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Annual Meeting on the Management of Patients With Relapsed and/or Refractory Multiple Myeloma

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Welcome! My name is Dr Keith Stewart. I'm a hematologist at the Mayo Clinic in Arizona, and today I will be discussing with you the management of patients with relapsed and/or refractory multiple myeloma.

Faculty

I'll be joined by Professor Paul Richardson from the Dana-Faber Cancer Institute at Harvard University in Boston and Dr Sagar Lonial, Head of the Cancer Center at Emory in Atlanta.

Educational Objectives

These are the educational objectives for today's meeting, and today we will be talking about multiple myeloma.

Multiple Myeloma at a Glance

Multiple myeloma as you know is the hematologic malignancy characterized by the presence of excess plasma cells in the bone marrow. Those plasma cells secrete a monoclonal protein, often found in the blood or urine, and can be associated with organ dysfunction, classically, crab features, high calcium, renal failure, anemia, bone disease, and recurrent infection.

It is estimated that 30,770 new cases of multiple myeloma will be diagnosed in the United States in 2018. This accounts for 1.8% of all cancers and 18% of hematologic malignancies.

Treatment today continues to be divided into those patients who are younger, more fit and who are eligible for autologous stem cell transplant. Although some centers no longer have an upper age limit, generally speaking that tends to fall out around the age of 70 to 75 years.

Less aggressive systemic treatment can be offered for older and frailer patients, and it's important to remember, of course, that myeloma is a disease that becomes more common in the elderly, and thus, many of our patients do fall into this category.

In recent years, we have been blessed with the approval of multiple new drugs and novel therapies, which have improved both the quality, depth, and duration of response. Nevertheless, despite the introduction of proteasome inhibitors, immunomodulating drugs (IMiD) and recently monoclonal antibodies, many of which we will discuss today, most patients eventually continue to relapse with their disease.

Unmet Needs in RRMM

We thus have ongoing unmet needs in relapsed/refractory multiple myeloma (RRMM) that need to be addressed. Today, we do have more effective therapies that can prolong remission. Certainly remissions are becoming more common, they are lasting longer, but we still need better ways to maintain remission, prevent recurrence, and prolong the duration of response.

Increasingly, we are beginning to use more sophisticated technologies to measure multiple myeloma remission, particularly the use of minimal residual disease and improvements in minimal residual disease negativity seem to correlate with improved progression-free and overall survival, and we will discuss that to some degree today.

We also now, with the advent of many new therapies, have to be more cognizant of side effects and look for more well-tolerated therapies, particularly in our more elderly and frailer patients, because patients may have experienced multiple adverse events during prior lines of therapy.

Strategies to Address Unmet Needs in RRMM

Some of the strategies to address the unmet needs in RRMM are shown on this slide. The unmet need is that we need better therapies, even although we have good drugs today, they are still not curing most patients. We need drugs that will improve the depth of response, either alone or in combination. We have understood recently that continuing therapy for longer periods of time than we traditionally have done has been effective in improving progression-free survival. We also understand today that it is important to identify patients who are either genetically at higher or lower risk disease, so that in high-risk patients a more aggressive approach can be applied.

And finally, because we aren't curing most of our patients today, we still need to work towards the development of novel therapies with unique mechanisms of action. We will describe a couple of those emergent therapies later during this discussion.

Finally, because we are treating patients with combinations of more drugs, with deeper responses and for longer, we now need also to turn our attention to the tolerability of therapy, both by improving the way we give our current agents through dosing, frequency or mode of delivery, and we need to develop prevention or management strategies, including dose adjustment plans, careful patient selection, and again, understand better the side effects that might come with novel therapies, how to predict and how to prevent those.

Discussion Outline

So, today, this is the outline of our discussion. Following this short introduction, we will hear from Dr Richardson, who will discuss the role of proteasome inhibitors, particularly from the recent American Society of Hematology meeting, the role of carfilzomib and ixazomib. Dr Sagar Lonial will then give us an update on the use of the monoclonal antibodies targeting CD38, daratumumab and isatuximab. I will conclude the formal part of the presentation by describing some novel therapies that were presented at the ASH meeting and are looking quite promising, following which we will have some discussion and commentary from Dr Lonial, Dr Richardson, and myself. We look forward to moving into the heat of the discussion now.

Dr Paul G Richardson MD

Hello everybody, my name is Dr Paul Richardson, and I'm the Clinical Program Leader and Director of Clinical Research here at the Jerome Lipper Multiple Myeloma Center at Dana-Faber Cancer Institute in Boston. It is my privilege today to be sharing with you data presented at the ASH 2017 meeting on the role of proteasome inhibition for the treatment of RRMM.

Role of proteasome inhibitors

Now, as I am sure many of you know, proteasome inhibition has become a backbone approach to the therapeutic management of myeloma, and it has become an integral part of combination therapies. What I am seeking to do today with you is to review some of the key data presented at the ASH meeting this last December in Atlanta.

Now, in that context, I am going to be speaking about the role of carfilzomib in three specific trials, ASPIRE, ENDEAVOR, and the so-called MUK FIVE randomized Phase 2 trial. These were Abstracts 743, 1850, and 835 respectively, presented at the meeting.

Proteasome inhibitors: Mechanism of Action

Before we start, I wanted to first remind people of the mechanism of action. Essentially, what we have come to realize is that the proteasome is a fundamental intracellular structure that is responsible for the degradation of ubiquitinated proteins that are absolutely vital to cellular homeostasis and appropriate cellular function.

Obviously, in the context of myeloma, which are veritable protein factories, the accumulation of proteins in myeloma is a particularly important therapeutic strategy because, as a result of the accumulation of misfolded proteins in the cell, there is a downstream effect of endoplasmatic and reticular stress, and then that leads to an unfolded protein response, which in itself results in cell-cycle arrest and apoptosis. This particular cascade of events has become a fundamental therapeutic strategy in the treatment of myeloma. It is summarized in this slide as you can see through interactions at the beta sub-unit, which is characteristically reversible when we use boronate peptides like bortezomib and ixazomib in this setting, but importantly, in the context of the epoxy ketones, which are characterized by the first in class in this space being carfilzomib, where there is irreversible inhibition at the chymotrypsin-like site in the β-ring of the 20s subunit of the proteasome, and this has a remarkable effect as illustrated in the slide on the accumulation, as I mentioned, of the misfolded proteins with an unfolded protein response that results in cell death.

There is a specific effect on proteasome inhibition that is fundamental to the way these drugs work.

Abstract 743: Overall Survival of Patients With RRMM Treated With Carfilzomib, Lenalidomide, and Dexamethasone (KRd) Versus Lenalidomide and Dexamethasone (Rd): Final Analysis From the Randomized Phase 3 ASPIRE Trial

With that in mind, let's talk first about the ASPIRE trial, which was Abstract 743 presented at the meeting as an oral session by my colleague, Dr Keith Stewart, who was the principal investigator of this pivotal study.

