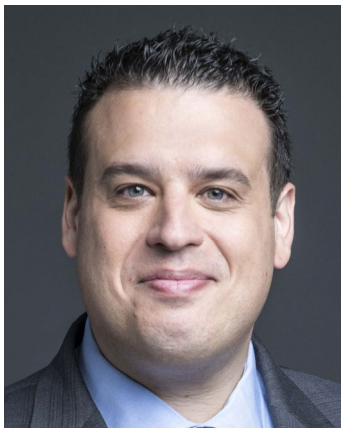

Joshua Richter, MD, FACP
Associate Professor of Medicine
Tisch Cancer Institute
Icahn School of Medicine at Mount Sinai
Director of Myeloma
Blavatnik Family Chelsea Medical Center at Mount Sinai
New York City, New York

Andrew Yee, MD
Clinical Director, Center for Multiple Myeloma
Massachusetts General Cancer Center
Massachusetts General Hospital
Assistant Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Joshua Richter: Hello, and welcome back to the second episode of our three-part series on CD38-directed strategies and the treatment of multiple myeloma. My name is Dr. Joshua Richter and 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. I am joined by the esteemed Dr. Yee. Sir, please introduce yourself.

Andrew Yee: Thank you, Josh, for starting the introduction. I'm Andrew Yee. I focus on multiple myeloma at Massachusetts General Hospital, where I'm the Clinical Director of the Center for Multiple Myeloma, and I'm an Assistant Professor of Medicine at Harvard. Thank you, Josh. Looking forward to talking about CD38.

Dr. Richter: I'm sure we'll get right into fighting words here. So, for those of you who tuned into our first episode where we talked about CD38-directed strategies in the newly diagnosed patients, today we'll be talking about the evolving role of anti-CD38 strategies in the relapsed/refractory setting of myeloma. And if you missed the last one, don't worry, you can find it in our series playlist.

Today, we're going to look at relapse, and much of this discussion will focus on the early relapse setting. In myeloma, we generally define early relapse as one to three prior lines of therapy. As anti-CD38 therapy has become a mainstay of our induction strategies, it's become a key component of our early relapse and refractory strategies, as well. So, Andrew, I'll throw

In MM, early relapse is generally defined as one to three prior lines of therapy.

it to you. Tell me how you approach treatment in early relapsed myeloma patients, specifically around anti-CD38-based strategies.

Dr. Yee: Right. If you've listened to our first podcast, we talked about how amazing the CD38-based regimens are and how myeloma therapies have evolved dramatically since their approval. However, the reality is that patients do relapse. Fortunately, though, when patients do relapse, we have great therapies and combinations of therapies. Some of the principles that I consider when I'm thinking about relapsed disease are basic oncology 101: I think about the patient's performance status, comorbidities, prior treatments, the patient's wishes. It's standard oncology practice.

Biochemical relapse: rises in monoclonal protein or free light chains without symptoms

I do think myeloma's a little different, though, in the sense that we need to consider the type of relapse the patient is experiencing, specifically a biochemical relapse versus a clinical relapse. In myeloma, once patients have started therapy, they're usually monitored more frequently. And when a patient is monitored more frequently, you're more likely to detect rises in monoclonal protein or light chain – and hence, biochemical relapse. One distinction between a biochemical relapse, in which the patient generally doesn't have symptoms but the clinician detects a rise in one of the myeloma-related markers, versus a clinical relapse is that, in a clinical relapse, the patient develops symptoms – a new bone lesion or a new anemia or renal dysfunction. These are different scenarios and the question of biochemical versus clinical relapse influences how I think about treatment.

