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Advancing Clinical Expertise in CELMoDs: Transforming Multiple Myeloma Treatment

Announcer:
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Dr. Richter:
Hi. My name is Dr. Josh Richter. I'm an Associate Professor of Medicine at the Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, and the Director of Myeloma at the Blavatnik Family-Chelsea Medical Center at Mount Sinai.

And I'm really excited today to be discussing the latest and greatest in multiple myeloma and, in particular, advancing clinical expertise in CELMoDs, transforming multiple myeloma treatment.

Our learning objectives are as follows: we're going to discuss the mechanisms of action underlying CELMoDs and their clinical utility in the treatment of patients with myeloma. We're going to go through some of the latest and greatest data in both the upfront and relapsed settings, and how we can incorporate them into the utilization of MRD in decision-making in the world of multiple myeloma.

So let's begin.

So ultimately, we talk about unmet needs in myeloma, and although globally the unmet need still remains cure for all patients, we recognize that there are significant barriers that we have yet to overcome in myeloma, and we're seeking newer and better ways to achieve disease control and ultimately durable, long-term remission—and one day, cure.

So really, what we understand is that the lymphoma docs have achieved something that we are still grasping at in the myeloma world—and that's better understanding disease biology at the time of diagnosis. Insofar as the lymphoma doctors have been able to better parse out the differences between mantle cell, marginal zone, CLL, and diffuse large B-cell lymphoma—and you would never treat these diseases the same way.

In 2025, we recognize that multiple myeloma continues to represent a variety of different disease pathologies. However, we continue to group them under the umbrella of multiple myeloma, and we recognize that one size is not going to fit all, and we need to come up with newer and better ways to deal with more resistant disease, extramedullary disease, and some of the more difficult phenotypes.

Now again, we recognize that as we go from relapse one to two to three, we can incur newer and more aggressive cytogenetic abnormalities, extramedullary disease, and a number of other high-risk features of myeloma.

This is where we're at in the current landscape. And for the most part, when we consider treatment of myeloma, most of these therapies are given in combinations of three and four drugs. However, some of them are still being studied only as monotherapy.

On the left side of the screen are some of the therapies that most people will be familiar with at this point, including some of the classic agents that we've used to manage both upfront, newly diagnosed, and relapsed and refractory multiple myeloma. This includes drugs

like the immunomodulatory agents, the proteasome inhibitors, and the monoclonal antibodies.

At the moment, in the time of this recording, histone deacetylase inhibitors are not currently approved in the United States. Antibody-drug conjugates are slated to be approved in October of this year, and hopefully by the time you're viewing this, they're already reapproved in the United States, with belantamab mafodotin. And we have a number of other small molecules, including drugs like selinexor and the as-of-yet not FDA-approved BCL-2 inhibitors like venetoclax, lisaftoclax, and sonrotoclax. We have a number of targeted agents, including the CAR T-cell therapies, currently two approved, and now four bispecific antibodies approved—teclistamab, elranatamab, talquetamab, and linvoseltamab—with many others under continued evaluation in clinical trial, as well as a number of other immunotherapies involving CAR T cells, bispecifics, and trispecifics.

However, what we're going to focus on today is really the next generation of the immunomodulatory drugs, the so-called CELMoDs, focusing on iberdomide and mezigdomide. And although much of the data is going to be focusing on utilizing these drugs the way we've used a lot of our therapies in myeloma for their anti–plasma cell therapy, one of the additional facets of these drugs is their marked impact on immune modulation. And ultimately, these drugs will likely be incorporated with some of our newer, advanced therapies like CAR T-cell therapy and bispecific antibodies, not just for their anti–plasma cell activity, but for the ramping up of a T-cell response.

In the relapsed/refractory world of myeloma, we don't have clear genomic guidance on which therapy to choose for which individual patient. Ultimately, we decide our therapies based on three dimensions of factors: patient-related factors, disease-related factors, and treatment-related. Is the patient old or young? Fit or frail? What comorbidities do they have? Is the disease growing fast or slow? Is it high risk? Is there extramedullary disease? Is there plasma cell leukemia? But most importantly, we really focus on treatment-related factors. We focus on what therapies the patient has had before. What are they naïve to, sensitive to, refractory to? What class or classes of agents has the patient done well with? What have they not done well with? And this really helps guide us to choose which therapy may be more optimal for a patient in the relapsed setting.