What Keith showed was the final overall survival analysis in which this study compared the three-drug combination of carfilzomib, lenalidomide, and dexamethasone to lenalidomide and dexamethasone as a control arm in patients who had received one to three prior therapies and had either relapsed or refractory MM after initial treatment.

The study design was a classic phase 3. The primary endpoint included overall survival and progression-free survival, and critically carfilzomib was administered at a dose of 25 mg/m^2 intravenously in combination with lenalidomide given in the classical fashion.

ASPIRE (KRd vs Rd): Study Design

In this study—and what was presented by Keith so nicely at the ASH meeting— was the final overall survival analysis, which showed across both arms, in which were enrolled

approximately 400 patients per arm, that there was a significant difference in survival in favor of the three drugs over the four. Median overall survival measured in months was 48.3 for the three-drug combination compared with 40 for the doublet, and the hazard ratio for this was 0.794 with a P value of 0.0045, which was obviously highly statistically significant.

ASPIRE (KRd vs Rd): Final OS Analysis

In practical terms, this resulted in a 21% reduction in the risk of death compared with Rd alone and thus this approach, in addition to the PFS advantage that was so striking, now shows a survival benefit, affirming in my view that it is a standard of care now in the treatment of relapsed myeloma to use this particular three-drug platform.

ASPIRE (KRd vs Rd): Efficacy and Safety

When one then thinks about the potential for side effects from this combination – we will come to some of those in a minute—but just to be aware of the fact that the side effect profile for this combination proved to be generally very manageable, and that is really summarized in this next study when you can see that treatment discontinuation due to side effects was 19.9% for the KRd arm and 21.5% for the doublet, so very similar. In that regard, there were no meaningful differences between the two arms in terms of Grade 3 and Grade 5 events, which I think is an important key set of parameters to share.

What was also true was an additional to the median overall survival benefit, the median progression-free survival benefit was striking at 26.3 months compared with 17.6, and that generated a hazard ratio of 0.69.

What was also very interesting was that the overall response rate was 87% for the triplet compared with 67% for the doublet, but I think what particularly caught my attention from the results of Keith's presentation was complete response (CR) or better was seen in 32% of patients compared with just 10% for Rd, and indeed KRd generated (as the acronym now is commonly used) 70% very good partial response (VGPR) or better compared with just 40% for Rd. So, high qualities of response, both in terms of CR and VGPR being seen with the three-drug platform compared with the control. So, excellent results overall.

Abstract 1850: Overall Survival of Patients With RRMM Treated With Carfilzomib and Dexamethasone Versus Bortezomib and Dexamethasone According to Prior Line of Therapy and Previous Exposure to Bortezomib: Secondary Analysis of the Phase 3 ENDEAVOR Study

As we move on and think about other studies that were presented at the ASH meeting, probably one of the most important in my view for the carfilzomib-based studies that were presented, is that of the ENDEAVOR study, and this was Abstract 1850.

This particular study was presented by Dr Katja Wiesel, and what she showed in this very, I think, elegant subgroup analysis was a comparison of overall survival and safety with carfilzomib and dexamethasone versus bortezomib and dexamethasone, according to prior lines of therapy and exposure to prior bortezomib.

I think this is very important from a clinical standpoint because the original ENDEAVOR trial compared carfilzomib and dexamethasone with bortezomib and dexamethasone, and patients had to have had one to three prior therapies, and there was a one-to-one randomization. So that is ultimately 464 patients were enrolled to both carfilzomib and dexamethasone, and 465 to bortezomib and dexamethasone.

The primary endpoint for the study was overall survival.

ENDEAVOR (Kd vs Vd): Study Design

Bortezomib was given, according to the classical schedule, at 1.3 mg/m^2 intravenously or subcutaneously, and carfilzomib, interestingly, was given at a dose of 20 mg/m^2 intravenously that was then increased to 27 mg/m^2 and then ultimately to 56 mg/m^2 in the study, so this was an important point because their ultimate dosing of the carfilzomib was obviously higher than we typically use at 27 mg/m^2 or 36 mg/m^2.

ENDEAVOR (Kd vs Vd): Subgroup Analysis PFS and OS

In any event, when you look at the actual results of carfilzomib and dexamethasone compared with bortezomib/dexamethasone across a variety of different subgroups, most importantly in those who had had one prior therapy versus two to three, and those that had had prior bortezomib and those who had not, I think some interesting information emerges.

First and foremost, there was a consistent signal in favor of progression-free survival advantage to the carfilzomib index compared with bortezomib and dexamethasone. I think this was particularly striking in those patients who had received prior bortezomib, and that would be an important take-away for practice. I think at the same time, in terms of survival benefit, what was seen was also a suggestion of survival benefit in favor of those patients particularly who had received prior bortezomib receiving carfilzomib-based treatment, and similarly for those patients who had received two to three prior therapies, the median overall survival was significantly superior for carfilzomib-based treatment.

However, in those patients who received only one prior therapy, this survival difference was not yet apparent. So, in aggregate the efficacy of carfilzomib and dexamethasone, regardless of number of prior lines of therapy, was clear, but importantly, progression-free survival was much more strikingly improved by carfilzomib and dexamethasone for those patients who had had prior bortezomib.

ENDEAVOR (Kd vs Vd): Subgroup Analysis Key Adverse Events

When you look at further aspects to this, including, very importantly, the side effect profile, I think it is very important to recognize that, although there is the clear advantage for carfilzomib-based therapy of lower rates of peripheral neuropathy, there is relatively uncommon but critically higher rates of high blood pressure, cardiac failure and dyspnea for patients receiving carfilzomib and dexamethasone, and this needs to be borne in mind in the context of patient selection. Personally, in my own practice, I am very careful about patients who have hypertension as an underlying issue for that reason, and certainly with patients with any kind of significant cardiac history or pulmonary history such as prior pneumonitis or similar.

Very encouraging, though, peripheral neuropathy is obviously significantly lower with carfilzomib-based treatment, which I think is a very important aspect of its therapeutic and safety profile.

Abstract 835: Carfilzomib, Cyclophosphamide, and Dexamethasone (KCd) Versus Bortezomib, Cyclophosphamide, and Dexamethasone (VCd) for Treatment of First Relapse or Primary RRMM: First Final Analysis of the Phase 2 Muk *Five* Study

Finally, I want to talk about some very nice combination data presented by Dr Kwee Yong, the 835 abstract, which was the Phase 2 MUK Five Study. In this, Kwee presented results from a randomized phase 2 trial, comparing the efficacy of carfilzomib, cyclophosphamide and dexamethasone, which is an increasingly widely used triplet, compared with bortezomib, cyclophosphamide and dexamethasone, which has become a standard of care in a variety of settings, particularly in patients with renal failure.

Phase 2 MUK FIVE (KCd vs VCd at First Relapse): Study Design

In this study design, patients were randomized 2:1 to receive carfilzomib, cyclophosphamide and dexamethasone compared with bortezomib, cyclophosphamide and dexamethasone, for 24 weeks. The primary endpoint was to look at the quality of response.