Clinical relapse: the patient develops symptoms such as new bone lesions, anemia or renal dysfunction

MM patients treated at biochemical relapse demonstrated improved OS compared to patients treated at clinical relapse.[1]

A related question then is, should you wait for a patient to have a clinical relapse? If a patient has a biochemical relapse, but has no symptoms, should you hold treatment until a clinical relapse occurs? In looking at a retrospective analysis from Mayo Clinic in which they studied patterns of relapse following stem cell transplant, they looked at patients who were treated at the time of biochemical relapse versus those who were treated at clinical relapse, and they found that the patients who were treated at biochemical relapse tended to do better.[1] Now, you might think that the patients who had biochemical relapse simply had better biology, and that's why they did better, right? Because those patients are all going to have low-stage disease. But it turns out that, when you look at the ISS staging and the FISH, the data is very similar between the biochemical and the clinical relapse groups. And yet the patients who were treated for biochemical relapse tended to do better.

So, when you think about the extent to which treatment strategies have changed in myeloma, you think about how often we're now using CD38 antibodies as part of our initial treatment; if you had listened to our first podcast, you may be thinking about using CD38 antibody upfront. But we do still have patients who are CD38-antibody-naive. For the purposes of this discussion about early relapse following one to three prior lines of therapy, let's focus on the patient who is not CD38 antibody-naïve, someone who's relapsed following treatment with a CD38 antibody. Of course, I could throw a monkey wrench into this whole discussion and talk about CARTITUDE for CAR T-cell therapies[24], but we won't do that.

Dr. Richter: I think you bring up a great point, because if you look at the NCCN guidelines for early relapse, the first page says bortezomib-refractory or lenalidomide-refractory. They don't have a section on CD38-refractory[2] because right now, that's still a minority of patients in the US. As we talked about in the upfront setting, newly diagnosed patients are classified as either transplant-eligible or transplant-ineligible and in the US, the majority of patients in the US filter down to lenalidomide. The patient either gets Dara-Rd or VRd upfront and then many people continue on lenalidomide until relapse, or the patient gets VRd or Dara-VRd, transplant and then lenalidomide maintenance.[3] So, I think many people enter relapse either CD38-naive or had a response to CD38 and didn't progress on it and so are still CD38-sensitive. I think that's a great jumping off point: we have a patient for whom a CD38 could still be an option. How do you approach that patient? Does your approach differ between biochemical or clinical relapse?

NCCN guidelines for early relapse in MM address bortezomib- and lenalidomide-refractory disease, with no guidance yet for CD38-refractory patients.[2]

Many patients in the US are treated with DRd or VRd upfront with lenalidomide until relapse, or VRd or Dara-VRd to transplant followed by lenalidomide maintenance.[3]

Dr. Yee: Right. So, for the purpose of the framing discussion, let's take the stereotypical patient: they had RVd plus or minus transplant and are now on lenalidomide maintenance. So, thinking about the patient in front of you, is it a biochemical relapse or is it a clinical relapse? As a starting point, if the patient hasn't had a CD38 antibody yet, in general, now is a good time to think about treatment with a CD38 antibody. It's one of the best therapies we have and if the patient hasn't had it already, now is the opportunity to use it. The next question then becomes, what's the partner drug? We've had multiple trials to help us think about the partners to choose. It's not like a marriage where you're looking for a partner or like you're going to a dance.

Choosing the partner therapy to a CD38 mAb isn't like a marriage; it's more like a dance partner

Dr. Richter: No, I think about CD38 more like a dance partner.

Dr. Yee: So, maybe the analogy isn't that far off?

Dr. Richter: You know, myeloma drugs don't follow the Billy Idol principle of "dancing with myself". They want to follow the Whitney model, "I want to dance with somebody". And that's where we have to say, who's the dance partner?

MM-014b: phase 2 trial of pomalidomide-dexamethasone-daratumumab immediately after lenalidomide treatment[4]

Dr. Yee: Right, right. So, CD38 antibody: I typically think of the partner drug, because I think, in general, combinations with CD38 antibodies work better. We can think of either partnering with pomalidomide or with carfilzomib. There are four types of trials: some are with daratumumab and some are with isatuximab, and, for the partner, some are with pomalidomide and some are with carfilzomib. Just to keep it simple, for patients who have a clinical relapse, I

think about the MM-014b study, which was daratumumab-pomalidomide-dexamethasone in lenalidomide-refractory patients.[4]

The patient on lenalidomide maintenance is a patient who's been through a lot with their initial therapy. They may have had a transplant and now they're on Len maintenance; they have a great quality of life, they're back to the routine. And then you tell them, "Oh, I think you have relapsing disease". For a biochemical relapse, I think a CD38 antibody plus pomalidomide-dex is a great regimen because of the schedule and the side effect profile. I tend to lean towards that regimen. On the other hand, for a patient who has a clinical relapse with a new lytic bone lesion, the carfilzomib-based regimen can sometimes be more effective.

