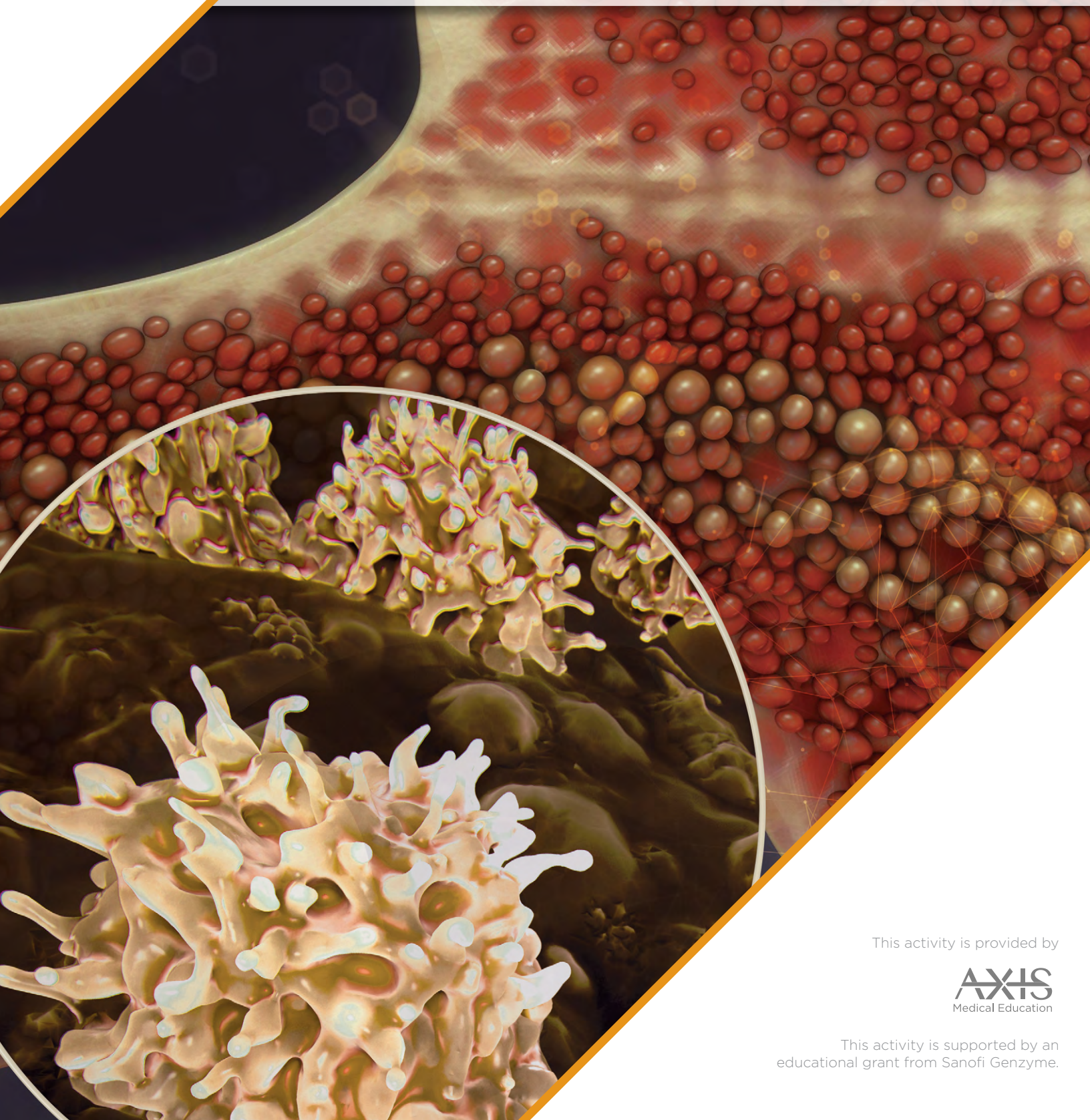
Medical Education

# Autologous Hematopoietic Stem Cell Transplantation and Mobilization in Multiple Myeloma:

## Current Debate and Developments

This transcript has been edited for style and clarity and includes all slides from the presentation.



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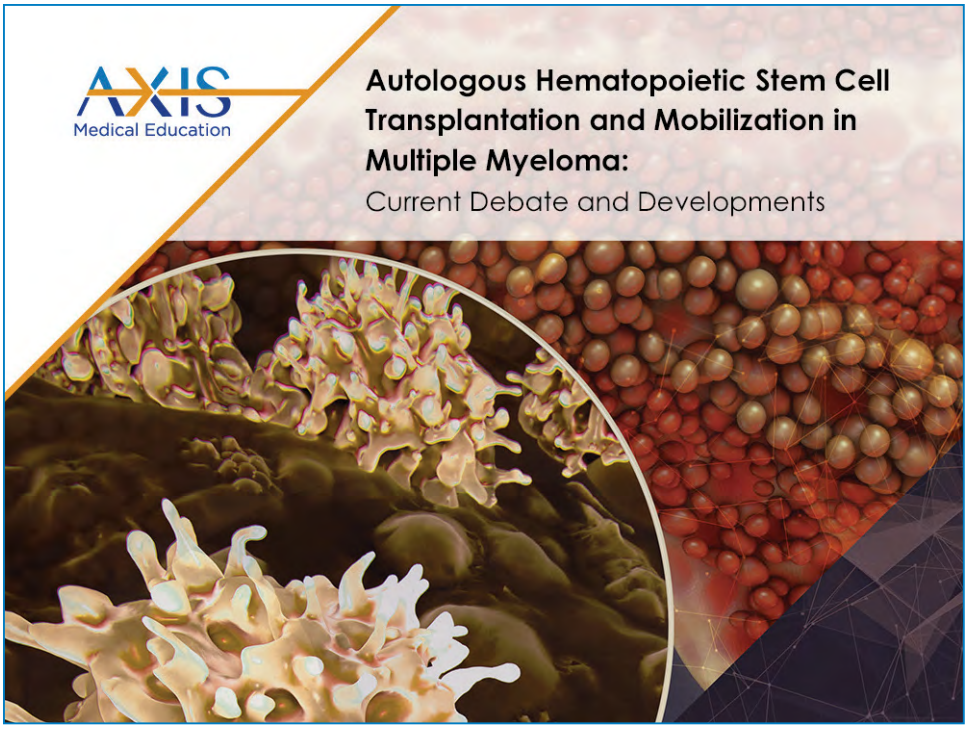
# Autologous Hematopoietic Stem Cell Transplantation and Mobilization in Multiple Myeloma:

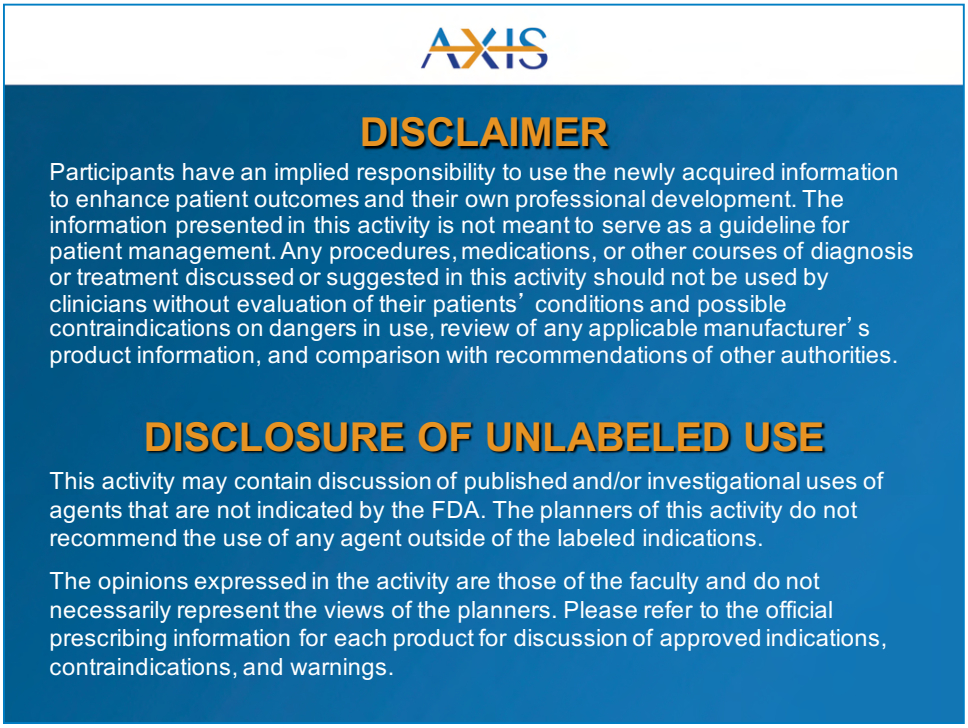
## Current Debate and Developments

Parameswaran Hari, MD & Nina Shah, MD

## SEGMENT 1




**Parameswaran Hari, MD**: Hello, welcome to the CME-certified activity entitled *Autologous Hematopoietic Stem Cell Transplantation and Mobilization in Myeloma: Current Debate and Developments.* I am Parameswaran Hari, Professor of Hematology at the Medical College of Wisconsin. And joining me today is Dr. Nina Shah, Associate Professor of Medicine at the University of California, San Francisco. We have a two-part presentation. In part one today, we'll be discussing the most recent clinical data on autologous hematopoietic stem cell transplantation and mobilization in multiple myeloma and provide evidence-based updates and some expert insights on this topic.

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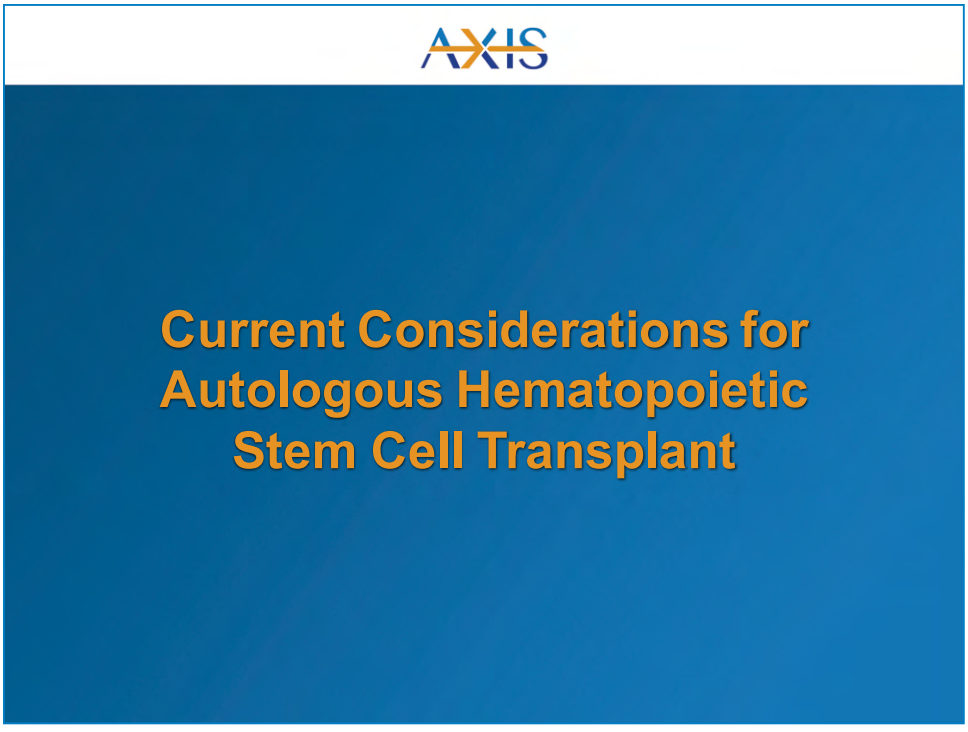
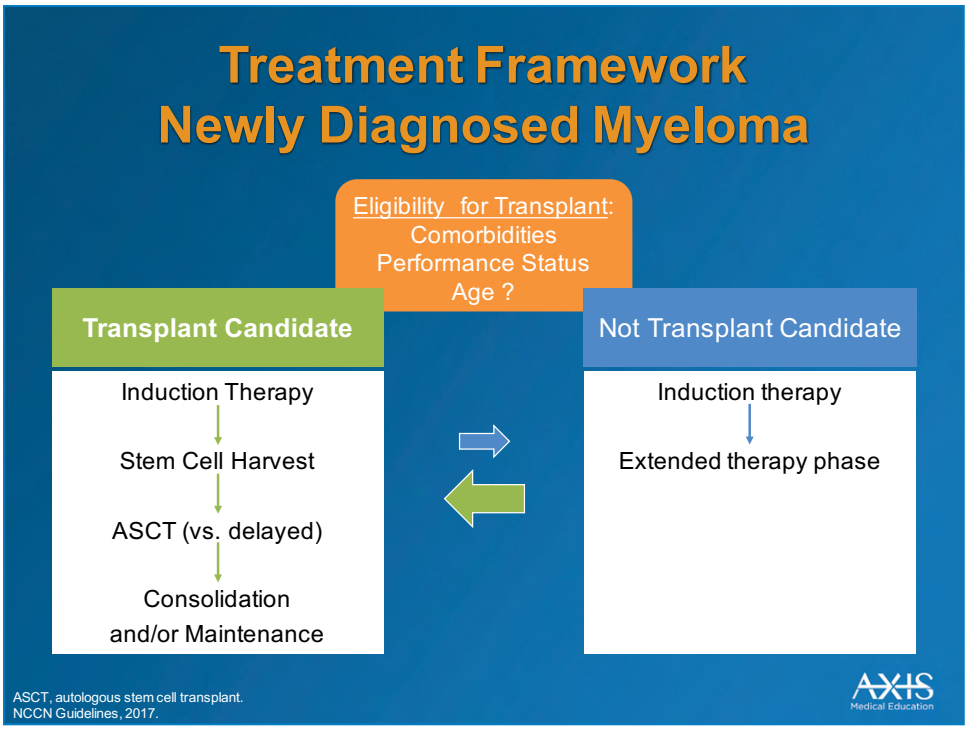