Now, very typically, the carfilzomib-based treatment was administered at a dose of 20 mg/m^2 to start with, and then escalated to 36 mg/m^2 intravenously as part of the combination. Bortezomib was given at a dose that was standard of 1.3 mg/m^2 subcutaneously.

Now, obviously bortezomib was administered over a 21-day cycle with carfilzomib combination treatment given over 28 days.

In this setting, what was particularly interesting was to see the comparison of response rate being strongly in favor of the three-drug combination using carfilzomib, so carfilzomib, cyclophosphamide and dexamethasone showed a higher rate of very good partial response at 40.2% compared with 32% for bortezomib, cyclophosphamide and dexamethasone.

This was a non-inferiority study and so this actually achieved its desired endpoint with a hazard ratio or an OR of 1.48 with a 90% confidence interval of 4.95 to 2.31, so this noninferiority design proved fruitful in that regard.

Phase 2 MUK FIVE (KCd vs VCd at First Relapse): Results

Now, I would say that it's important to note that toxicities were more common for bortezomib, cyclophosphamide and dexamethasone, leading to discontinuation, but in that same context, what is important to also note is that with the overall response rate being superior for KCd versus VCd, there were some side effects that we should obviously be careful about. Importantly, those included the cardiac signal, which occurred in 4% of patients for the KCd arm, compared with just 1% for VCd, but otherwise, the most important difference really was in favor of KCd when neurological toxicity that was considered serious occurred in 8% of patients on VCd, whereas it just occurred in 1% or less of the patients on KCd.

Phase 2 MUK FIVE: Safety

When you look at neutropenia and thrombocytopenia, what I think was particularly interesting to me anyway, was that there were higher rates of neutropenia, thrombocytopenia and anemia for the VCd combination, and at the same time, similar rates of infection. Conversely, however, there was twice as much hypertension seen in the context of carfilzomib, cyclophosphamide, and dexamethasone. I think encouragingly, though, there was no difference in renal toxicity, which I think is an important positive to be shown, but in fairness, this study did enroll patients with satisfactory renal and normal renal function, which I think is an important practice takeaway, because what we do know is that carfilzomib needs to be used with some caution in patients with renal dysfunction.

Discussion: Protease inhibition

Moving on to other data, I want to spend a little bit of time on ixazomib, because this, I think, was a very important series of data presented at the meeting. There was a very nice abstract presented by my colleague, Meletios Dimopolous, in which I was also a co-investigator, which looked at ixazomib maintenance therapy. Basically, we showed in this particular analysis, improved depth of response and long-term outcomes in newly diagnosed

myeloma, and we also confirmed the efficacy and safety of the ixazomib/lenalidomide/dexamethasone triplet in RRMM.

What Are the Factors Influencing the Decision to Use Carfilzomib-Based Therapy

Moving on from that, I would simply say that we were able to demonstrate that the combination of ixazomib with other drugs is another platform to go forward with obviously, but also most importantly, that ixazomib maintenance was a safe and effective strategy for a significant number of patients with improvements in quality of life as well as response seen across therapies. So, encouraging data in that regard.

In aggregate, I would conclude by saying the summary of experiences with proteasome inhibition presented at the ASH meeting encompassed the highly provocative and exciting results of ASPIRE in particularly for overall survival benefit, continued impressive results from subset analysis from ENDEAVOR, and obviously I think some informative information from the randomized phase 2 study that compared carfilzomib, cyclophosphamide and dexamethasone with bortezomib, cyclophosphamide, and dexamethasone.

I would conclude by saying there were also some very important studies incorporating ixazomib as maintenance in particular that were informative, in addition to other combination approaches. I would finally say that what I found particularly exciting at the ASH meeting was to see a multitude of new drugs emerging, monoclonal antibodies targeting BCMA. There were also data, interestingly and importantly, on elotuzumab in maintenance, which could become important, particularly in combination with proteasome inhibitors. And of course, there was discussion— although no primary data presented—on the impact of HDACs in the same setting where they could be combined reasonably with a variety of other drugs, including proteasome inhibitors to improve outcome.

But in aggregate, this whole spectrum of data suggests to us that the use of proteasome inhibitors as a backbone in treatment remains an absolutely key platform for the management of myeloma.

At that point, I would like to conclude and say thank you very much for your kind attention.

Dr Stewart: Dr Richardson, thank you very much for your presentation, particularly updating us on the role of novel proteasome inhibitors that were presented at the ASH meeting in 2017. I am kind of curious to get some discussion going with you here on

the factors that influenced your decisions to use a carfilzomib-based therapy. What sort of patient selection and at what stage of their disease do you see this drug being most frequently applied?

Dr Richardson: Keith, thanks very much, it's my pleasure to join. I would say that where I use carfilzomib in my practice is in first relapse and beyond, according to the label, although outside, in the context of clinical trials obviously, we do use it in the initial treatment setting as well. In selected patients upfront, I have used carfilzomib-based treatment where I have been concerned that neurotoxicity from bortezomib as an alternative treatment approach could be a challenge.

I think particularly in patients that I feel are potentially vulnerable to neurotoxicity do I consider it, by frankly, based upon the strength of the ASPIRE information and ENDEAVOR, I'm very comfortable recommending it in first and second relapse now, given not only the remarkable activities seen but also the reassuring aspects of efficacy in terms of activity and tolerability overall for the majority of patients who receive carfilzomib-based therapy.

Dr Stewart: Do you use carfilzomib at first relapse, or are you inclined to use carfilzomib, or would you retry bortezomib if patients had previously been sensitive to that?

Dr Richardson: What governs my choice there, actually, Keith, is more issues of the possibility of improved tolerability using carfilzomib-based treatment, in particular patients who are younger and have any evidence of residual neurotoxicity from bortezomib or had a particularly challenging time with it.

Conversely, if I have an older patient, frailer, who may be more at risk of the vascular challenges that we sometimes see with carfilzomib, I am cautious then about recommending it and would rather recommend a rechallenge with bortezomib in combination with something more active. Also of course, we are very impressed by the safety and tolerability of ixazomib, and in that setting, obviously, we consider that also as another option.

Dr Stewart: Right. Is your tendency, if you do choose carfilzomib in a first-relapse setting, to use it with dexamethasone as in the ENDEAVOR trial, or do you prefer triplet combinations as in ASPIRE or other studies?

Dr Richardson: That's a great question, Keith! In a patient in whom immunomodulatory treatment has been well tolerated and active, personally one of my favorite combinations in the triplet setting is carfilzomib, pomalidomide, and dexamethasone, which I find particularly active and well tolerated.

In a patient in whom immunomodulatory treatment may be challenge, for whatever reason, prior intolerance, rash, etc., I might consider carfilzomib and dexamethasone as a

doublet, recognizing that it's very powerful. But generally speaking, I like to use triplets because we have in multiple-settings data that show triplets to be preferred.

Dr Stewart: I would tend to agree with that, Paul, and of course, in the United States, where we use so much lenalidomide at diagnosis and in maintenance, we are often faced with this dilemma of what to combine with carfilzomib. Certainly pomalidomide is also one of our choices. Sometimes even, if insurance allows, a combination with daratumumab can be applied. You did present some data with the use of cyclophosphamide, do you ever use that in your own practice?