For the patient who has a biochemical relapse on lenalidomide maintenance, a CD38 mAb-Pom-Dex regimen may be a good option, based on schedule and side effect profile.

OPTIMISMM: phase 3 trial of pom-Vd in patients who have become lenalidomide-refractive[5,6]

Another point to think about is the question of an IMID: if you have a patient on lenalidomide and they're progressing on an IMID, would an IMID still work in the relapse setting? I think pomalidomide definitely has efficacy in patients who are lenalidomide-refractive based on the OPTIMISMM study.[5,6]

Dr. Richter: Dara-Pom was the focus of another study: the MMCC4047-014 study specifically looked at Len-refractory going to Dara-Pom.[7]

CC4047-MM-014: Dara-pom-dex in patients who have become lenalidomide-refractive[7]

Dr. Yee: Exactly. And they showed a PFS of about two years. You know, Josh, if you were to put me to a wrestling mat and say, compare carfilzomib with pomalidomide (obviously I know you would win), but I don't think there's going to be a head-to-head trial of carfilzomib and pomalidomide. I will acknowledge that carfilzomib-based regimens probably have more juice to them. If there would be a head-to-head trial of CD38-carfilzomib versus CD38-Pom, I think the CD38-carfilzomib would probably be more effective than CD38-Pom. That's just extrapolating from studies like CANDOR[8] and IKEMA.[9] Initially, with CANDOR and IKEMA, about 50% of the patients were lenalidomide-naïve; but, if you looked at the lenalidomide-refractory patients in these two carfilzomib studies, you still saw a significant benefit in those patients. For the patient who has a clinical relapse and you need a regimen with a little more juice to it, I would lean towards a CD38 antibody plus a carfilzomib-based regimen.

CANDOR: phase 3 trial of Dara-Kd vs Kd in RRMM[8]

IKEMA: phase 3 trial of Isa-Kd vs Kd in RRMM[9]

Dr. Richter: I would completely agree. If you look at the treatment patterns in the US, there are many options in the relapsed setting. The number one prescribed regimen in early relapse is going to be Dara-Pom, with about 10 to 12 percent of patients getting that regimen in the first relapse.

Dr. Yee: 10 to 12% doesn't sound like a lot, Josh.

Dr. Richter: Yes, but if you think about the literally dozens and dozens of options, 10 to 12% is actually pretty high. I think we have to draw from both the EQUULEUS study[10] and from ICARIA[11] looking at either Dara-Pom or Isa-Pom. And I agree, I always separate patients with different types of relapse: you call them clinical and biochemical relapse, I tell patients it's the "I-tell-you" or "you-tell-me" version. The "I-tell-you" is you come in, you feel fine and yep, your M spikes up, so we need to switch. Or, you have new bone pain or a similar problem and you come in feeling horrible and you're telling me.

EQUULEUS: trial evaluating the safety of Dara-pom-dex in RRMM[10]

ICARIA: Isa-pom-dex vs pom-dex in RRMM[11]