- To start off, let's talk about the treatment framework for people with newly diagnosed myeloma. So, we typically divide these patients into transplant eligible and ineligible. Nina, would you agree with this framework?




**Nina Shah, MD**: Yes, I think this is one of the things that we've come to as a decision point when we first meet a patient is who is transplant eligible and who is transplant ineligible, and that's something we're going to talk about a little bit later. But, it's a big decision point because it changes sort of how we approach each patient, right?

**Hari**: Right, exactly. But, on the other hand, there is some nowadays with model induction therapy there are a bunch of people who we would have thought transplant ineligible at the beginning whose main problem was multiple myeloma and with induction treatment they get better, and then they become eligible. And as we have moved away from melphalan in the initial induction regimens, almost anyone can be stem cell mobilized these days. And, it's very important to keep the eligibility question in mind when you see a person upfront, but we also need to consider that people could go back and forth between this eligibility versus ineligibility buckets so to speak.

**Shah**: Yes, I think that's a really important point you make because the person that you see at the beginning may not be the same patient that you see two cycles into their therapy. So, what we have here on the slide with people being transplant eligible or ineligible may change and be a dynamic course after they have some cycles of therapy.

**Hari**: Yeah, I think for the people watching this CME I would say the arrows going back and forth between the transplant candidacy question is very important to focus on

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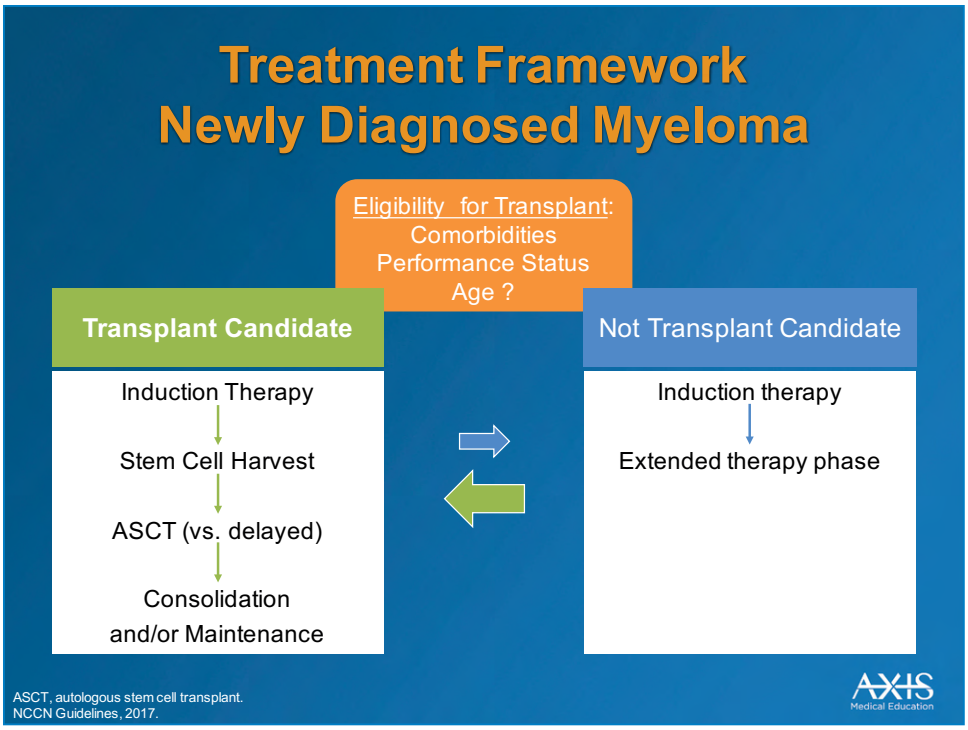


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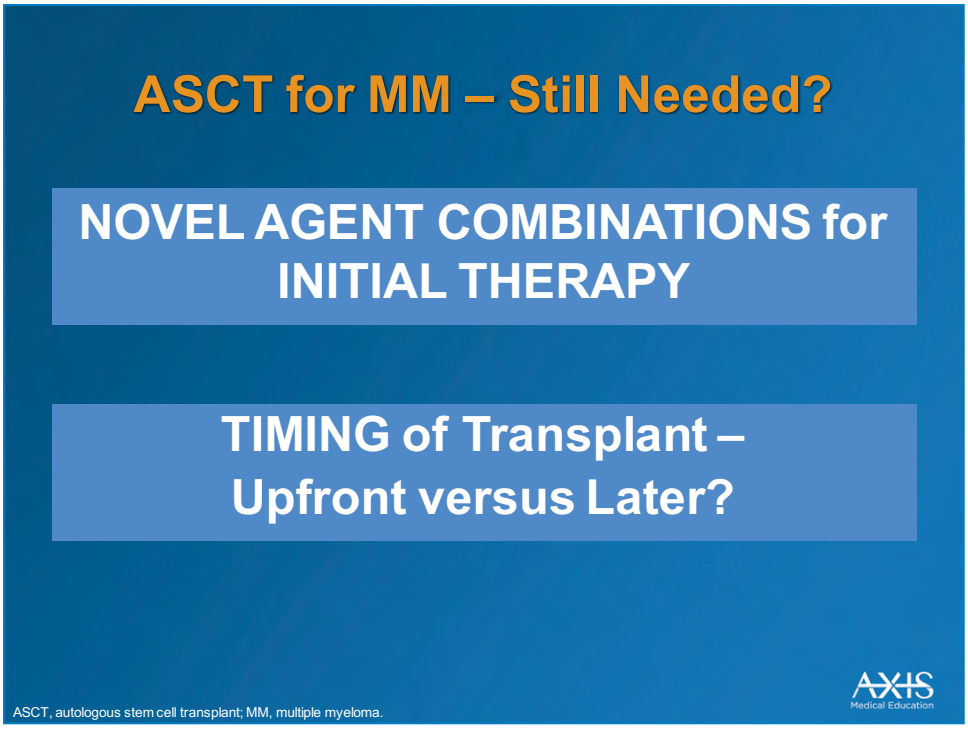
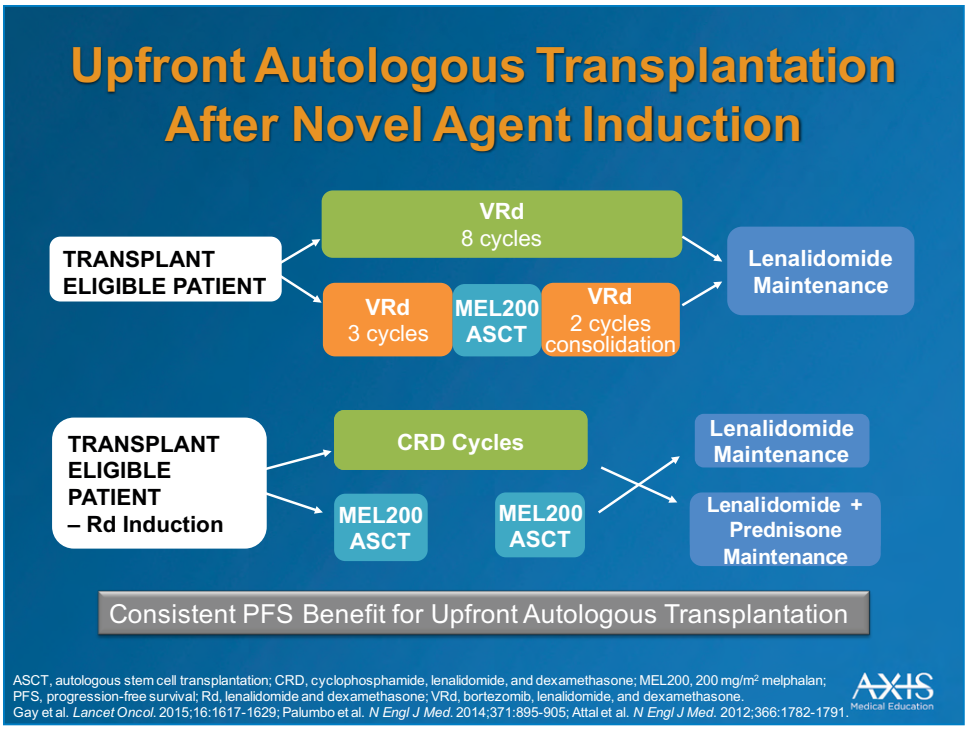
because, you know, you don't want to commit somebody against something very effective such as transplant by putting them up using their eligibility question just at the beginning of their disease.




- **Hari**: So one of the questions that's always been asked in myeloma ever since transplant became so to speak standard of care is is it still needed? As chemotherapy pretransplant gets better and better, we get more and more people go into complete remissions. And then the question always comes up do those people need a transplant? Who needs a transplant? Can you defer transplant? So I think these are some of the things that we should answer today—upfront versus later? Is there a role for transplant still in the era of modern very effective induction regimens?




So, here's a couple of studies that we have for our viewers. And, these are the two big studies that we should focus on.

**Shah**: So on the top of the slide, you can see how there is an ongoing study. This study actually has been performed in Europe and is also now being performed in America, but the results from the European study have been available to us sooner, and so we've been able to look at that. So, this study allows patients who are transplant eligible to receive bortezomib, lenalidomide, and dexamethasone, which is our standard induction regimen (and we'll get to that later). And they get it but they're upfront randomized. So, half of the people will be getting just the bortezomib, lenalidomide, and dexamethasone for eight cycles without going to transplant right away.