Dr Richardson: Absolutely. In fact, you have anticipated exactly what I was going to add, which is that another particularly active combination that I am pleased by is informed by Kwee's data where basically carfilzomib, dexamethasone combined with cyclophosphamide has been very active.

I am particularly pleased because, at the same time as you know from our work together, Keith, with bortezomib, cyclophosphamide, and dexamethasone, that's a particularly effective triplet, and although we recognize that typically a PI-immunomodulatory drug (IMiD) platform is preferred, because of the greater synergy that is typically observed with that approach, nonetheless, in patients in whom an IMiD may be contraindicated for whatever reason, I personally find that carfilzomib/cyclophosphamide/dexamethoasone combination very active, and actually generally well tolerated, and again with the usual cautions that we tend to deploy around electrocardiogram monitoring. We will use brain natriuretic peptide monitoring, and we will also use echocardiography, particularly when we are using carfilzomib and cyclophosphamide, simply because I tend, Keith, to prefer to use IV cyclophosphamide, I am not a great fan of the oral route, and as a result of that, I tend to be a little bit extra cautious about any potential risk of cardiac issues. But, I have to say, from my experience with carfilzomib and cyclophosphamide and dexamethasone, I have been very pleased that actually we haven't seen too much in the way of cardiac issues with that triplet.

Dr Stewart: Yes. As you know, we have tended to use the cyclophosphamide orally, but it does cause a bit of nausea as you point out.

Just to close on carfilzomib, we have been using this drug for a while now in the real world and we have had some more experience with it. You talked about using it in preference to bortezomib to avoid neuropathy, but you have also alluded to the fact that some caution is maybe required in the most elderly, frail patients. Are there any other clinical nuggets you would like to share with the audience about selecting patients for carfilzomib use?

Dr Richardson: Yes, absolutely. We tend to be more cautious about dose. We don't tend to necessarily go to the higher doses of 56 mg/m^2 or up to 70 mg/m^2. We tend to be much more comfortable around 27 mg/m^2 and 36 mg/m^2. I do actually think that hydration does help, but it has to be given with some caution. You don't obviously bolus, but you infuse. We find that useful with bortezomib as well, actually. We have always felt that hydration matters, albeit with just appropriate caution.

I think the kind of nuggets I found with carfilzomib-based treatment is that there are a significant proportion of patients who tolerate it very well. Fatigue can be issue, thrombocytopenia can be, but basically they do very well with it. The subset of about one in five, or 20% of patients, who run into difficulties with either thromboembolism, hypertensive-type issues, the rare but real issue of cardiac difficulties, renal dysfunction, and so forth, I tend to be very careful with those patients, and as soon as we see those kinds of issues emerging, be prompt to back off if that is becoming a challenge.

I think that it's a generally very well-tolerated drug, and what I have been struck by is that there are a group of patients who do very well with it. The thing is just understanding better that subset who emerge, who can be a little bit unpredictable actually, as to whether they get a cardiovascular issue, but fortunately, as we have discussed before, Keith, the incidence of this is relatively low, so that makes it obviously very attractive, particularly in younger patients.

I really want to close with one final comment, which is it is clearly very potent, and I think particularly in patients who I am worried about, they have high-risk disease, aggressive relapse, and we are looking for rapid disease control where carfilzomib is part of a rational backbone, with an IMiD, with an alkylator, with other drugs, I find it a very appropriate partner in those settings.

Dr Stewart: Thank you for your comments. I would tend to concur with them all. I think with some relatively careful patient selection, this is a very powerful drug and as long as we are not putting the wrong patients on the studies, I think this is safe to use. I would encourage our listeners, if they haven't a lot of experience, not to shy away from this because it is probably one of the best drugs we have for controlling disease.

Thank you very much for your comments on that, Paul, and we will move on to the next discussion topic perhaps.

Dr Richardson: My pleasure, Keith, thank you.

Dr Sagar Lonial MB, FACP

Hello! I'm Dr Sagar Lonial, Professor and Chair of the Department of Hematology and Medical Oncology at the Winship Cancer Institute of Emory University in Atlanta, Georgia. Today I'm going to be discussing data presented at the ASH 2017 meeting on the role of anti-CD38 antibodies for the treatment of patients with relapsed and refractory myeloma.

Role of Anti-CD38 Monoclonal Antibodies

As you know, daratumumab is probably the most forward in terms of data as well as clinical use of the monoclonal antibodies, and in specifically anti-CD38 and the management of patients with myeloma. The three abstracts I want to briefly cover are the CASTOR update, the POLLUX update, and then new data on the role of subcutaneous delivery of daratumumab.

Mechanism of Action

Let's go ahead and begin talking a little bit about mechanism of action. We know that CD38 is an antigen that is expressed ubiquitously on plasma cells and so antibodies such as daratumumab and isatuximab both bind CD38.

Now we know that there are some effects of killing a myeloma cell directly through binding of CD38 on the surface of a malignant plasma cell, but many of the mechanisms that are really important for killing myeloma with an anti-CD38 antibody involves immune anti-tumor effects such as ADCC or other immune-mediated mechanisms of cell death.

You can see that described here on the bottom part of that figure as well as the top part of the figure where you see the importance of effector cell function as part of a mechanism of action of patients with daratumumab and isatuximab.

We are also learning other things about these antibodies in terms of their ability to stop some of the immunosuppressive effects that occur with myeloma, particularly removal of T-regulatory cells and myeloid dendritic suppressor cells, which represents a way to reactivate immune surveillance and reactivate normal antitumor immune function that may be a by-product of the use of antibodies such as daratumumab and isatuximab.

Abstract 3145: Daratumumab, Bortezomib, and Dexamethasone (DVd) Versus Bortezomib and Dexamethasone (Vd) in RRMM: Updated Efficacy and Safety Analysis of CASTOR

Let's talk a little bit now about the use of, or an update from, the CASTOR study. As you may recall, the CASTOR study was a randomized trial of daratumumab in combination with bortezomib and dexamethasone, versus bortezomib and dexamethasone in RRMM. Remember, this was basically a series of patients who had one to three prior lines of

therapy. Again, it was a randomized trial. The daratumumab was given in a standard dosing schedule, and again, the primary endpoint of this trial was progression-free survival.

CASTOR (DVd vs Vd): Study Design

What we see in this, if we begin to look at updated data in terms of median progression-free survival, is a more than doubling in the median PFS favoring the group that received daratumumab with bortezomib and dexamethasone, the triplet over the doublet.

CASTOR (DVd vs Vd): PFS and PFS2

PFS2 is an endpoint that really is becoming more and more important as we test the impact of early relapsed salvages on long-term outcomes. It has not been reached in either treatment arm, but specifically if you look at PFS2 in the high-risk genetic group, this is really quite striking, and I think it's important for a couple of reasons.

