ASH 2020 Meeting Highlights in Myeloproliferative Neoplasms

Ruben Mesa, MD
Director
Mays Cancer Center
UT Health San Antonio
MD Anderson Cancer Center
San Antonio, Texas

Aaron T. Gerds, MD
Associate Professor of Medicine
Cleveland Clinic Lerner College of Medicine
Case Western Reserve University
Cleveland, Ohio

John Mascarenhas, MD
Associate Professor of Medicine
Tisch Cancer Institute, Division of Hematology/Oncology
Icahn School of Medicine at Mount Sinai
New York, New York

Dr. Ruben Mesa: Hello, my name is Ruben Mesa, and I'm the Executive Director of the Mays Cancer Center at UT Health San Antonio MD Anderson. Welcome to this *ASH 2020 Highlights in Myeloproliferative Neoplasms*. I'm joined tonight by two very good friends and wonderful MPN experts, Dr. Aaron Gerds, Associate Professor of Medicine at the Cleveland Clinic, and John Mascarenhas, Associate Professor of Medicine at Mount Sinai. It should be a great discussion today.

We're going to be having a review of some of the challenges and unmet needs in your management of patients with MPNs. We're going to have a high level summary of some of the key data coming from this year's ASH and how it might impact your practice. We'll discuss some of the new therapies and how they might fit into managing MPNs. Now, when we're speaking of myeloproliferative neoplasms, today, we're going to be focusing in particular, on polycythemia vera in myelofibrosis. Now, polycythemia vera and essential thrombocythemia are our earlier MPNs. We know these diseases start with driver mutation acquisition, JAK2, CALR, or MPL. There are now additional modifying mutations, ASXL1, amongst others, that occurred during the progression of the disease. Now, early on in the course of these illnesses, there is a risk of vascular events, difficulty with symptoms, occasional splenomegaly, and as the disease has progressed into overt myelofibrosis, there can be splenomegaly, cytopenias, extramedullary hematopoiesis, bone marrow fibrosis. In that phase, the disease becomes typically more life-threatening, and finally, the diseases can progress to acute myeloid leukemia.

Now, these patients have quite a variable disease course. They are heterogeneous, there's even three diseases worth speaking of. When we are developing our treatment plans, we need to be mindful of what are our goals. Is it avoiding thrombosis and bleeding? Is it improving symptoms? Is it increasing activity or decreasing splenomegaly? Are we working to improve low blood counts in myelofibrosis? Are we working to decrease progression, prevent progression, or live longer? All of these are important considerations as we assess both where we currently stand, but several of the new therapies we're discussing as they try to broach new areas of efficacy.

Let's kick off with polycythemia vera.

Now, in 2021, we would need an accurate diagnosis, develop our treatment plan, and develop our frontline medical therapy, and then we want to be certain to be evaluating for potential progression, movement into second-line if need be, or shift gears altogether if we are treating AML.

Now, we developed NCCN guidelines over the years. I was the inaugural panel chair and now Dr. Gerds is the current panel chair. With these, we stated in polycythemia vera the importance of monitoring counts, the importance of phlebotomy and aspirin in lower-risk patients and cytoreduction in higher-risk patients.

There was a nice analysis done by our colleagues at Yale, demonstrating the importance of appropriately starting frontline therapy for these patients. They were able to look at overall survival as well as thrombosis-free survival, demonstrating the importance of utilizing hydroxyurea, utilizing that frontline therapy when appropriate.

Now there are treatment gaps that remain in polycythemia vera. There are both in the guidelines that are out there, hydrea and interferon both as considerations for frontline. Which of those should we use? How do we prevent disease progression? JAK inhibition is approved in the second-line setting with ruxolitinib. How early should we be weaving that into consideration?

Indeed, there are two types of interferons that are actively being explored. Ropegylated interferon alfa-2b, which is approved in Europe, and there was data at ASH in use in low-risk PV and pegylated interferon alfa-2a, that those of us in the MPN Research Consortium, John, and I, and our colleagues, performed trials either alone as single-agent or as second-line.

Now, one of the first abstracts from this year's ASH, the long-term use of ropegylated interferon, the five-year results from the randomized controlled study.