But let’s focus on newly diagnosed myeloma at the moment. Currently in 2025, we recognize that for newly diagnosed myeloma patients, we still group them into the transplant-eligible and the transplant-ineligible cohorts. Now, although in the United States there are no clear guidelines, we recognize that on the whole, eligible patients tend to be younger and fitter, while ineligible patients tend to be older and frailer.

Here, we can see a list of the commonly recommended and approved regimens for transplant-eligible, newly diagnosed multiple myeloma. For the most parts, we've moved beyond triplets into the realm of quadruplets, and you can see some of the most recommended regimens are quadruplet-based therapies like Dara-RVD and Isa-RVD; however, there’s ongoing data about incorporating carfilzomib as the proteasome inhibitor of choice in these types of patients.

Additionally, there are some patients who may be transplant-eligible but may have some contraindication to one or more of these therapies, in which case there is still applicable data to use a triplet in these populations. However, on the whole, a dose-adjusted quadruplet is probably better than a full-dose triplet.

We also see here some of the updates from Europe with the EHA-EMN guidelines, which are very similar in many ways to what we utilize in the U.S. However, some of the countries still utilize thalidomide as their upfront IMiD of choice. Based on the CASSIOPEIA data, we see guidelines here recommending the potential use of Dara-VTd as opposed to Dara-VRd. Ultimately, these patients who are eligible will go on to autologous stem cell transplant. There are still some countries and some institutions that will consider a tandem autologous transplant for a select group of patients, and ultimately, we land patients in the realm of maintenance therapy post-autograft, with the standard of care being lenalidomide, although there’s ongoing data about the role of doublet maintenance in some higher-risk patient populations.

Now, we also have patients who are older and frailer that we would group into the non–transplant-eligible population. Now again, these patients, through a variety of clinical trials recently, such as IMROZ and CEPHEUS, have seen the clear benefit of quadruplet-based therapy, with median progression-free survivals of around 100 months. However, in general, as these patients may be older and frailer, triplet regimens are still applicable, most notably the MAIA regimen of DRd, which gives us a median progression-free survival north of 5 years.

There may be some extremely old or frail patients where doublets may still be appropriate. And again, looking at the European guidelines, we see this mimic what we have in the NCCN, noting that quadruplets are still applicable for patients even if they’re not considered transplant-eligible. However, frailer patients may still benefit from triplet-based therapy with DRd or VRd.

Now, once we get into the first and second relapse, the realm of treatment options becomes quite expansive, and it becomes, in my mind, very akin to a game of chess or a game of Go. Ultimately, we still have to refer back to the discussion before about our choices in

the relapsed setting, focusing on patient-related, treatment-related, and disease-related factors. However, what's notable in the NCCN guidelines, as well as some of the other guidelines outside of the United States, is that the first branchpoint of decision-tree making is treatment-based.

So we look at: Is the patient refractory to IMiDs or proteasome inhibitors or monoclonal antibodies? And this kind of logic tree will drive us into which therapies may be better or worse.

Now, one of the things that's changed across the last 5 to 10 years is many patients who were not previously lenalidomide-refractory, now the majority of patients in the U.S. are IMiD-refractory going into the second line. And although CD38 refractoriness was once quite rare, it is becoming more and more common, estimated that at the time of this recording, somewhere between 25% and 50% of myeloma patients will enter first relapse CD38-refractory.

And again, despite the heavy use of proteasome inhibitors globally in transplant-eligible and -ineligible patients for the last 15-plus years, given regimens like MAIA, we have a new class of patients entering early relapse that are actually proteasome inhibitor–naïve.

And we can see here, once you ascertain what therapies the patient is refractory, sensitive, or naïve to, we have a bevy of different choices. However, once we get into later-line therapies—and in myeloma, we describe early relapse as one to three prior lines, late relapses as four plus—we start to look at some of our T-cell redirection therapies like CAR Ts, as well as some of our small molecules like selinexor. Again, clinical trials are always an option, especially for relapsed and refractory patients.

Based on the NCCN guidelines, once we get to later relapses, the current recommendations really do recommend CAR Ts and bispecific antibodies. However, we must remember a couple of options, including small molecules like selinexor, BCL-2 inhibitors for patients who harbor translocation 11;14, as well as the role for classical chemotherapeutics like bendamustine and cyclophosphamide.

Once we go beyond the class of BCMA-based therapies, there are a number of considerations we must take into account. One is patient preference, of course, and the time since their relapse from BCMA-based therapies, because we know that we can sequence them.

