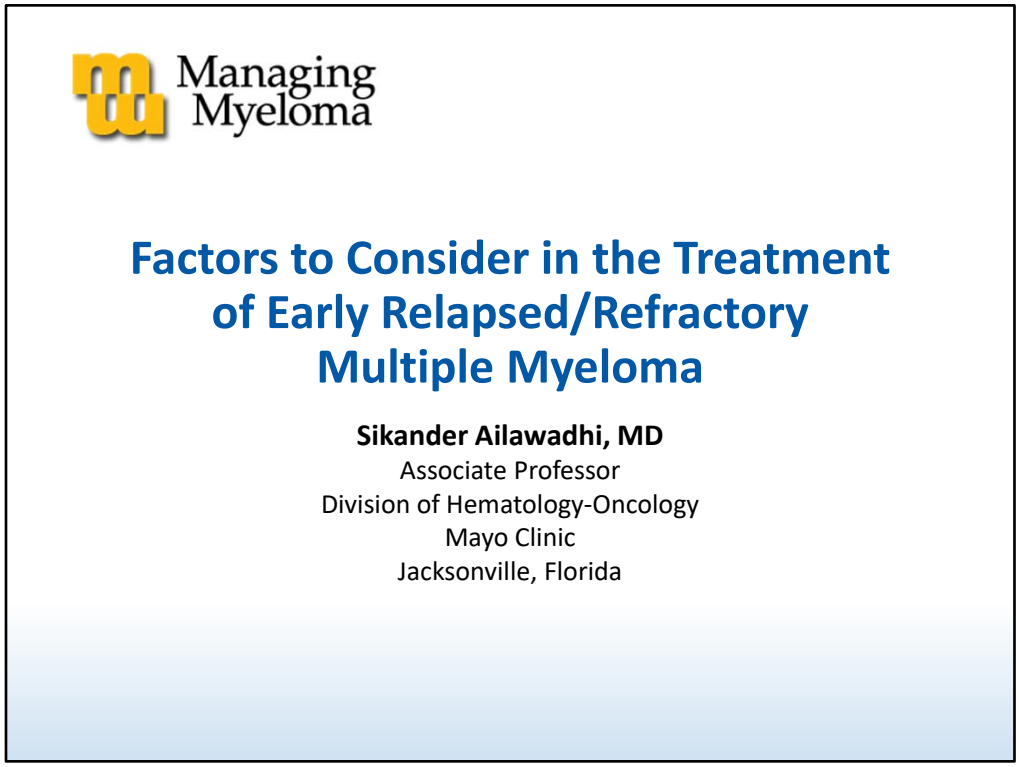
# Factors to Consider in the Treatment of Early Relapsed/Refractory Multiple Myeloma




Hello everybody and welcome to this program on *Managing Myeloma*. I'm Sikander Ailawadhi. I'm one of the hematologists focused on multiple myeloma care at Mayo Clinic in Jacksonville, Florida.

Treatment for multiple myeloma has become very complicated with a lot of treatment options, a lot of clinical data that comes from different meetings, journals, clinical trials, but it has also brought with it a lot of opportunity for patient care. Outcomes of patients are improving, but it's also important to put the things in perspective so that we as practitioners, as physicians focused on multiple myeloma, can try to take the most appropriate treatment decision for patients. So, today's activity, we'll be focusing on factors to consider in the treatment of early relapsed/refractory multiple myeloma.

## Multiple Myeloma Can be Divided into Three Categories

- Management of a newly diagnosed patient
- Management of patients who are relapsed/refractory but within the first few lines of therapy (generally three to four lines of treatment)
- Relapsed/refractory patients with disease treated much more heavily with many different regimens

You will realize that multiple myeloma can be divided into three broad categories: the management of a newly diagnosed patient, management of patients who are relapsed/refractory but within the first few lines of therapy, generally three to four lines of treatment, and then relapsed/refractory patients with disease that has been treated much more heavily with many more different regimens.

So today, we will be focusing on management of a multiple myeloma patient within the first few lines of therapy after the disease has relapsed or has become refractory.

## Learning Objectives

- Outline factors to consider when selecting therapy for patients with RRMM, including patient age and frailty, history of prior treatments, early versus late relapse, and others
- Summarize current evidence regarding available therapeutic options in RRMM and strategies to select the most optimal option for a given patient

The learning objectives for today's talk and today's program are outlining the factors to consider when selecting therapies for patients with relapsed/refractory multiple myeloma, including factors such as patient age, frailty, history of prior treatments, early versus late relapse, etc.

And also, summarizing the current evidence regarding available therapeutic options for relapsed/refractory multiple myeloma patients and strategies to select the most optimal option for any given patient based on what they have been treated with before, their clinical features, etc.

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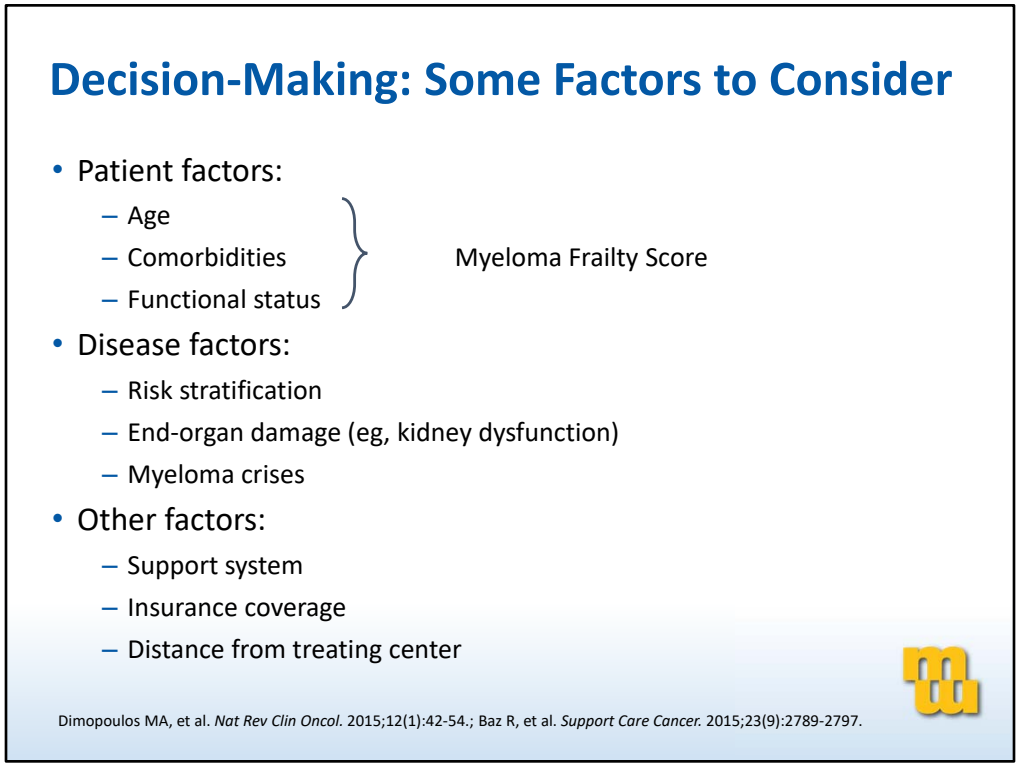