The first is, we think of proteasome inhibitors as being very active in the context of high-risk myeloma. Again, if you look at the PFS compared with all patients in the Vd arm, clearly the PFS is longer in the high-risk group, speaking to the importance of proteasome inhibitors in that sub-group. But even more importantly, you can see the added benefit of adding in a monoclonal antibody where the PFS of high-risk patients is almost as high as 21 months, suggesting that the antibody clearly has an important role in long term establishment of remission, even with subsequent therapies, because we know that daratumumab is so present in the blood stream at that timepoint.

CASTOR (DVd vs Vd): Response rates

If you begin to take this one step further and then look at overall response rate and depth of response, this is also quite amazing if you think about the fact that we never really consider MRD negativity to be an important endpoint in relapse trials. You can see here that about 12% of patients in the daratumumab arm achieved MRD negativity at 10^{-5}, and 5% achieved MRD negativity at 10^{-6} compared with much lower numbers in the bortezomib/dexamethasone alone arm.

This is really reflected in the fact that the VGPR and the CR rates for the daratumumab arm are clearly significantly higher than we see in the bortezomib/dexamethasone alone arm.

Now again, if you begin to think about that in context, this really does potentially put bortezomib with daratumumab as an important salvage therapy, and we are going to talk about potentially some ways to think through what the best partner is for daratumumab as we begin to get to some of the Q&A.

Abstract 739: Daratumumab, Lenalidomide, and Dexamethasone (DaraRd) Versus Lenalidomide and Dexamethasone (Rd) in RRMM: Updated Efficacy and Safety Analysis of POLLUX

The next study to talk about is the POLLUX study, and this was also a randomized Pphase 3 trial that compared daratumumab, with lenalidomide/dexamethasone versus lenalidomide and dexamethasone.

POLLUX (DaraRd vs Rd): Study Design

Again, standard dose of daratumumab was used, median of one prior line of therapy is what we saw in this trial, and the median follow-up is a little over 2 years with PFS really being the main primary endpoint of this clinical trial.

POLLUX (DaraRd vs Rd): PFS

Again, I think one of the highlights of the POLLUX trial is the fact that the median PFS with a follow-up of 2 years was 68% for the group that received daratumumab, versus only 41% for the group that received lenalidomide and dexamethasone. The reason why I think this is really so striking is if you look at this curve in terms of follow-up, it does appear as if the median PFS for the daratumumab/lenalidomide/dexamethasone arm maybe somewhere close to 4 years, and that would put it as one of the longest PFS of any trial in relapsed myeloma. This really speaks to the fact, not only of the synergy between IMiDs as well as monoclonal antibodies, but in my mind, more importantly to that effector cell mechanism that I showed you earlier on in the antibody discussion.

POLLUS (DaraRd vs Rd): Overall Response

We know that IMiDs can in fact enhance effector cell function and by enhancing that, you may make the monoclonal antibody a better drug than if you give it either by itself or with other drugs that perhaps don't enhance effector cell function to the same degree that the immunomodulatory drug class appears to do. Again, this is an updated follow-up from the *New England Journal of Medicine* paper, which was published with much shorter follow-up that demonstrated pretty significant magnitude of benefit as you can see in this slide here.

Now, again, if you begin to look at response overall, you can see 79% of patients achieved a VGPR or better in the daratumumab arm compared with only 48% in the lenalidomide/dexamethasone arm, and that this depth of response was really quite striking, and as I showed you on the previous slide, was really quite durable. I think that we clearly have data looking at daratumumab in the context of early relapse, one to three prior lines of therapy, and choosing the partner is something again that I think is a clinical decision and is a decision we can discuss in a few moments as well.

Now, what about new approaches or innovations in the delivery of daratumumab? We know that the infusion time, particularly in the early infusions can be a real issue for patients as well as for infusion centers to keep patients in the chair for that period of time, and we also know that infusion reactions occur about 46% of the time in patients who were receiving intravenous daratumumab.

While those infusions and infusion reactions can be managed, they do potentially prolong the duration of infusion, making it a little bit more difficult sometimes for patients to receive daratumumab in the community setting.

Abstract 838: Subcutaneous Delivery of Daratumumab in Patients With RRMM: PAVO, an Open-Label, Multicenter, Dose Escalation Phase 1b Study

Now the trial that we are going to talk about is the PAVO trial, which was an open label, multicenter dose-escalation phase 1 study, really looking at RRMM in patients with ECOG performance status of less than 2, and received subcutaneous dosing of daratumumab in this clinical trial.

PAVO: Study Design for Subcutaneous Delivery of Daratumumab

The first thing that I think is worth noting is that you were able to escalate to 1800 mg, which is the standard mixed component of the diluent in combination with daratumumab, and the injection time here was about 3 to 5 minutes, which is certainly a much better infusion time than we see with intravenous daratumumab.

PAVO (SC Daratumumab): Dose Regimens

If you begin to look at the frequency of infusion reactions, what you see is any infusion reaction was basically about 13% in this group here and Grades 3 to 4 was about 13% as well, which is again really low, much lower than what you would see with intravenous infusion reactions. Again, it suggests the importance of potentially an alternative mechanism of infusion, reducing the severity and time commitment for patients in terms of receiving daratumumab.

PAVO (SC Daratumumab): Safety

If you begin to look at what some of those reactions were, again you can see that most of them are what you would expect with daratumumab. I think the real benefit here is a much lower incidence of infusion-related reactions and certainly early on, there is preliminary data suggesting that the response rate may be just as good as daratumumab and perhaps maybe even a little bit better, although we need larger trials to really fully feel comfortable with that dataset at this timepoint.

Abstract 1887: Updated Results From a Phase 1b Study of Isatuximab Plus Pomalidomide (Pom) and Dexamethasone (DEX) in RRMM

What about other anti-CD38 antibodies that are in development? I am going to spend just a moment talking about isatuximab, another anti-CD38 monoclonal antibody that binds a different epitope on CD38, so potentially binds in an area where daratumumab does not and may have some different properties and mechanisms of action and immune effects than what we see with daratumumab.

Phase 1b Study (Isatuximab + Pomalidomide + Dexamethasone): Study Design

If we begin to look at this Phase 1b study that was presented by Dr Richardson, what you see is that again it was a standard 1b dose escalation and expansion, patients that had two or more prior lines of therapy and the primary objective was recommended dose of isatuximab in combination with pomalidomide, with secondary endpoints being efficacy, safety, and pharmacokinetics.

Phase 1b Study (Isatuximab + Pomalidomide + DEX): Results

As we begin to look at some of this, I think it really does suggest that there are exciting data here. You can see the dose of 10mg/kg was chosen as the isatuximab dose to move forward with. Grade 3 adverse events (AEs) were about 78% with serious AEs about 47%, not significantly different than what we would see with daratumumab in combination with pomalidomide, and again, most of the toxicities were chemotherapy-related. The response data certainly looked very encouraging as well, suggesting that this is a very important and active mechanism by which we can continue to try and treat patients with a different monoclonal antibody targeting CD38 as we go forward from here.