The other half of the people will get the bortezomib, lenalidomide, and dexamethasone for three cycles and then undergo stem cell collection and then transplant thereafter getting two more cycles of what we call consolidative bortezomib, lenalidomide, and dexamethasone. And I just want to point out that in both groups the patients are allowed to collect stem cells. And this is something very important that we should talk about. And so the comparison is between these groups who get an early transplant that is after their three cycles versus those who wait until relapse to get a transplant. And all of the patients have gone on to get lenalidomide maintenance, which we consider standard

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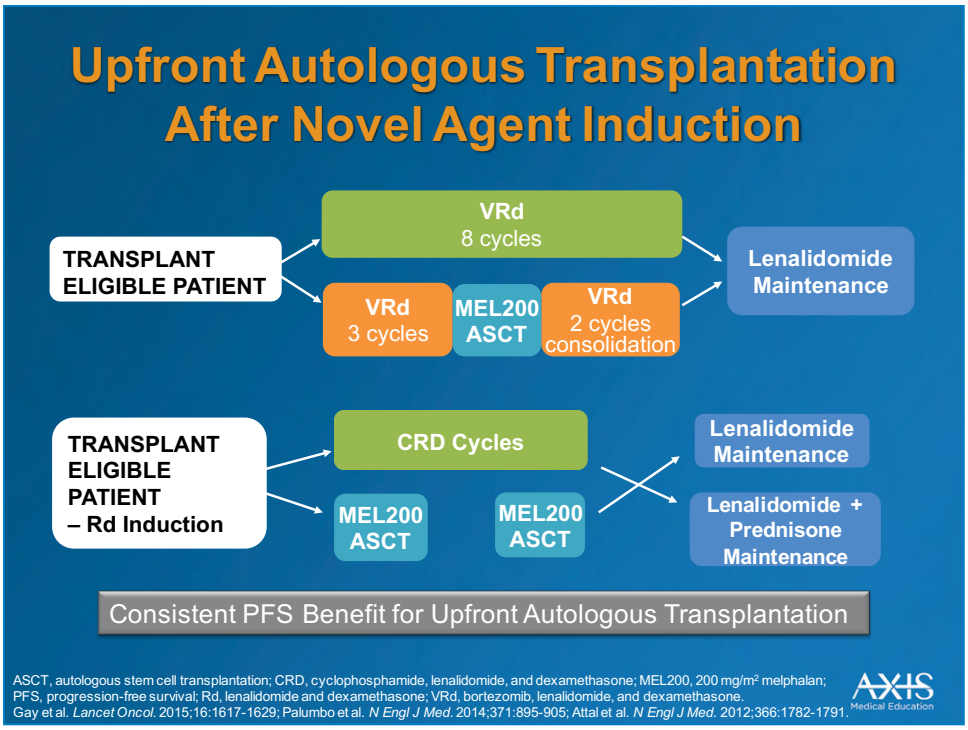


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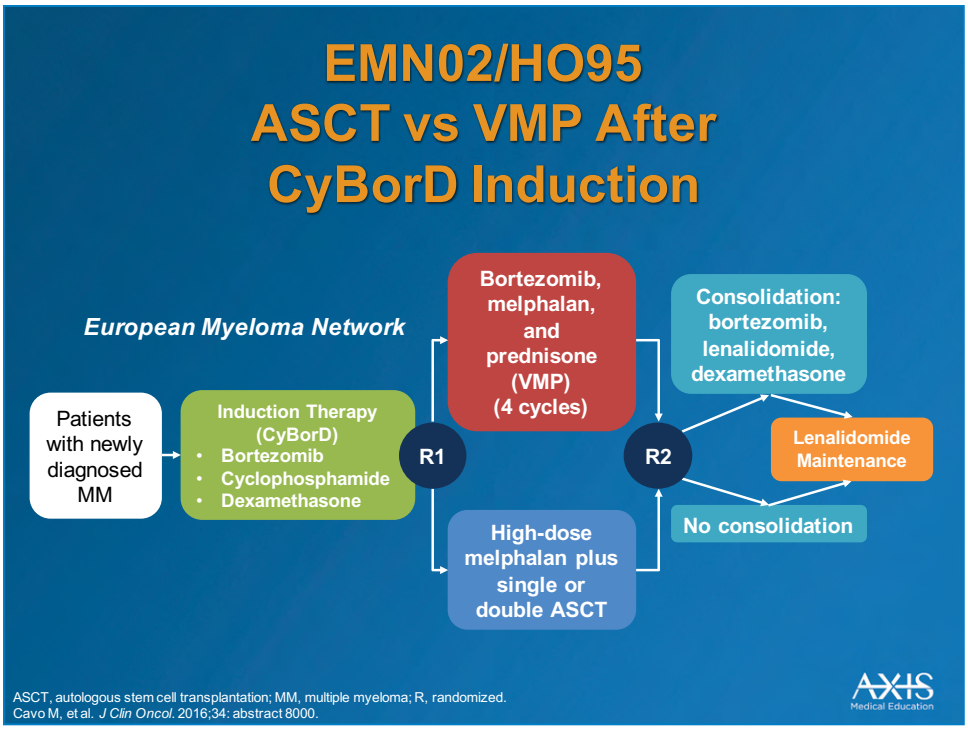
of care. And so, this is very interesting because it's one of the first trials in the novel era—one of the major trials—that's been able to help us answer this question.




**Hari**: This is another major study that actually asks two or three different questions, a large European study known as the EMN02, European Myeloma Network 02 study. Here again, the induction is specified as what we call CyBorD, which is cyclophosphamide, bortezomib, and dexamethasone. Then there is a randomization to transplant. And again, within the transplant subgroup, there is another randomization to single transplant versus double transplant. And the people who are not randomized to transplant end up on a combination of bortezomib/melphalan/prednisone. And turns out that cumulatively you get almost the same amount of melphalan in that cycle as you would for those you transplant.

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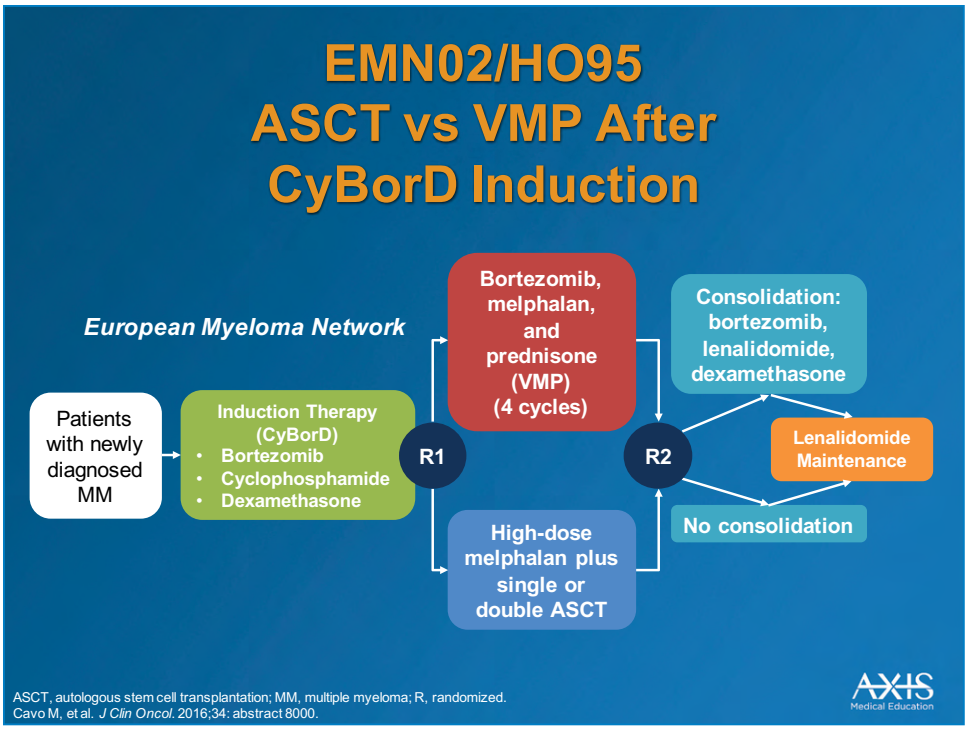


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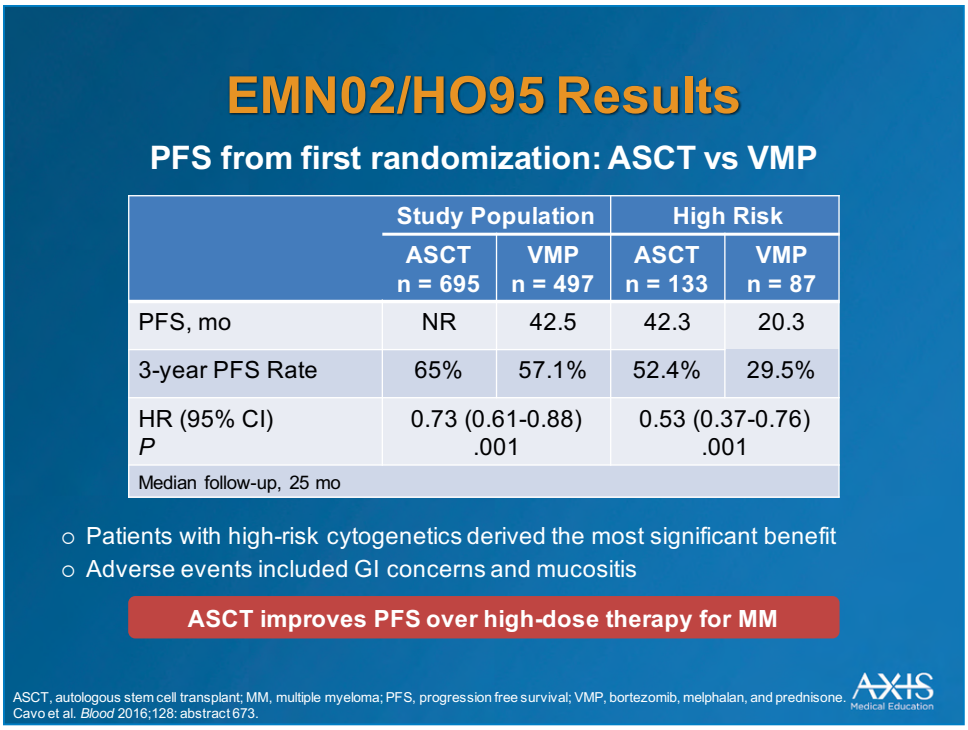
And then, patients get re-randomized to consolidation, which is bortezomib/lenalidomide/dexamethasone consolidation versus no consolidation, and then lenalidomide maintenance is uniform for everyone. I think the important thing about these two studies is that they both involve bortezomib, a proteosome inhibitor; they both involve lenalidomide. In the EMN study, the lenalidomide comes in a bit later at maintenance only. So we actually have data from previous studies that bortezomib—or a proteosome inhibitor—is an important part of the induction therapy.

**Shah**: Right, which I totally agree with.

**Hari**: Absolutely. And then, the second thing is that lenalidomide maintenance is no longer a question because both of these studies mandate lenalidomide maintenance in everyone.




**Hari**: So here are the results from the EMN study, which were actually presented at the ASH meeting recently. And here again, you can see that the progression-free survival for the autotransplant population was not reached; whereas it was 42.5 months for the VMP, or the non-transplant or the late transplant population. The 3-year progression-free rate was also pretty significant, which means that about two-thirds of the patients were progression free at 3 years in the transplant arm. Now the difference becomes even more drastic for people who are high risk by cytogenetics. And that's a pretty impressive result wouldn't you say?

**Shah**: Yes. I think this is one of the most difficult populations that we treat in the high risk, and we'll get into that a little bit later also. But, it's good to know that when you have a high-risk patient or if you're high-risk myeloma that going for a transplant in some ways ***early*** may be beneficial. The reasons for that are not clear; we don't know the biology of why that's clear. But this study seems to indicate that for those patients it is a good idea to consider transplant early.