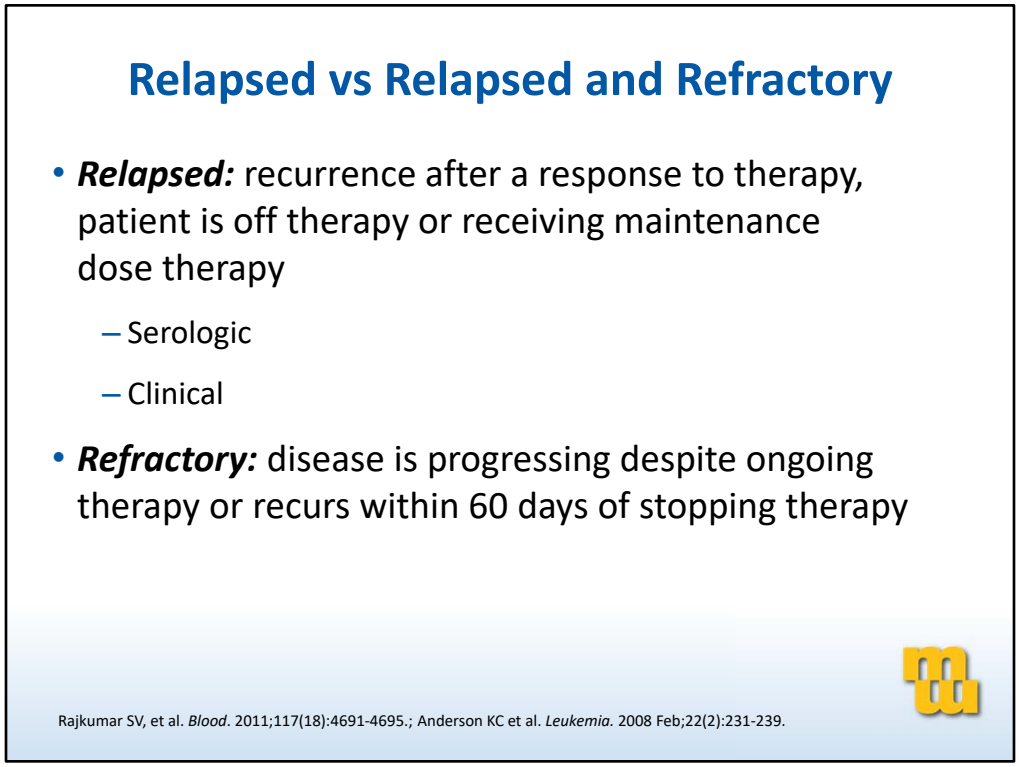

When we look at a patient who has had a multiple myeloma diagnosis, and we are trying to figure out what is the most appropriate treatment for them, there are several factors that we need to consider. Now, very frequently, a lot of these factors have been mentioned for patients who are newly diagnosed with multiple myeloma. But as you will realize from your practice, and I'm sure you have seen in your day-to-day work, most of these factors actually apply for patients with relapse or refractory disease also. So, for example, patient factors including age, comorbidities, how functional is the patient with their activities of daily living or instrumental activities of daily living, called ADLs, and IADLs, all of this goes into the myeloma frailty score. In fact, most recently modified myeloma frailty score has been brought up which has simplified the frailty calculation for patients a little bit better. It is important to note that while the frailty score has been mostly reported with newly diagnosed patients, the same can be used practically for relapsed patients as well. Of course, that has not been validated in large data sets, but in day-to-day practice at least, it provides a very practical source or guide to figure out what may be appropriate for patients and what they may tolerate.

Similarly, there are factors associated with the disease itself like risk stratification, (ie, whether a patient is high risk or standard risk). While we utilize that in newly diagnosed patients, again, patients who have high risk of relapse disease are probably going to be treated a little bit different as compared to patients who are standard risk disease. Similarly, is the patient presenting with any end organ damage like kidney dysfunction? So, which may be the most appropriate treatments to choose there, what dose adjustments need to be made, etc. Also, is the patient presenting with what is called a myeloma crisis?

For example, large plasmacytoma, hypercalcemia, so that our treatment may have to be directed towards that crisis first while in the background, we are trying to select the right most appropriate therapy for them.

Similarly, there are some other very important factors, which bring into discussion the social aspects of patient care. So how is the patient support system? How frequently can they come to the clinic? How far is the clinic for them? Who's going to drive them? What is the insurance coverage for any particular drugs that we want to prescribe for them? Is it injectable? Is it oral? Does the patient have the prescription drug coverage or not? How far do they live from the treating center? How frequently can they come, etc. So, all of these factors, in my opinion, are important at every single juncture whenever we are trying to decide the treatment for a patient.

# Factors to Consider in the Treatment of Early Relapsed/Refractory Multiple Myeloma




Let's talk about what is relapsed and what is refractory; you will hear this term very frequently in the myeloma literature. So relapsed means that the patient has had disease recurrence after response to a prior treatment. Generally, the patient is off therapy or receiving maintenance dose therapy and the relapse can be either serologic - or also termed sometimes biochemical - where only the disease is progressing in form of lab abnormality or it can be a clinical relapse. The clinical relapse could be worsening pain, new fractures, kidney dysfunction, worsening anemia, etc.

Refractory disease, on the other hand, is when the disease is progressing despite ongoing therapy or if it progresses or recurs within 60 days after stopping the treatment. Again, it's important to make this distinction, partly because we will be able to understand how a particular drug was tested and which patient population it is active in, but at the same time, patients who have refractory disease tend to have a more aggressive disease or a more rapid disease course, just because biologically, that disease, that myeloma clone, may be resistant to the drugs it is progressing on. So important to keep in mind.

