Experts Explain MDM2 Inhibition and Clinical Trial for MPN Patients

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Andrew Schorr:
Hello and welcome to Patient Power. I'm Andrew Schorr. Joining me once again is a leading expert in the MPNs. Today we're talking about a new trial for people with myelofibrosis. Dr. Srdan Verstovsek joins us from MD Anderson.

Dr. Verstovsek, welcome back to Patient Power.

Dr. Verstovsek:
Pleasure to join you again. Thank you for having me on the program.

Andrew Schorr:
Dr. Verstovsek, so many of us with myelofibrosis, like me, have become familiar with the JAK2, maybe V617F gene and know that that could be active for us, and some of us have been taking a drug called ruxolitinib or Jakafi. But I understand now you're looking into in a clinical trial something else called MDM2. What is MDM2?

Dr. Verstovsek:
So MDM2 is a protein that binds in the cells, in any cell, to another protein called the p53. This is the very important protein in general, and particularly in cancer. This is so-called tumor suppressor and transcription factor. In other words, p53 is involved in the regulation of what the cell does and the survival of the cell.

When we have a normal situation in the human body and the cell is under stress, p53 is activated and leads to cell death. That would then mean that in a cancerous cell there is lots of stress to the cell. It's not normal. It's uncontrolled growth. There should be death to that cell because of the activation of p53. However, it doesn't happen because there are inhibitors of p53 functioning in the cancer cell.

One of those inhibitors is called MDM2. So it's an inhibitor of p53 function. It's a little bit of biology here that we are talking about that is important for the survival of the cell itself. So cancerous cells, instead of dying, they are surviving because one of the major regulators of their survival and and hat p53 protein is inhibited. And one of them is called MDM2.

And here we are talking about a clinical study where we have an opportunity to provide patients with inhibitor of MDM2 protein. So it's inhibitor of inhibitor of the p53 function allowing cells to die off. That would be the ultimate, allowing cells, cancerous cells to die off and normal cells to flourish again and become--the bone marrow to become normal in myelofibrosis patients.

Andrew Schorr:
So, Dr. Verstovsek, I understand you're a principal investigator in myelofibrosis of this study for MDM2 inhibition, a pill. The study is KR T232. So who would that be right for?

Dr. Verstovsek:
Right. You are right. So that's a pill. Company Kartos is sponsoring this study in multiple different centers in the United States and Europe, and it's a pill that is taken for seven days out of a 21-day or 28-day cycle. We have three schedules. Patients will be randomized between the three schedules to find the best way to deliver the medication in possible active and safe way in a second-line setting.

In terms of the patient eligibility, it is therefore because it's a second-line setting, focus on the patients with prior exposure to JAK inhibitors, that is ruxolitinib. Ruxolitinib is the only JAK2 inhibitor approved so far, and it's usually frontline, first-line therapy for patients with myelofibrosis that have the symptoms or a big spleen that is symptomatic.

So if you are failing that therapy or you failed the JAK therapy that is ruxolitinib, then you would be eligible for a study with an MDM2 inhibitor. The standard eligibility criteria would be that there is a presence of symptomatic splenomegaly, systemic symptoms, and that of course you have a good organ function meaning the liver and kidney and other organs in the body functioning very well.

Andrew Schorr:
Okay. So if someone is no longer benefitting from ruxolitinib, a JAK inhibitor, and they are otherwise doing pretty well but they have that enlarged spleen, other things you discussed, then that would be something to discuss with their doctor and consider whether this trial is right for them. Is that correct?

Dr. Verstovsek:
Absolutely. We are pretty excited about this new way of looking at it because we know that the resistance to JAK-STAT pathway leads to other activation of other biological markers in the cancer cells, so this is one of the novel ways of attacking the problem in patients who are failing or progressing after the JAK inhibition.

Andrew Schorr:
And lastly, Dr. Verstovsek, what side effects would you be watching for—well, I guess, what benefit would you be looking for and what side effects would you be watching for in this study?

Dr. Verstovsek:
It is always a balance between the two. You are right. So the benefit. The patients' needs to have a spleen, the symptomatic splenomegaly, and the symptoms to participate. So you would look obviously therefore on improvements in the spleen, elimination of the symptoms and the activity on the bone marrow itself, decrease in fibrosis, improvement in the function of the bone marrow with increasing anemia or increase in the regulators eliminating anemia, perhaps improvements in the platelets, improvement in the body composition, and if we are really successful then you would talk about partial response and complete response.

Partial response is normalization of everything except there are some fibers still in the bone marrow, and complete response means complete elimination of the disease. For now, the hope is clinical improvement in the spleen and symptoms of anemia and platelets, so there would be improvement in a quality of life and perhaps longevity of the patients in the second-line setting.

The toxicity, we are seeing some of them. We are seeing already in the (?) inaudible is acute myelo-leukemia and solid tumors and there are two types that we will watch closely in the myelofibrosis study. One is some nausea or diarrhea can happen. I would call them a GI-related side effect. Remember the study calls for us to give a drug for seven days, not

continuously, seven days out of a 21-day cycle or seven days out of a 28-day cycle, so we want deliver this in a safe way without too much of the GI upset. And it can also lower the platelets in some patients, so we will be watching the blood cell counts and the GI tract and adjust those as necessary.

Andrew Schorr:
So there you have it about myelofibrosis, but what about for people with polycythemia vera? Well, here's an explanation of a trial there with a leading expert investigator. Thanks for being with us, Dr. Gotlib.

