Sagar Lonial, MD, FACP
Chair and Professor
Department of Hematology and Medical Oncology
Chief Medical Officer
Winship Cancer Institute
Emory University School of Medicine
Atlanta, Georgia

Thierry Facon, MD
Professor of Hematology
University of Lille, France
Lille, France

Dr. Sagar Lonial: Hello and welcome to *Managing Myeloma*. My name is Sagar Lonial and I am a Professor at the Winship Cancer Institute at Emory University in Atlanta, Georgia. Today, I am talking to Dr. Thierry Facon, who is a Professor of Hematology at Lille University Hospital in Lille, France. We are very happy to have him here to talk about his session at the ESH 3rd International Conference on Multiple Myeloma, titled Treatment of Relapsed Patients. Professor Facon, thank you for joining us today.

Dr. Thierry Facon: Thank you.

Dr. Sagar Lonial: So, you chaired a session that really talked a lot about the individual parts of how we approach relapsed treatments. Can we go through a couple of the highlights from some of those lectures, starting off with the lecture on the IMiD class of drugs?

Dr. Thierry Facon: Yes, we had a nice session dedicated to relapsed/refractory myeloma. The first part was dedicated to IMiDs, and so we presented studies, especially on pomalidomide for relapsed/refractory myeloma patients, and, most importantly, pomalidomide-based regimens. Not only pomalidomide in combination with dexamethasone, but some other new regimens such as the combination of pomalidomide and bortezomib, pomalidomide combined also with cyclophosphamide and dexamethasone, so that was an important part. Then, we had the presentation on proteasome inhibitors, which is a long story. As you know, bortezomib was approved many years ago in 2004, but recently, we got new PIs; we got carfilzomib, we got ixazomib recently in 2015 in the US, and very recently in Europe as well. We also cite some words on potential new PIs such as oprozomib, and in the same way, these PIs have been combined with IMiDs, and these regimens are very effective, especially for the high-risk patients. Then, we had one part dedicated to antibodies, and so we got the results of some important studies with elotuzumab and daratumumab and isatuximab as well. Finally, Philippe Moreau did a very nice summary, all of these studies on each slide, to say some words on sequencing. This is, as you can expect, a very challenging part, with sequencing being very likely different across different countries, so he did very well and he had the most difficult part I would say, but he did very well.

Dr. Sagar Lonial: So, let me ask, just to bring you back a little bit to some of the discussions that were had during the session. A drug that we have all had some experience with now for a number of years is carfilzomib. How is that being utilized in your practice now in terms of the dose that is used, as well as the schedule that is used? Because that is a big question I know in the US.

Dr. Thierry Facon: No, that's definitely a big question for us as well. So, at the present time, I do believe that the majority of European physicians, they use carfilzomib in combination with

lenalidomide and dexamethasone, which was established in the context of the ASPIRE study. So, as you know, the dose is 27, so it is not too challenging, and I do believe this regimen is quite well accepted. The most challenging part is likely carfilzomib is at 56 or that could be also at higher doses given weekly, so that is a significant discussion because as you know, we have got a cardiac safety signaling from patients, and as far as I know, some of my colleagues are still a little bit reluctant to use a high dose of carfilzomib, and some of them have some concern with the cardiac safety, especially for the frail patients. Otherwise, I would say the carfilzomib with lenalidomide and dexamethasone is well-accepted, and we have to say that carfilzomib is a very active drug in myeloma.

Dr. Sagar Lonial: Yeah, I completely agree, and I think there is no question that it is an active drug; in that, at a higher dose, it is probably more potent than bortezomib. I think the question that we all struggle a little bit with is if it is going to go to weekly, what is the weekly dose and if it is going to go twice weekly as a partner with other drugs, what is the dose in that situation as well? And I think that is something we are all struggling a little bit with.

Dr. Thierry Facon: No, no, I agree with you. So, looking at the weekly dosing that could be 70 weekly,* but in my opinion, it is still not so well-defined. At least, in terms of treatment, it is not approved, and so, I do believe that at the present time, we basically stick with a carfilzomib-lenalidomide-dexamethasone regimen which is not too much in terms of dosing and which seems to be very effective and safe.
*This dosing of carfilzomib is not FDA-approved in the United States.

Dr. Sagar Lonial: So, let's talk a little bit about the antibodies which I think, given some of the data we have seen in the last few months, is really, really very exciting. How are those getting used in daily practice in France for instance or in Europe in general, given the data we saw from CASTOR and POLLUX and other trials?

Dr. Thierry Facon: These studies are extremely impressive. In my opinion, the lenalidomide and daratumumab study is very, very impressive, and if you look at the POLLUX study, if you try to speculate on what could be the median PFS for these patients. So, some people will tell you that will be 36 months. Some people will tell you that will be up to 40, something like that, but we have to keep in mind that these patients are relapsed/refractory myeloma patients, so that is extremely promising, and then you try to speculate on what will be the situation for the newly diagnosed patients using lenalidomide, dexamethasone, and daratumumab.* So, in my opinion, the bortezomib is a little bit less impressive, but it will be definitely useful for some patients and especially these patients taking lenalidomide and dexamethasone continuously, for example, they may receive daratumumab in combination with bortezomib and dexamethasone at the time of relapse. My perception is that these regimens will be clearly game changers, and we will see as soon as these regimens will be formally approved and reimbursed, I think we will see the majority of myeloma patients will receive in relapse a daratumumab-based regimen, and then we will have the same regimen for the frontline, and as you know, we may get VMP in combination with daratumumab and also lenalidomide and dexamethasone in combination with daratumumab. My understanding is that for the US doctors the lenalidomide, dexamethasone, and daratumumab will be a key regimen, and for us, in my country in France, I think lenalidomide, dexamethasone, and daratumumab will also be a very key regimen for newly diagnosed elderly myeloma patients, and also because the daratumumab will be subcutaneous

daratumumab in a few years, so that will be very effective. I do believe it is safe and that will be also more convenient for patients.
*This regimen (lenalidomide, dexamethasone, daratumumab) is not FDA-approved in the United States.