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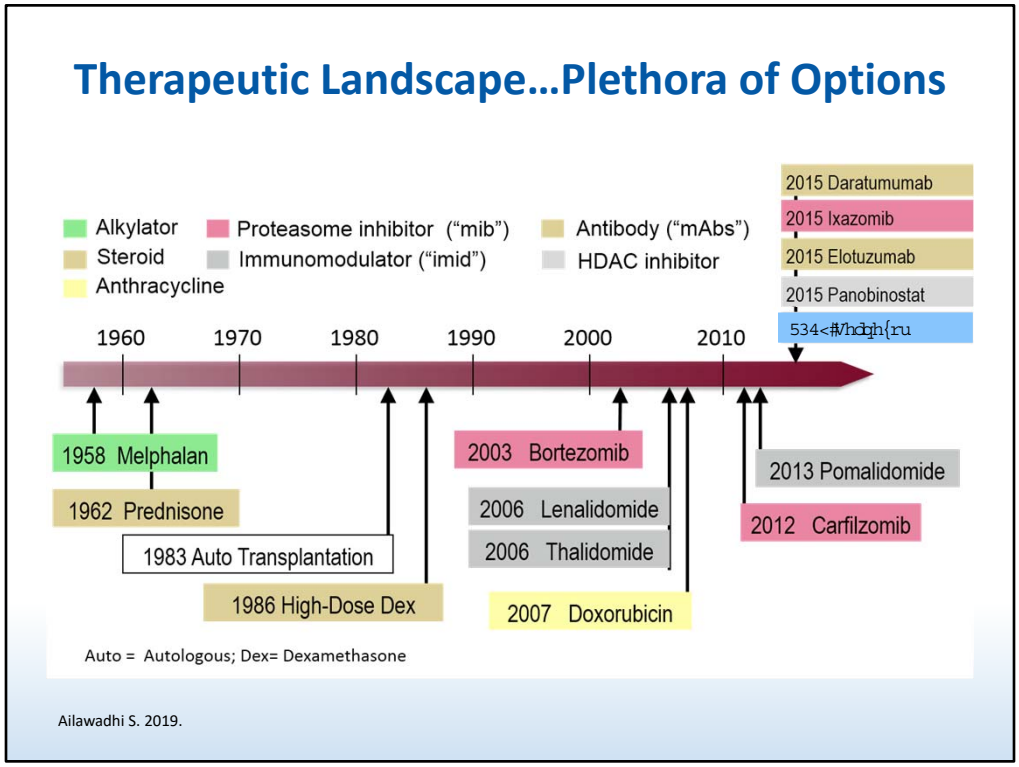
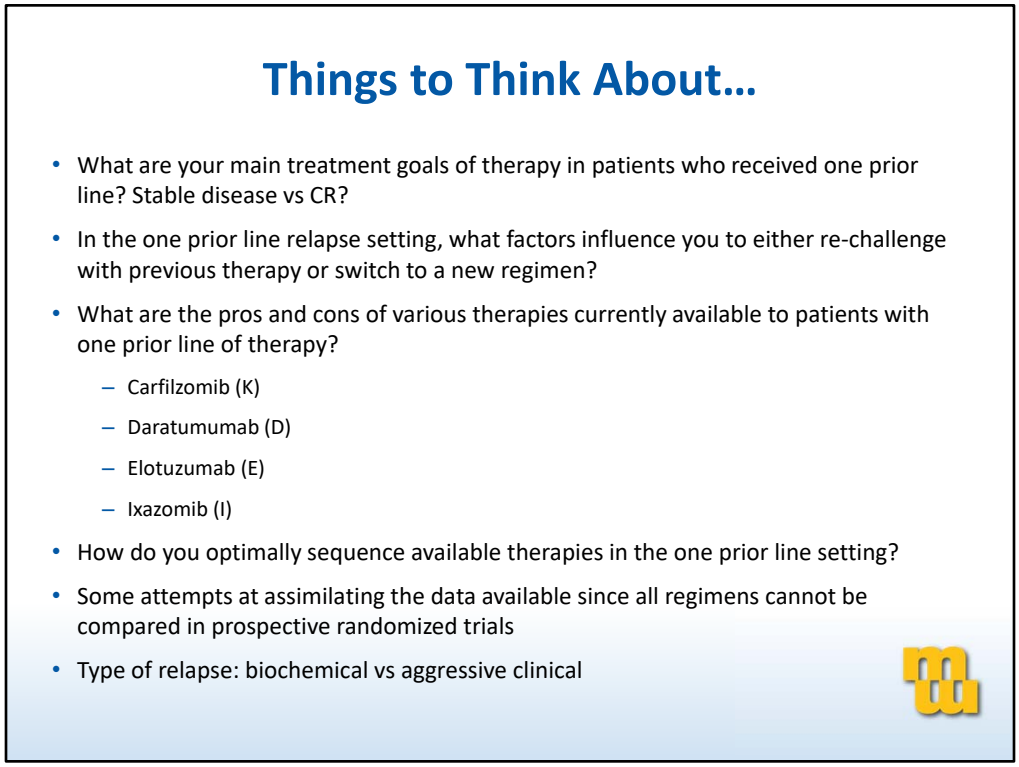



The therapeutic landscape for multiple myeloma has changed significantly. I've mentioned here that there is a plethora of options. So, while on the one hand, it is a great opportunity for patients, at the same time, we who are focused on treating the patient need to figure out which out of these options and, more so in which combination, is most appropriate for the patients. As this particular slide shows, historically there were not many options, just some alkylators like melphalan, cyclophosphamide, steroids, and even going from high-dose dexamethasone to standard or low currently used dexamethasone at 40 mg weekly; that was a huge landmark. But since then, we have bortezomib, carfilzomib, and ixazomib, in the proteasome inhibitor category; we have thalidomide, lenalidomide, and pomalidomide in the immunomodulatory drug category; and then we have the monoclonal antibodies, namely daratumumab and elotuzumab; and now we have newer molecules including panobinostat and selinexor, which are all FDA approved. And I think I forgot to mention doxorubicin, which would also have been used in the past, much less frequently used now, but is also FDA-approved for the treatment of relapsed multiple myeloma. So, several options. We just need to figure out what may be right for the patient at any given time.

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I think it's good to think about some general concepts or thoughts. For example, what are your main treatment goals of therapy in a patient at that given time? So if a patient has received one prior line of therapy or let's say two or three prior lines of therapy, what is our goal of treatment? Are we looking for stabilization of disease? Or are we looking for a deeper response with let's say, a complete response or for that matter, even MRD or minimal residual disease negativity? In the one prior line treatment setting, what factors influenced you to either rechallenge with the previous therapy or switch to a completely new regimen? So, if a patient is let's say, progressing on while getting treatment, mid bortezomib, cyclophosphamide, and dexamethasone, do we just switch the cyclophosphamide to lenalidomide? Or do we just completely change the regimen to let's say lenalidomide, daratumumab, and dexamethasone? These are all things to think about because unfortunately, we do not have enough clinical trial data to answer each of these questions.

What are the pros and cons of the various therapies currently available to patients, especially those who have had one prior line of therapy? I'm focusing on this one or one to two prior line therapy area because that is where a lot of our drugs are currently FDA approved. So, whether the patient should get something with carfilzomib, daratumumab, elotuzumab, ixazomib, and then with which immunomodulatory drug whether it's lenalidomide or pomalidomide, or for that matter even thalidomide, which has been used in quite a few regimens.