Discussion on the Use of Daratumumab

In summary, what you have seen are some really exciting data, targeting CD38, both with daratumumab and isatuximab, trying to find ways to partner them with other drugs, to enhance efficacy, as well as looking at alternative ways to deliver the drug, to reduce the burden and side effect profile for patients as well as their practising physicians.

I think it's important at this time to really think about the use of daratumumab in combination with lenalidomide/dexamethasone as an appropriate choice in patients with first relapse therapy as well as patients who have been on prior lenalidomide-based therapy, and this really important practical question as we manage patients with myelomas.

I think based on some of the data that we've seen, there is no question that daratumumab should be considered as a first option in patients with early-relapse disease, and I think the real question is, is lenalidomide the better partner, is bortezomib the better

partner, or is there perhaps another opportunity to use daratumumab in the early-relapse setting?

In our practice, certainly among patients who have not been exposed to lenalidomide maintenance and may only have received lenalidomide for a limited duration during induction, using daratumumab/lenalidomide/dexamethasone as a salvage therapy is our first go-to option because of the very long progression-free survival that I showed you from the POLLUX trial, as well as the well-tolerated approach that that brings and the fact that it seems to be such a synergistic interaction between two very important and potent drugs.

At the same time, if patients are progressing on lenalidomide-based maintenance therapy, our approach for using daratumumab with lenalidomide/dexamethasone is perhaps a little bit less enthusiastic, mostly because we think we want to switch to a different drug so that the myeloma can be exposed to something different with a higher benefit to the patient in the long term. In that case, the discussion becomes, do you partner with bortezomib, as I showed you from the CASTOR trial, which certainly looks very exciting and very active, or do you partner with a different IMiD? Certainly in our practice, one of the approaches that our group often takes is the use of pomalidomide in combination with daratumumab and dexamethasone. This was published by Ajai Chari about a year ago now, and again the advantage of pomalidomide is that it brings in that IMiD synergy that we have seen before, and does allow us to get that synergistic effect between the IMiD and the daratumumab.

I think those are really important discussions.

How you choose whether you do an IMiD or a proteasome inhibitor as the partner with daratumumab, in many ways depends on how a patient presents and the rapidity with which you think you need to get a response. We know that among high-risk patients, for instance, proteasome inhibitors and bortezomib/dexamethasone certainly are very encouraging, and as showed you, not only is PFS longer for high risk, but PFS2 is actually quite long for patients who received daratumumab and bortezomib in the salvage setting, suggesting that that might be an approach for certain high-risk patients.

For other patients, where you want to go back to a more oral approach outside of the daratumumab, the use of daratumumab in combination with either lenalidomide or pomalidomide, depending upon their previous treatment history, I think are really important.

When we begin to think about delivery of daratumumab, there clearly are some improvements we can make from the patient experience perspective, as well as from side effect management. It is very clear to me from the data we have seen so far that the use of subcutaneous daratumumab clearly reduces the burden of time for the patient in the chair, but also reduces the overall side effect profile and infusion reaction burden that patients

experience as well. This to me is really an exciting opportunity to make this drug even easier to give than it already is. One of the points that always has struck me with giving daratumumab is that outside of those first two infusion reactions, most patients tolerate daratumumab better than they do almost any other drug we use in myeloma. So I think if we can do things to mitigate the time that it takes to give it, as well as the early infusion reactions, that would be a real win for patients in terms of subcutaneous delivery and reducing the burden of time on our patients.

Promising Developments With Anti-CD38 mAbs in RRMM

Finally, I want to spend just a moment talking a little about other emerging strategies in patients with RRMM. I think that really revolves around partnering with daratumumab or with second generation anti-CD38 antibodies such as isatuximab.

One of the advantages that drugs like isatuximab may have is because their mechanisms and their epitopes are slightly different, it may raise the opportunity that if a patient receives daratumumab early on in their treatment course, that perhaps switching to a different antibody with a similar target but not the same target, such as isatuximab, may be really important. As we have seen in some of the early data with isatuximab, it does partner quite nicely with pomalidomide, as we saw from Dr Richardson, but also with lenalidomide and bortezomib as well. Having more options for our patients in the relapsed/refractory setting, really does give us additional opportunities that are important as we prolong and improve the quality of life and the longevity of patients with myeloma.

Dr Stewart: Let's move on now to discuss some of the new and exciting emergent therapies that were described at the recent ASH meeting, and I will describe four of those for you today.

Emerging Therapies in RRMM

The first one that we would like to talk about is the very important target that has emerged in myeloma therapy, called BCMA, or B-cell maturation antigen. This is a cell surface receptor in the TNF super family which is expressed on myeloma cells and on normal plasma cells.

Abstract 741: Deep and Durable Responses in Patients With RRMM Treated With Monotherapy GSK2857916, an Antibody Drug Conjugate Against B-Cell Maturation Antigen: Preliminary Results From Part 2 of Study BMA117

We have two potential therapeutics that were discussed at the ASH meeting targeting BCMA. The first one is an antibody-drug conjugate that is composed of an anti-BCMA monoclonal antibody linked to a microtubule disrupting agent.

Anti-BCMA Antibody-Drug Conjugate GSK2857916: Phase 1 Study Design

The objective of this target study, which was a phase 1 trial, which was presented at the meeting, was to assess the safety and efficacy of GSK 2857916 in patients with RRMM. Patients were eligible if they had received a prior alkylator proteasome inhibitor, immunomodulator and stem cell transplantation. Treatment was a 1-hour infusion every 3 weeks for 16 cycles, with a primary endpoint of establishing a maximum tolerated dose and safety.

Thirty-five patients who had been heavily pretreated were enrolled in this study. Notably, 57% of these patients had had more than five prior therapies, so a very heavily pretreated population.

Anti-BCMA Antibody–Drug Conjugate GSK2857916: Results

Common adverse events were mostly related to the cytotoxic conjugate and were side effects that we have become used to with some of these similar drugs that are already being used in our practices. They include the usual myelosuppression with thrombocytopenia and anemia being quite common, elevation in AST in 29% of patients, and cough 26%. Corneal events in 63% of patients, which may be one of the side effects we are not so used to dealing with as hematologists, these were however mostly Grade 1 and 2 and reversible, but quite frequent at 63% of patients enrolled having some kind of corneal adverse event.

The most common Grade 3/4 adverse events with thrombocytopenia and anemia, eight patients had infusion reactions, three of which were Grade 3. Again, this is something we are becoming quite used to with the infusion of antibodies.

What was most exciting about this presentation was that the overall response rate in these pentarefractory patients in many cases, was 21 out of the 35, or 60%, with a healthy progression-free survival in this population of 7.9 months.

This trial shows then that this anti-BCMA antibody-drug conjugate was active, and had a manageable safety profile in heavily pretreated patients.

Abstract 740: Durable Clinical Responses in Heavily Pretreated Patients With RRMM: Updated Results From a Multicenter Study of bb2121 Anti-BCMA CAR T-Cell Therapy

The second therapy trial BCMA that was presented was one of a number of presentations on chimeric antigen receptor (CAR) T-cell therapy. This particular presentation involved the drug bb2121. This was obviously one of the therapies that has attracted a lot of interest and attention as the earlier results have begun to come in.