So, I completely agree: for convenience's sake, and the fact that you can spread out the doses, I give a CD38 with Pom for the kinder, gentler regimens. And while it's difficult to compare trial to trial, you mentioned PFS ranges around two years and we then start getting into the CANDOR[8] and IKEMA[9] world, Dara plus carfilzomib and Isa plus carfilzomib. I couldn't agree more: there are two reasons to worry and to think about more aggressive treatments. For the patient who's in clinical relapse with big time renal failure or bone lesions, I tend to be more aggressive. I also use aggressive regimens with the functionally high-risk. Yes, you can go from IMID to IMID and if you were on lenalidomide maintenance for five years, I have no problem switching to pomalidomide. But if you were on lenalidomide maintenance for six to 12 months, I'm pushing quicker to those other regimens. When we look at CANDOR and IKEMA, we're getting PFS rates that go from around 30 months to around 40-month median progression-free survival in IKEMA, which rivals some of the outcomes that we're seeing in some of the early CAR T studies. Of note, those studies that compared CAR T-cell therapies head-to-head with CD38-based therapies excluded CD38 plus carfilzomib, for exactly your point. And I love the term, I'm going to steal it: it just has more juice.

Dr. Yee: I think the timing of the relapse is key, right? Because if somebody's been on Len maintenance for five years, it's not necessarily going to be high-risk; whereas if you progress within a year on Len maintenance, that does feel high-risk. From a practical standpoint, in the pomalidomide arms of APOLLO[12] and ICARIA[11], for example, we saw a fairly high rate of neutropenia with pomalidomide four milligrams. Because of that, I think you have to be generous with the use of GCSF and, for some patients, I do think about using a lower dose of pomalidomide – not necessarily four milligrams; you can think about three milligrams, and some people use two milligrams.

APOLLO: phase 3 trial of Dara-pom-dex vs pom-dex in RRMM[12]

ICARIA: Isa-pom-dex vs pom-dex in RRMM[11]

Dr. Richter: Yes, I was going to ask, are you a "go low and then raise it up"? Or are you "max dose and then back off" kind of guy?

Dr. Yee: I generally split the difference and start at three, actually.

Dr. Richter: I have to admit, I used to be a four and I started reducing so much that now, I agree: I do a lot of three and I see a lot of my colleagues even using two, for exactly the reasons you talked about.

Dr. Yee: I think pomalidomide three milligrams is probably easier. And then, with carfilzomib, I think about the dosing schedule. You mentioned IKEMA[9] and CANDOR[8], and you know, in those studies, they used a twice-a-week carfilzomib. But in clinical practice, I think once-a-week is the way to go. So, Josh, are you a 70 mg/m^2 carfilzomib with CD38? Or are you more of a 56 mg/m^2 weekly?

IKEMA[9] and CANDOR[8] used twice-weekly carfilzomib dosing, but in clinical practice, once-weekly carfilzomib may be more appropriate

Dr. Richter: I completely agree: it's once-a-week and I have to admit that I'm not so bold as 70 mg/m^2 once-a-week as we saw in CHAMPION[13] and some of the older trials. I'm a 56 mg/m^2 once-a-week. How about you?

Dr. Yee: Exactly, I do 56 mg/m^2. In the trials, they used carfilzomib twice-a-week on weeks one, two, three out of four. Once patients have a response, I'm pretty quick to change the dosing to carfilzomib every other week.

Dr. Richter: Absolutely. That's another great point: we think about induction and maintenance in the upfront setting very readily, and the point that you just made isn't always thought about in the relapsed setting. But I do exactly what you do: I start patients off at days one, eight and 15 weekly, and when we get 4 to 6 months down the road, I switch to an every other week schedule. So, if you're using a Dara-carfilzomib combination, you get Dara and carfilzomib this week, carfilzomib two weeks later. For isatuximab, this schedule actually dovetails nicely because then, when we move into the maintenance setting, both drugs are given every other week.

For daratumumab-carfilzomib and isatuximab-carfilzomib, consider adjusting dosing schedules

Dr. Yee: I just want to emphasize that how we practice doesn't always reflect what's published in the clinical trials. So, when you hear about the results of a trial, what's missing is, how does Dr. Richter actually use these agents in Chelsea? I think it's just different.

Dr. Richter: We've talked about the CD38 plus carfilzomib and the CD38 plus pomalidomide. Andrew, are there any other secret hidden pathways of using CD38s, either by itself or in combination with other drugs, other dance partners?