How do you optimally sequence the therapies from one prior line to two to three prior lines of therapy?

There has been some ongoing attempts to assimilate some of this data into meta- analyses and some large real-world analyses because it would be impossible to do prospective randomized comparative clinical trials for all of these regimens.
Also, as I mentioned, the relapse could be biochemical or serologic or it could be clinical, sometimes also called aggressive relapse. So how do we select the right treatment?

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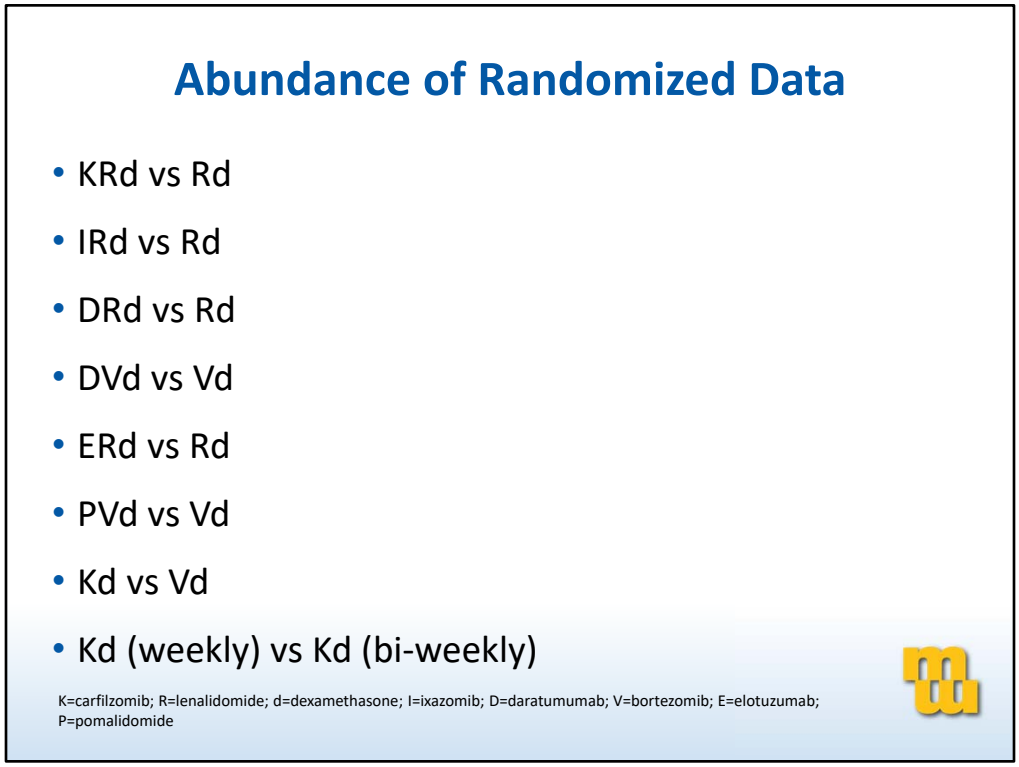


There is a lot of randomized data as I said; there is carfilzomib, Len, Dex versus Len, Dex; ixazomib, Len, Dex versus Len, Dex; daratumumab, Len, Dex versus Len, Dex; daratumumab, bortezomib, Dex versus bortezomib, Dex; elotuzumab Len, Dex versus Len, Dex; pomalidomide, bortezomib, Dex versus bortezomib Dex; and then of course the doublets of carfilzomib, Dex versus bortezomib, Dex, or weekly versus biweekly carfilzomib, Dex.


As you will notice, most of these regimens are comparing triplets to doublets. So that brings up the thought that triplets are going to be used much more frequently because they have come out superior as compared to doublets. It's also important to keep in mind that progression is practically more frequently nowadays while the patient is on maintenance. Because maintenance is the norm for all myeloma patients. Everybody who has responded to a certain line of therapy typically is transitioned to maintenance, generally including some of the agents that were used in the induction therapy. And then after that, the patient can continue on the maintenance for as long as they respond or tolerate the regimen. But again, very important to keep in mind that the triplet versus doublet trials that I mentioned, especially the ones which had Len, Dex as the competitor, majority of those trials did not include patients who were previously progressing on Len, Dex. And come to think of it that was the ethical thing to do because if these were randomized trials, the patient had a 50% chance to going on to the doublet. If they were already refractory to lenalidomide, then putting them on Len, Dex would not have been the appropriate choice. So prior Len refractoriness was not included in any of those clinical trials. Similarly, patients who were getting bortezomib-based treatment, if they were refractory to bortezomib, they were not included in the trials which had bortezomib, Dex versus some triplet. So that's a very important thing to keep in mind, because that is not how we see our patients in the clinic when we are treating them day in and day out.

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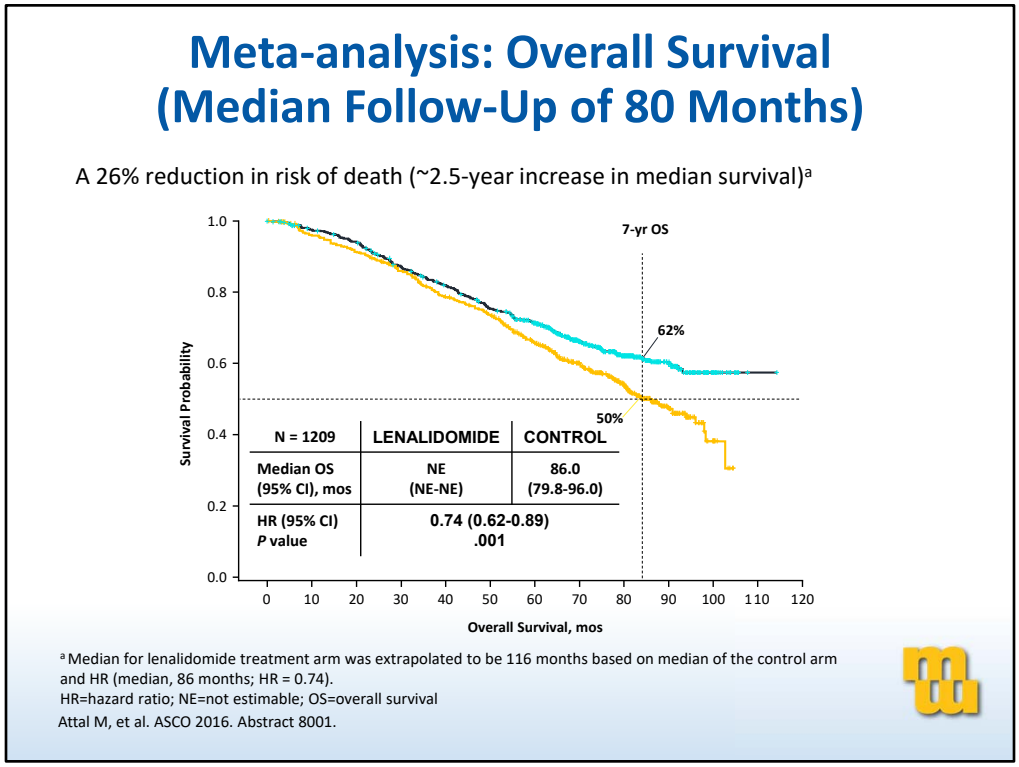