CAR T-cell therapies, or chimeric antigen receptor engineered T cells, have had robust activity in several blood cancers and are now approved by the US Food and Drug Administration (FDA) in use in acute lymphoblastic leukemia in children, and non-Hodgkin's lymphoma in adults, with trials in myeloma now emerging.

bb2121 is a second generation CAR T-cell therapy construct that targets BCMA on the myeloma cell and is a T-cell enhancer. This trial was a phase 1 multicenter dose escalation trial. Patients had to have had at least three prior therapies or be double-refracted to proteasome inhibitor IMiD, and for this particular study, had to have evidence of BCMA expression on at least 50% of the plasma cells.

CAR T-Cell Therapy (bb2121) in RRMM: Study Design

Again, the primary endpoint was safety.

CAR T-Cell Therapy (bb2121) in RRMM: Results

21 patients had been treated at the time of this presentation, and 18 were evaluable for response. The median number of prior therapies was seven with a range of 3-14, and 100% of patients had a prior transplant, 67% had high-risk cytogenetics. No dose-limiting toxicities were observed on the doses studied. However, cytokine release syndrome occurred in 15 of 21 patients, or 71%. Again, this is a feature in toxicity of similar CAR T-cell products that we are becoming acclimatized to, and seems to be prevalent even with this construct.

However, some encouragement, most of these 71 cases were Grade 1 to 2, only two patients had Grade CRS that resolved in 24 hours, although later we learned that there has subsequently been a patient who did develop a more severe toxicity with this treatment.

What has really got people excited is that, despite this sometimes quite difficult toxicity to manage, the overall response rate was 89%, and if it looked at patients who received at least 150 million CAR T cells, was 100%.

bb2121 CART T-cell therapy, therefore, shows very promising activity at doses above 100 mg/million or 150 million cells, and no upper limit to the cell number that can be delivered on this trial, but again quite frequent cytokine-release syndrome which can, on occasion, be serious.

Other Emerging Therapies Being Investigated in RRMM

Just to close, there are two other small molecules that are worthy of mention in RRMM. The first of these that we will discuss is selinexor. Selinexor is a novel drug, and there are targets, exportin 1, XPO1, which has been shown in previous studies to be one of

the targets that were knocked down genetically as most able to eliminate myeloma cells. Selinexor has been used as a single agent with dexamethasone with success, and is reported in this meeting in combination with bortezomib and dexamethasone where it also appears to be very active.

The single agent response rate has just recently been reported as 25%, at least when used with dexamethasone, and an ongoing phase 3 trial is now comparing selinexor with bortezomib/dexamethasone versus bortezomib/dexamethasone alone.

So this drug seems to meet the threshold for drugs that are likely to be approved for the use in myeloma. However, it can be a tough drug for patients to take, fatigue, anorexia, nausea are all quite common, but as we learn how to use this drug more efficiently, I think we will be able to control those side effects more frequently.

The final drug I would like to mention is venetoclax. Venetoclax is a selective, small molecule inhibitor of the anti-apoptosis protein B-cell lymphoma 2 (BCL2). Venetoclax is already FDA-approved for the treatment of chronic lymphocytic leukemia, and is showing activity across the spectrum of hematologic malignancies.

In early studies – again updated at this meeting – it has been demonstrated to be active in myeloma in the clinic, particularly in those with a trans-locational (11;14) where the response rate seems to be in the 40-60% range, particularly within that cytogenetic sub-group. When combined with bortezomib, venetoclax has shown even higher activity with up to 90% of patients responding to the combination of bortezomib and venetoclax. It seems to be a relatively safe drug to use. Tumor lysis syndrome was a concern early on, but doesn't seem to be as prominent in myeloma as it is in chronic lymphocytic leukemia, and again, the higher response rate in patients with t(11;14) is quite impressive.

Paul, we talked today about some emerging therapies in RRMM. What are the emerging therapies do you think are most promising for this disease that we discussed?

Dr Richardson: The extraordinary thing, Keith, is that the breadth and depth of new treatments available for myeloma continue to stun me in terms of their number and their variety and their potency. What is so interesting is to see beyond next generation immunomodulatory treatment, next generation proteasome inhibition. We have some very novel targets, and some great drugs which go after them.

I personally am very impressed with selinexor. I think it is an entirely novel mechanism of action, and the idea of the selective inhibition of nuclear export protein mechanisms being taken advantage of therapeutically to essentially what I think is one of the

most important, especially late stage changes, which is the overexpression of C-MYC in myeloma—and of course that is how selinexor works—is particularly impressive. I think that all drugs can be challenging in early development from a side effect point of view, but what we are learning with selinexor is that they are manageable and particularly in combination. I think selinexor, to me anyway, is a very interesting and exciting new avenue. I think beyond that there then become obviously some very exciting other drugs in that space. I think we can go through the list, but essentially, we are fascinated by obviously the expanding space of immunotherapy. This is dramatic. It has put CAR T-cell therapy to one side because it's a discussion in and of itself, but obviously beyond that, we need off-the-shelf strategies that are effective. I think the antibody-drug conjugates are very promising in that space, and obviously there were tremendous data at ASH from 916 which has obviously shown great promise, and that work - led by Suzanne as you know – showing really remarkable single agent activity, so that space continuing to grow.

I think that in terms of other new agents, I would want to emphasize a drug we have had some experience with which is a modified, or rather a targeted, cytotoxic, melflufen, which actually is peptidase-activated and really takes the concept of melflufen to a new level. It is highly more effective within the myeloma cell, but also beyond it, selective in how it works.

Then I think we move into other new drugs as well, which we can talk about, but I want to have you chime in here at this point.

Dr Stewart: I agree. I think selinexor is clearly an active drug. It is a very promising target as we described. It is, in our experience, challenging for patients, and we hopefully are learning better how to manage those side effects. My experience with venetoclax has been quite promising too, Paul. I have had some very dramatic responses that were quite rapid, particularly in the (11;14) population. Have you had a chance to use that in many of your patients?

Dr Richardson: I want to especially acknowledge the really seminal work of Shaji Kumar and his team in this because, targeting (11;14) and going after BCL2 I think was tremendously important because, actually it was my colleague, Constantine Mitsiades who years ago demonstrated that a very important mechanism of bortezomib resistance was BCL2 up-regulation.

In there lay an important clue, because I think what it really told us was that this particular target matters, and then with the development of venetoclax and the targeting of BCL2 and the emergence that the (11;14) subgroup could benefit from the approach, I think

was just seminal work by Shaji and his team. Then, of course, Philippe Moreau took it to the next step, combining it with bortezomib, and really, the results there are great.