The initial study was a PROUD-PV Ropeg versus hydrea at 12 months, and then the CONTINUATION-PV, 60-month interim analysis to look at the long-term. Indeed, with PV, we're thinking of a long-term suppressive therapy, so long-term data is very relevant as we consider these patients. Our colleagues, Heinz Gisslinger and colleagues, reported that when we take the long view that perhaps at a year, hydrea and interferon are roughly similar in terms of CHR, but as we get further and further out in terms of follow up, it's very clear that there is superiority of ropegylated interferon over hydroxyurea for these patients.

There also seems to be a better control of the JAK2 allele burden for these patients, which again, makes it potentially intriguing as a more disease-modifying therapy. Terms of rate of vascular events, roughly equivalent, although the numbers are quite low in both arms, so difficult to see much daylight between those, lower rates of disease progression in the ropegylated arm versus the control arm. In terms of safety, good safety with the ropegylated arm, and not a clear, major difference in terms of SAEs between these agents.

Let me open it up. First, Aaron, what do you think are some of the greatest unmet needs in PV?

Dr. Aaron Gerds: Well, thank you, Ruben, and it's a pleasure to be here with you and John to discuss these topics. I think there are a lot of needs still in PV. I think you hit the nail on the head there with disease modification, stuff that can really delay progression, delay disease moving forward in time, or even resetting the clock back to earlier forms of the disease would really be

wanted, because although a lot of patients will stay in a chronic phase, a lot do progress. I think a lot of times too, these agents can-- hydroxyurea interferons can control counts, but in some people, it doesn't control their symptoms and I think additional agents to help really directed at their symptoms they be may having can be a big help as well. I think those are the two main categories in my mind.

Dr. Ruben Mesa: Great. Now, John, you and I have chewed on this issue of interferon with our own analysis of the MPN-RC studies. How compelling do you think US-based hematologists would find, particularly, this last set of longer-term data on ropegylated interferon?

Dr. John Mascarenhas: I think the trick, when you're looking at treating a PV patient, particularly with interferon, is the long game. One doesn't really look to achieve immediate responses with interferon alfa-2a or 2b for that matter. I think if one is looking for instant gratification, I think really hydroxyurea is probably the agent that will achieve that. If one is looking for the potential for disease course modification and using the JAK2-V617F as a surrogate marker of that, then one really needs to be invested and temper expectations for the patient, for the physician, for everyone involved. That really takes time to achieve those kinds of responses and patients have to be followed over the course of years. I think the biggest obstacle is likely going to be in experience with interferon. I think most hem-onc docs in the community are pretty comfortable with hydroxyurea and oral therapy, for the most part, well-tolerated. Older docs who've had use of interferon with CML, but prior to the TKIs, probably are comfortable. Those of us that do a lot of MPN are comfortable. I think it's going to take time to achieve that comfort level through education and other mechanisms so that docs and patients are likely to feel comfortable using a biologic-like interferon.

Dr. Ruben Mesa: Wonderful. Now, let's pivot a bit. That's a discussion really in frontline. Patients clearly can fail frontline for a variety of reasons. Toxicity, maybe they have a vascular event, maybe they have other issues in terms of inadequate efficacy, so let's pivot to an abstract I was involved with but John, you presented this. I'll quickly run through your slides but it's regarding an agent idasanutlin in hydrea-resistant or -intolerant polycythemia vera patients. Now, this was again the second-line study, they had PV, they had failed hydroxyurea, they were phlebotomy dependent, and they were receiving idasanutlin with looking at response, and this was a phase II study.

You presented, good clinical activity, control of hematocrit, CHR, and again, this is in second-line patients, European LeukemiaNet responsible CR and PR, in the majority of individuals in composite response of the majority of individuals realizing it's a phase II trial.

There was reduction in spleen violence, some patients. Now mind you, only a subset of patients clearly have splenomegaly, but you see the waterfall plots with these individuals, also saw a reduction in platelet counts in, again, not all patients are valuable for platelet count response, control of the leukocyte count ,an area of my interest improvement in MPN related symptoms. Again, clearly saw that there could be improvement in MPN related symptoms and individuals again, who had failed hydroxyurea.

Now, the MDM2 inhibitors do have some issues with toxicities, in GI toxicities really all being kind of at the top of the list there. If you see across the board, the grade 1/2 nausea did lead to dose reduction in a few patients as well as some dose interruptions. John, maybe I'll have you

first comment, as you've chewed most on this data, what are your thoughts in terms of both the efficacy as well as the tolerability of this agent for PV?

