know I mentioned that these patients can have symptoms, so are your symptoms worse if we make you iron deficient probably yes, so there are negatives to phlebotomy.
- 00:31:52We learned that controlling the hematocrit tightly under 45% is really critical.
- 00:31:59So, again that's the hematocrit we calculate that you spin it to the blood down and it's truly the percent of blood by volume in the bottom of the tube.
- 00:32:08That are red blood cells and value is above that truly have been shown to be higher risk in terms of blood clots.
- 00:32:18So, for your standard in a We found that you had PV at the time of a pre employment physical let's say you've come to work at uva in as a medical assistant you're in your 30s you otherwise feel fine phlebotomy and aspirin might be how we treat you.
- 00:32:35Now many individuals will be higher risk because their age over 60 they've had a blood clot or reading event I previously had mentioned.
- 00:32:45If you see people with sprang thick vein thrombosis portal vein thrombosis.
- 00:32:50sajid or vein thrombosis is very atypical areas of thrombosis there's a much higher correlation of an occult Milo proliferative neo Plaza.
- 00:33:00For reasons that we don't fully understand, we think that has something to do with the the end affiliates in those individuals why that particular basket or distribution, but we don't know 100% yet why that specific basket or distribution.
- 00:33:18In these individuals will use medical treatment to control the accounts and the hematocrit also if they aid over 60 prior blood car or.
- 00:33:30If they're not tolerating phlebotomy or if they're having difficult symptoms, sometimes patients can have bad PR itis.
- 00:33:39Sometimes for riotous has been so severe there have been suicides from the practice in P Vera were.
- 00:33:45A water seems to aggravate it, in particular, we think white cells migrate to the skin they react with water some patients really have to dramatically change how they baby because of that, and it can be an incredibly impactful thing on their quality of life.
- 00:34:03Our frontline therapy very much alike et is interferon or hydroxyurea there's now an approved interferon that I mentioned that got approved in the fall of last year.
- 00:34:14For P Vera additionally individuals if they fail front life therapy may receive a jack inhibitor we'll talk more about the jak inhibitors in the therapy of myelofibrosis.
- 00:34:27But the jak inhibitors are a group of drugs that may have implications in a range of different disorders inflammatory disorders and autoimmune disorders.
- 00:34:38I mentioned that interferon has been approved, since fall of last year, and part of that was on the basis of studies, I was involved with from Europe then looked at this long at the interferon that's given every two weeks, compared to hydroxyurea.
- 00:34:56And they treated individuals in a randomized study and then had a continuation study.
- 00:35:02there's a parallel study that we had done here in the US, we have an nci supported mtn research consortium where we hadn't done a trial between regulated interfere on alpha to a.
- 00:35:13or Pegasus versus hydroxyurea that showed the two drugs are fairly similar through one year, but the longer people are on the more an advantage of interferon over hydroxyurea because of progression free survival.
- 00:35:30And a greater impact on potentially the malignant stem cell clone.
- 00:35:35These were data that we're just shown just a few weeks ago in Vienna at the European hematology association.
- 00:35:44again showing better control of complete hematologic response of the rope regulated interferon versus hydroxyurea as well, as you know, even more striking data as a related to molecular response.

