A Review of Current and Developing Therapies for MPNs

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Andrew Schorr:
Wow. Reset. So, John, so people know many of the medicines that are available for these conditions now, whether it's a JAK inhibitor—and we'll talk in a minute about where there'll be others—hydroxyurea (Hydrea) and other medicines that people take for some of these conditions, but she was talking about hedgehog inhibitor.

So I just want to ask a question—are there medicines that are developing for other cancers that may apply here because you're learning of some commonality or some other pathway—things like that?

Dr. Mascarenhas:
Yeah, so the repurposing of therapies or agents that have shown success—or may not even have shown success—in other malignancies or even non-malignant conditions, in some cases, can sometimes be utilized in MPNs. And there's actually, if you sit back and look at all the abstracts that are being presented at ASH this year or last year—even in the last five years—you'll notice there's a lot of promiscuity.

There's a lot of agents that are being used in lots of different fields. And I'll give you one prime example, because it's something that I've been interested in for the last 5+ years, which is *p*anobinostat (Farydak), which is a histone deacetylase inhibitor which, when we first started working on it, didn't have a name—it was just called LBH589.

And it basically is an agent that inhibits or affects the protein scaffolding in which DNA is wrapped around and enables cells to produce or to transcript genes that would normally be silenced. So this was what's called an epigenetic-type therapy that was being looked at in a lot of different hemotologic malignancies and then saw positive signal, for example, in multiple myeloma. And, now, today, there's a drug, *p*anobinostat, approved for myeloma. It's still struggling in

myelofibrosis and other diseases—but I think it has activity—but it's an example of where there is the ability for multiple agents in multiple different related hematologic malignancies to have a promising effect.

Andrew Schorr:
Okay. And then let's get to the nitty gritty of where we are now. So we have ruxolitinib that's been approved for a few years now. I've been on it. It doesn't work for everybody. We have other JAK inhibitors that have been in trials. Is there any news about that?

Will we have others? And then we'll continue our discussion about other kinds of drugs, but let's just talk about JAK for a minute.

Dr. Mascarenhas:
Sure. So I think the abstract that many of us are waiting and interested to be presented will be a late-breaking abstract on Tuesday morning which will be the result from the PERSIST 2 Study with pacritinib—one of the other JAK inhibitors. And this is a drug that has gone through a couple twists and turns but, amongst the notable features are that this drug seems to cause less effect on the platelet count and so, perhaps, would have a specific role for many are aware, the drug has been on hold by the FDA due to safety concerns but the results that will be presented on Tuesday are updated results from the PERSIST 2 Study so we'll see what they have to say in terms of both safety and efficacy.

In the best-case scenario, if this drug were to be shown to be efficacious and safe, then, ultimately, again, it could have a potential role—particularly for those patients that have low platelet counts.

Andrew Schorr:
Okay. And momelotinib is another one and there was some data I saw, if I understood it right, that said it has effectiveness but didn't seem to be as exciting as they thought.

Dr. Mascarenhas:
Yes, so momelotinib, again, another JAK inhibitor. Perhaps one distinction with that – and compared to ruxolitinib pacritinib is that, in the early phase study, there was a significant proportion of patients who had improvement in anemia. And that is, of course, a major issue in patients with myelofibrosis and something that does not typically improve on treatment with ruxolitinib. And, as you alluded to, just before this meeting, there were topline results released from two Phase III studies with momelotinib and myelofibrosis.

And, if I recall correctly and to simplify, one study which was randomizing patients to receive either momelotinib or ruxolitinib, they conducted what's called a "noninferiority analysis" basically saying, "Is this drug not inferior?" and that was found to be true in terms of spleen response. However, they did not meet the secondary endpoint of symptom response. It's a mixed bag there.

The other part, I think, that's unsatisfying at this point is we don't have detailed information about anemia response in that study because of the way that, I think, the statistical analysis was designed—they did not conduct that. There happens to be a separate study that's ongoing that we are participating on which is focused specifically on this anemia question. So it's enrolling patients who have transfusion-dependent anemia and all of those patients will be treated with momelotinib.

So that's a smaller study but, hopefully, we'll gain some clarity as to the potential benefit of momelotinib for anemia.