Dr. John Mascarenhas: It's bittersweet. It's clearly an active agent. We saw that early on through the Research Consortium-115 study of idasanutlin, and that really informed the phase II study. What we've learned from that study is, you can have an effective drug, and what we didn't show in today's webinar, the molecular responses that were presented at the meeting as well, which were quite dramatic, and we had 85% VAF reduction, within four to six months of therapy. I'm not really aware of other therapies that have such dramatic changes in meeting allele burden. It's clearly active and on target and informed by preclinical studies conducted by Ron Hoffman and Min Lu. The problem is, is that the tolerability is such from the GI toxicity that it's very challenging to deliver it month after month. If you're treating patients with acute illnesses, like AML, with a very set number of cycles of therapy, that may be doable. If you're giving patients with chronic disease therapy on a basis of a monthly basis, every four weeks for five days, and there's GI toxicity, even grade 2, that becomes difficult after multiple cycles of therapy. The lesson learned here is as good as the drug may be, if it's not really well-tolerated. It ain't that good. I think the mechanisms on target and I'd love to see other MDM2 inhibitors perhaps KRT-232, or HDM-201 from Novartis. Other drugs in the class, take a try, both in the PV and MF space, and maybe the toxicity profile will be better and the on-target activity will be there.

Dr. Ruben Mesa: Yes, very true. Now, Aaron, as a current panel chair for the guidelines. Clearly, ruxolitinib is a second-line therapy for PV, what do you think some of the characteristics, whether it be an MDM2 inhibitor or perhaps some of the agents we will end up discussing about myelofibrosis might, of course, pivot to be tested in PV. What do you think a second-line agent needs to show in PV to really be a credible option?

Dr. Aaron Gerds: I think a couple of things, I think at a fair minimum, controlling the blood counts I think would be the first criteria to be in a second- or third-line drug in PV. The one thing that we know that ruxolitinib can do pretty well is address symptom burden. I think that's really its niche there in the second-line setting in addition to controlling counts, but like John mentioned, with the idasanutlin. The exciting part was, what it was doing under the hood, the reductions in allele burden that we saw would really prove the on-target effect. I think the one thing that the study didn't really capture was some of the patients that, when their treatment was done, they went many months without needing phlebotomies, even after coming off study. A couple of my patients went roughly 12, 13, 14 months without needing phlebotomies after coming off study. Getting back to that earlier point about disease modification, I think it's something really exciting for polycythemia vera. I think a lot of these agents that we are looking right now in the second- and third-line setting, and even in myelofibrosis, when they drift over to PV and when we really start to explore them in PV, we're hoping to see some more of that evidence that they do modify disease.

Dr. Ruben Mesa: No, it's very true. I was doing telemedicine visits earlier this afternoon. A few new patients with PV, some of them are fairly new to the diagnosis. Again, I try to frame this disease. It's a neoplasm it clearly can be progressive, but it's a chronic disease. Some people have PV for decades, so I try to frame it in their own mind, because they're thinking neoplasm, and they hear that word, and they're thinking pancreas cancer, breast cancer, colon cancer. The dynamics are really dramatically different on many levels, I try to frame it more accurately, like a disease like lupus. The mechanism is different, but it's a chronic disease, requires a chronic

therapy. There are many individuals that will live out their normal lifespan, but there are some that it can become progressive and have very difficult complications or fatal complications. I do think the chronicity is an important fact. As John says, the patient's willingness to put up with toxicity is clearly and appropriately more limited. If any of us need to withstand four cycles of intensive chemotherapy to overcome a cancer, we'll do it. We'll hold our noses, we'll struggle through it, we'll take time off from work. Whatever, but that's for curative therapy. Maybe will evolve to the point where , again, we have curative therapy, but it has a period of recoverable toxicity that maybe we'll choose to do for PV. A chronic day in and day out therapy, that issue of tolerability is key. For particularly when the current landscape is overall pretty well tolerated. Hydrea for most people can tolerate pretty well. Ropeg is, we saw, most people, not all, but most people tolerated it pretty well. Ruxolitinib, we saw that nice response to data presented the five-year data at this year's ASH from Pasamonte showing five-year durable improvements in splenomegaly symptoms or symptoms, hematocrit control, that was the trial that they did not need to have splenomegaly, so all good.

Let's pivot now. Let's loop in another interesting drug, again from one of your colleagues, John, at a group PTG-300. This is a hepcidin mimetic, which acts to basically simulate anemia of chronic disease make people phlebotomy independent, hopefully, that their iron levels come up.