- 00:36:02They showed improvement in disease associated symptoms in individuals now with long follow up.
- 00:36:11As well as an improvement from freedom from phlebotomy why we think that's helpful for bottom me if you're on medical therapy.
- 00:36:21One if you're needing too many phlebotomy is, you may have a higher risk of blood clots are bleeding it's a hassle.
- 00:36:27You know if I told Karen today that she had to go for phlebotomy tomorrow and ruin her Saturday.
- 00:36:34You know it's a whole day of things, and it may ruin Sunday because she's going to feel light headed and the next day, maybe she's a tough stick, you know and needs to get stuck several times, so it really can be a lot of hassle it can be a real negative.
- 00:36:53Additionally, this is showing the difference in control as a relates to that jack to a little burden at six years, so it shows quite a difference between these two groups.
- 00:37:06And this next slide is probably one of the most interesting that we've not had this mature data set in this sort of group of patients before, but this is overall event free survival.
- 00:37:18Between rope regulated interferon and hydroxyurea you know, and you see here really, really quite what a difference with events being listed as death disease progression or thrombosis symbolic events.
- 00:37:33So we're going to prove in November.
- 00:37:36Now the interference, for those that have not using their sub Q injection they can cause mood disorders, that can cause elevated liver function tests.
- 00:37:45really can cause an autoimmune disorder so definitely things that need to be kind of closely observed, but most individuals tolerated pretty well.
- 00:37:56And we tight trade up the dough so they started putting me on a low dose and we tight rate up till we get control of counts as well as adequately monitoring their response and any side effects or toxicities.
- 00:38:12Now, another drug and this is a very interesting class of drugs is are they have cited in mathematics, so I have decided from iron metabolism.
- 00:38:22And again, making the non he people almost cringe just to hear the word have cited is associated with inflammation.
- 00:38:30And anemia of chronic disease so it's really interfering with the utilization of iron, so people have the idea, what about if we give a hub site in Mimetic could we simulate an era of chronic disease control the red cells, but in a way that wasn't psycho toxic.
- 00:38:48So that was kind of the preclinical rationale for this this agent, and again it kind of preclinical models was helpful.
- 00:38:57In clinical studies, this one from mount Sinai in New York, they were able to show that it was quite effective and helping people become phlebotomy independent or control the, the number of phlebotomy he's.
- 00:39:12not unexpectedly, it was relatively neutral as related to controlling the platelets or the white blood cells, so if your goal really is controlling mathematical that's helpful I if all of the encounter elevated in May really only be a partial therapy.
- 00:39:31Now, part of the benefit of this approach is that it may help to control the degree of a retro psychosis would out inducing iron deficiency and the they were to show that the iron levels could increase.
- 00:39:47Overall, the drug had we always say everything is relatively well tolerated, but that was the case here now relatively low grade of adverse events.
- 00:40:01So this is currently undergoing another phase three study the verify study where they're really adding an on two additional therapy for individuals that are ready need for bar.

- 00:40:12So let's say you're only getting phlebotomy.
- 00:40:15Is this versus just flow batteries let's say you're already on hydroxyurea but you need phlebotomy is this is being added on in addition.
- 00:40:23When with an open label extension so we're going to et and PV between them, probably 350,000 patients in the US.
- 00:40:34So we really historically had very few approved therapies, so now several more in the mix, as we learn more about the disease.
- 00:40:42Now things coming down the Pike some other interesting approaches curriculum, which is present, about a third of the patients with et is present on the surface.
- 00:40:53of cells sort of potentially more easily targeted then jack to which is more in the nucleus.
- 00:41:01And there are vaccine studies and other cider based studies under evaluation actually was a vaccine study presented at ej in Vienna.
- 00:41:12There was a complete dud so it did it was not effective, but the first of them again as we learned with the vaccine studies isn't the right vaccine is it hitting the right way is being absorbed.
- 00:41:24So, like all things I was shared with patients, you know science is very much like watching the sausage being made, you know it, that it can take a bit, but it will be very interesting to see as those approaches evolve.
- 00:41:38And myelofibrosis has been where the majority of therapies have been developed or tested because it's been the most severe disease.
- 00:41:47can lead to the greatest amount of morbidity and mortality, the majority of patients with Milo fibrosis if they live long enough will pass away from their disease.
- 00:41:58This is a disease we're fundamentally we consider the disease burden.
- 00:42:03And we truly consider is this an individual, in which we really turn to our colleagues who do stem cell transplant and proceed with a transplant.
- 00:42:11Or do we move from medical therapy still probably about 90% of the patients in the US we're getting medical therapy, and this is roughly 25 to 30,000 patients in the US.
- 00:42:25We now have three approved drugs in Milo fibrosis rock solid food random and prescriptive that are all jak inhibitors with other drugs can have on the heels that I'll touch base on another jack inhibitor as well as drugs, looking at other mechanisms of action.
- 00:42:44that people will look at it try like this sometimes and say you know boy reuben.
- 00:42:48You know you got 30,000 patients, you know, is it worthwhile, you know developing all these different sort of drugs for a small group.
- 00:42:55What we're learning is that a lot of these is he's already quite interconnected and you really never know what other things will be helpful for.
- 00:43:04So I was involved with the development of each of these but rock solid and we started with model fibrosis and then it got approved and policy MIA Vera.
- 00:43:11And then it got approved in psoriatic arthritis and then it got approved in graft versus host disease, and then they realized that dogs that have itching they could put it into creams.
- 00:43:23You know and veterinarians can use it for dogs that have a range of disorders, so you never know where these things are going to go also as we think about the greater stable of my thyroid disorders monitors plastic syndrome MPs overlap acute leukemia clone automatic police's.
- 00:43:46Things really start to blend from one area to the other.
- 00:43:53Directive in the first drug approved in myelofibrosis now over 10 years ago and it was approved, based on two studies randomized compared to placebo, which was our North American study or compared to best alternative therapy.
- 00:44:10In patients in Europe.
- 00:44:14And it was approved with endpoints of showing a benefit in terms of the spleen.

