**ASCO Highlights from Robert Z. Orlowski, MD, PhD**

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Thanks for joining me. My name is Bob Orlowski, I am the Director of the Myeloma Section at the University of Texas MD Anderson Cancer Center in Houston, Texas, and also the interim chair for the Department of Lymphoma/Myeloma. I am coming to you today from the 2018 ASCO Annual Meeting here in Chicago, Illinois. Usually ASCO is full of solid tumor abstracts, but there are a number of important myeloma studies that are being presented; and one of them is an update on the so-called ENDEAVOR study. This was a trial for patients with relapsed or refractory multiple myeloma where almost 1000 patients were randomized either to get bortezomib and dexamethasone, or carfilzomib with dexamethasone. The carfilzomib regimen here was the higher-dose combination, which means 20 mg/m$^2$ IV on days 1 and 2 of cycle 1; and then 56 mg/m$^2$ on days 8, 9, 15 and 16 of cycle 1; and then all of those days of later cycles. The characteristics of the patients on the two arms were really well-balanced, and what was reported was an update on the overall survival. The difference in overall survival between the two arms was a nine-month improvement for the group that got the high-dose carfilzomib with dexamethasone. It went from 38.7 months on bortezomib-dexamethasone to 47.7 months for carfilzomib and dexamethasone. This was also true for all of the relevant subgroups including patients with one prior therapy, two or more prior therapies, older patients, younger patients, and those with either standard-risk or high-risk multiple myeloma. These data, I think, are really exciting because we have many combinations that have been shown to improve progression-free survival, but not all of them have improved overall survival which, of course, is our ultimate endpoint. Now you can have much greater confidence to use carfilzomib and dexamethasone at the higher-dose regimen given that it improves survival with a good safety profile.

One that I wanted to tell you about is the so-called IKEMA trial which is for patients that have relapsed or refractory myeloma, and they will be randomized to receive either high-dose carfilzomib with dexamethasone as the control arm, or high-dose carfilzomib with dexamethasone plus isatuximab, which is an anti-CD38 monoclonal antibody. The rationale for this study, of course, is that CD38 antibodies really combine well with a variety of different agents including immunomodulatory drugs and proteasome inhibitors. Also, we know that carfilzomib with dexamethasone (with a high-dose carfilzomib) has recently been shown to be superior to bortezomib and dexamethasone compared to patients with relapsed and refractory disease, with a better overall survival. The other benefit, particularly in the U.S., is that patients after transplant often are on lenalidomide-based maintenance; and when they progress on lenalidomide, you probably should not put them on, for example, lenalidomide and daratumumab because the approval of that was based on a study which excluded patients with lenalidomide-refractory disease. Therefore, it makes senses to go ahead and use a proteasome inhibitor-based combo, and something like carfilzomib-dexamethasone with isatuximab would be an ideal candidate. So please look to enroll patients to the study, and I think we are very optimistic about its success.

Another trial to mention is the so-called IMROZ study, and this is another isatuximab-containing trial but is for newly diagnosed patients who are not eligible for stem cell transplant. One of the standards of care in this area is the so-called VRd lite or bortezomib with lenalidomide and dexamethasone; and based on the SWOG S0777 study, VRd is a great induction both for transplant-eligible and for transplant-ineligible patients. CD38 antibodies like daratumumab really add to the benefit of induction therapy. We know that because of the ALCYONE study which was recently published in the *New England Journal of Medicine* which looked at bortezomib, melphalan, and prednisone, plus or minus daratumumab, and the daratumumab-containing arm did substantially better; but VMP is not a regimen that we commonly use in the U.S. whereas VRd is. This trial looking at VRd plus/minus isatuximab, it is actually enrolling quite quickly, and we would encourage you that if you have patients to get involved and enroll them on this study because we really feel that adding an anti-CD38 like isatuximab to VRd will really improve not only progression-free but also overall survival for transplant-ineligible patients who so far have not benefited as much from some of our novel agents.

Thanks very much for tuning in and hopefully the next time I'm speaking to you, we'll have data from some of these studies to present. Best of luck with your myeloma patients.

**Abstracts:**

Orlowski R, Moreau P, Ludwig H, et al. Carfilzomib and dexamethasone (Kd56) vs bortezomib and dexamethasone (Vd) in relapsed or refractory multiple myeloma (RRMM): Updated overall survival (OS), safety, and subgroup analysis of ENDEAVOR. ASCO 2018. Abstract 8032. *https://meetinglibrary.asco.org/record/160712/abstract*

Martin T, Dimopoulos M, Yong K, et al. Phase III (IKEMA) study design: Isatuximab plus carfilzomib and dexamethasone (Kd) vs Kd in patients with relapsed/refractory multiple myeloma (RRMM). ASCO 2018. Abstract TPS8060. *https://meetinglibrary.asco.org/record/165519/abstract*

Orlowski R, Goldschmidt H, Cavo M, et al. Phase III (IMROZ) study design: Isatuximab plus bortezomib (V), lenalidomide (R), and dexamethasone (d) vs VRd in transplant-ineligible patients (pts) with newly diagnosed multiple myeloma (NDMM). ASCO 2018. Abstract TPS8055. *https://meetinglibrary.asco.org/record/165518/abstract*