This was the design, open-label in individuals either with or without cytoreduction but in a stable way. John and his colleagues demonstrated very nicely control of the need for phlebotomies in these individuals. You see kind of a need for a phlebotomy is on the left and kind of freedom on the right. A nice graphical way of showing complex data, a well-done control in the decrease in the hematocrit and red cell count, of course, part of the premise improvement in iron and improvement in ferritin to go along with that.

Again, it warms my heart to see that as a field, we continue to look closely at patient's symptoms as part of efficacy, which we should, just in parallel with other parts. Again, some improvements. Now are these from improved the counts, more even control of hematocrit, decrease in iron deficiency? It may be some of each. Difficult to know how much each contribute, but probably all are relevant. In terms of toxicities, overall fairly well tolerated. This is an injectable drug, some mild injection site reactions, no serious toxicities, no grade 3 or 4 toxicities, some mild GI toxicities, but looks overall better tolerated than the MDM2 inhibitor.

Here, a different agent, non-cytoreductive agent in the traditional sense, for control of hematocrit and possibly could be a role for even low-risk PV patients that currently get phlebotomy and aspirin. Maybe I'll ask Aaron the first question. Currently, lower-risk patients, we're doing phlebotomy and aspirin. If all of this held up through a positive phase III, what would you need to see to have, you think that that could be an option for lower-risk patients?

Dr. Aaron Gerds: Thank you. I think this could potentially be a great option for lower-risk patients. Phlebotomies can be a burden and people can really feel the effects of iron deficiency, and this could potentially alleviate that in addition to controlling their counts. It would save time away from work, you don't have to go into the infusion room, you could just give yourself the shot at home, which is great. It could be a self-administered medication because it's subcutaneous. I think these things are all really important. Showing efficacy, I think the way the phase II trial was designed here, it took all-comers, folks who were getting just phlebotomies and hydrea, interferons, and added this on top. I would anticipate more information coming out of the phase II on what

populations this seems to work the best in. Traditionally, after phlebotomy, becomes difficult for a patient who is low risk, we think about hydroxyurea or interferons, so this might have to be something where we think about patients who are really receiving phlebotomies, not tolerating phlebotomies, and then potentially randomized against one of those other agents. I know I'm kind of sliding into the next [chuckles] question and sorry about that, but I think it would have to show similar response rates to these other agents that we would often reach for after phlebotomy.

Dr. Ruben Mesa: Great. Well, John, maybe I'll have you comment, because you have the most first-hand experience. Maybe comment on the agent, but again, what do you think of phase III needs to show with--obviously, only discussing what's in the public domain?

Dr. John Mascarenhas: As Aaron pointed out, mechanistically, it's a really interesting agent that takes a different spin on treating the disease because it's really affecting hepcidin and iron metabolism distribution, and essentially choking off red blood cell production. What it probably doesn't do necessarily is have clear anti-clonal activity, and once you stop the drug, one would presume that the red cells would go up again, and one is not expecting white count and platelet count control nor significant JAK2 V617F burden reduction. To me, the trick will be trying to figure out how best to run a phase III study that clearly defines a population that this drug would address an unmet need. I'm not quite sure that low-risk patients, per se, would meet that criteria. I can definitely think of a few patients, at least, in the practice, that have significant tolerability issues with phlebotomy, and those patients, if they were unable to tolerate cytoreductive therapy or unwilling, this may be a therapy to offer patients like that. Although, I think this is a great example of brilliant science, really interesting mechanism, but if you start to really think it through all the way through, I'm not totally clear what the patient population would be that's best suited for this. Although I can definitely think of patients here and there in the context of a trial where one needs to have a defined patient population and then an outcome measure that can be even between the two groups, requires, I think, some serious thought.

Dr. Ruben Mesa: Well, good. Very interesting mechanism of action. I think much for us to learn, and I think as we end up talking about momelotinib, it's interesting, this hepcidin question where-- here, we're using a hepcidin mimetic to create a decrease in erythrocytes, and on the flip side, we see with momelotinib, as we'll discuss, a reason to increase erythrocytes. Let's pivot to MF, myelofibrosis. Now, this, for many, is more like a solid tumor malignancy in terms of its natural arc or seriousness. Not for all, but for many.

