# The Role of Histone Deacetylase Inhibitors in MPN Treatment

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**Dr. Verstovsek:**
The other interesting and exciting result presented in a poster session here with the highlights was a combination of the JAK inhibitor with the panobinostat, which is the histone deacetylase inhibitor. What is the panobinostat, and why would they still work together?

**Dr. Odenike:**
Right, so panobinostat, as you mentioned, is a histone deacetylase inhibitor, and histone deacetylases, we know, help to stabilize the JAK protein.

By inhibiting a histone deacetylase, one can actually effectively cause acetylation of a protein called HSP90, and that targets the JAK protein for degradation by the, this pathway called the proteasome pathway.

Anyway, that is one of the potential mechanisms by which, maybe, these drugs may work in this class of diseases, but the important thing is also that in mouse models, when this, when ruxolitinib, or Jakafi is combined with panobinostat, this combination seems to be synergistic in, you know, fighting of tumors in mice.

So it makes sense, then, to try to see that approach would work in humans and to make sure that this, two drugs could be safely combined.

What the results show is that this combination is feasible. There is some effect of, or the suppression of the bone marrow and the blood counts, but in general they were able to arrive at a dose that seemed safe enough to move forward into subsequent trials. The remarkable thing, also, is that there was significant shrinkage in, you know, more than two-thirds of patients, you know, exposed to this…

**Dr. Verstovsek:**
In the spleen.

**Dr. Odenike:**
…in the spleens, significant spleen shrinkage, so again, this is a combination to watch. I think, ultimately, if this moves forward, it would be nice to see, to have a study where we would randomize patients to the combination versus the single

agent, ruxolitinib or Jakafi to see whether, in fact, the combination in a randomized trial produces a superior efficacy in our patients with myelofibrosis.

**Dr. Levine:**
To me, there's two, I think, fundamental challenges that we don't have an answer to yet. The first, which you already heard about from Olatoyosi, is that I think there are a number of putative mechanisms about how we think this drug works in different contexts. We tried in T-cell lymphoma and myeloma and many other diseases, and I actually think we understand less than we want to about how these drugs work.

And that does lead to challenges. I's just a reality. Sometimes there are drugs that work, and we don't really understand the why or sometimes, drugs work through a multitude of different things. It's not simply they do one thing, and that's all they do. That's okay. But I think that's the first challenge. The other challenge, specifically to this drug, that I always, I'm watching in the studies, is that this drug, in earlier studies, particularly in higher doses, lowered platelet counts.

And I think the biggest question's going to be can you get enough efficacy at a dose that doesn't lead to significant reduction of platelet counts? And I think we just need more time, more patients, more data, and I think one of the questions will be, because this won't be the first, last combination tried, I bet, by the hematology meeting if we sat at this table in six months, there would be five combination studies presented.

So the question will be not only efficacy, but which of these is easiest to give? Which of these is safest? Are there ones that are two oral drugs? And I think it's exciting, as you suggested, Srdan, we have to get it in combination space. We need to get off the sidelines and do it. It's happening in breast cancer. It's happening in lung cancer, so why should our patients be any different?

But I think we need to be a bit of a careful consumer, and I tell my patients, you should carefully look at all this data and not jump on the bandwagon of one combination. This one looks great. But there could be three others that look just as great or may be a little bit easier to give, and we'll find out. And so I think we need to sort of see what the next six to 12 months bring.