**Hari**: Right. So for the high-risk patients in this study, which is about 133 people who received transplant, the median progression-free survival was 42 months, which is very similar to the standard-risk patients who didn't get a transplant. So it, again, brings to the point that high-risk people do benefit from transplant but not as much as the standard-risk patients. So this is not a good reason to deny transplant to

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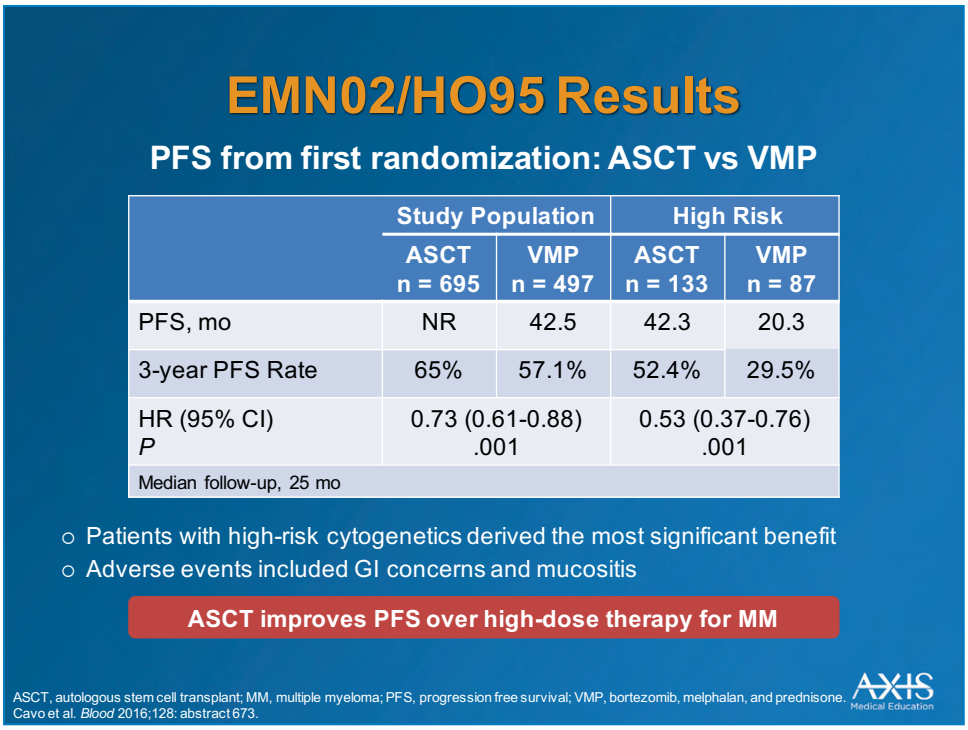


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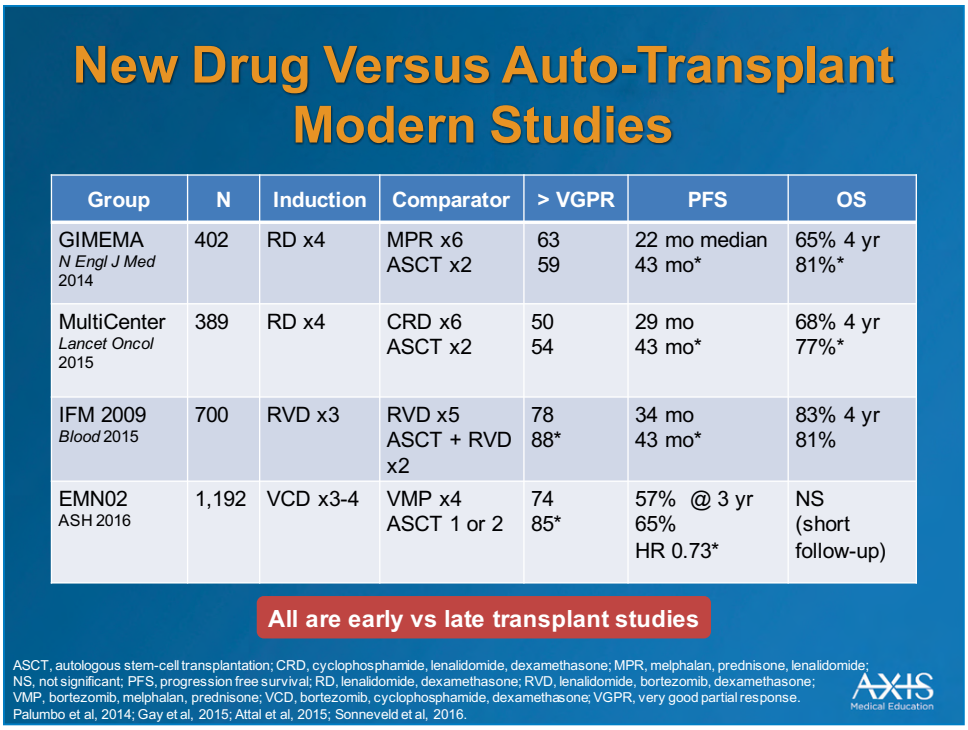
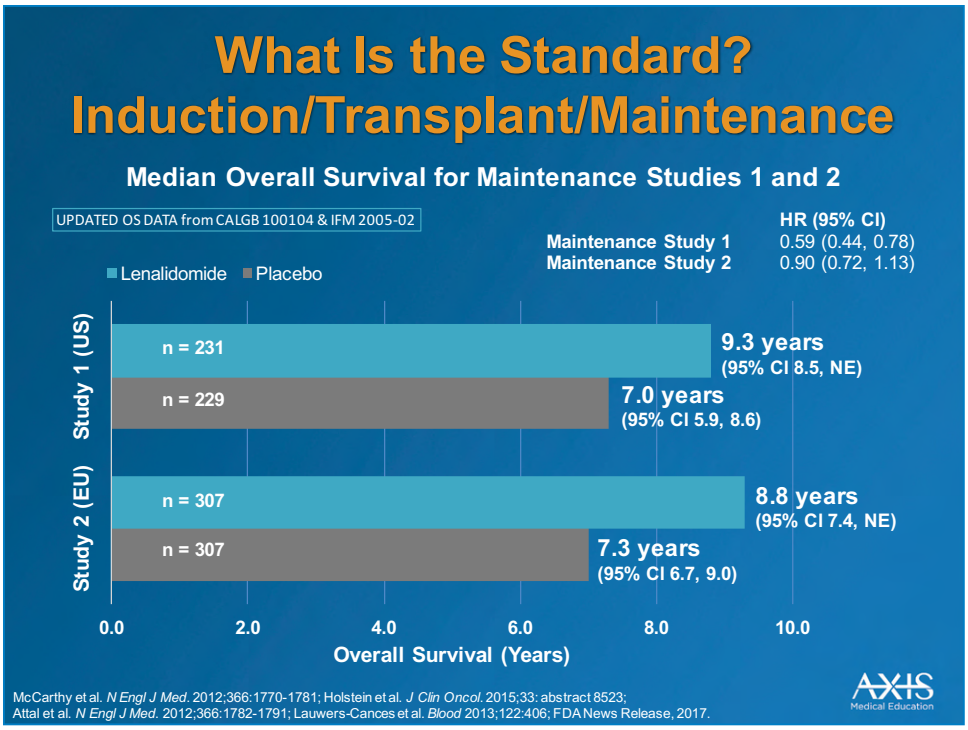
high-risk patients, which was one of the thoughts—prevailing thoughts—probably about 5 to 6 years ago. I think we should get away from that. You know, high-risk people do get benefit from intense chemotherapy. And perhaps they are the patients who need to get to what we call a minimal residual disease negative remissions, and transplant remains an important tool to get there.

**Shah**: Yes. I was going to say the same thing that one of the reasons we think the benefit exists is because you get a deeper response, you get more of the disease eradicated from the body. And we know that depth of response is related to length of remission or time before people will progress again. And even more now—and we'll talk about this later—with minimal residual disease (MRD) monitoring you can sometimes overcome the bad risk of the cytogenetics by getting to that MRD negativity. So, if transplant can help with that, this will be good for our patients.



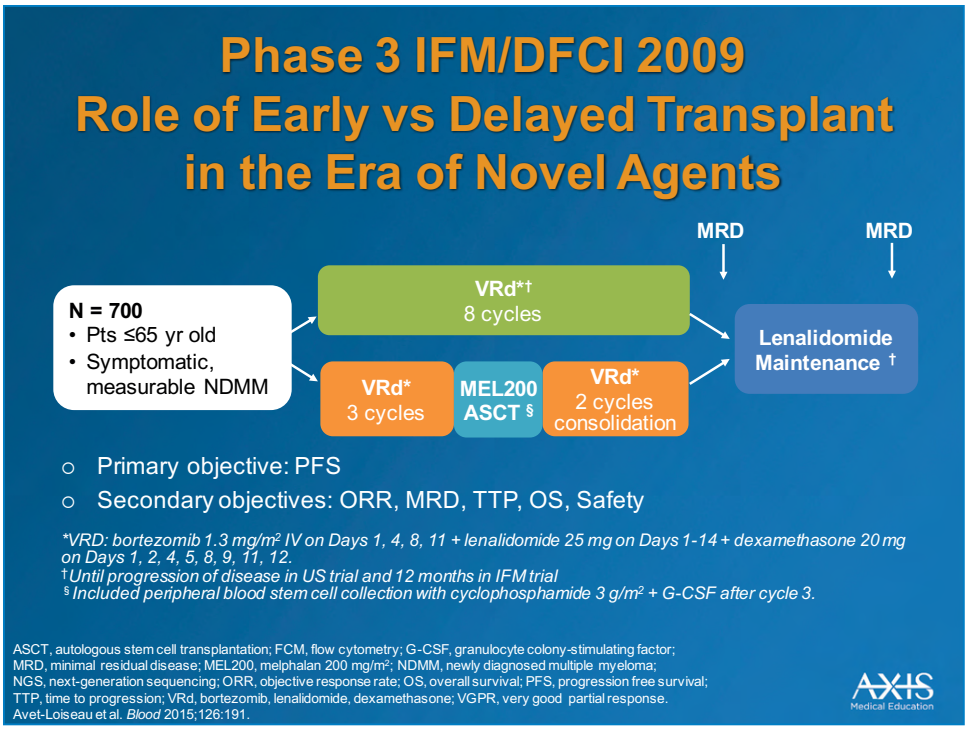

**Hari**: Absolutely. So here is a summary slide of all the new drug versus auto-transplant studies in the modern era. I would point out that the top first two are studies that did not involve proteasome inhibitor or bortezomib older studies. And those are the two studies that show an overall survival advantage for transplant. And the criticism against that is that they didn't have bortezomib in the induction regimen or, in fact, nowhere in the regimen at all. The bottom two are the ones that we just discussed.

**Shah**: So, that's one of the reasons why I think these discussions in the clinic are so important because you never want to say you ***have*** to do this or you ***have*** to do that. We can present data, but we should also remember that, so far, all of the data is in favor of early transplant.



