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Managing Myeloma **recently talked with Dr. Jatin J. Shah of the University of Texas MD Anderson Cancer Center about panobinostat, and when this agent should be used.**

The question of when panobinostat should be used is a very important one in clinical practice. In 2015, four new drugs were approved in managing relapsed myeloma, including panobinostat, ixazomib (an oral proteasome inhibitor), and two different monoclonal antibodies. With the advent of these new drugs, it is important to understand how to sequence and how to use these drugs appropriately. Importantly, as we look at our options in relapsed/refractory myeloma, there are several options including IMiD-based therapy, proteasome inhibitor-based therapy, alkylating-based therapy, elotuzumab in combination with lenalidomide plus dexamethasone in early one to three lines of therapy, and daratumumab in later lines of therapy in patients who have refractory disease both to IMiDs and proteasome inhibitors.

Panobinostat also has been approved now in the relapsed/refractory setting, and it is clearly a very important option for our patients. Panobinostat was approved in combination with bortezomib and dexamethasone based on a phase 3 trial. There is strong phase 3 data, when we look at bortezomib and dexamethasone in combination with panobinostat, suggesting significant improvement in the depth of response. First, we know that there is improvement in the CR rate from 15% to 27% in patients with relapsed myeloma. This is clearly statistically, as well as clinically, significant improvement, and we know that depth of response matters in patients and improves both overall survival and duration of response. Secondly, the addition of panobinostat improved progression-free survival by approximately 7 months in patients who had both the prior IMiD as well as bortezomib. So, clearly there is a role for panobinostat in patients with refractory myeloma used in combination with bortezomib, and also a significant improvement in response rates.

When using panobinostat, it is important to keep in mind some of the agent's side effects; in this case, the data presented used panobinostat in combination with IV bortezomib. In clinical practice, many of us use subcutaneous bortezomib, and the data presented for panobinostat in combination with subcutaneous bortezomib is significantly better, with an improved side effect profile. There is also data with panobinostat in combination with carfilzomib which shows a very limited GI toxicity, and suggests that this is a very well-tolerated combination. Panobinostat has also been used in a phase 2 study in combination with lenalidomide, in lenalidomide-refractory patients, showing a 50% response rate, again with a very different side effect profile with limited GI toxicity.

Importantly, panobinostat can also overcome bortezomib resistance. In the PANORAMA study, there is an approximately 40% response rate in bortezomib-refractory patients with a combination of bortezomib and panobinostat. So, there is clearly utility for the use of panobinostat, as demonstrated by one phase 3 study in combination with bortezomib, and in phase 2 studies in combination with

lenalidomide and carfilzomib. The dose can be modulated from 20 mg down to 10 mg as necessary, and with appropriate side effect management, it can be a very well-tolerated and very active regimen. In a subset of patients, it can clearly be an important combination. Therefore, I think panobinostat is an important option in patients with relapsed/refractory myeloma, when used in combination with appropriate side effect management and dose reduction, as necessary.

Thank you for your attention.