Dr. Yee: Other dance partners, yeah. I think one emerging area involves translocation 11;14. When I think about relapsed disease, knowledge of whether or not the patient has a translocation is increasingly important, because we need to think about BCL-2 inhibition, specifically with venetoclax. I know that the CANOVA data that was presented in Greece was interpreted as a negative study,[14-17] but there were some complicated factors with how IMWG response is interpreted, et cetera. I think in clinical

Translocation 11;14 is an important consideration in identifying treatment regimens in RRMM

Daratumumab-venetoclax combination therapy has demonstrated efficacy in patients with translocation 11;14[18]

practice, Josh, venetoclax for patients with translocation 11;14 can have amazing efficacy. And so, if a patient has translocation 11;14 and has not been treated with a CD38 antibody, there is data that suggests that the combination of daratumumab and venetoclax can work quite well.[18] Concerning the dosing of venetoclax, I think about 400 milligrams, not 800 milligrams as it's been presented. Again, dosing is important in minimizing possible side effects.

Then, we've talked a lot about triplet and quadruplet combinations, but there is the occasional patient for whom daratumumab or a CD38 antibody as a single agent can work quite well. The problem, though, is that you don't know ahead of time who those patients are going to be, the ones in which a single agent just works exceptionally well.

STOMP: Phase 2 trial of oral selinexor, pomalidomide and dexamethasone (XPd) in RRMM[19]

Dr. Richter: I completely agree. I have two other CD38 combinations that I think are important. One of them involves the emerging data about CD38 and selinexor. This has been studied in the STOMP trial, but there's been some genomic work recently on non-overlapping genomic sub-cohorts, where the type of disease that tends to be refractory to selinexor is more sensitive to Dara or Isa and vice versa.[19] It turns out that CD38 takes about 4 to 6 months to repopulate on the cell surface.[20] With daratumumab moving into early lines, if I have someone who gets Dara early on and then gets carfilzomib-pomalidomide-dex in the next line, and then 4 to 6 months later or beyond relapses, I've been using a fair amount of isatuximab along with selinexor in the clinic, both to reintroduce the CD38 and the synergy with selinexor.

Consider isatuximab-selinexor regimen if a patient relapses following Dara, carfilzomib-pomalidomide-dex treatment

The other area that I've had some success with, is the combination of CD38 monoclonals and oral cyclophosphamide. I've been using this combination in some older patients, if single agent Dara isn't quite effective enough and they have issues either tolerating or affording IMIDs; and, as we've talked about, carfilzomib and bortezomib can both have their own toxicities. In these patients, I've had some good outcomes in getting immunogenic cell death with oral cyclophosphamide in combination with a CD38 monoclonal antibody, either Dara or Isa. So, I agree – with everything we've discussed this time and in our last podcast, I think it's clear that CD38s are turning out to be the Swiss army knife of myeloma therapies.

Consider combinations of CD38 mAbs-oral cyclophosphamide in some older patients

Dr. Yee: Right. CD38 can partner with just about anybody; it's a flexible partner. Thinking about partners like cyclophosphamide, there's also the Canadian study that looked at daratumumab with cyclophosphamide and pomalidomide.[21] I really can't think of a specific situation where you couldn't use a CD38 antibody, actually. There are so many different permutations that have been studied and with very few exceptions, there just aren't many limitations on the agents you can combine with a CD38 antibody.

CMRG 004: phase 2 trial of daratumumab-dexamethasone-cyclophosphamide with or without pomalidomide in RRMM[21]

Dr. Richter: I think the only area that you have to proceed with a little extra care involves possible pulmonary side effects. We know that CD38 is expressed in the pulmonary vasculature.[22] While this is more of a concern in the package insert for daratumumab than it is for isatuximab, the caution concerning patients with severe reactive airway disease applies to both of our currently approved CD38 antibodies. I don't know how you approach these patients, Andrew; I give montelukast (Singulair) for at least three days prior to the first dose, to prevent any untoward bronchospasm or reactive airway events.[23] I don't know if you have any tips or tricks for patients with severe COPD.