Here, again, an accurate diagnosis. We assess survival and disease burden. Do they have splenomegaly? Do they have anemia? Are they progressing? We need to be considering the role of stem cell transplant. Frontline medical therapy has been ruxolitinib for almost a decade, now, we have fedratinib as a frontline option. Of course, people don't consider that in those with moderate thrombocytopenia. If they progress, do we move on to transplant? Do we go to second-line fedratinib, as an approved agent in that space if someone got ruxolitinib or a trial, and then if not, moving to AML type therapy?

Now, the landscape, we've got fedratinib with ruxolitinib which I mentioned, we've got two coming up on their heels, pacritinib for that myelodepleted phenotype, people with low platelets, exciting data coming out there, possible approval in the near future. Momelotinib, JAK1, ACVR1, JAK2 inhibitor from Sierra, ongoing trials at the moment. With that, I'll share a trial that I presented at this year's ASH related to survival and efficacy of momelotinib for patients with MF.

There was the SIMPLIFY-1 study, this was the frontline study, SIMPLIFY-2, this was the second-line study. It showed that one, a differentiator in SIMPLIFY-1 that people were able to take the full dose of momelotinib. Its heme profile, as it related to tolerability for anemia and thrombocytopenia, allowed more fuller dosing, which it could be potentially an advantage. There are frequent times we know that there's way overutilization of suboptimal doses of ruxolitinib in the community. Perhaps part of that could be improved, but way too many people out there on five, twice-a-day of ruxolitinib, a dose that, although can provide some symptom improvement, may be modest for efficacy.

We see here nice data as it relates to spleen response and duration of spleen response. We see nice data as it relates to both transfusion independence and duration of transfusion independence for that momelotinib, as well as the Rux to momelotinib crossover. Part of that mechanism we now believe is due to the inhibition of ACVR1, that is doing, again, the opposite of that PTG-300, in inhibiting hepcidin, decreasing that inflammation, allowing erythropoiesis to occur.

Again, improvements in anemia in that SIMPLIFY-2 study, the second-line study. Data we presented as well was the median overall survival of 53 months in the Rux to momelotinib patients, and a median not achieved in those who have been on momelotinib the whole time. These are survivals. Again, there's not a long-term control arm, but these are survivals, really much better than we would have thought going into this study based on the risk of the patients. Similarly for SIMPLIFY-2, this is second-line, normally second-line patients survivals can be poor, two years or less by data from MD Anderson, and here, three years or more.

Let me ask you, Aaron, first. We're seeing some improvement in survival with momelotinib. We've seen improvement in survival with long-term analysis from the COMFORT study. We're going to get around to John's imetelstat study in little bit, that also speaks of survival advantage. Do you think that any therapy that clearly has an impact, you improve spleen, you improve symptoms, do you think we're there yet to say that that likely is predictive of improvements in survival?

Dr. Aaron Gerds: Yes and no. Clearly, patients, as you mentioned, on these trials are living longer when getting the active agent or getting the ruxolitinib or getting the momelotinib, which is I think a great thing. We're all aching for this disease modification, right? That is technically disease modification when they're living longer, but I think a lot of that might be because they're lowering cytokine levels long term, decreasing complications, shrinking spleens, better nutrition, improved in the case of momelotinib perhaps fewer transfusions and avoiding some anemia, are all helping translate into this improved survival, but this ultimate goal of eradicating the clone or reducing the amount of the malignant clone on the bone marrow. I don't think any of those types of agents were seeing now, imetelstat that we're going to talk about in the future, might be doing some more deeper changes there. I think that's what we're really looking for, but certainly, there is a place for momelotinib. I think, really the most telling part of that analysis was that even in the relapsed/refractory setting, patients were getting transfusion independence on average of 50 weeks, which is phenomenal. That's better than a lot of the other agents that we have to improve anemia. Then in the frontline setting, the patients were getting transfusion independence for three to four years, at least. I think those are really impressive numbers, and can really be a big benefit to that population who are anemic and need JAK inhibitor therapy as well.

Dr. Ruben Mesa: Now, John, obviously we spend a lot of time, the three of us thinking in the MPN Research Consortium, about myelofibrosis, how do we cure the disease and how do we prolong survival? Why do you think we're seeing improvement in survival with these agents, even with different mechanisms of action?