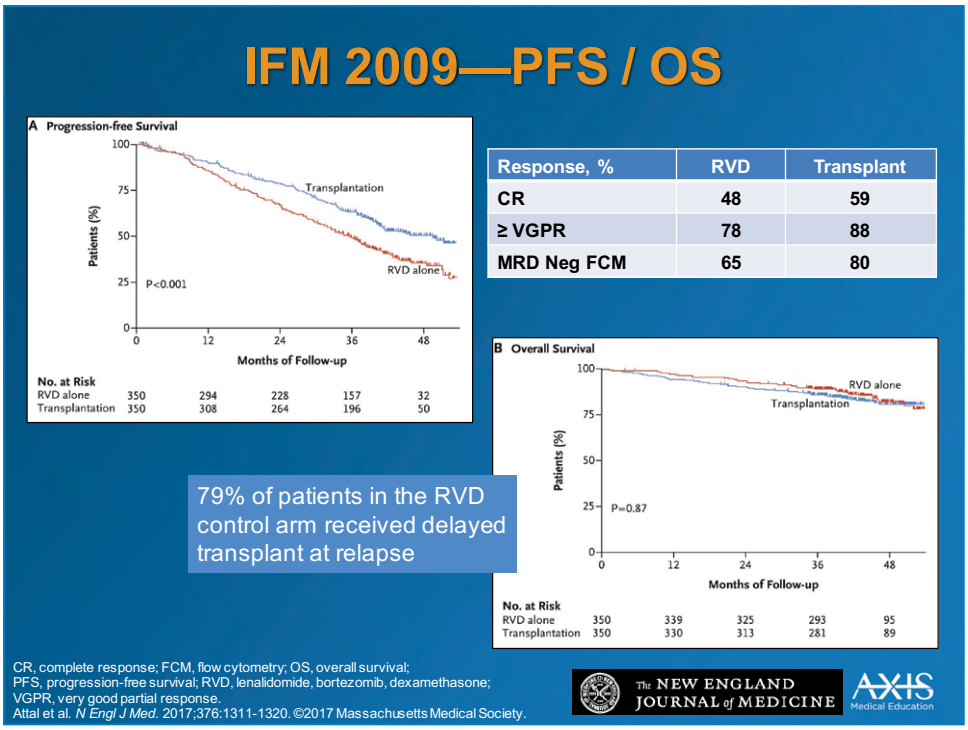

**Hari**: Absolutely. And again, you know, I'm always humbled by this slide, which shows us the advantage that maintenance gives to patients. When I started my career, I still remember the early half of my career we used to say that the majority of patients after a single autologous transplant relapsed in the second or third year, between the second and the third years 50% of patients who relapsed. Now in the era of maintenance, these are data that were submitted to the FDA, which has now approved lenalidomide maintenance in the United States. And you see that study 1, which is the US CALGB 100104 study, the median overall survival in patients who took a single transplant and lenalidomide maintenance was in their tenth year, 9.3 years, which means that 50% of all the patients in the 2004/2005 era who went onto a single transplant followed by lenalidomide maintenance were alive 10 years later, which is amazing.

**Shah**: It's amazing, especially considering what it used to be.




**Hari**: So here we go at the IFM/DFCI study, which I talked a little bit about, that's the IFM 2009 part is the part that's already been reported by Dr. Attal from France in *The New England Journal of Medicine* this year. Whereas the DFCI part, which is the Dana-Farber part also done by The BMT CTN—The Blood and Marrow Transplant Clinical Trials Network, as the determination trial (which is still ongoing and almost accrued at this point), this study—again, as you said Nina—randomizes patients after a collection to ongoing bortezomib/lenalidomide/dexamethasone, which then amounts to eight cycles for people who don't get a transplant. And for people who get a transplant, it turns out to be three cycles and induction. A single stem cell transplant with high-dose melphalan followed by consolidation with bortezomib/lenalidomide/dexamethasone for two more cycles, and then lenalidomide maintenance for a year as reported by the French.

**Shah**: Right. Although longer for the Americans.




**Hari**: And indefinite maintenance for the Americans. So here are the final data from *The New England Journal of Medicine* paper by Dr. Attal. As you can see, the transplant arm, as expected, had a higher complete remission rate; higher percentage of people getting to very good partial responses or more; and more importantly, as you said, the MRD negativity by flow cytometry.

**Shah**: Right. I think this is really important because it really brings the question of early versus late transplant into the modern era. As you mentioned already, that it's triple-drug regimen, which is pertinent to our practices now and bortezomib-containing regimen. And this is something that people can take back to their clinics and say okay I do this in my clinic, or I got this from my doctor, and I have data to show that there's some benefit from my getting a transplant earlier. And again, it's a decision that everybody has to make together, but it helps patients to sort of have more clarity in this respect. Also, as you mentioned, that there are deeper responses in the transplant group. And, like we've talked about, it seems that deeper responses correlate with better outcomes long term.

**Hari**: Exactly. So this study was important in that it didn't show an overall survival difference for the transplant versus non-transplant arm, but functionally these arms turned out to be early transplant versus late transplant. Because the patients who were randomized to no transplant—80% of them—ended up getting a

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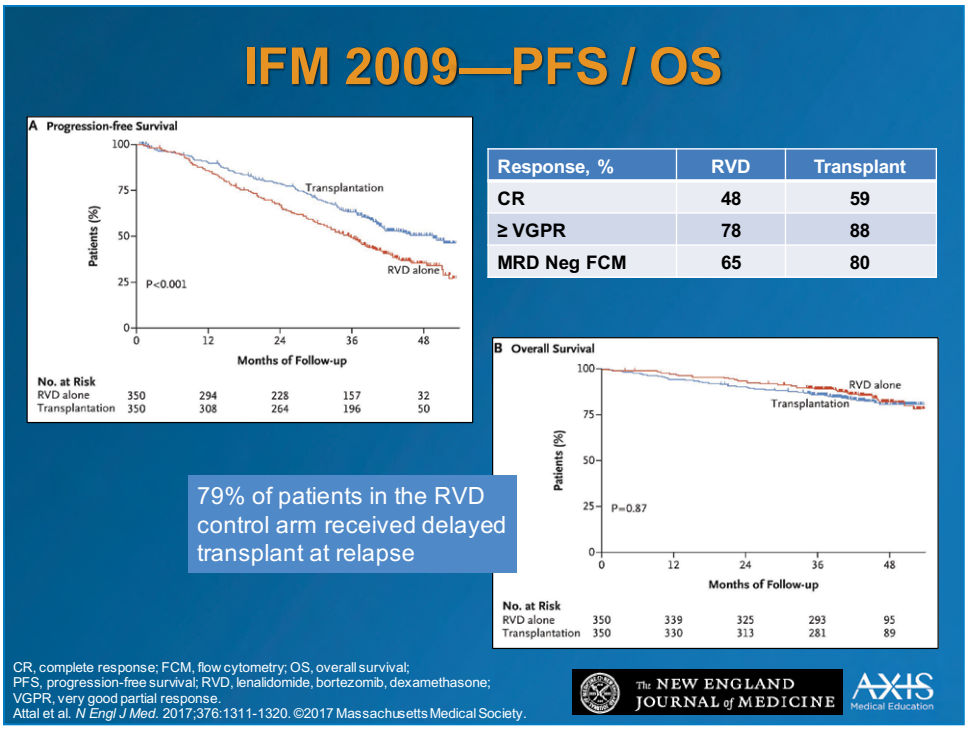


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transplant in their first progression. So the progression-free survival was significantly better for transplantation, but the overall survival was not. But at progression, remember the non-transplant arm really ended up being a late transplant arm. So I think it tells us the following points. One, the importance of a transplant giving you a long first progression-free interval. And again, going back to the natural history of myeloma, it turns out that for the majority of patients with myeloma the first progression-free interval is probably going to be the longest progression-free interval because we know that the disease morphs—clonally evolves—and badness comes a little bit further upfront during relapses. It becomes more difficult a disease to control at relapse. So I think the first progression-free interval cannot be and it has to remain an important consideration when we choose treatments.

**Shah**: Right, we have to optimize that.

**Hari**: We have to optimize that. And increasing that would be, again, the way to get to a cure.

**Shah**: And things happen, as you mentioned, and 20% of people may not be able to get that transplant later. So, it's something to consider. Also I think it really drives home the point that stem cell collection is very important. And whether you're going to use it now or later, it's something to consider after a few cycles of therapy.

**Hari**: Exactly. So, 80% could get to a transplant at relapse provided they had stem cells in storage. If you didn't get

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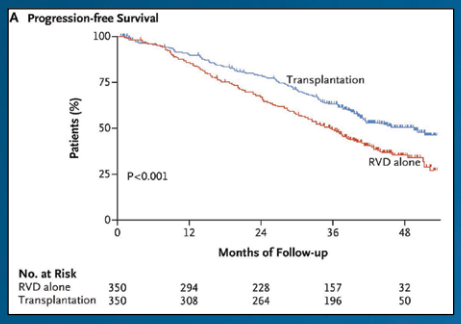
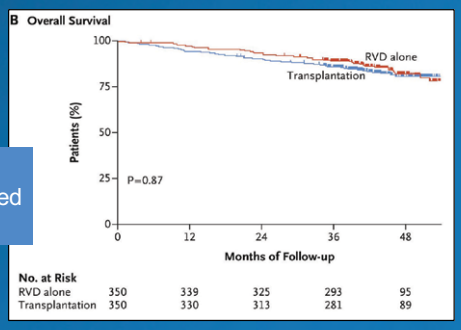
# IFM 2009—PFS / OS




| Response, % | RVD | Transplant |
|---|---|---|
| CR | 48 | 59 |
| ≥ VGPR | 78 | 88 |
| MRD Neg FCM | 65 | 80 |




79% of patients in the RVD control arm received delayed transplant at relapse

CR, complete response; FCM, flow cytometry; OS, overall survival; PFS, progression-free survival; RVD, lenalidomide, bortezomib, dexamethasone; VGPR, very good partial response.
Attal et al. *N Engl J Med*. 2017;376:1311-1320. ©2017 Massachusetts Medical Society.

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a transplant referral or if you didn't get the collection done at the early time point, that 80% is not going to happen, it will be much lower. So that's why...

**Shah**: You have to think in advance about that.

# When to Refer to a Transplant Center?

- Data strongly in favor of early transplant in multiple myeloma
- Even if delaying transplant – when to collect?
  - Earlier the better for collection
  - "Collect, Hold, Transplant at relapse"
  - Avoid repeated induction cycles that reduce collection yield

**Timing of Referral:**

**Early in induction**

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- **Hari**: ...think in advance about that. It is an effective option. And if you didn't—for whatever reason—if you didn't have it upfront, it's important to keep that option open for later. Which brings us to this point, which is when should you refer to a transplant center.

**Shah**: I always encourage referring providers—and even in our own practice with newly diagnosed myeloma—to start the transplant referral right away. Number one, people, as you mentioned, may be considered ineligible initially. But after having a couple of cycles of therapy, they feel better, they're more functional, they're getting back to who they were, and they now become eligible. So you don't want to close the door right away. It takes time to plan for a transplant, so I like to see them upfront. What about you?

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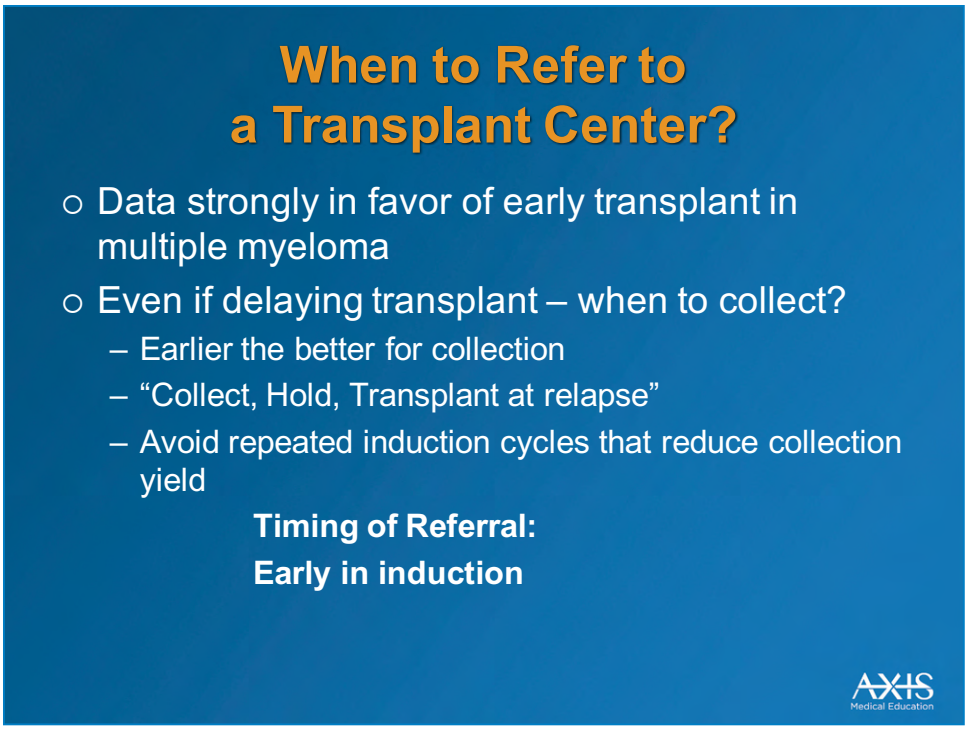


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**Hari**: That's exactly my view, too. I think every patient with myeloma if they're eligible or borderline eligible for a transplant they should come and have a discussion about it. And transplants have become substantially safer in the last decade or so.