However, if you're progressing within 1 or 2 months of a BCMA therapy, we may not want to go on to another one. However, for patients last BCMA therapy was a CAR T given several years ago, BCMA is likely still going to be re-expressed and remains an option in the relapsed setting.

We also have to consider the risk of second primary malignancies, as some of the CAR T-cell therapies have been associated with an increased risk of this. What options do we have? Well again, if it's been a long time since your first BCMA therapy, you can go back to the well. However, we recognize there may be a role for newer antigens like the GPRC5D bispecific antibodies, such as talquetamab, reintroducing some of the standard IMiDs, proteasome inhibitors, or monoclonal antibodies—perhaps those are the patients never progressed on it in the first place.

And now we're really going to start talking about some of our smaller molecules like BCL-2 inhibitors, selective inhibitors of nuclear export, as well as the CELMoDs.

So again, in the world of myeloma, despite our marked improvement in outcomes, we continue to have large gaps and unmet needs within our patient populations.

One is patients who progress beyond multiple lines of therapy, and we recognize that once we go beyond some of these key classes, regaining disease control can be extremely difficult. Additionally, patients who are older or frailer may not have access or be eligible for some of the more aggressive therapies. Additionally, we recognize that the achievement of MRD negativity may be key in certain patient groups to achieving durable remissions, and we're not always able to achieve these levels of depth. In addition, we want to make sure that we're taking into account, for patients who are on chronic therapy—oftentimes from diagnosis to death, exceeding a decade—that the patients may have desires not to go back and forth to the hospital, may prefer oral oncolytics, and ultimately may not have access to some of the more advanced therapies.

Our current data of what the landscape looks like once we get to triple-class refractory, and indeed penta-refractory—refractory to Revlimid, pomalidomide, bortezomib, carfilzomib, and daratumumab—comes from the MAMMOTH study. And here we can see data showing that, despite the fact that in newly diagnosed and even early-relapsed patients we continue to have unbridled enthusiasm about amazing outcomes. Once patients become penta-refractory, their median survival is under 6 months.

And although this used to be a phenomenon reserved only for patients with extensive prior lines of therapy, you can imagine that if a patient has Dara-RVd up front and then gets KPd in the second line, you can be penta-refractory nowadays after only two lines of therapy. So being able to go above and beyond these core classes into some of the newer agents is absolutely crucial to optimize outcomes in the relapsed setting.

So we see here from additional data from both PREAMBLE, Connect MM, and Flatiron what happens when patients are simply post-lenalidomide and CD38, because we have a rising number of patients who continue on regimens like Dara and lenalidomide directly from the upfront therapy and may ultimately progress on to regimens like Dara and Rev. Now though this occurred in a median of three prior lines of therapy. We see once this happens, there is no standard of care for how to approach these patients, especially for patients who are suboptimally responding to these two types of classes. We ultimately need to continue to find better strategies to manage these patients.

So let's get into the rationale for the use of CELMoDs in the treatment of multiple myeloma. So CELMoDs are the cereblon E3 ligase modulators, and they're currently in development with two key assets that are getting closer and closer to FDA approval. This includes iberdomide, formerly known as CC-220, and mezigdomide, CC-92480. And although in many ways, shapes, and forms these drugs are simply advancements of the immunomodulatory class—from thalidomide to lenalidomide and pomalidomide—there are certain features of these drugs that make them even more effective, and in some cases better toxicity profile, making them more advantageous for a chronic disease.

And we can see here that, in reality, CELMoDs do represent the next-generation IMiDs. And they can enforce their disease-control mechanisms through the same ubiquitin-based pathways, emphasizing their role of action on Ikaros and Aiolos, ultimately leading to downstream activity. However, we recognize that this is also impacted not just by direct myeloma cell kill but by true immunomodulation and ramping up of NKT cell activity.

This is becoming more important now than ever, seeing as that the majority of our treatment in advanced-stage myeloma involves utilizing T-cell-directed therapies. So any type of augmentation that can improve T-cell response can be combined with modern-day bispecifics and CAR Ts to optimize disease control.