Dr. John Mascarenhas: I think Aaron said it best. I've thought about this a lot. Is it really the shrinkage of the spleen that predicts the survival? Or is it what you're doing to shrink the spleen that's really associated with the survival. Perhaps, as the data has been shown before, the deeper the spleen response with ruxolitinib, perhaps the better the survival outcome, but I'm not entirely sure I believe that's because the spleen is literally smaller, but it might be you're just optimizing the amount of JAK2 inhibition. That's really the goal of therapies like this. A lot of time and attention has been spent trying to analyze, the patients don't go into molecular remissions, they don't go into pathologic remissions. There is a believable survival benefit from both COMFORT studies when you follow them long term, it's there, and I think Aaron hit it. I think their cachexia is reversed, their performance status is improved. I think they're less likely to have inflammatory-mediated complications, and patients do better. Unfortunately, most patients have actually progressed too. There's still so much more to do, and I don't know that every drug that can shrink spleen to a comparable level will have that survival benefit. I'm enthusiastic or optimistic that we have trials now that actually look at survival as an endpoint that moves the dial forward. Whether we're going to figure out whether there's a clear biomarker that associates with survival, and I thought Aaron said it really well. It's probably the most important disease course modification we can offer our patients to prolong their life. Even JAK2, we don't have a clear marker that achieving a significant reduction in JAK2 means the patient will necessarily live a longer and better life. There's still a lot of research interests dedicated to figuring that part out so that we can design trials that can hopefully have early reads and move drugs forward quickly.

Dr. Ruben Mesa: Good. I agree. I think improvement in splenomegaly and symptoms are biomarkers of response. I don't think we still fully know what is the exact aspect of the response that is most crucial? How do we drill that up or down? There certainly is no magic to just the fact that the spleen is smaller, they'll undoubtedly improve symptoms, but it's really a marker of response.

Well, let's pivot to the final part. There's four agents with different mechanisms of action, each with intriguing data at ASH that we'll quickly go through and compare and contrast a bit where they might fit. Indeed, there's a very robust pipeline of agents, but we're going to delve a little deeper into four of these agents. The BET inhibitor from Constellation, imetelstat, navitoclax, and IMG-7289. CPI is extend BET inhibitor working on myeloid diseases, suppressing cytokines, promoting erythrocyte differentiation, normalizing megakaryocyte differentiation.

John, you presented this but it's almost a panel of different abstracts as it relates to this agent, but probably the one that's the most interesting is in the upfront setting.

In this part and they've looked at in each of the segments, all three have activity, but here, initial experience CPI-0610 plus Rux JAK inhibitor naive patients, impressive spleen volume responses. Again, response rates of 67% overall. Again, with the COMFORT studies, we saw response rates more in the low 40s. Now, obviously, this is combination. Impressive

improvements in symptoms, response rates of almost 60%, quite a bit higher than the COMFORT studies, but obviously, this is not randomized.

Improvements in hemoglobin, particularly in individuals that had some anemia, that could be a differentiator. Suggestions in a non-controlled fashion of impact on fibrosis. Suggestion of disease modification, toxicities can cause some anemia or thrombocytopenia, some GI toxicities. Then there was the MANIFEST-2, the phase III study, this is going to be opening, it is opening now at my center, I think probably all of our centers who are on the call today, this should be interesting. Typically, if you have newly diagnosed patients know that there's some frontline studies out there, Rux plus this agent versus Rux. Not a lot of downside is what I'm telling patients, again, maybe a little higher risk of tox but maybe a deeper response, nothing underneath.

Now, before we pivot to talk about the drug, there was also data as it related to using this in patients who were refractory or intolerant. Obviously, tougher group of patients. This was the non-transfusion-dependent cohort. Improvements in splenomegaly are relevant in the second-line, improvement in symptoms in the second-line was impressive. Again, here are some improvements in anemia, particularly those individuals without transfusions, the toxicities again, similar to what we saw on the frontline.

Looks active. What do you think is going to be the sweet spot? That upfront combination, obviously, you can use it possibly in the second-line, but if it was available tomorrow, would you use this in everyone in frontline? If this data carried out, would you use it in a subset? Aaron, why don't you kick us off?

Dr. Aaron Gerds: I'll jump in. Sure. Thank you. I think that's really the tricky part about all this. The response rates, as you mentioned, in terms of spleen size and symptom reduction, were almost double that in the frontline setting in what we see what the COMFORT study, ruxolitinib alone. We're also seeing lots of responses in the second-line setting in patients who are intolerant of ruxolitinib or ruxolitinib didn't get them in a great response. The big question in my mind is where to sequence this? You mentioned there is increased toxicity. Is this something where we start off with ruxolitinib, go three months to see if ruxolitinib is going to cut the mustard then we add in CPI-0610? Or is this something we need to start off right from the beginning doing combination therapy? Definitely, like you said, I'm looking forward to working on the MANIFEST-2 study to really get some more of these answers. I think, really digging into that frontline setting, and seeing what comes the MANIFEST-2 study is really, really exciting for patients, again, because the response rates were so much higher than what we would normally expect with ruxolitinib alone.