I'll just bring up this data, which I'm pretty sure most of us are now aware of and I've seen repeatedly. This data was presented a couple of years ago and since then, has been published in a manuscript which shows that even on a long-term follow-up, seven years out, the patients who were getting maintenance with lenalidomide after their induction therapy, mostly in the post-transplant setting, had a better overall survival. Based on this data, even those who were not fully in favor of maintenance therapy have adopted it and rightly so, because this is the right thing to do for the patient. So, practically every single patient is on maintenance therapy. Now mind you, this data is only pertaining to lenalidomide, but there is data to support bortezomib as maintenance and also ixazomib maintenance. Again, not everything may be FDA approved, but the idea being that maintenance therapy is extremely important and most of the clinical trials did not address patients who were progressing on maintenance. This is the 26% reduction in risk of death. So that is a couple of years increased median overall survival, extremely important.

# Factors to Consider in the Treatment of Early Relapsed/Refractory Multiple Myeloma

## FDA Approved MM Therapeutics in the U.S.

| The "Big Five" | | | | | | |
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| | Use | Route | Mode of Action | Plus | Minus | Clinical Benefits |
| Thalidomide | ND, RR | Oral | IMiD | Safe in kidney dysfunction, minimal myelosuppression | Neuropathy, fatigue, thrombosis | ORR; especially in combinations even in late disease |
| Lenalidomide | ND, RR | Oral | IMiD | Little neuropathy, safe over long durations | Thrombosis, GI side effects, cytopenias, fatigue, secondary malignancies | ORR; especially in combinations in early and late disease, Most extensive maintenance data |
| Pomalidomide | RR | Oral | IMiD | Little neuropathy, more combination data emerging | All similar to Len. May need lower dose (2 mg) in triplet combinations | ORR |
| Bortezomib | ND, RR | SC/IV | Proteasome | Excellent efficacy, use in renal dysfunction, high risk, manageable cytopenias | Peripheral neuropathy (SC and weekly) | ORR, OS benefit, extensive efficacy and safety data including maintenance |
| Carfilzomib | ND, RR | IV | Proteasome | All benefits as bortezomib, minimal neuropathy | Twice/once weekly, cardiopulmonary toxicity | High CR rate, OS benefit |

ND=newly diagnosed, RR=relapsed/refractory, SC=subcutaneous, IV=intravenous, ORR=overall response Rate, CR=complete response, OS=overall survival

So, I'm not going over all of these drugs which we use very frequently, but I have tried to summarize some of the data from the FDA-approved drugs. These were the five kind of mainstay of drugs that we've had for quite some time, including thalidomide, lenalidomide, pomalidomide, bortezomib, and carfilzomib. They all have their use where they are FDA approved, how they are administered, what their mode of action is, their pros and cons, and what their clinical benefit is. But when I'm trying to select a treatment options for a patient, I'm trying to keep some salient features in mind, which is oral versus IV versus subcutaneous? How did these drugs work? So, what is the patient progressing on and how can I bring in a different mode of action into that patient's regimen when they are progressing, let's say on maintenance? What is safe in kidney dysfunction? What causes neuropathy or less neuropathy because that is a common symptom we have to deal with in myeloma patients. Risk of clots, what are the side effects like fatigue, secondary cancers, etc?

# Factors to Consider in the Treatment of Early Relapsed/Refractory Multiple Myeloma

## FDA Approved MM Therapeutics in the U.S.

| The "New Three" | | | | | | |
|---|---|---|---|---|---|---|
| | Use | Route | Mode of Action | Plus | Minus | Clinical Benefits |
| Ixazomib | RR | Oral | Proteasome | All benefits as bortezomib, minimal neuropathy | Specialty medication, GI side effects, thrombocytopenia | ORR; being studied wherever bortezomib used, maintenance |
| Daratumumab | ND, RR | IV | Anti-CD38 | Less overlapping toxicities with other agents, well-tolerated, significant efficacy even as a single-agent | Long infusion time, infusion reactions, some safety data in renal failure | ORR; Extensive triplet data emerging. Deepest MRD negativity with lenalidomide among all regimens |
| Elotuzumab | RR | IV | Anti-CS1 | Less overlapping toxicities with other agents, well-tolerated | Not much efficacy as single agent, no reported efficacy in patients who are IMiD refractory (even patients progressing on Len maintenance) | ORR, better MRD than doublet. Consider when planning lenalidomide + dexamethasone |

MRD=minimal residual disease

And then the newer drugs which have been approved have been ixazomib, daratumumab, and elotuzumab. Similar to the prior drugs, the first five, I'm looking at also the mode of action, the mode of administration, and then what are the pros and cons that I can use in a particular patient at a given time? So that let's say if a regimen of Dara, Len, Dex is applicable to a patient, Elo, Len, Dex may not be applicable to it or vice versa. So, while all of these agents are approved in a very similar treatment landscape, especially these three over here, Ixa, Dara, and Elo, and also for that matter carfilzomib. While all of them have very overlapping FDA approvals, it's important to keep in mind that what's applicable to one patient may not be applicable to another based on all of these considerations that we are talking about.