Here we can see a breakdown of both the immunomodulatory drugs as well as the CELMoDs—going from lenalidomide to pomalidomide to iberdomide and mezigdomide—and we can see that there are similarities in the structures. However, ultimately I would draw your attention to the ability for the drug to provide a close confirmation for cereblon. And although drugs like lenalidomide and pomalidomide cap out at about 1/5 to 1/4, with using drugs like mezigdomide we can lead to 100% close confirmation, and even iberdomide leads to about 50%. Ultimately, this translates to better cell kill overall. And we can see that there are again some similarities but also some notable differences, especially in terms of half-life and approach in renal and hepatic dosing.

Comparing some of the key classes, the biggest thing I'll note is in the bottom—the immune stimulation characteristics of the drug. As we recognize that the entire class has both immune modulation as well as VEGF and apoptotic pathway involvement, we can see here that the apoptotic pathway as well as immune stimulation is markedly improved as we go from the IMiDs to iberdomide to mezigdomide, leading to enhanced cell kill overall.

And most notably, in the world of myeloma we're constantly talking about dance partners, recognizing the importance of drug synergy to provide multiple mechanisms of cell kill, to kill multiple subclones and engender deeper and more durable responses, especially in the world of relapsed and refractory disease.

On the right, you can see the curves for cell kill when we start looking at both controls, single-agent IMiDs, and CELMoDs. And then when we start combining them, particularly with proteasome inhibitors, we see marked synergy between the agents. And ultimately, this is what's needed to kill as much of the myeloma as possible.

Additionally, we see enhanced immune stimulatory activity, especially when evaluating in in vitro studies comparing the CELMoDs versus lenalidomide and pomalidomide. Ultimately, we see here that the impact on Ikaros and Aiolos is many logs improved, and this is what leads to adjustment in immunocytokine release and ultimately a decrease in myeloma cell survival.

Additionally, we focus not just on the myeloma cells as well as the immunocytokine milieu but also the bone marrow microenvironment. And we can see here that when we look both at iberdomide as well as mezigdomide, we can see significant effects on the bone marrow microenvironment, which is part and parcel of the drugs inducing better disease control overall.

We see increased effector cell abundance, increased cellular activation, decreased signals of T-cell exhaustion across the board, and recognizing that T-cell fitness is one of the key components of preventing resistance and intolerance to both the bispecific antibodies as well as the CAR T-cell-based therapies.

Now, this has become one of the key areas of myeloma. Leading into T-cell redirection, we want to make sure that our T cells are not exhausted. Whereas we want to avoid drugs like heavy-duty alkylators such as bendamustine and cyclophosphamide, we also need to focus on what happens once we start therapy with either CAR Ts or bispecifics—that we continue to have activated T cells and strike the balance between exhausted T cells and T cells that continue to be so active in a redirected fashion that we lead to other toxicities

such as infection. And we can see here a variety of data that's been presented from recent studies looking at CELMoDs to overcome T-cell exhaustion phenotypes.

So let's transition to assessing the efficacy and tolerability of CELMoDs in the world of relapsed and refractory multiple myeloma. So here we see data from the first-in-human study in the phase 1/phase 2 trial of mezigdomide and dexamethasone. As we know, we continue to evaluate many of our therapies either in monotherapy or in combination with corticosteroids, and this comes from the CC-92480-MM-001 study. We recognize that if we think back across the last 10 to 20 years of approvals in myeloma, the majority of monotherapy or drugs with dexamethasone in late-line settings have led to FDA approval with between a 22% and 30% response rate. However, we recognize that end-stage myeloma now, or advanced myeloma, is now progressed beyond all of those therapies.

And we can see here, at the expansion cohort, an overall response rate of 41%, which is extremely impressive for an all-oral regimen.

Of note, even patients with plasmacytomas had significant responses, and although to date this has been a very difficult-to-control group. And some of the best data coming out of the RedirecTT-1 study combining teclistamab and talquetamab, we continue to need to find better options and better tolerated options for patients with myeloma that behaves like lymphoma.

And of note, this is some imaging data from one of the patients who was treated with mezigdomide and dexamethasone, where you can see there is significant evidence of extramedullary myeloma, which goes into remission both from a serologic and a radiographic standpoint after treatment with this combination.

Again, here's another patient with extremely extensive extramedullary disease treated on the 001 data. And we can see that in the pre-treatment PET scan, there are extramedullary foci of myeloma from stem to stern. However, after 4 months of treatment with a standard dosing of mezigdomide and dexamethasone, there has been marked resolution of this type of disease.