Dr. Ruben Mesa: I agree. Even as I try to predict the discussion, you guys will have in the panel sessions, is this everybody? I suspect not. I suspect there will be subgroups. Do you do it upfront based on a molecular phenotype or other feature or do you add it in after three or six months if not an adequate response? I don't think you need to wait four years. I think this concept of somebody's got to completely fail and then switch to another agent. I suspect things will be a bit more fluid.

Well, I have John coming up with us, let me jump into our next agent. This is imetelstat. Again, in many participating with this one, that John was kind enough to present this one at ASH is this initially tested by my colleagues at Mayo in Rochester, this is a telomerase inhibitor, different

mechanisms of action, and again as we all strip to get more gray hair, we're all much more interested in lengthening our telomeres.

An active agent they look at two different doses, they saw improvement in survival of the higher dose versus the lower dose and that in particular. Yes, improvements in symptoms and some in spleen, but again a suggestion that perhaps with this mechanism of action, improvement in spleen in symptoms may not be the perfect litmus test for what's going with the agent. I'm mindful of agents like azacitidine that can improve survivor on MDS but it's not necessarily correlated 100% with how well it improves cytopenias, it's doing other stuff.

Here's it's showing that difference in improvement in survival that lower risk of death correlated with improvement in bone myelofibrosis. Again here perhaps that is a litmus test, it's doing something else in the bone marrow. Undoubtedly, bone marrow and progressive disease in myelofibrosis, acquisition of additional mutations, perhaps toxic microenvironment may be a range of different things that are going. The patient with symptom response, again lower risk of death and again that may be indicative of a variety of surrogate markers, as well as those that did have a spleen volume response if they had it, certainly it was beneficial. There is a phase III study ongoing, it's an interest study that the primary endpoint is survival. Here they're looking at refractory high-risk patients, imetelstat versus best available therapy, certainly a strong consideration. Aaron, if you think about imetelstat, again further reinforcing this issue of survival, why do you think these patients might live longer on this agent?

Dr. Aaron Gerds: I think as we've been talking, there might be a deeper effect on the disease than just lowering cytokine levels improving spleen signs and symptoms. I think the most telling piece of data from that presentation that John gave was the correlation between survival and fibrosis grade and changing fibrosis grade and trying to connect the dots to associating some sort of tangible biomarker with better survival, and I think that's so, so important. There's been agents in other diseases that proved in the past where there has been a survival advantage but no clear mechanism why or no biomarker to follow and it's been really difficult to employ those agents. The one might we think of is the dendritic cell therapy from Dendreon for prostate cancer. There was no connection there and that made it really, really difficult to employ in the clinics. I think that's a really important thing and I really think that this is a gutsy trial going for the survival advantage**.** I'm really looking forward to seeing the results from this one as well.

Dr. Ruben Mesa: It certainly raises in my mind that perhaps, and this is speculative, but the litmus test from improve survival with JAK inhibition is spleen and symptoms, but agents for the other mechanism action it might be different. I think one way we need to be mindful in terms of a dose intolerability but it certainly raises whether this agent combine with JAK inhibitor could be complementary. If you could get enough of the drug in that the thrombocytopenia, again that might suggest some of the momelotinib or fedratinib they may have less cytopenias might be natural to combine up with this.

Another agent taking the approach, this presented by Naveen, navitoclax, in individuals with relapse or refractory myelofibrosis. They too are looking at different niches, although this year they actually presented this niche, but they're also looking upfront, like CPI-0610, this is impacting apoptosis in myelofibrosis a topic near and dear to my heart. It was the topic of my K award long ago, 20 years ago when I had that K award, but this as Bcl-xL inhibitor.

This was the single-arm, second-line study for patients who have failed a ruxolitinib and they were adding it on to ruxolitinib as opposed to a complete swap out. Which I do think is a bit more patient-friendly approach when it can be employed, it's not either/or, you add it on. I think that makes it easier in terms of both transition but also judging the incremental impact. They saw a nice improvement in spleen and symptoms. Again this was from a baseline of being on a stable dose of the agent as a single agent. It was nice to get this incremental benefit. Most common adverse events, thrombocytopenia, and GI. Again somewhat of a recurring theme in our realm, mainly these agents active in MF can cause some cytopenias, can cause some GI side effects.