Dr. Sagar Lonial: Yeah, I think you hit a couple of really important points and that is having an antibody really does change the entire potential treatment landscape. In the US where many patients have received lenalidomide maintenance after transplant, the question about the applicability of POLLUX to this patient population does come a little bit into question. What I think we are very fortunate to have is data not from a phase 3 trial but from a phase 2 trial that combined pomalidomide with daratumumab and dexamethasone and showed an equally impressive high response rate in that relapsed and refractory patient population that appears to be very active among high-risk patients as well. We at our center put several patients on that trial, three or four of which were 17p deleted that had progressed very quickly after the IFM trial. They were on the original IFM/DFCI trial and have been in remission longer on pomalidomide, daratumumab, and dexamethasone,* and they were with their RVD induction and transplant and maintenance for that protocol. So, I think even for patients that have progressed on lenalidomide there is an IMiD combination that can be very potent for them.
*This regimen (pomalidomide, daratumumab, dexamethasone) is not FDA-approved in the United States.

Dr. Thierry Facon: I fully agree with you. In fact, everything with daratumumab is impressive, and the pomalidomide combination regimen is impressive as well, and we may expect that this is basically for relapsed/refractory myeloma patients, but in the frontline setting I think we all agree that we will see four-drug regimens including a PI, an IMiD, and a CD38 antibody, so we may see patients on VRD, daratumumab, or even carfilzomib, RD, daratumumab, both for induction and consolidation before and after stem cell transplantation and when we would have to manage the maintenance part, so that is the very often question that as you say the combination of some lenalidomide on some daratumumab for maintenance will be likely extremely effective as well.

Dr. Sagar Lonial: Yes, I agree, and I think for the wallet hawks in the room, when people talk about four-drug induction or two- or three-drug maintenance, to me the benefit of doing one or both of those is that patients do not have to stay on maintenance indefinitely. The goal would be to figure out whether you can get patients to MRD negativity with this approach and potentially stop therapy and see whether you have cured a bigger subset of patients.

Dr. Thierry Facon: That is a very good point. I think these kinds of regimens will likely may cure at least some of these patients. Then we still have the issue of the high-risk myeloma patients. I do believe that CD38 antibodies would make a difference as well because what I say to my young people is that if you look at the POLLUX PFS curve which is so impressive, and if you say that the high-risk patient should benefit from lenalidomide, dexamethasone, and daratumumab. Otherwise, that means that some of these patients will be cured basically because the curve is so high. So, my expectation is that we will have some good news for high-risk patients as well. As you know, it remains a very, very great challenge; at least 10% to 20% of high-risk myeloma patients still have a poor clinical outcome and many colleagues have said that the antibodies are in a certain extent agnostic to cytogenetics, so I do not know exactly what it means. I would say that probably they do not care too much about the alternatives that I

think it is probably premature to say that, but I do believe they will make some difference for the high-risk patients as well.

Dr. Sagar Lonial: Yes, I think it is very, very exciting. Were there other targets that may have come up in the relapsed/refractory setting worth mentioning, perhaps PD1 or venetoclax or selinexor or other new targets or new drugs that might be worth just a moment or two of mention?

Dr. Thierry Facon: Okay. That was briefly mentioned and I believe that that will likely be part of the next American Society of Hematology meeting, but that is also good news. For example, venetoclax* has shown some activity. We got also some good study results with selinexor,**and then we have the PD1 story. In my opinion, the PD1 story is still an ongoing story. It is not totally clear, so we got very impressive results in a very limited number of patients that, for example, at ASH last year, Dr. San Miguel presented a couple of patients who did very well on lenalidomide in combination with pembrolizumab.† As you know, the phase 3 studies are ongoing with both pomalidomide and lenalidomide, pomalidomide in the relapsed/refractory setting and lenalidomide in the frontline. We will see. I think we need to wait, but the good news is that for some drugs, that is not so impressive as antibodies for sure, but we can find some good patients for venetoclax and selinexor, for example, as these drugs will play a role in myeloma in the next few years as well.

*Venetoclax is not FDA-approved for this use in the United States.

**Selinexor is under investigation and not FDA-approved.

†This regimen (lenalidomide in combination with pembrolizumab) is not FDA-approved in the United States.

Dr. Sagar Lonial: All right, well good. It sounds like an exciting session. You want any closing thoughts before we conclude this? I think it was a really important and exciting session about a lot of new targets on how to use these drugs more effectively.

Dr. Thierry Facon: Exactly.

Dr. Sagar Lonial: All right. Thank you, Professor Facon, for highlights that you provided today, and thank you all for joining us today. For additional resources, please view the other educational activities on *ManagingMyeloma.com*.