Montelukast (Singulair) may be used to reduce bronchospasm or reactive airway events in patients treated with CD38 mAbs[23]

Dr. Yee: With Dara sub-Q, we do use Singulair as part of the prophylactic regimen. I haven't been pre-treating patients with Singulair, but on the day of treatment, they do get Singulair; I just haven't seen any issues with patients with reactive airway disease. Also, as a side note, there's an observation period required after the CD38 antibody. We used to watch patients for four hours after sub-Q Dara, but we realized that nothing was happening in those four hours. So now, in our practice we watch patients for 30 minutes after their very first dose and then they're discharged. I think this really emphasizes how CD38 is just a great dance partner for almost any drug.

Dr. Richter: Absolutely. So, as you and I continue to dance our way towards the end of this podcast, just like in our last episode, you go into the office of a hematologist/oncologist and you have two minutes with them in between patients number 35 and 36 for the day. You want to talk to them about the role of CD38 and relapsed/refractory disease. Can you give us a couple of bullet points that you would absolutely hammer home?

Dr. Yee: Right. I think the key is that, if the patient hasn't been treated with a CD38 antibody by now, this is the time to use it. I think about some of the key combinations and the stereotypical patients, the lenalidomide maintenance patient, I think about clinical relapse versus biochemical. If it's a biochemical relapse, I tend to think about pomalidomide; if it's a clinical relapse, I tend to think about carfilzomib. I'm also careful with the dosing of both carfilzomib and pomalidomide: I think a lower dose translates into better tolerability and patients are able to stay on the drug longer.

Patients who have relapsed and are CD38 mAb-naïve should be treated with a CD38 mAb regimen at relapse.

Adjust dosing and choice of carfilzomib vs pomalidomide based on patient- and disease-specific characteristics.

Dr. Richter: I couldn't agree more: the dose of pomalidomide is absolutely key to the success of that regimen. You brought up earlier that this is not classical chemo, so, judicious use of myeloid growth factors is needed. I would also say prior to a carfilzomib-based regimen, I like to get a baseline echocardiogram, although I completely agree with you that the majority of patients don't have any issues. It's just always nice to have a good baseline at the

Consider baseline echocardiogram prior to carfilzomib-based therapy.

Consider montelukast (Singulair) in patients with non-cardiac dyspnea treated with carfilzomib.

beginning, because if you haven't done an echo in a while and the patient gets a little short of breath, you want to know what's going on. I've had a few patients with non-cardiac dyspnea who were treated with carfilzomib and we just give them more Singulair, which works pretty well.

So, I agree, CD38 loves to dance with everything. If you haven't used CD38 in early relapse, it's time to bring in that dance partner with its fancy shoes. That'll take us to the end of this podcast. We'd really like to thank you for joining us today as we evaluate some of our options in the relapsed and refractory setting using CD38 monoclonal antibodies.

Looking forward to our next podcast, where we're going to be talking about future directions in clinical trials and some of the cutting-edge approaches that we'll be seeing in the next five, ten years and beyond. If you have any questions concerning any of the information that's been presented today, you can simply scan the QR code on the screen and submit your questions.

All questions will be answered in a series of e-newsletters following the release of this podcast series. Please complete the continuing education evaluation to claim your credit, and be sure to download the reference resource associated with this podcast. Please don't forget to either check out the podcast before or after this one. On behalf of myself and Dr. Andrew Yee, I'd like to thank you for joining us on this series of understanding the role of CD38-targeting agents in multiple myeloma. Thank you.

We hope you found this discussion informative and insightful. If you have any questions about the content discussed, please scan the QR code or visit https://www.surveymonkey.com/r/YTFYWMR to submit your questions.

Questions will be answered in a series of e-newsletters following the conclusion of the podcast series.

References

1. Sidana S, Tandon N, Dispenzieri A, et al. Relapse after complete response in newly diagnosed multiple myeloma: implications of duration of response and patterns of relapse. *Leukemia.* 2019 Mar;33(3):730-738. doi: 10.1038/s41375-018-0271-1. Epub 2018 Oct 15. PMID: 30323358.