- 00:44:19Again, which I had mentioned the spring same name is going to be massively enlarging cause pain, it can cause discomfort.
- 00:44:25That can be weight loss, there can be early satiety there can be sporadic infarcts can be harmful in a range of ways, or to improvement an individual disease symptoms or syndromes can have a huge impact in terms of quality of life.
- 00:44:40This was one of the first drugs approved because of a significant benefit in disease associated symptoms.
- 00:44:50Now over time we've learned that, in addition to those things which we can measure in the short term and the long term it's clear that patients are living longer it's not a cure does not lead to a complete remission in a way that we might recognize like chronic myeloid leukemia.
- 00:45:09But quantifying this, this was a analysis done by my colleagues over in Houston where they looked with a large number of patients that they treat over there.
- 00:45:17and saw that there was an improvement in survival over the last decade now still you could see so much room for further improvement, far from a from a universal cure.
- 00:45:29But a significant improvement nonetheless and fairly tied to taking a jack inhibitor.
- 00:45:36Now, why do they live longer, we think that it may be a range of things you know one they're less debilitated so the more active or not dying of pneumonia heart failure and things of this nature.
- 00:45:49To it may improve what's usually hit been a very hostile bone marrow micro environment with inflammatory cytokines you know, chronic inflammation the body is never good wherever it is whether it's the bone marrow whether it's the esophagus you know whether it's another tissue.
- 00:46:08And that inflammation may really be a pressure to accumulate additional somatic mutations that may take people down the path of moving from model fibrosis towards acute leukemia that can be much more fatal.
- 00:46:23Now we've learned several things over time, you need to use enough of the medication to really have the impact as it relates to survival.
- 00:46:32And indeed we've been able to show a nice analysis that dose as it relates to kind of short term endpoints like screen or symptoms.
- 00:46:41matter, but also that the quality of the response, even as measured by Spain volume can be a strong predictor of improvement in survival, but greater than 10% improvement in the volume of this being made dramatically improve survival.
- 00:46:58The next jack inhibitor was approved, just in August of 2019, and this may have implications in acute leukemia and other diseases.
- 00:47:08This is both a jak two and a flip three inhibitor with react can be a common invitation in acute leukemia and other Milo disorders and it was approved on a similar study that had been occurred temporarily around the same amount of time.
- 00:47:25In the Jakarta study with two different bills is a progression of compared to placebo with similar endpoint as to the studies with wrestling it.
- 00:47:36Improvements in spleen on the left in these kind of waterfall plots where you see an improvement or a decrease in the size of the spleen as well as symptoms.
- 00:47:48Now this agent, and this was a bit of a fascinating story ended up having a toxicity.
- 00:47:54that there was a delay in recognizing because us as hematology and medical oncologists were unexpected in seeing this sort of Texas, which was Warner keys encephalopathy.
- 00:48:06That the drug possibly slightly impacts, the metabolism of firemen so don't worry about 1% of patients but enough.
- 00:48:13That they could drop their Simon levels and develop or nikki's and again from our and we're used to dealing with side opinion we're used to dealing with GI side effects.