Dr. Gotlib:
Andy, thanks very much for having me. I very much appreciate your time.

Andrew Schorr:
So tell me, tell us about this trial in polycythemia vera. What are you trying to understand, and who is it right for?

Dr. Gotlib:
So let me give a little bit of background of why we're looking at this agent KR T232. This is a drug which is referred as an MDM2 inhibitor, and I think it's worth giving a little bit of background about what MDM2 is.

In cells there is a master regulator called p53, and it's important for controlling cell death. And in cells in PV they grow too much, and p53 in many cancer cells and in normal cells is responsible for the cells undergoing appropriate cell death. But in certain types of cancers and in PV the cells don't undergo cell death, and that's why it increased cell numbers.

So p53 is blocked from doing its job by a protein called MDM2, and this drug KR T232 is actually blocking MDM2 from blocking PV, so it's basically blocking the blocker of p53, which allows cells to undergo cell death, and that's what you want in cancers and in patients with PV, where they're making too many cells, particularly red blood cells. So it's a very interesting, different novel mechanism of action.

It should be noted that this is an agent that works only in patients that have normal or so-called wild-type p53, which is good in the case of PV because 95 percent of patients have normal p53 and not the mutated form.

Andrew Schorr:
Who could this trial be right for?

Dr. Gotlib:
So what we're looking to do is compare KR T232 to ruxolitinib (Jakafi) to see if we can reduce phlebotomy needs and also decrease spleen size, and this is in patients who have hydroxy resistance or intolerance.

And why this patient population? Well, we know that patients with hydroxy resistance or intolerance have about a six-fold increased risk of death and a seven-fold increased risk of transformation to myelofibrosis, myelodysplastic syndrome or acute myeloid leukemia. So this is a patient population we need to do better with, and that is why we're looking at KR T232 in this Hydrea-resistant or intolerant PV population.

Andrew Schorr:
So, Dr. Gotlib, for our patients who are watching their PV, what should they ask their doctor? What situation might they be in where they should say is there a trial, this trial perhaps, that could be right for me?

Dr. Gotlib:
So this trial would be appropriate for patients who have PV that are on Hydrea and are showing themselves to be Hydrea resistant or intolerant. Let me give you a little bit of flavor what that means. So Hydrea resistance, for example, would mean someone who has been on Hydrea for at least 12 weeks who is at least on 2 grams per day or lower than 2 grams per day but are not achieving the goals of being phlebotomy free or have an elevated white blood cell count or platelet count, so that would be some examples of Hydrea resistance.

Hydrea intolerance, for example, would be patients that are having, for example, oral ulcers or skin ulcers or GI intolerance or have low blood counts and are not able to necessarily achieve their phlebotomy goals with their doses, for example, 2

grams per day or lower than 2 grams per day. So that would be a Hydrea resistant or intolerant population that would be well suited for this trial.

Andrew Schorr:
So what concerns would you have? Would there be any side effects that you would be watching for in people who are in this trial?

Dr. Gotlib:
So, Andrew, we know from some initial studies where this drug has been used, for example, in patients with multiple myeloma, or acute myeloid leukemia or patients with advanced solid tumors or melanoma, at some of the higher doses that have been used we have seen some GI intolerance such as nausea, vomiting or diarrhea. There has been some lowering of the platelet count and the white blood cell count or neutrophil count and some fatigue.

Now, having said that, we're exploring in part A of this trial three different dose regimens of KR T232. For example, one arm is 120 milligrams given for seven days every 21-day cycles, a second dose at 240 milligrams given for seven days on 21-day cycles, and then a third arm with 120 milligrams given on 28-day cycles. So we're seeing which of these doses, which of these arms is the most well tolerated with regard to those issues of tolerance that I noted earlier and the most efficacious and well tolerated arm, and we'll be looking at both safety, tolerability and efficacy, will be moved into part B of the trial where we pick a dose of KR T232 and then look at it versus ruxolitinib. And patients will be randomized to either KR T232 or ruxolitinib, and that will be the basis of part B of this large trial. So it will be randomized. There will be no placebo.

Andrew Schorr:
And, Dr. Gotlib, as far as patients' access in this trial, so obviously at Stanford, you're one of the centers, so there'll be trial sites proliferating where patients might be able to have this treatment?

Dr. Gotlib:
So that's correct, Andrew. So in part A, which is the three-dose arms, I believe there will be about 50 sites, and in part there will be about 70 sites. In part A we're looking to accrue about 75 patients, 25 patients per each of those three dosing arms or 75, and then in part B it will be 110 patients for the KR T232 arm and 110 patients in the ruxolitinib arm. So altogether there are 220 plus 75 or 295 patients that we plan to accrue at 50 to 70 sites.

Andrew Schorr:
Okay. Well, I think a good opportunity for patients, MPN patients specifically with PV to look into this. And thank you for your dedication to progress, Dr. Jason Gotlib from Stanford.

So start thinking about this. MDM2 inhibition, can it be really what's the next wave of therapy for those of us dealing with an MPN, whether it's myelofibrosis, polycythemia. And please consider finding out about a trial to see if it's right for you. And we have a map that makes it very convenient for you to see where the trial sites are and how you can get involved. Please consider clinical trial. It can help all of us move science forward for the benefit of the community and for us as well.

I'm Andrew Schorr with Patient Power. Remember, knowledge can be the best medicine of all.