Andrew Schorr:
So, Catriona, we hear this drumbeat of pipeline drugs—not yet approved—and we want these drugs to come to market so they're available to us or, maybe before that, available in a trial with the hope that it will improve things. So, when there are FDA holds and you're talking about noninferiority, it's not really exciting. Maybe you could put this in perspective because it dampens the enthusiasm, if you will.

Dr. Jamieson:
Well, it certainly does for us, as well. We've all been in this field for a little while, so it's not a great ASH for us, because it's a wake-up call. Maybe monotherapy is really not sufficient. In a disease like myelofibrosis, it's fairly complex—either because

the drugs that we give as single-agents long term can have long-term side effects or just not sufficiently effective over the long term to eradicate the malignant clone or clones plural.

So I think that what we're looking at is some drugs that have very specific effects—whether it's momelotinib actually not inducing as much anemia or NS018 which is made by NS Pharma—very selective JAK-2 inhibitor, not quite as potent but doesn't cause the low platelet counts—pacritinib, same thing, JAK2617F inhibitor—very good as a drug, doesn't cause low platelet count but maybe bleeding in some patients so, maybe, if we lower the dose—imetelstat's another one, a telomerase inhibitor.

We may be able to get away with combination strategies so that we'll be able to have what I like to think of as the future of care, which is a treatment-free remission. Now, that's a very ambitious strategy, but we've done that with chronic myeloid leukemia where, now, that's part of the lexicon, "Of course, you come off therapy." Who would even have thought that that would be the case? But the way to do that is to determine, in individual groups of patients—and I don't mean in individual patients but groups of patients—what have they activated in terms of other pathways?

Will they be able to respond to an epigenetic modifier as you were alluding to, or do we have to come in with these other, more interesting agents that we have to develop with one of them being a splicing modulator? So there's a lot of great science going on, and this is happening because the MPN support groups that are so strong. So we saw this with HIV—completely changed everything. So my husband works on HIV—has done research in that area for a long time—now, he has to work on preemptive treatment of HIV. Those are called the prep studies. So I think what we're doing with MPNs is we're dialing back the clock and saying, "When is the earliest time we should direct and treat these disorders? When can we redirect them safely to not allow this abnormal scarring in the bone marrow?"

So that's really the issue that we've been talking about in our NCCN panel meetings—"How soon is too early to start treatment?" And that's when clinic visits become quite long. "I have the JAK2 mutation, I have the TET2 mutation, I have scarring, but I don't have a big spleen, and I don't have symptoms." So those are great discussions to have, because we'll understand how to move forward in terms of tailoring therapy.

Andrew Schorr:
Okay. So, Stephen, we've talked about the analysis and I think you're all doing it now and you're all in your labs, looking further which gives us a lot of hope. But you're detectives, but you don't know all the answers yet, so let's go back to the medicines we have.

So we talked about the medicines even in development for the JAK. Now, she mentioned telomerase—where does that come in?

Dr. Oh:
Yeah, imetelstat's a telomerase inhibitor. There was a lot of excitement a couple of years ago with the initial results reported from Mayo Clinic from their relatively small study and actually seeing some patients with myelofibrosis have a complete remission on treatment, which is almost unheard of for anything other than stem cell transplant for this disease. So, as we need to do, we followed it up with a larger study, and that study is now ongoing at multiple sites.

But also, have received some disappointing news recently about that study in which there have been two dose levels, and, on the initial analysis, the lower dose level did not appear to have any efficacy, and so that arm has been closed. The higher dose level, I guess the best way to say this is there is, perhaps, some hint of activity, but it requires longer follow-up and further analysis.

So that study is currently suspended in terms of further enrollments until there is more follow-up and more analysis.

Andrew Schorr:
Okay. And there's also been study of a drug—I know at least one—to try to reduce the scarring.

Dr. Oh:
Yes.

Andrew Schorr:
Where does that stand?

Dr. Oh:
So PRM-151 is, I think, the drug you're talking about and that's, I think, very promising. I don't think there's any results being presented at this year's ASH but there have been earlier results presented in years past and it does appear that some patients have had improvement in their fibrosis treatment with this medication. And it's being looked at in combination with ruxolitinib, as well. So I think there's certainly optimism with that. In comparison, I participated in a study with a different anti-fibrotic agent, simtuzumab, a LOXL2 monoclonal antibody, and that study was negative. So this one, PRM-151, is looking promising. We'll need to see what the next update shows.