**Shah**: Yeah, we can do them as an outpatient now.

**Hari**: Actually, a vast number of patients are actually getting these transplants in out-patient now. And secondly, as we just said, if you don't get it collected at the beginning, you are very unlikely to make it happen. And, outside of a well-designed clinical trial, I think the standard of care should still involve an upfront transplantation for anybody who is eligible. And if you are on a clinical trial, it's again important to collect the stem cells in hold because there's no study that shows that transplant has disadvantages in myeloma, such a study doesn't exist.

**Shah**: Right, that's never been shown. If anything, there may have been noninferiority or equality or equivalence, but it's not that it's ever been shown to be inferior, even though it's an intense therapy. I mean I think just this issue of when to collect stem cells. I would think maybe after somewhere between four to six cycles in that range of induction therapy. What do you think?

**Hari**: I agree. And it has gone between three to six cycles in that range. And it's important to—we will get to mobilization in a second—so even with very effective mobilizing drugs, some people become ineligible

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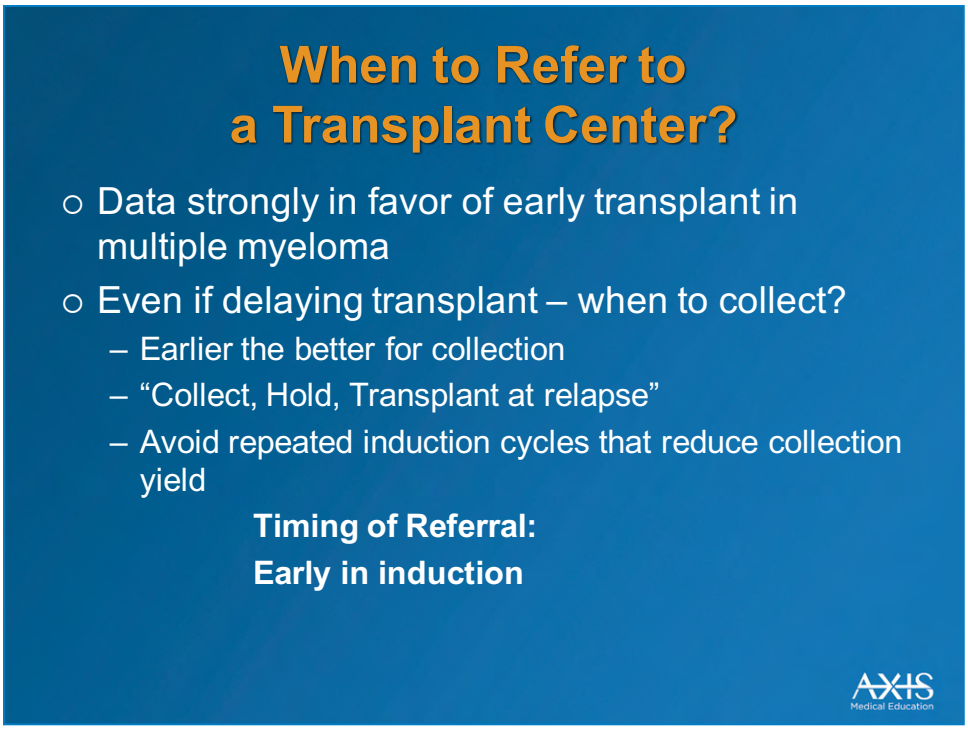


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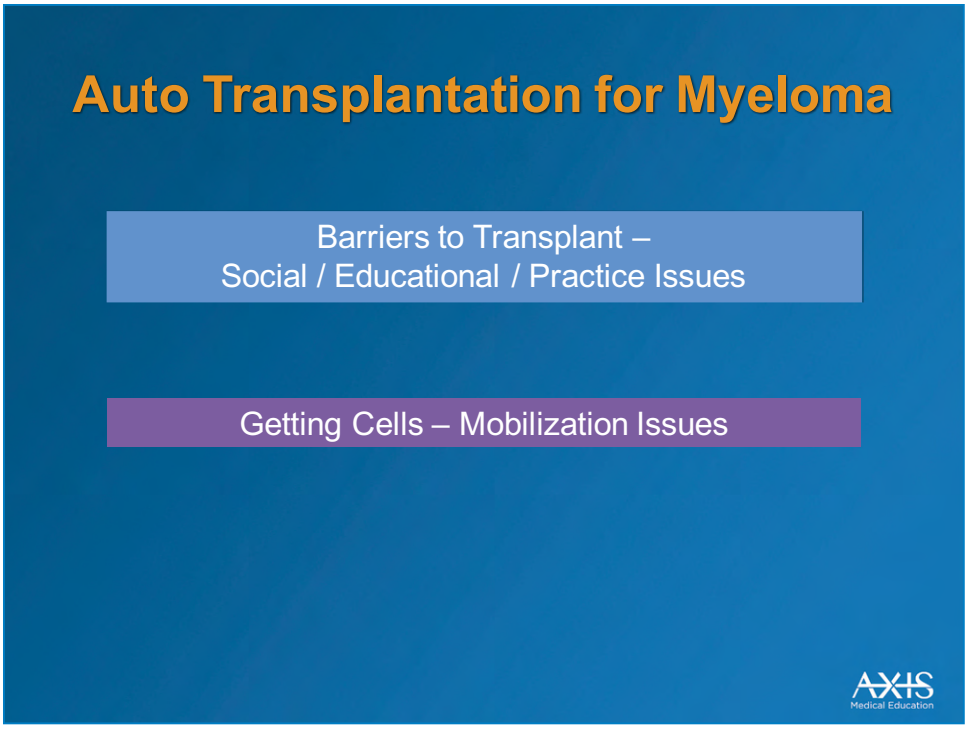
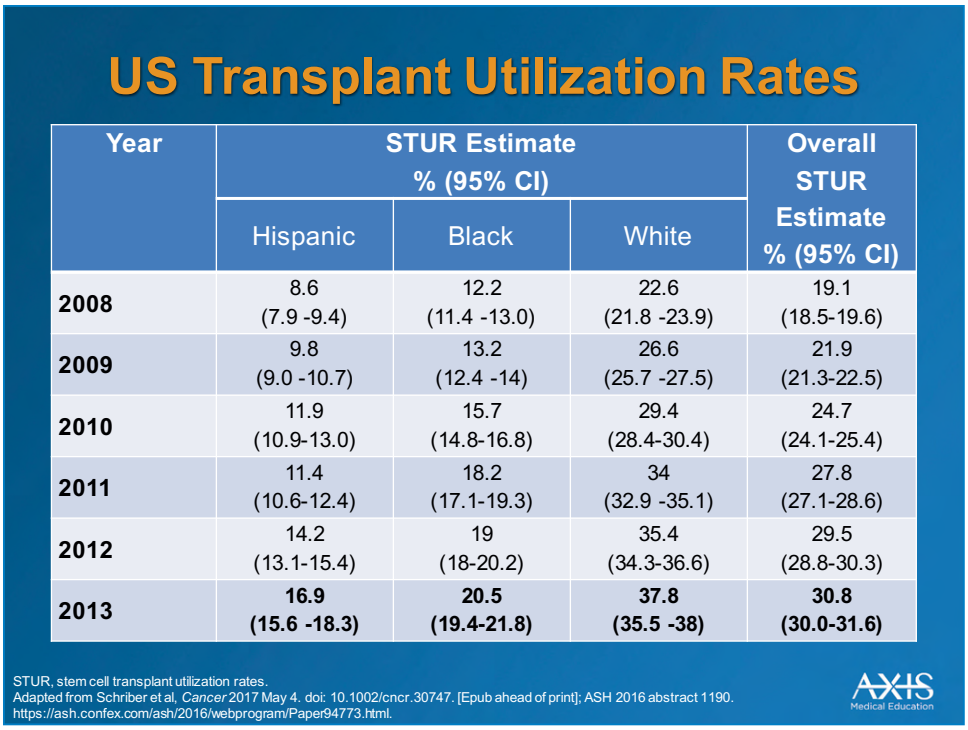
for mobilization or are unable to mobilize stem cells because of repeated cycles of therapy. So you get them early.




- So again, what are the barriers to this happening? You know, there are some sobering data that has come out from CIBMTR (Center for International Blood and Marrow Transplant) type comparisons, which talk about the barriers to transplant. And we have analyzed some of the social, financial, and other barriers. And then, even if you get referred to a transplant center, there is a barrier to transplant in terms of mobilization issues. So we will discuss those in a second.




**Hari**: So here are the US transplant utilization rates. This is a paper that just came out in the journal *Cancer*. And so this basically gives you a percentage of patients with myeloma who get to a transplant. And it's only for patients below the age of 65, so that there wouldn't be much questions about eligibility. So here we see that only about 30% of the patients who are eligible for transplant end up getting a transplant in the United States even in 2013.

**Shah**: Which I found surprising because I would think that more would be getting a transplant based on the data that exists. But, we often don't see the people that don't get referred right?

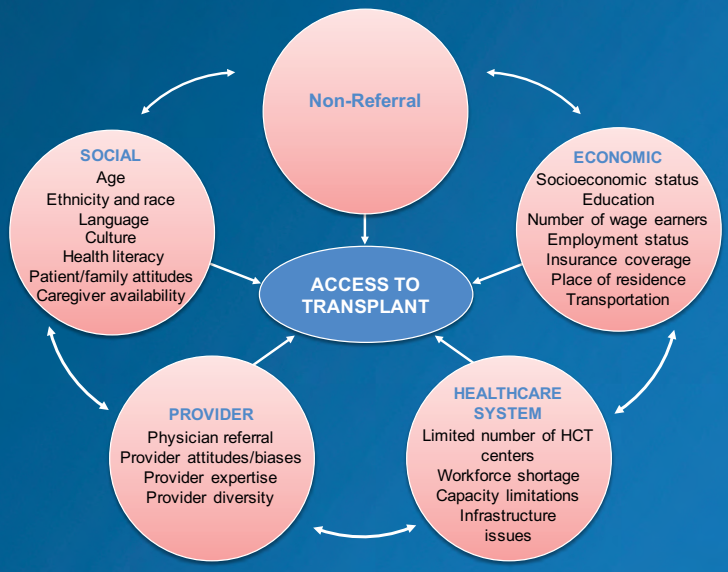
**Hari**: Exactly. And the disparity is even wider for patients who are of ethnic minority like blacks or Hispanics. So in those populations, it drops down to 20% or lower than 20%.