2. Kumar S, Callander NS, Adekola K, et al. NCCN Clinical Practice Guidelines in Oncology, Multiple Myeloma, Version 2.2024. *J Natl Compr Canc Netw*. 2023;21(12):1281–1301. doi: https://doi.org/10.6004/jnccn.2023.0061

3. Rajkumar, SV, Kumar, S. Multiple myeloma current treatment algorithms. *Blood Cancer J.* 2020 Sep 28;10(9):94. https://doi.org/10.1038/s41408-020-00359-2

4. Bahlis NJ, Siegel DS, Schiller GJ, et al. Pomalidomide, dexamethasone, and daratumumab immediately after lenalidomide-based treatment in patients with multiple myeloma: updated efficacy, safety, and health-related quality of life results from the phase 2 MM-014 trial. *Leuk Lymphoma.* 2022 Jun;63(6):1407-1417. doi: 10.1080/10428194.2022.2030477. Epub 2022 Feb 8. PMID: 35133221.

5. Richardson PG, Oriol A, Beksac M, et al. OPTIMISMM trial investigators. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2019 Jun;20(6):781-794. doi: 10.1016/S1470-2045(19)30152-4. Epub 2019 May 13. PMID: 31097405.

6. Dimopoulos M, Weisel K, Moreau P, et al. Pomalidomide, bortezomib, and dexamethasone for multiple myeloma previously treated with lenalidomide (OPTIMISMM): outcomes by prior treatment at first relapse. *Leukemia.* 2021 Jun;35(6):1722-1731. doi: 10.1038/s41375-020-01021-3. Epub 2020 Sep 7. PMID: 32895455; PMCID: PMC8179841.

7. Pierceall WE, Amatangelo MD, Bahlis NJ, et al. Immunomodulation in Pomalidomide, Dexamethasone, and Daratumumab-Treated Patients with Relapsed/Refractory Multiple Myeloma. *Clin Cancer Res.* 2020 Nov 15;26(22):5895-5902. doi: 10.1158/1078-0432.CCR-20-1781. Epub 2020 Sep 14. PMID: 32928795.

8. Dimopoulos M, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study. *Lancet.* 2020 Jul 18;396(10245):186-197. doi: 10.1016/S0140-6736(20)30734-0. Erratum in: *Lancet.* 2020 Aug 15;396(10249):466. PMID: 32682484.

9. Moreau P, Dimopoulos MA, Mikhael J, et al. IKEMA study group. Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial. *Lancet.* 2021 Jun 19;397(10292):2361-2371. doi: 10.1016/S0140-6736(21)00592-4. Epub 2021 Jun 4. PMID: 34097854.

10. Chari A, Suvannasankha A, Fay JW, et al. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. *Blood.* 2017 Aug 24;130(8):974-981. doi: 10.1182/blood-2017-05-785246. Epub 2017 Jun 21. PMID: 28637662; PMCID: PMC5570682.

11. Attal M, Richardson PG, Rajkumar SV, et al. ICARIA-MM study group. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. *Lancet.* 2019 Dec 7;394(10214):2096-2107. doi: 10.1016/S0140-6736(19)32556-5. Epub 2019 Nov 14. Erratum in: *Lancet.* 2019 Dec 7;394(10214):2072. PMID: 31735560.

12. Dimopoulos MA, Terpos E, Boccadoro M, et al. APOLLO Trial Investigators. Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial. *Lancet Oncol.* 2021 Jun;22(6):801-812. doi: 10.1016/S1470-2045(21)00128-5. PMID: 34087126.

13. Berenson JR, Cartmell A, Bessudo A, et al. CHAMPION-1: a phase 1/2 study of once-weekly carfilzomib and dexamethasone for relapsed or refractory multiple myeloma. *Blood.* 2016 Jun 30;127(26):3360-3368. doi: 10.1182/blood-2015-11-683854. Epub 2016 May 12. PMID: 27207788; PMCID: PMC4929927.