Now, of course, where we're really going to focus in the new age of utilization of CELMoDs is in combination, specifically taking advantage of the synergy between CELMoDs and the proteasome inhibitors. Here we see some data from the phase 1/2 study of the 002 trial combining mezigdomide with bortezomib as well as with carfilzomib. Overall, almost 1/2 of these patients had high-risk cytogenetics, an average of three prior lines of therapy, with many of these patients already refractory to both IMiDs, proteasome inhibitors, and monoclonal antibodies. But ultimately, we see extremely high response rates of these different combinations that are exceeding 75 and in some cases 84% overall response rate. Again in a somewhat mid- to heavily pretreated group of patients, this is an extremely impressive response rate and drugs that are readily available at all centers.

Again, despite the amazing efficacy of both CAR Ts and bispecifics, they remain available only at a limited number of centers, whereas CELMoDs and proteasome inhibitors can be given essentially anywhere.

Moving on to some of the monoclonal combinations, we see here additional data combining mezigdomide with daratumumab as well as with elotuzumab. Again, these patients had a median time since diagnosis of over 8 years, a median of two prior therapies, and many of them again being refractory to some of our classic agents. We can see here response rates of over 75% when we start combining mezigdomide with any of the monoclonal antibodies, and again, even in the ELO arm, the overwhelming majority of these patients were refractory to CD38 monoclonal antibodies like daratumumab and isatuximab. So ultimately, we continue to have increased options for this patient subgroup.

So especially in the world where the treatment of myeloma continues to be a chronic phenomenon, we're always seeking to find rational oral combinations to provide to our patients, to allow them as much time outside of the clinic as possible. And we look here at some of the true mechanism of action of how the CELMoDs work, we do recognize that they start to involve a number of downstream pathways that we already have targetable agents for, including drugs that impact the RAS/RAF/MEK/ERK pathway.

We can actually see some data here of some additional combinations of mezigdomide, including combinations with BET inhibitors, MEK inhibitors, and the EZH2 inhibitor tazemetostat. Again, these are relatively small numbers but still represent a very heavily pretreated group of patients—1/3 of them with high-risk cytogenetics, an average of five prior lines, and more than 2/3 of patients with prior T-cell–redirecting therapy. So again, at the current time, T-cell–redirection therapy seems to be noncurative, so we continue to need options in the post-BCMA world.

And we can see here that in this very heavily pretreated group of patients, specifically the patients treated with mez, dex, and tazemetostat, that we see an overall response rate of 50%, many of these patients with deep responses.

Additionally, we see a number of deep responses as well when we start combining with the MEK inhibitor trametinib. So especially for patients who may already have derangements in the RAS/RAF pathways, these are all-oral combinations that can be provided, including to patients who are post–T-cell–redirection therapy and will be active despite some of these patients already having significant exhausted T cells.

Really looking forward to the next generation of therapies where we utilize the CELMoDs to combine with some drugs like bispecific antibodies, again, not just for their anti–plasma cell properties but their ability to augment T-cell response. Here we see the workup for the MELT-MM study, a phase 1/2 study evaluating the role of mezigdomide plus elranatamab in relapsed and refractory myeloma. This is across different dosing cohorts, but ultimately this represents a nice, convenient approach, especially with the fixed dosages of elranatamab.

So here we see the paradigm of clinical trials evaluating the role of iberdomide in multiple myeloma. And more clearly, the 001 study was a basket study looking at a variety of different combinations utilizing this new CELMoD. We see combinations here of just single agent with dexamethasone or some of the classic agents in multiple myeloma, including the proteasome inhibitors and the CD38 monoclonal antibodies.

Now, when we look at the doublet data of iberdomide and dexamethasone, we see, again, decent responses in heavily relapsed patients. These are patients with a median of six prior lines of therapy, all of them being IMiD-refractory, all of them being CD38-refractory, most patients being PI-refractory, and about 1/3 of them having high-risk cytogenetics. Despite this, we see patients at the cohort of iber-dex of 36.8% which is a very impressive response rate in these heavily pretreated groups of patients. Particularly, that Cohort I was even BCMA-exposed, and these patients had a median of seven prior lines of therapy.

But really where the drug lies in the future is in the combinations. We can see here additional data from different combinations, including iber-dara-dex, iber-Vd, and iber-Kd—responses of around 50% overall. Again, once you start to get to this type of heavily pretreated groups of patients with a median of four prior lines, we start to see higher and higher rates of extramedullary disease, and over 16% of patients did have EMD in this cohort, as well as even higher rates in the iber-Kd arm. Patients who were heavily pretreated still were able to achieve deep remissions across the board. Of note, iberdomide has a lower incidence of hematologic malignancy than most of the other IMiDs, making it an ideal drug for combinations, especially long-term treatment strategies.