- 00:48:23But sometimes it's kind of that that pre existing bias of what you're expecting to see, whereas a different group of physicians might have picked up on that right away, so there was a bit of a delay got put on hold.
- 00:48:36We learned over time, that if you check the fireman levels to forgive them Simon probably not a problem that there's an FDA black box warning.
- 00:48:45diamonds pretty inexpensive and largely it's not been a big issue after its approval, I didn't show you there can be GI side effects, as well as a risk of suicide opinion.
- 00:48:57So these individuals we give them for granted, we assess Simon we replaced by a man and we monitor for response like rock solid.
- 00:49:06And currently we primarily use this in individuals in which REX 11 was not effective in the frontline setting it has a label that it could be used in the frontline setting but.
- 00:49:18Given people's comfort level with a drug they've had now for over 10 years is primarily used in second line setting.
- 00:49:25And there is data in its use in second line setting, which was a travel I lead with colleagues from the UK or this can be a helpful therapy.
- 00:49:36The third approved drug is called predictive, and this was just approved in February.
- 00:49:42And this one was a bit unique in that it also can be given to individuals with a very low blood counts.
- 00:49:48Particularly very low plates, which is sometimes eliminate the other two had bills leveling toxicities of dropping the planet, so you are frequently in a difficult spot.
- 00:49:58You wanted to use the drug, but you couldn't use enough of it because of the plane account there was found that this drug both inhibitor object to but an additional.
- 00:50:08Protein called Iraq, one that may have to do really with the inflammatory home and may allow it to be given in individuals with mark thrombocytopenia.
- 00:50:19And without a limitation on who could enroll in in these studies so again, including individuals that had played accounts below 50,000 it was shown to be able to improve spleen and symptoms kind of it, regardless of that low plated issue for these individuals.
- 00:50:39they're showing that the players for these individuals were stable or improve, so this is different than the other ones so again good Victor we're slowly putting each of these in their own niche in terms of as we're thinking about trying to manage individual patients.
- 00:50:54Including can have an impact in terms of improving anemia so less impact for individuals with low blood counts might be stable for a little plate it's helped to improve anemia.
- 00:51:07And side effects fairly typical of that have fed rats in it as well with diarrhea GI side effects and low count, but without the issues of their work is encephalopathy, so that is somewhat unique and again this approved just recently.
- 00:51:26Fourth, drug that I just presented an oral presentation at asco just a few weeks ago is called a mom a lot in it, and this is an agent that we've seen in the past, may help to improve anemia so we had done a phase three study of this drug versus Dennis all and individuals that had failed.
- 00:51:46rock solid and had an email.
- 00:51:50Now this drug and again coming back to have cited it said that in P Vera, we were giving patients that have cited Mimetic to cause a decrease in red cells.
- 00:52:03Here, this drug may help to inhibit it have cited so that patients with anemia might have an improvement.
- 00:52:12In red blood cells, so this may surface in other diseases with chronic anemic states to inhibit have cited through ACR one there was another drug from inside being developed this inhibitor of our to that again may inhibit have sidon and have cited may have negative impact in other.
- 00:52:33Diseases that we may see in a variety of diseases that it may see across medicine.