14. Kumar S, Kaufman JL, Gasparetto C, et al. Efficacy of venetoclax as targeted therapy for relapsed/refractory t(11;14) multiple myeloma. *Blood.* 2017 Nov 30;130(22):2401-2409. doi: 10.1182/blood-2017-06-788786. Epub 2017 Oct 10. PMID: 29018077.

15. Gupta VA, Barwick BG, Matulis SM, et al. Venetoclax sensitivity in multiple myeloma is associated with B-cell gene expression. *Blood.* 2021 Jul 1;137(26):3604-3615. doi: 10.1182/blood.2020007899. PMID: 33649772; PMCID: PMC8462405.

16. Touzeau C, Dousset C, Le Gouill S, et al. The Bcl-2 specific BH3 mimetic ABT-199: a promising targeted therapy for t(11;14) multiple myeloma. *Leukemia.* 2014 Jan;28(1):210-212. doi: 10.1038/leu.2013.216. Epub 2013 Jul 17. PMID: 23860449; PMCID: PMC3887407.

17. Mateos MV, Beksac M, Dimopoulos MA, et al: Results from the randomized, open-label phase 3 CANOVA study of venetoclax-dexamethasone versus pomalidomide-dexamethasone in patients with t(11:14)-positive relapsed/refractory multiple myeloma. International Myeloma Society 2023 Annual Meeting. Abstract OA-52. Presented September 29, 2023.

18. Bahlis NJ, Baz R, Harrison SJ, et al. Phase I Study of Venetoclax Plus Daratumumab and Dexamethasone, With or Without Bortezomib, in Patients With Relapsed or Refractory Multiple Myeloma With and Without t(11;14). *J Clin Oncol.* 2021 Nov 10;39(32):3602-3612. doi: 10.1200/JCO.21.00443. Epub 2021 Aug 13. PMID: 34388020; PMCID: PMC8577687.

19. White D, Chen C, Baljevic M, et al. Oral selinexor, pomalidomide, and dexamethasone (XPd) at recommended phase 2 dose in relapsed refractory multiple myeloma (MM). *J Clin Oncol.* 2021;39(15_suppl):8018. https://doi.org/10.1200/JCO.2021.39.15_suppl.8018.

20. Dwivedi S, Rendón-Huerta EP, Ortiz-Navarrete V, Montaño LF. CD38 and Regulation of the Immune Response Cells in Cancer. *J Oncol.* 2021 Feb 27;2021:6630295. doi: 10.1155/2021/6630295. PMID: 33727923; PMCID: PMC7936891.

21. Sebag M, Bahlis N, Venner C, et al. CMRG 004: A Randomized Phase II, Open Label, Study of Daratumumab, Weekly Low-Dose Oral Dexamethasone and Cyclophosphamide with or without Pomalidomide in Patients with Relapsed and Refractory Multiple Myeloma. *Blood* 2019; 134 (Supplement_1): 3121. doi: https://doi.org/10.1182/blood-2019-124457

22. Guedes AG, Dileepan M, Jude JA, et al. Role of CD38/cADPR signaling in obstructive pulmonary diseases. *Curr Opin Pharmacol.* 2020 Apr;51:29-33. doi: 10.1016/j.coph.2020.04.007. Epub 2020 May 29. PMID: 32480246; PMCID: PMC7529733.

23. Chari A, Mark TM, Krishnan A, et al. Use of Montelukast to Reduce Infusion Reactions in an Early Access Treatment Protocol of Daratumumab in United States Patients with Relapsed or Refractory Multiple Myeloma. *Blood*. 2016;128(22):2142. doi: https://doi.org/10.1182/blood.V128.22.2142.2142

24. San-Miguel J, Dhakal B, Yong K, et al. Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma. *N Engl J Med.* 2023;389:335-347 DOI: 10.1056/NEJMoa2303379

Provided by MediCom Worldwide, Inc.
This activity is supported by an educational grant from sanofi-aventis US LLC