Additionally, there are a number of phase 2 studies looking at all-oral triplet combinations for the use of this CELMoD. Here we can see two studies—the I2D study and the ICON study—combining iber with ixa/dex and iber with cy/dex. Again, in both of these patient groups, the patients have had multiple lines of therapy; however, were still able to achieve deep and durable remissions with an all-oral triplet, including overall response rates of over 60% in the I2D study with a median progression-free survival of over a year. And we see in the ICON study overall response rates of over 80% with median progression-free survival of around 18 months. Again, these represent great options, especially for patients post–BCMA-based therapy.

There are a number of ongoing phase 3 studies evaluating CELMoD triplets in the relapsed/refractory world of myeloma—most specifically, we have the SUCCESSOR-1, SUCCESSOR-2, and EXCALIBER studies. We're expecting these studies to read out toward the end of 2026 and hopefully get approval toward the end of 2026/early 2027, with combinations of mezi-Kd as well as the combinations of iber-dara-dex and iber-vel/dex.

Here we come to a case study. Case #1 is a 66-year-old female who was part of the SUCCESSOR-1 study. She has relapsed and refractory IgA lambda multiple myeloma. She received RVd ×3, followed by autograft in 2014, followed by RVd consolidation and lenalidomide maintenance. Now presenting with progressive disease in 2024, with an increase in lambda light chains, increase in bone marrow plasmacytosis, as well as symptomatic fatigue and bone pain. She started on therapy with mezi-Vd according to the clinical trial and achieved a VGPR with a decrease in lambda light chains and negative immunofixation.

Overall, the patient tolerated the therapy quite well. There was some mild anemia that was treated with erythropoietin-stimulating agents. There was some GERD; however, this may have been related to dexamethasone. The patient continues to have grade 1 neuropathy without pain, and GFR remained stable.

Given your following options, what will be your next step in the management of this patient? Continue current cycle as planned, supportive care only; Hold treatment due to cytopenias and reassess marrow; Reduce mezigdomide dosage; or Discontinue bortezomib to reduce overlapping toxicity.

And generally, we would say the answer is A) Continue current cycle as planned, supportive care only. In general, the patient has some minor, supportive care manageable toxicities and remains in excellent disease control.

Here's the second case: a 69-year-old male patient on SUCCESSOR-2. This patient was diagnosed with IgG lambda multiple myeloma, underwent a variety of different therapies, including dara-pom-dex, RVd, cyclophosphamide-VAD, and autotransplant. The patient does have several high-risk features, including revised ISS stage III, CKD stage 3/4, and functional hypogammaglobulinemia. The current therapy is mezi-Kd, based off of the DFCI 24-302 trial, and again, this is a combination of carfilzomib and mezigdomide, with mezigdomide being administered 1 mg orally days 1 through 21 of a 28-day cycle.

Now on cycle 5, day 1, the patient is having a decreasing M-spike, which is currently nonquantifiable, but without a bone marrow, we would call this a very good partial response. Overall, hematologically, tolerating well—mild anemia, mild leukopenia, some renal insufficiency; peripheral neuropathy is stable. GI tolerance is having a little bit of issues; we had to reduce the dose of dex, and due to issues with infections, the patient is on monthly IVIg.

Now, given the following options, what will be your next step in managing this patient? A) Continue current regimen with close monitoring; B) Hold treatment and perform bone marrow biopsy; C) Discontinue mezigdomide and switch to a BCMA-directed therapy; or D) Add G-CSF and transfusion despite stable counts.

And again, the answer is A) Continue current regimen with close monitoring. The patient seems to be otherwise tolerating therapy quite well and may, in fact, be heading toward a complete remission.

I'm wanting to move on to the next session where we evaluate the role of MRD negativity, particularly in the realm of newly diagnosed multiple myeloma. So there are a number of studies that have been looking into the upfront world of myeloma and the role of CELMoDs there. Here we have the GEM-IBERDARAX study using iberdomide and dex as a CELMoD doublet for newly diagnosed, non–transplant-intended patients. Overall, the iberdomide was given at 1.6 mg, 3 weeks on and 1 week off, in a fashion that we've come to administer all of our immunomodulatory drugs, here along with weekly dexamethasone.