Although we have not had a direct role at our center in the development of venetoclax, increasing my partner, Jacob Laubach, is embracing that and actually exploring it in various combinations. My own clinical practice with it, using it off-label, has been really exciting. I think for the (11;14) subgroup, it is a particularly interesting drug. I have found it useful, well tolerated. I am also very excited by its potential, Keith, in plasma cell leukemia, where, as you know, expression of (11;14) is enhanced. I have seen it without a doubt help me salvage patients who otherwise basically would not have been salvageable. I am very impressed by it, very.

Dr Stewart: One wonders if amyloid will be the same story, because that's very enriched for (11;14) as well.

What is the Role and Position of Venetoclax and CAR T-Cell Therapy in RRMM?

Let's move on to the big one, CAR T-cell therapy. Give us your thoughts on that and your experience.

Dr Richardson: With CAR T-cell therapy, our own group is led by my outstanding colleague, Dr Nikhil Munshi, and basically Nikhil and our team have embraced this, especially with the BCMA-targeted approach, which obviously I have alluded to earlier with the antibody-drug conjugate 916 that targets BCMA.

What we have seen with the BCMA-targeted approach in CAR T-cell therapy has been remarkable. I would say there have been other efforts, CD19 on the one hand, also at the Dana Faber we had our own particular home grown target that didn't really pan out, sadly, for myeloma, but certainly the BCMA one has done.

Although we have a relatively small number of patients who have been successfully treated, the results are extremely compelling. What we have seen is activity despite incredibly resistant refractory disease, and what we have seen is durability. Although I know there is some concern about long term durability, I think as a starting point, the results we have seen with our CAR T-cell approaches have been nothing short of spectacular, recognizing it's a highly selected population. I think that's an important thing to share with our listeners because obviously when you see nine out of nine responses, you say to yourself 'wow!', but it is also important for listeners to realize that the waiting lists for each CAR T-cell program—certainly speaking to our own—are substantial. This is not an intent-to-treat analysis, but rather a highly selected group of patients who are able to do it.

That notwithstanding, I think the results are extraordinary.

Dr Stewart: Yes, I would agree with all of those comments. Very encouraging, very difficult to get to today, but obviously coming quickly in this space.

Discussion: Impact on Clinical Practice

Let's move on and wrap up for the audience here, and I think in this context let's include discussion of daratumumab, which Dr Lonial has presented on this morning and given us some commentary on. What do you generally think the addition of carfilzomib, daratumumab, the arrival of some of these therapies, what has that done in your daily practice, Paul?

Dr Richardson: I think it has been incredibly important because I think what, unfortunately, is the reality is that myeloma is, as always, a highly formidable foe. At the end of the day, once proteasome inhibition and immunomodulatory treatment has failed our patients, we definitely need next steps.

I think there is an array of options. Daratumumab is clearly the game-changer targeting CD38. I personally use it very widely. Obviously from our very first time of getting involved with daratumumab in the 501 experience, which was the original phase 1, we have been so impressed by its efficacy and it has generally well-tolerated therapeutic profile in terms of side effects. Then in combination, the results have been again spectacular.

There is a lot to learn about daratumumab, about schedule, weekly versus twice weekly. Certainly we have seen situations where administering the drug weekly and then once every 2 weeks and then monthly, we have seen loss of response and been able to go up to every 2 weeks and then back to weekly to get response back. We have then been able to combine it with a variety of other drugs, including carfilzomib for that matter as well as other proteasome inhibitors and IMiDs. I think it has become a new backbone and transformed our therapeutic opportunities for our patients, but I think we have to be very realistic though and remember that it does fail, that we have plenty of patients sadly now who have become refractory to daratumumab, and that we, importantly, need options for them.

Dr Stewart: Yes, I would agree with all of that, and say that one of the big changes here has been almost at time of first relapse our best drugs are now available. The use of carfilzomib, the use of daratumumab, the use of pomalidomide, probably the three most powerful agents are the ones we are now using in first relapse, and hopefully soon even earlier.

I would say that one of the biggest changes for me has been the fact that we see such deep remissions, including molecular remissions that we almost never saw 5 years ago

where patients are not only morphologically and biochemically depleted of myeloma but also at the molecular level, we can't even find the myeloma in very sensitive assays when daratumumab and pomalidomide or carfilzomib/ lenalidomide or carfilzomib/ pomalidomide are employed, or even, as you point out, carfilzomib and daratumumab in combination.

Just one thing to close, I think these have both been transformative drugs in the treatment of myeloma, and with some of the new drugs we are discussing here again today including CAR T-cell therapies, I think we continue to see progress and improving survival.

Denosumab: FDA Approval in Multiple Myeloma

In our last minute, Paul, supportive care. We have all used zoledronic acid for a decade now, denosumab was recently approved by the FDA. I am just wondering what your thoughts are on the use of denosumab in these patients—it's a drug we haven't discussed already.

Dr Richardson: I think denosumab has again been an important addition to the supportive care armamentarium. I am very pleased with it because it provides us with a safe option in renal disease, which is obviously so common in our patients, especially over time. I think denosumab as an alternate to zoledronic acid and to pomidronic acid becomes a very attractive option, recognizing that it also has the convenience of a once-a-month administration subcutaneously, which is a big value-add in my view.

I think denosumab has been a great addition. We certainly view it as a critical additional treatment. Whether it becomes a replacement to zoledronic acid in all patients is a more challenging question. We personally reserve it for patients with renal dysfunction and in whom, for any reason, zoledronic acid may be not tolerated and/or relatively contraindicated. So we therefore use it in that setting.

Dr Stewart: I think that is very similar to our own practice today, although I suspect we will use more denosumab moving forward.

Dr Richardson: I agree.

ASH 2017 Key Messages

Dr Stewart: Let's summarize here.

Today we have heard of the incredible advances in myeloma, particularly the use of new proteasome inhibitors, carfilzomib, ixazomib, the introduction of monoclonal antibodies targeting CD38, and daratumumab, and how transformative they have been in both the frequency and depth of response and the resulting overall improvement in progression-free and overall survival.

We have also talked about the future a little bit, about where things seem to be going and new drugs that are coming along to help us, and how this has really changed, together these factors have changed how we treat myeloma on a daily basis.

Some of the key messages we have conveyed to you today that were communicated at the American Society of Hematology meeting in 2017 were that new data are now available to help us refine the use of proteasome inhibitors and CD38-targeted therapies in the treatment of patients with RRMM.

Analysis of efficacy according to prior therapy can help inform treatment decisions for individual patients, and new methods of delivery, for example, subcutaneous daratumumab, weekly carfilzomib, and novel regimens such as combining carfilzomib with cyclophosphamide or carfilzomib with daratumumab continue to be explored as optimal use of these agents in relapsed disease.

We have also described today several promising new therapies with unique mechanisms of action, such as selinexor and venetoclax, and agents targeting the cell surface receptor BCMA.

I would like to conclude by thanking you for your attention and participation. I would like to thank Dr Lonial and Dr Richardson for their discussion and commentary and remind you that this is a CME activity supported by an independent educational grant from Amgen and is provided by the Elsevier Office of Continuing Medical Education.

Thank you for your participation, and we hope this was useful for you in your practice.

[*Ends*]