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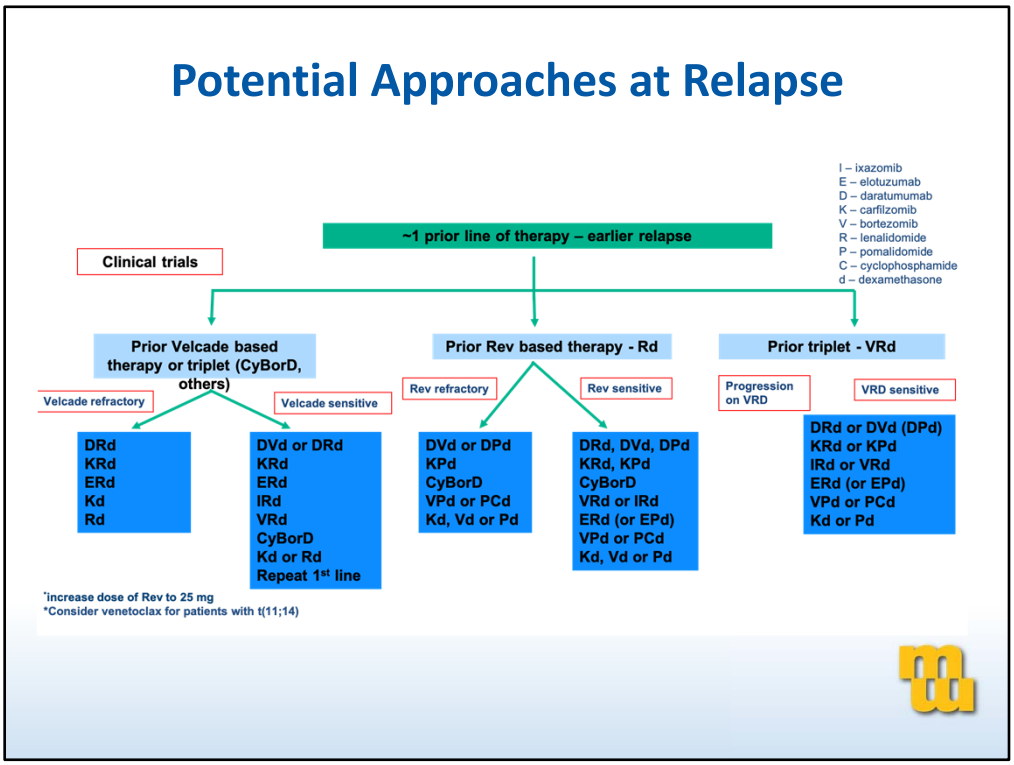
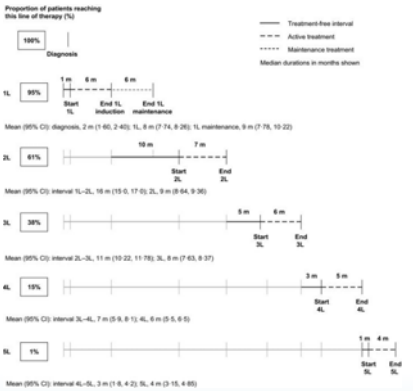



There are several approaches for selecting treatment for relapse patients and while this particular slide talks about several of those options, I can tell you when preparing this data, these are not even all inclusive; there are actually more options than this that we can use. That is what makes it a little bit confusing. But what we need to keep in mind is, and this is one schema talking about one approach, but for example, if a patient has had prior, let's focus on prior lenalidomide-based therapy and the patient has had, let's say, Len, Dex, or something with Len, Dex for initial therapy, or is progressing while on lenalidomide, then they would be Len refractory. In that case, we could consider for that patient, let's say Dara, bortezomib, Dex, so we are completely eliminating Len. We could also consider Dara, Pom, Dex. So, again we are increasing the immunomodulatory drug. We could consider carfilzomib, Pom, Dex. Some patients may end up going back to a regimen like CyBorD. They could get bortezomib, Pom, Dex. There is also some data with Pom, Cytoxan, Dex; carfilzomib, Dex; Pom, Dex. The thought is we would always prefer to use a triplet, but whether we are using IV, subQ, oral, etc., that would all depend on the factors we've talked about, and whether the patient is progressing rapidly. Do we think switching the class completely would be beneficial? Do we think that keeping the same class but changing the agent would be helpful, etc.? In common practice very frequently, if a patient is progressing on a certain drug, the regimen is kept the same or the drug is kept the same, but the dose is increased. I should say that there is not a lot of data to support that. In fact, there has been some data from frontlines studies where patients were progressing on maintenance with lenalidomide, some European clinical trials, where increasing the dose of lenalidomide recaptured the response, but the duration of that response was relatively shorter. And I should also point out that in the US where we have all of these treatment options available,

the drugs available, the thought has always been, or the thought is moving towards the factor that we need to provide a deeper response for patients whenever possible. So if a patient is progressing while on treatment with a certain agent, the thought is to increase the potency of that family, or to switch the class in some cases, to try and get a deeper response, and to try and get to that complete response, but hopefully even MRD negativity at every juncture possible.

# Factors to Consider in the Treatment of Early Relapsed/Refractory Multiple Myeloma

## High Rate of Attrition with Subsequent Lines




Yong K, et al. *Br J Haematol*. 2016;175(2):252-264.

It is also important to note that this paper that was published now, two or three years ago actually, that with every subsequent line of therapy, there is a significant attrition in the number of patients. In other words, every time we have progression of disease, the number of patients that are able to go on to the subsequent line or the number of agents that we have available dwindles. So, there is absolutely no need to save the best option for later. Whatever we can use now to give a deeper response, we should try to do that.

# Factors to Consider in the Treatment of Early Relapsed/Refractory Multiple Myeloma

## Some Prominent Considerations…

- General
  - Dose reductions may be done for symptom control, but optimal benefit may be obtained only when the clinical trial regimen and treatment plan is mimicked
  - For example, DRd after 6 cycles should not be changed to *"maintenance"* with Len 10 mg and no Dex. Will adversely affect PFS
  - Deeper response should be a goal, even in RRMM
  - In frontline setting for non-SCT eligible patients, it has been shown that discontinuing Dex after 9 cycles OK and has better PFS. Dex discontinuation in RRMM not studied yet

Now some other general principles that I'll talk about. So dose reductions may be done for symptom control, but the optimal benefit is obtained from a particular regimen when we tried to mimic a clinical trial, and keep with the regimen that was given in that clinical trial, which led to the drugs approval, so I'll use an example. For example, the Pollux Clinical Trial compared daratumumab, Len, Dex versus Len, Dex. After six cycles of treatment with Dara, Len, Dex, the Dara goes once a month, but the Len and Dex remain at the same dose and regimen in the clinical trial. Now, if in our real world, we treat the patient for the first six months with Dara, Len, Dex, and then after the six months we go to Dara monthly. Sometimes it has been noted that the term maintenance is applied and at the six-month mark, the Dex is eliminated and the Len is dropped to 10 milligrams. While that may sound like a maintenance, that is not how the drug was approved or how the clinical trial showed its efficacy. So, in my mind, this would be taking the treatment off or diluting the treatment too soon. If this is being done in response to side-effect management, I think it's very appropriate, but if after six months, we are decreasing the Len and eliminating the Dex because we think that is the maintenance, that may be decreasing the dose too soon. Deeper responses I've mentioned a few times should be the goal even in relapse refractory myeloma.

Also, in the frontline setting in the non-transplant eligible patients, it has been shown that dexamethasone can be discontinued after the trial looked at nine cycles, so the progression-free survival was maintained. Dexamethasone discontinuation in relapsed/refractory disease has not been studied yet. But some people have started using that same concept and saying that after 8, 9 or 10 months, if the patient has had a

plateaued response, then just for the fact that they may be able to continue on the treatment longer, the Dex may be reduced or sometimes even eliminated. But as I said, this is practice, this is not evidence-based medicine, at least as of yet. We're hoping that a lot of these studies will be done in due course.