These patients were generally older, with a median age of 79 years, a number of them with high-risk cytogenetic features, and overall, with the doublet, we're still seeing response rates of over 80%, with almost 1/2 the patients achieving a complete remission. Again, overall, the patients are tolerating this well, with relatively low rates of hematologic toxicity.

Here we look at some triplets in the world of transplant-ineligible myeloma. And although the MAIA regimen—dara-rev-dex—has become an absolute standard in this world, we see here results from the 001 study combining iber-dara-dex in the same patient population. We have a number of patients at each dose level, and overall, almost everyone is responding. In fact, to boot, we're actually seeing MRD negativity rates topping out at around 60%.

Just to put this into perspective, in the realm of transplant-ineligible myeloma, the current quadruplet data from regimens such as CEPHEUS—Dara-RVd—has an MRD negativity rate of around 60%. So we can see here that we can actually achieve similar rates of MRD negativity with a triplet as opposed to a quadruplet—and again, in an older, frailer patient group, this may be very advantageous to spare them any potential toxicity of proteasome inhibitors.

Now, although dara-len-dex has become an absolute standard based on the MAIA study, one of the more utilized regimens based off of the SWOG 777 study in newly diagnosed transplant-ineligible patients has been VRd. Additionally, we see here iber-bortezomib-dex in a similar patient population of transplant-ineligible, newly diagnosed myeloma. This gave bortezomib on days 1, 4, 8, and 11 on a 21-day cycle, along with iberdomide 2 weeks on/1 week off.

We're seeing a median time to response of 0.7 months, a 100% overall response rate, and 1/2 the patients achieving a CR or better. These still represent small numbers, however, again, this is an excellent option for patients with relative or absolute contraindications to CD38 monoclonal antibodies, which can include more advanced reactive airway disease such as asthma and COPD.

One of the things that has evolved in the last 5 years of myeloma is our ability to achieve extremely deep and durable remissions, such that we have now started to incorporate the evaluation of MRD—or minimal residual disease—into our analytics, both in terms of disease response as well as clinical trial development and FDA drug approval.

This has been seen with a variety of available data from the i2TEAMM meta-analysis, the EVIDENCE meta-analysis, and this has been incorporated into a presentation for the U.S. FDA ODAC, which ultimately led them to approve the utilization of MRD negativity rates as a viable clinical endpoint in myeloma clinical trials.

This is critical because, at the current time, the overall survival for newly diagnosed myeloma patients is measured potentially in decades, which is not appropriate to get drugs approved in a reasonable amount of time. Additionally, progression-free survivals can range from 10 to 20 years in transplant-ineligible and -eligible patients, making that additionally an inappropriate clinical endpoint.

So MRD is allowing us to achieve endpoints much sooner and ultimately get drugs to the clinic in a much quicker fashion. Ultimately, where we go from here is to utilize MRD in the clinical management of our day-to-day patients. And one of the things that's becoming clear is that MRD is really a moving platform, and we need to evaluate it at multiple time points. So the current definition is evaluating MRD at two time points at least 1 year apart, and if they're both negative, we refer to that as sustained MRD negativity.

Where we're going with this is that when we first started treating patients with newly diagnosed myeloma, our drugs were simply too toxic to keep them on long term. However, once they became better tolerated, we were able to keep patients on from diagnosis to

death. However, we do recognize that there are probably a number of patients in modern-day therapy that have achieved such a deep remission that we could probably stop their therapy and they will do just the same.

The question is, who is that?

And one of the ways we're looking to achieve this is by identifying patients who achieve sustained MRD negativity as an approach to stopping long-term maintenance therapy—especially for those who remain on lenalidomide maintenance after autograft—in a world where lenalidomide maintenance after autograft has certainly shown an increased risk of second primary malignancy.

And we can see here that patients who do discontinue are able to maintain long remissions even off therapy.

Here we see updated data from the GEM2012MENOS6 study that, again, is trying to evaluate MRD negativity status for stopping maintenance-based therapy. At the start of maintenance, we had a number of patients who were MRD negative and positive, but patients were elected to stop if they were MRD negative for at least 2 years. And again, ultimately, we recognize that patients who are able to maintain these deep levels of remission for multiple years are potentially at the possibility of being cured, but most notably, probably will have limited difference in their overall outcomes, whether or not you continue or stop their maintenance-based therapy.

So in the quest to not only cure patients but to stop patients from the toxicity of long-term therapy, achievement of sustained MRD negativity may be the pathway to achieve that.