- 00:52:40Now we had shown an earlier studies that mama laudanum could improve spleen symptoms but probably had a much better anemia profile than the drug we typically use, which was rock solid.
- 00:52:52So we designed this phase three trial that ended up being conducted exclusively during the time of Kobe we put the first patients on in.
- 00:53:01April of 2020 mom a lot net versus Dan has all that is all again a relatively accepted second line agent for anemia in these patients.
- 00:53:12With really trying to improve symptoms spleen and anemia.
- 00:53:17So we show that it was not it was vastly superior to Dennis offer improving us of symptoms, which is our primary endpoint.
- 00:53:27Much better for improvement of spinal magnetic which again was not a surprise, but it was good to see.
- 00:53:33and significant improvement as a related to improvement in anemia, whether it be the achievement of transfusion independence or improvement in hemoglobin levels.
- 00:53:45The toxicities overall were as expected GI and some side opinions now interestingly.
- 00:53:55A much higher rate of death of code in the pre vaccinated period on the jack inhibitor arm versus denzel.
- 00:54:04In Israel has been learned over time that androgens may have a protective effect against coven for reasons that we were kind of unexpected, but it has been identified, that being on a jack inhibitor.
- 00:54:19Stopping a jack inhibitor is probably a bad thing to do in the setting of active co would particularly early on in the pandemic.
- 00:54:28And, of course, this being a study that's exactly what occurred you're on a study you get sick with Cobra they stop the study drug.
- 00:54:34Probably the wrong thing to do, so I don't think it's an issue kind of long term but, but it certainly was a real covert viral phenomenon.
- 00:54:42And although it wasn't not a survival city certainly a leaning of an improvement in survival through week 24 between the arms.
- 00:54:50And we've previously seen that the decision may have an impact on survival and that the achievement of transfusion independence is probably associated with an improvement in survival for these patients.
- 00:55:07So how might these drugs kind of fit together.
- 00:55:11We got three that are approved, so if you're proliferative and frontline rucks 11 is our primary choice proliferative and second line probably fit right in it.
- 00:55:23If you're cited penis you got low counts for today, that would be recruiting and particularly if you had a low platelet count.
- 00:55:30After my millennium is approved, if you're anemic that may be frontline so again ways that we think is we try to evolve treatment guidelines, both in the US and elsewhere in terms of options people might consider.
- 00:55:43Now there's a lot of interest to see okay well.
- 00:55:47You know the jak inhibitors space has been pretty well fleshed out that they overlap a lot, there are niches within them, how do we really kind of kick it to the next gear in terms of deeper impact try to get closer to a more complete remission or other issues.
- 00:56:04So there are a whole range of different approaches that are being looked at usually in combination with a jack inhibitor.
- 00:56:12To try to make a deeper impact for these patients.
- 00:56:16The drug that's probably the furthest along.
- 00:56:20is one that is called a bet inhibitor.
- 00:56:25That again associated with it, with brd for again at active in terms of really the molecular pathogenesis of the disease, with good preclinical data that both drugs may be synergistic together.