# Factors to Consider in the Treatment of Early Relapsed/Refractory Multiple Myeloma

## Some Prominent Considerations…

- General
  - Patients progressing on lenalidomide were not included in most triplets that have been approved for RRMM – ERd, IRd, DRd
  - Is progression on 10 mg Len maintenance = Len refractoriness? *(Should it be followed by another Len-based regimen with higher doe of Len or should pom be used as the IMiD?)*
  - While bortezomib and Len have been reused, is the same true for carfilzomib and Dara? *(eg, now data on Kd-Dara, KCd. But what if prior KRd?)*

Similarly, patients who are progressing on lenalidomide were not included in most of the triplet clinical trials, which have led to drug approval. For example, Elo, Len, Dex; Ixa, Len, Dex; Dara, Len, Dex, these were trials done where lenalidomide progression was not included.

Also is the progression while on lenalidomide happening when the patient is on a maintenance dose of 10 mg, is that Len-refractoriness? Generally, the thought has been that if a Len-based regimen is supposed to be used there, then the Len should be increased to a full dose, but there are different schools of thought. Some would consider that they can increase the Len to full dose in that follow-up regimen and some would think, “Well, no, let's switch to pomalidomide completely.” Again, more data, which will be coming hopefully in the near future.

While bortezomib and Len have been reused, the same data has not yet been presented for carfilzomib and daratumumab for example. So, if a patient has had progression on carfilzomib,  Len, Dex, can they go to carfilzomib Dara, Dex? Carfilzomib, Cytoxan, Dex? We don’t know. But some of these studies are being done. It's important to again, figure out do we need to switch an agent, or do we need to switch a whole regimen? Practically, a lot of times when biochemical progression is happening, sometimes agents are changed. But when a patient is progressing clinically and it has an aggressive relapse, then for sure the regimen should be changed and modified completely.

# Factors to Consider in the Treatment of Early Relapsed/Refractory Multiple Myeloma

## Some Prominent Considerations…

- Elotuzumab
  - Dependence on IMiDs for activity (ELOQUENT trial; ERd vs Rd)
  - Consider ERd for relapse off of bortezomib-based maintenance, aka IMiD-naïve
  - Being used more with pomalidomide and Dex (EPd) in later lines of therapy *(but benefit after prior daratumumab failure not known)*

A few thoughts about elotuzumab, a drug that unfortunately is not utilized that frequently because of the way its clinical data has been telling us that elotuzumab depends on immunomodulatory drugs for its activity. This was shown in the Elo, Len, Dex versus Len, Dex trial and also the fact that Elo by itself does not have much anti-myeloma activity. But now since the Elo, Pom, Dex has been available, this regimen has been used much more frequently. We don't know what happens to Elo after patients had refractory to the daratumumab because we're using Dara early on in a lot of patients, but hopefully that data is also coming down the road soon.

It’s important to consider that we should keep Elo, Len, Dex in mind in patients who are Len naive. So, let's say if the patient was on a frontline treatment with CyBorD, bortezomib, cyclophosphamide, and Dex, or let's say for that matter bortezomib, Dex for some reason, and they are naive to lenalidomide, then when they progress, Elo, Len, Dex may be an excellent option.

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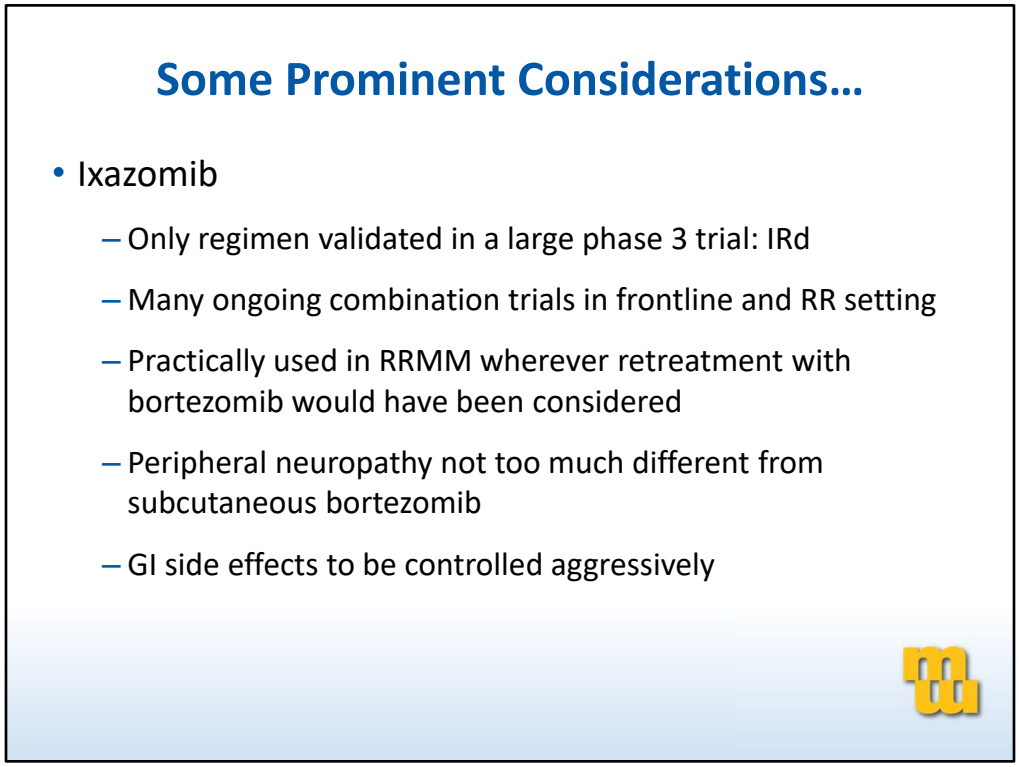



For ixazomib something to consider that the only regimen that has been validated in a large phase three randomized clinical trial is Ixa, Len, Dex. I know there has been use of Ixa, Cyclophosphamide, Dex; Ixa with Pom, Dex; some have thought of using Ixa with Daratumumab, Dex. It's just too important to keep in mind that not everything has been FDA approved or has been looked at in clinical trials. There are many ongoing combinations of Ixa in the frontline and relapsed/refractory setting, which will hopefully clarify the use of this drug in different settings. Practically it is used in relapsed/refractory multiple myeloma whenever we think that retreatment with bortezomib may be considered. So generally, in those settings, Ixa is brought up just for the sake that it's convenient to the patients – it's oral. Peripheral neuropathy from Ixa not too much different from subcutaneous bortezomib. It is clearly lesser than bortezomib when it was given IV or twice a week, but peripheral neuropathy can still happen, so important to keep in mind. Also, GI side effects are known, so gastroenterological side effects like diarrhea, nausea, vomiting, etc., but they can be aggressively controlled and are generally quite manageable.