We have additional studies trying to evaluate the role of CELMoDs in not only achievement of MRD negativity but sustaining that MRD negativity as well. And we can see here that there are a number of clinical endpoints for these studies that are evaluating the primary endpoint of being MRD negativity at 2 years or the overall MRD negativity rate across the board, again hoping to use this data to get earlier readouts to incorporate this into our day-to-day clinical practice.

One of the most important studies to date has been the EMN26 trial evaluating the role of iberdomide as post-autograft maintenance. And in a world where lenalidomide has been the absolute standard, with ongoing studies looking at doublet maintenance such as proteasome inhibitor or CD38 monoclonal antibody added to IMiDs, we recognize that it's the achievement of and conversion to MRD negativity that probably leads to some of the better outcomes.

We've seen this even with the datasets from ORIGA comparing Revlimid to dara and Rev. Here, we can see in a variety of different cohorts the rates of conversion from MRD positive pre-maintenance to MRD negative during the maintenance period ranging from 30 to 53% is extremely impressive, noting that with lenalidomide maintenance alone, in a variety of studies, this caps out at around 18%. So the ability for us to achieve much deeper remissions with the CELMoDs and, again, overall having a better hematologic toxicity profile proves this to potentially be even a better option than multi-agent or dual maintenance therapy.

There are a number of ongoing studies evaluating the role of converting to MRD negativity in the post-transplant realm. Two studies listed here — both the COMMANDER study and the IBEX study. The COMMANDER study is looking at patients who received induction therapy with a proteasome inhibitor and IMiD plus or minus a CD38, followed by auto transplant, who achieved at least a PR, looking to see if we can further reduce their disease and get them to rates of MRD negativity with a combination of iber-dara-dex and iber-dara-Kd. And the IBEX study, looking at patients who had a daratumumab-based induction, who achieved at least a PR, is looking at iber plus dara to see if we can convert these patients to MRD negativity, really waiting to see some of the long-term readouts from these amazing studies.

One of the studies that I'm really excited to be part of at my institution is the DETERMINATION-2 study. This follows on the heels of the DETERMINATION-1 study, which was undertaken by Dr. Richardson and many others starting in 2009 and culminating in the *New England Journal of Medicine* publication in 2022. DETERMINATION-2 seeks to one-up that approach in newly diagnosed myeloma and provide a number of MRD-driven pathways to lead to either cure or extremely durable remission.

Ultimately, patients will receive induction therapy with a quadruplet regimen of isatuximab, iberdomide, bortezomib, and dexamethasone, and then be randomized based on their MRD status to either undergo maintenance with iber and isa and then either stop maintenance or continue, versus randomization to either receive high-dose therapy with autologous stem cell transplant or consolidation with the BCMA bispecific linvoseltamab, either of those two arms reserved for patients with either high-risk disease or MRD positive disease, ultimately going on to long-term maintenance with isatuximab and iberdomide until progression or intolerance.

And although this trial will take quite a long time to read out, we're hopeful that it will provide an MRD-driven analysis of how to pick the optimal strategy for a patient based not only on their presentation but their functional response to a variety of different upfront therapies.

So, in conclusion, there are a number of phase 2 and ongoing phase 3 studies looking at the role of CELMoDs, iberdomide and mezigdomide, both in relapsed/refractory and newly diagnosed myeloma. In the relapsed/refractory world, there's a number of

combinations, including combinations with CD38 monoclonal antibodies as well as proteasome inhibitors, which are probably going to lead to the first few approvals.

However, additional studies—particularly oral options targeting the MEK, RAS, RAF, ERK pathways, including drugs like tazemetostat—provide a number of interesting options in patients who are post-BCMA-based therapies. Additionally, other oral combinations with either ixazomib or cyclophosphamide provide additional well-tolerated and already established therapeutic options for patients who want an all-oral triplet.

Additionally, we're looking into the roles of combinations with bispecific antibodies to augment the T-cell response. In the newly diagnosed realm, we're looking to transfer some of our already standard approaches with triplets and quadruplets with lenalidomide to see if we can augment them with iberdomide and provide deeper rates of MRD negativity and better long-term tolerance, especially in the realm of hematologic toxicity. And along the way, utilizing MRD to help guide us in terms of when to start, when to stop, when to transplant, and when not to for our newly diagnosed patients, so that we don't have to keep them on forever therapy.

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