They did see some early molecular responses as well as some improvement of fibrosis. Again we have more flirting with this issue of disease modification, fibrosis is a challenging endpoint but several agents are flirting with this area. They also saw improvement in inflammatory cytokines. Again I think a lot going on in that bone marrow microenvironment, perhaps in the complex microenvironment within the spleen might be relevant as well. Obviously, phase II, but Aaron, this drug is following the same track as the BET inhibitor. Data is early, but what do you think are these parallel ships in the night? Where do you think they might fit together?

Dr. Aaron Gerds: Yes, exactly, I think that's the key, and like CPI-0610 where is it going to fit? And there are studies launching with the navitoclax in both phases, the upfront setting, and the relapsed/refractory setting. I think we'll get some phase III data to kind of sort that out. I think the devil is going to be in the details. We're going to look at subpopulations in all likelihood from these studies saying, "Well, this subpopulation did really, really well, we might choose navitoclax as a partner for a JAK inhibitor instead of CPI-0610 or vice versa." Some of that might be molecular driven, although part of that data that Naveen presented here in this abstract show that responses seem to be mutation agnostic. No matter what the molecular risk type was, there are high-risk mutation and there are low-risk mutations, response rates were similar. I think in the future we might actually hopefully use some of this molecular data that we get on a lot of our patients with these gene panels to help direct therapy when we're thinking about addback strategies.

Dr. Ruben Mesa: Wonderful. We had buzzed through navitoclax, CPI-0610, and imetelstat, but first let me ask you, CPI-0610, navitoclax both of these, well they're both looking at the same issue frontline, second-line, add-on strategies, what do you think these drugs are relative to each other?

Dr. John Mascarenhas: I think they're both active drugs. Personally, I would welcome both into the commercial space so we have multiple options. Right now the data looks best in my opinion for navitoclax as an add-on strategy, that's what they did in the phase II study. We haven't seen any data upfront, so that's unknown. CPI looks really active I think combined with ruxolitinib upfront but the only way to prove that will be the randomized phase III each study. As the data matures and there's more data to look at, I think Aaron's point is well taken, if there are clear molecular signatures that associate with a specific therapeutic, that will help guide the treatment decision. We're not quite there yet, but I see no real downside in having multiple options that can be cycled for any individual patient.

Dr. Ruben Mesa: I definitely agree, I think we're going to be learning a lot from those correlative studies. If you have ASXL1, if you have EZH2, if you have any number of things, how it might

impact these will be relevant. Well, the final one that we'll go through before we get to our question-and-answer session is the LSD1 inhibitor, bomedemstat IMG-7289, in patients with advanced MF. I've been participating in this study and also have an ET study that we have ongoing that we can discuss another time but active in both of those settings. This again working in megakaryocyte differentiation and this pathway may be disease-modifying in a range of ways; 49 patients second-line typical features in patients who had failed here are showing the enrollment and treatment duration. You've got really some long-term players out there well past a year. Overall, no dose-limiting toxicity. This agent does impact, it does have a bit of a peculiar thing, it can impact taste that can lead to nausea and some other things. I have found that to be something needed to manage around. Been a bit more of a factor perhaps in the ET study than has been reported in MF. Again, some of the rare SAEs, but these are obviously second-line patients. They're pretty high risk. Improvements in symptoms, as you see on the left, and some improvements in the spleen volume. The trial is of course earlier in its arc than some of the other agents that I have presented. There were some interesting improvements in the variability of frequency in a few different molecular phenotypes. Again, that might be of great interest, including a couple there with ASXL1. Early, but obviously, that would be a highly valuable group to be improving.

Where might this fit in? Do we need to really let this mature compare it with something else? John, why don't you kick us off?

Dr. John Mascarenhas: Also I think mechanistically a very interesting drug and I think there's some signal of activity here. I think compared to some of the other studies we've discussed where there's a lot more data, a lot more patients, it's a little bit more challenging here to really be definitive. The reality is if this was a drug that we were discussing seven or eight years ago where the field was different, there were a lot less agents being presented at meetings, this would probably be the lead compound. It's a competitive field right now. It's a little hard to say how best this fits in or compares and obviously, it needs more data and I think more time and the move to take it into ET makes sense. I look forward to seeing that data as well.