## Why Study Transplant Barriers in Multiple Myeloma?

- Most common disease treated with transplantation
- Transplant is SOC as initial therapy – strong evidence base
- Vast majority of transplants are autologous, therefore not limited by donor availability
- Higher incidence in blacks
- Incidence increases with age – less insurance issues (Medicare)

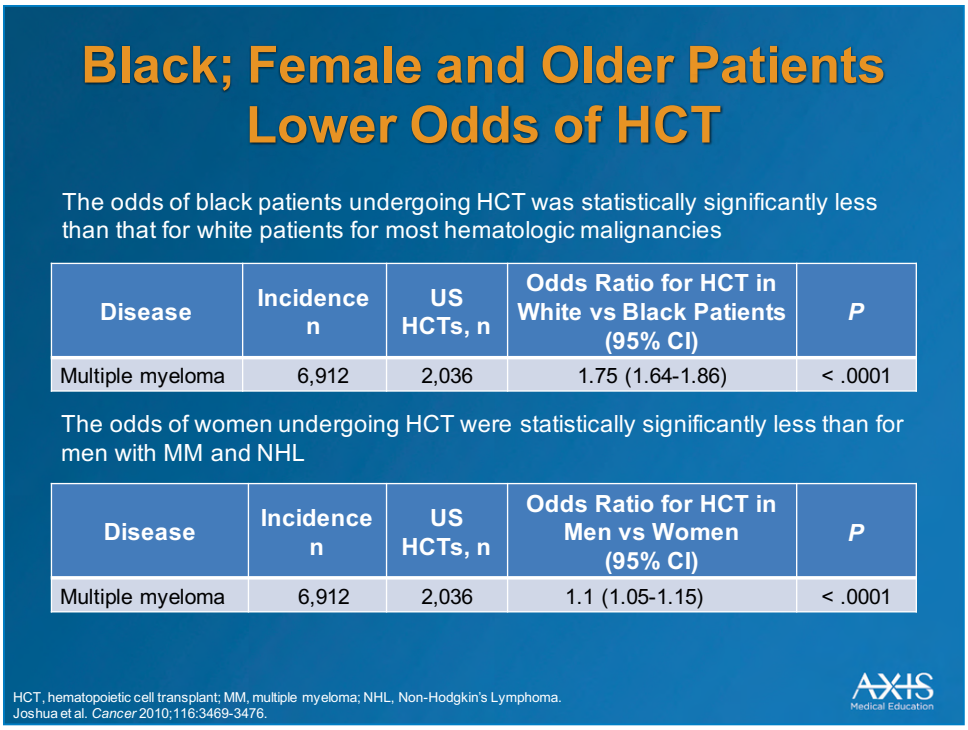
SOC, standard of care.

## General Barriers to Transplant Access



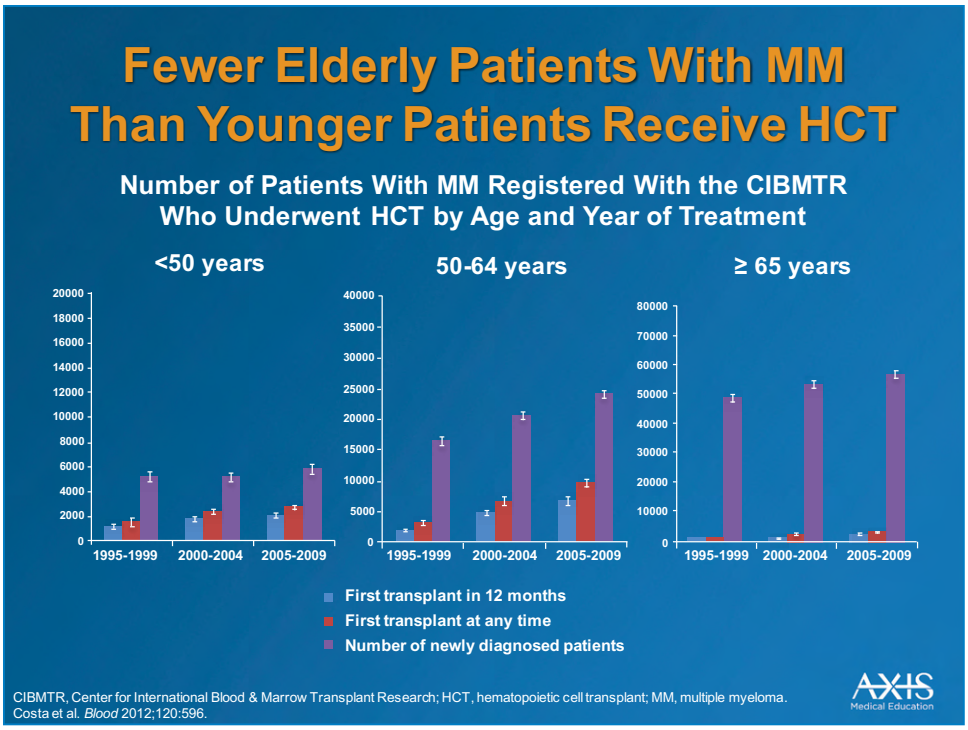

HCT, hematopoietic cell transplant.
Adapted from Majhail et al. *Biol Blood Marrow Transplant.* 2010;16:1070-1075.

**Hari**: And it's important to study the barriers to transplant because our treatments are only as effective as the people who get them. So you could have a thousand patients treated on a clinical trial which shows 10-year survival; whereas if it doesn't translate to the 25,000 patients living with myeloma, it's not effective. So it's important to study these barriers. Again, this slide actually talks about some of the barriers that you just mentioned: economic barriers, social support barriers, referral bias. And again, healthcare system in-network decisions; sometimes healthcare systems become very restricted and they don't want to refer out to another system that is not within their network, and I think it's ***very*** disadvantageous to patients if they don't get the expertise sometimes which exists in their own town because of narrow network practices and health systems who are only focusing on profit at that point.



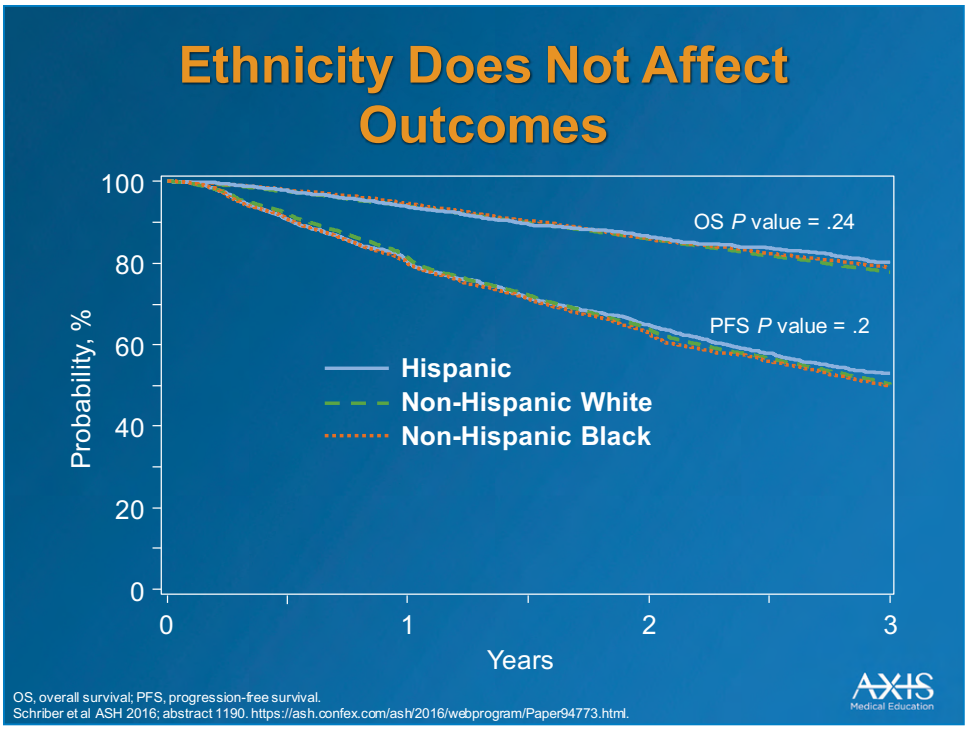

**Hari**: So here's, again, some data suggesting that the probability of getting a stem cell transplant for myeloma is significantly lower or is much higher odds if you are a white individual versus a black individual and male. And so we see that age, ethnicity, and female sex are the three biggest barriers that exist and for no good reason.

**Shah**: For no good reason. There are no differences in outcome. And this tells us that we should be more mindful that maybe we're not giving these opportunities… our own biases are coming in, and we're not offering these opportunities to these populations because we, as physicians, may not think that they're appropriate, but they are. And we shouldn't limit them based on any demographic information.

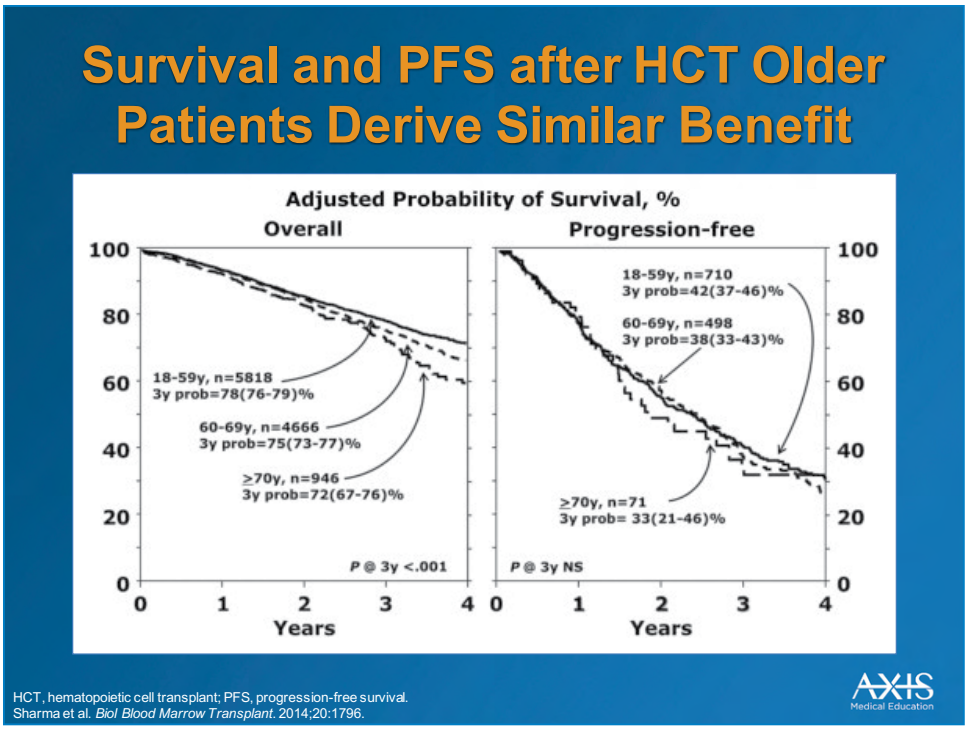



**Hari**: And again, you know, age being a barrier—here is data showing that. It's a very small proportion of patients who are above the age of 65 who get a transplant even this is in the United States. Even if you look at the people getting it within the 12 months of diagnosis as upfront transplant —or at some point during the course of their disease—still very, very low numbers. And remember the majority of patients with myeloma are above the age of 65.

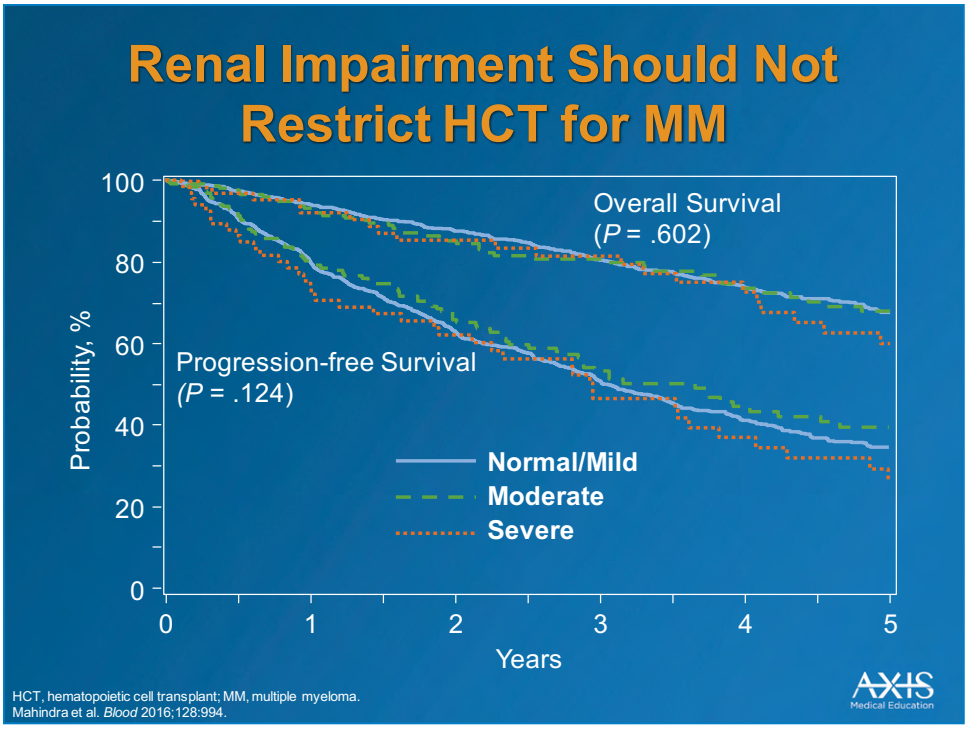
**Shah**: And people are willing to consider this as an option. So when I saw this data that so few of the patients above 65 are being referred for transplant, I thought we can make a difference here.