# Factors to Consider in the Treatment of Early Relapsed/Refractory Multiple Myeloma

## Some Prominent Considerations…

- Daratumumab
  - DRd regimen noted to have the most prominent PFS benefit among RRMM triplets as per a meta-analysis
  - Dara approved in frontline regimens – Dara-VMP, Dara-VTd, Dara-Rd
  - So far, limited Dara usage in frontline setting in the US as VMP and VTd not used much *but Dara-VRd coming down the road fast*
  - Subcutaneous Dara expected to get approval soon. So will change logistic considerations for Dara

For daratumumab, we need to note that daratumumab, Len, Dex regimen has been used extensively now and has shown the most prominent progression-free survival benefit amongst the relapsed/refractory myeloma regiments. Of course, it is difficult to make cross trial comparisons, but the Dara, Len, Dex regimen has provided excellent deep responses and very good progression-free survival. But as a reminder, I would say it is possible to mimic the benefits from a regimen if we try to keep the treatment as close to how the clinical trial intended to give those drugs. Dara is approved in frontline regimens like Dara, VMP; Dara, VTd; Dara, Rd, we don't use a lot of these regimens in the US. For example, Dara, Rd may be the only one that we would use in frail patients. So, it is important to keep in mind if this agent gets utilized more and more in the frontline setting, for example, there is Dara, VRd versus VRd data, similarly, Dara, KRd vs KRd, all of this data will be coming out in days and months to come. But when Dara is used frontline, how are we going to use it subsequently? So, keep in mind, there are some Dara retreatment clinical trials ongoing; we are awaiting the data for those. Subcutaneous Dara is also expected to be available in the near future, that will hopefully make this a much more convenient and easy to use agent, but there is some very encouraging data including the safety and efficacy that has been presented or is coming out.

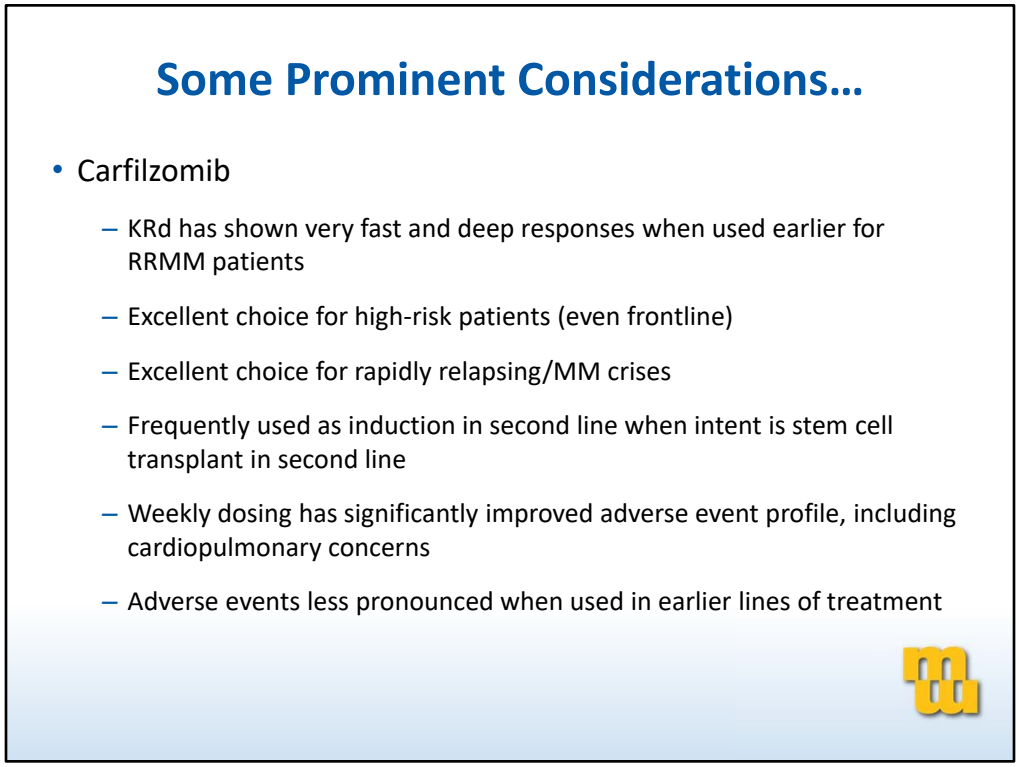
# Factors to Consider in the Treatment of Early Relapsed/Refractory Multiple Myeloma

## Some Prominent Considerations…

- Daratumumab
  - Dara-Rd gave deeper (MRD-) and longer (PFS) responses than Dara-Vd
  - In real-world, DVd being used more for high-risk patients, DRd in standard-risk *(no real evidence)*
  - Dara retreatment data not available so difficult to say how RRMM would shape up with increased frontline Dara usage
  - Typically not used as a transplant-preparatory regimen since not sure of post-transplant status with Dara yet

Dara, Len, Dex as I mentioned provides very deep MRD negative responses also have been seen with Dara, Bortezomib, Dex. In the real-world setting, Dara, Bortezomib, Dex has been used more so for high risk patients and Dara, Len, Dex for standard risk. I should say that there is no clinical trial data to support that sort of a utilization, but that has been seen in some real-world usage. As I've mentioned Dara retreatment, we still have to figure it out and it is not typically used for transplant preparatory regimen. So, for example, if a patient is in their second line treatment and they have not had a transplant before, should we give them a couple of months of Dara and then take them to transplant? That is not the norm because Dara is more frequently the long-term used drug. It is not something that we would use for a couple of months and then think of using again in the future, again, because we don't have retreatment data. So that is important to keep in mind. For example, if a patient is going to transplant in their second line, then it may be more beneficial to use a carfilzomib- or ixazomib-based regimen where we could give them a few cycles, get them the appropriate response and take them to transplant. On the other hand, if the patient is not going to transplant, Dara-based regimens are absolutely good to use.

# Factors to Consider in the Treatment of Early Relapsed/Refractory Multiple Myeloma




A few salient points about carfilzomib, again KRD or carfilzomib, Len, Dex has shown very fast and deep responses, excellent choice for high-risk patients; even in the front line, it is listed as per the NCCN Guidelines. Excellent choice for rapidly relapsing myeloma patients, provides very fast responses. It is frequently used, as I mentioned, for induction in second line when the intent is to prepare the patient to a transplant if the patient did not get a transplant before. With weekly dosing, the side-effect profile has become extremely favorable, including even the cardiopulmonary side effects which are very manageable when we use carfilzomib weekly. Adverse events are much less pronounced when carfilzomib is used and earlier lines of therapy. A lot of the very concerning side effects happened when it was used more in the relapse setting.

So, from my standpoint, these are mostly the things to keep in mind. I don't think it is complicated, but I think it is full of a lot of opportunities to treat multiple myeloma patients in today's day and age when we have a lot of treatment options available. Thanks a lot for listening to this presentation.