- 00:56:41So there was a crowd them they looked at a whole variety different scenarios, where do we add it from the beginning, do we added.
- 00:56:49After a period of time and people that have sub optimal response, do we use it as a second line I was created the greatest interest is the combination data from in jack inhibitor naive patients.
- 00:57:04Seemingly much higher rates of initial response in spleen and symptoms and individuals that are naive to jack inhibition.
- 00:57:14These are the second line data which are active but probably less so clearly than using both drugs up front so there's currently an upfront combination study accruing as we speak.
- 00:57:28But showing here just showing the durability of response with these individuals.
- 00:57:34The side effects again.
- 00:57:38Very much of a recurring theme, most of these agents can cause some GI side effects some potential simultaneous.
- 00:57:47No warning keys and stuff philosophy for any of them other than the Fed rational.
- 00:57:53There has been some evidence to show that there may be some benefit in terms of bone marrow histology like fibrosis which we've not seen to a great degree before so that's one reason that that's created.
- 00:58:04A variety of interest.
- 00:58:07And here again showing a correlation between improvements in the jack to mutation and this degree of bone marrow fibrosis.
- 00:58:17This is a current ongoing accruing phase three study, there are more phase three studies ongoing now an MP ends in there have ever been before.
- 00:58:27The second drug that's of interest.
- 00:58:30Is a BC l XL inhibitor called Nevada class about 100 years ago my my K award was actually on a potosi's in myelofibrosis.
- 00:58:42So as excited to see this kind of be developed, we didn't have specific inhibitors of bcl excel but he proposes or program cell death.
- 00:58:51We had recognized that there was this issue of resistance to to program cell death in these patients.
- 00:58:57And the there's probably issues in the development of this disease of now we're really studying, which is the issue of senescence.
- 00:59:06Where cellular senescence and the potential of see analytics you know may play a role in this kind of secondary harm process that is occurring in the bone marrow as well as seeing the lyrics may play a role in a range of other.
- 00:59:21approaches to other solid tumors coming forward as well.
- 00:59:26Now my most recent ha in Vienna, they looked again like the progressive they looked at all these different scenarios and here there they were reporting the scenario of using it for individuals who were treatment naive, so, in combination upfront.
- 00:59:46In short, they found that it probably has more side effects in a non randomized way compared to pelle abrasive.
- 00:59:53And that the initial response rates are active, but again, not as as profound as the Palo breasted, so this is also going on in randomized phase three trials.
- 01:00:06And again it's always difficult comparing drugs that aren't being compared directly against one another in a randomized study but we're waiting all of these results again to see where might these drugs fit do they have data this really strong enough to support their use.
- 01:00:24And do they are they effective enough to change the decision as people like Karen I sit and talk about an individual patient, so the patient.
- 01:00:34Go to transplant, so they not go to transfer, should we try another drug beforehand, you know, looking at these data very closely is a big part of how we do that analysis.

- 01:00:47So the current time there's really an unprecedented number of phase three trials, there are those are people that truly fail jak inhibitors.
- 01:00:55Another drug we won't get into today but that's an inhibitor of telomerase until armories involved with the caps of chromosomes involved with aging that may end up having implications in a range of different diseases.
- 01:01:09i'd say the approach that is the most.
- 01:01:12Patient focused is you know you're on a jack inhibitor but you don't have an optimal response can we add something else in.
- 01:01:18You know, realistically, to drugs for Milo fibrosis is probably going to cost north of $300,000 a year, which is a tremendous amount of money.
- 01:01:31So you know what is the impact, you know I'm the patient in terms of progression free survival, quality of life.
- 01:01:37In overall survival, you know, both in the USA and external to the US, and of course combination therapies from the get go, you know, is there a deeper response, or is there just a broader response rate.
- 01:01:53Which again begs the question, what do you really need to start to drugs at once, are you better off staggering it apart.
- 01:02:01So I didn't try to weave all this together.
- 01:02:04So one to think about the treatment, the next three to five years for people that are low risk we're thinking either observe interferon or a trial or if they need.
- 01:02:17Their symptomatic we think about rick Sullivan, if they need more than this, we really move to our more intermediate or high risk approach and we certainly start to consider, should we move towards stem cell transplant.
- 01:02:31Individuals with who need medical therapy intermediate or high risk we consider procreative if they're thrombocytopenia if they're an email potentially mom a lot name or another agent in combination.
- 01:02:43yourself standard mf patient not already set a penis big spleen symptoms rock solid number for dragging him or a subset that I think will find from phase three do we use a combination.
- 01:02:56And likewise in second line we really follow a very similar approach for where we weave in second line if they didn't get him in the front first line.
- 01:03:06A big area of unmet need is what if they're moving toward acute leukemia up to this point we've not had a tremendous amount of success.
- 01:03:14We largely have been running trials, if there is a target, we will try to use it target, along with jack inhibitor, so there are currently approved agents that are inhibitors of it H1 and H2.
- 01:03:28they're not common mutations in that setting, but they have her, and I have one patients that have beautiful response to a combined it to inhibitor and rock solid them, but we don't have enough situations like that, where we have a target that we can identify quite yet.
- 01:03:48Because I like to tell patients, you know as we evolve, you know we start with 30 advancing number therapies, we have a broader.
- 01:03:57understanding of the disease, but we really try to have to couch the management of these chronic diseases in terms of what the individual treatment goals are the patients goals their individual health factors again if a patient has a lot of cardiovascular risk we may be more aggressive.
- 01:04:17The individuals impact on symptoms and their quality of life so molecular understanding of a disease or hematologic neuropathy is critical, but it's kind of the starting place.
- 01:04:28And that kind of the end all be all in of itself, I could take two different coronal diseases and put it into two different people and it's going to behave differently.
- 01:04:37Based on their age, their fitness or comorbidities you know their wishes, I mean Karen can attest to this, I could send her to patients that are 65.

- 01:04:46Equally candidates for stem cell transplant and one will say yes and one will say hell, no, you know so there's a lot of injuries individualized factors that are key.
- 01:04:56to open up the questions were cleared everything I've shown you is really a lot of teamwork, so one tremendous teamwork really in the mtn community in the MP and patient community that really has been.
- 01:05:07Critical to a lot of these efforts, as well as my colleagues at work with the MP and quality by study group again trying to weave in the patient's voice and kind of understanding of these therapies, along with their efficacy and safety.
- 01:05:23And with that I'll open up to any questions.

Unknown Speaker

01:05:36questions.

UVA Internal Med

01:06:20it's a good question so for those who didn't hear the question from Ferris is for people that have earlier disease and have miles, fundamentally, is there a benefit in treating.

- 01:06:30December agree, I don't think we know, I do think there is an impact of jack innovation in terms of progression free survival.
- 01:06:38So in the that group of folks they typically will do next generation sequencing just to get a sense of you know what is there a greater risk with the disease.
- 01:06:47But I may just observe that group of patients, there may be a role particular if you're a very young patient, you know in long acting interferons in this group of patients as well.
- 01:06:59You know if you're really trying to improve progression free survival, particularly if it's a particularly young patient, you know with it is he someone.
- 01:07:07Again, we found patients who have primary mal fibrosis in their 30s and they have a general physical somebody notices just the tip of a spleen.
- 01:07:16You know, may have fairly early disease is that more aggressive than we need to be I think at this point it's unknown, you know, certainly strong to kind of involve the patient in those.
- 01:07:27In those thoughts, you know I could share with them, you know I, I believe, if I look at the population if I need 500 patients like that, with a jack inhibitor and 500 without.
- 01:07:38The group on a jack inhibitor are probably better off, but at the individual patient it's difficult it's difficult to know we still don't have.
- 01:07:48A good biological surrogate of what drives progression, which is really scientifically one of our limiters You know, as I try to work collaboratively with.
- 01:07:59The basic scientists are trying to understand the biology of the disease is trying to send will Why do people progress is a critical thing we don't know, because if we knew it, we could measure it, we could say okay well if I started a jack inhibitor does it improve that marker of progression.
- 01:08:18or it's improved some but I need to use more drug to to get it to where it wants to be so I am hopeful that we make that kind of critical biological discovery day because I think we're still largely flying blind in terms of that that progression free survival piece.
- 01:08:42Well, great well again, thank you very much and appreciate the wonderful hospitality, thank you.
- 01:08:55Great no.
- 01:08:58wonder these attendees there we go no no worries well Thank you so much now it's a great crowd so thank you much appreciated we love having you Thank you so much.