**Hari**: Absolutely. And as we said before, here is data suggesting that ethnicity does not affect outcomes—it's the same whether you're Hispanic or we didn't think this would be any reason biologically, but we had to prove it.




- And again, similarly we have data suggesting that the older versus younger progression-free survival from transplant is exactly the same whether you are 18 or whether you are 70. So it suggests that the benefit in terms of controlling myeloma is not restricted based on age.

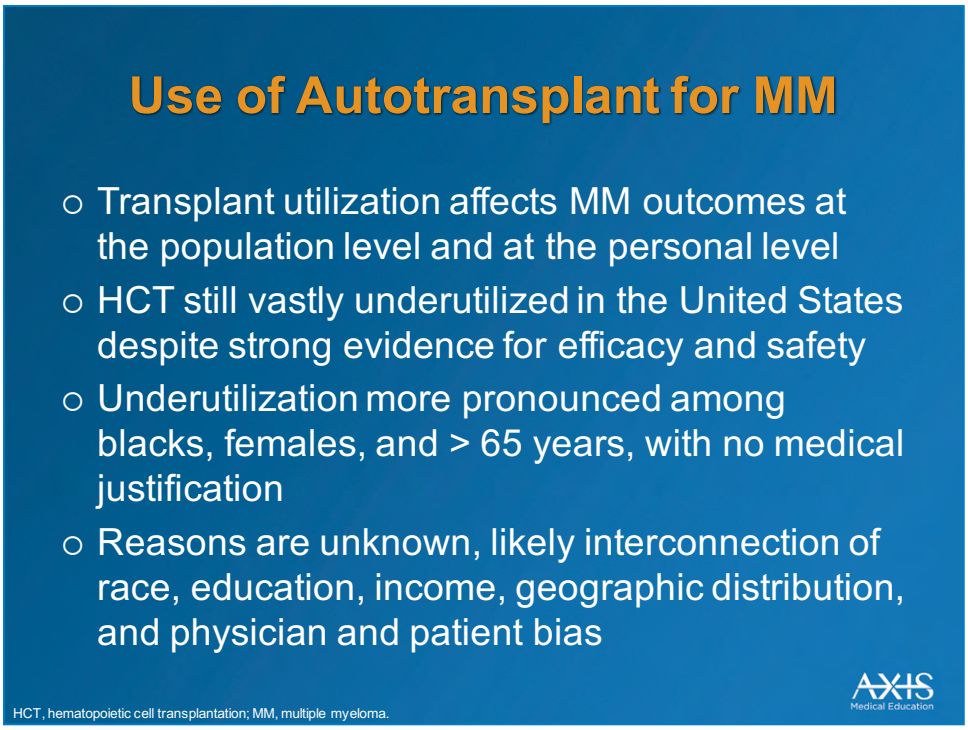



- **Hari**: Similarly, with renal impairment, even if you have severe renal impairment on hemodialysis, transplant physicians have perfected the art of giving melphalan even in people on dialysis.

  **Shah**: Yes, we routinely do this.

  **Hari**: Exactly. And that should not be a contraindication to referral for transplant.

  **Shah**: Right.




**Hari**: So here, again, is unlikely—but true—is that we have this effective therapy, which is transplant followed by maintenance, but we're not utilizing it as we should. And this is a huge challenge for our patients. And I think we, as physicians…

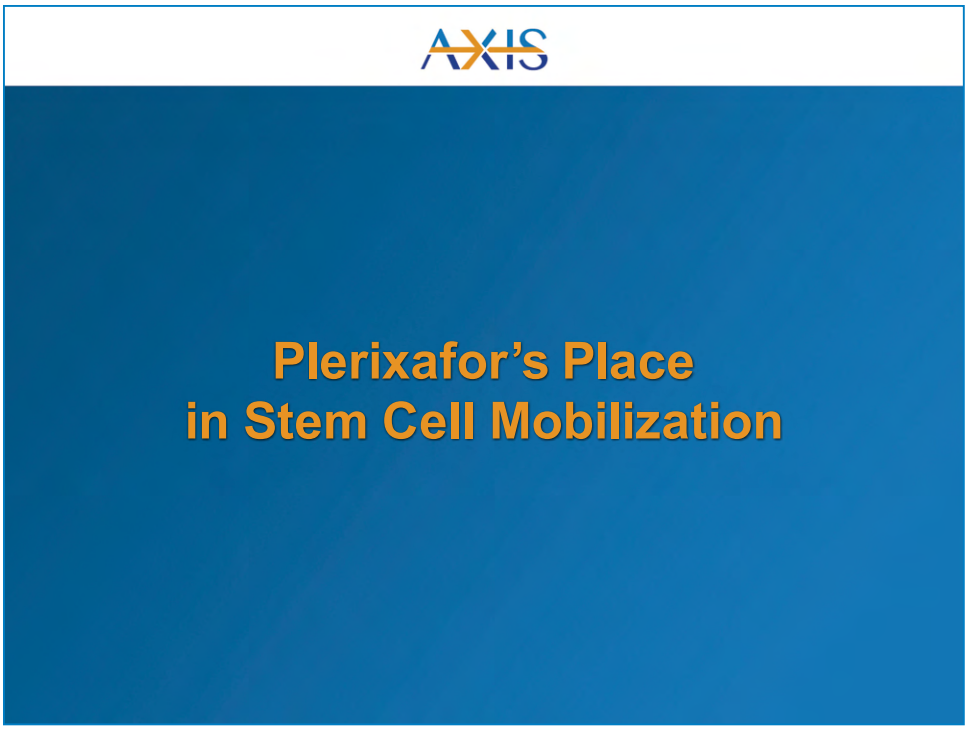
**Shah**: And for us…we have to make sure the word gets out and refer patients and not let our own biases get in the way when it's very possible to get this done for way more patients than we're doing it.

**Hari**: Right. And again, in some ways, when we have a new effective drug that comes out, there's always a hype about it, but it still turns out that every time a transplant is compared with non-transplant the benefits seem to be additive rather than bringing everything to the same level. So the newer drugs plus transplants now with maintenance are giving…50% of patients are alive at 9.3 years.

**Shah**: Yes, I mean this was unimaginable 15 years ago.

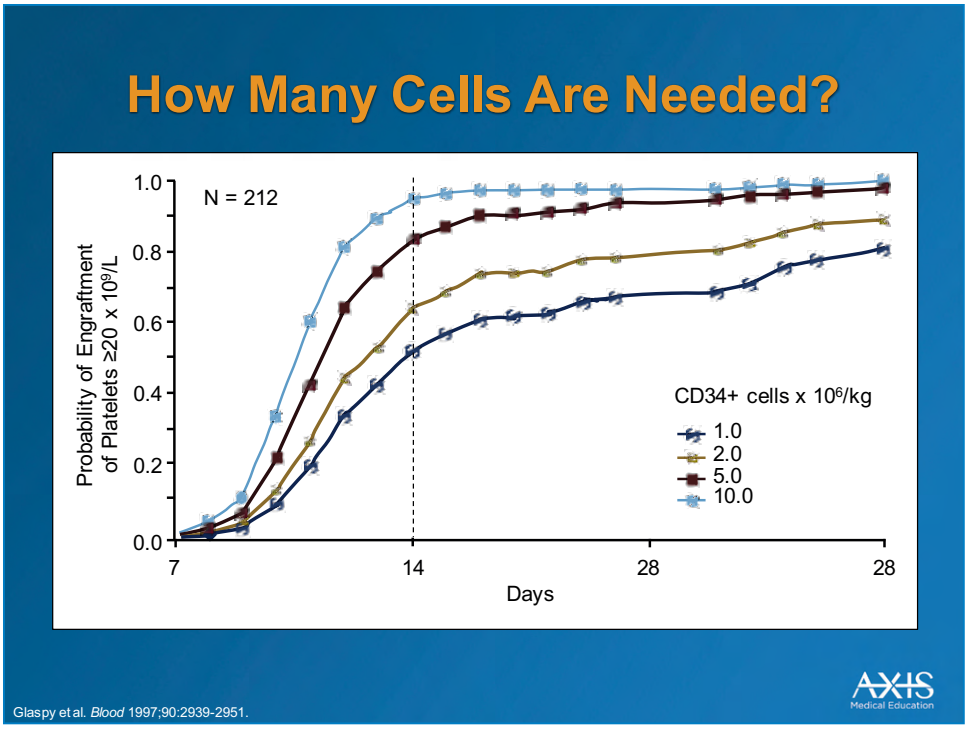
**Hari**: Unimaginable, exactly. So we have a lot of these old technologies which it still at some point it may go away, but right now right now it's here.

**Shah**: Right. And in the next session, we'll talk about how we can even utilize that for more novel therapies to be on top of it.



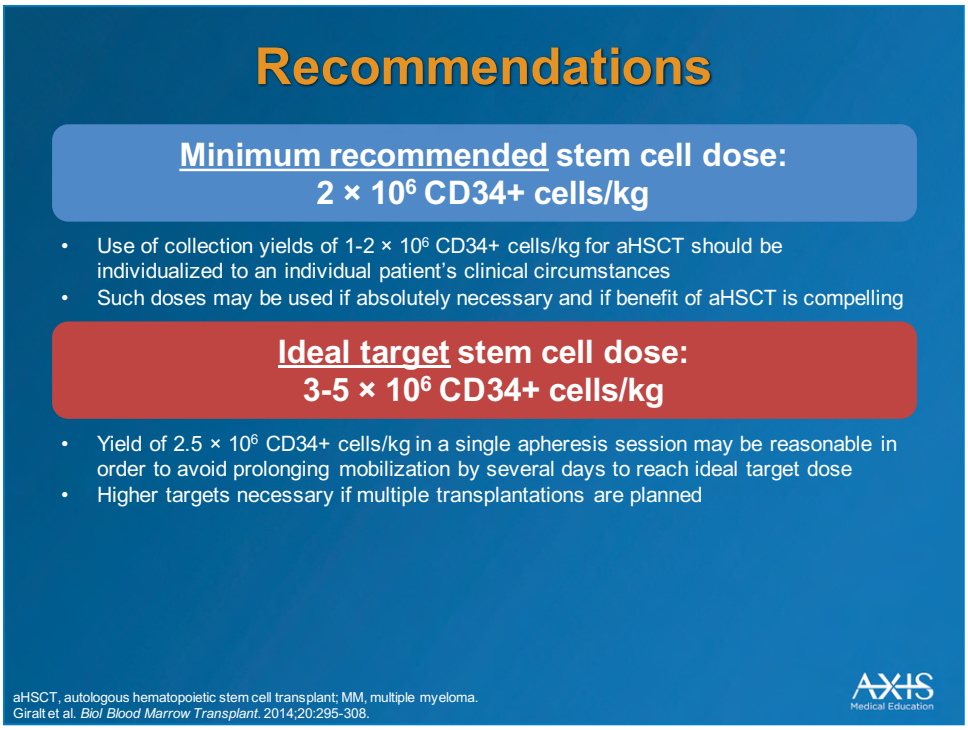

**Hari**: Exactly. So then, one of the other things that we should mention in this context is mobilization. Because when you get to a transplant center sometimes, especially if you come late after multiple cycles of induction treatment, there is a challenge in getting enough stem cells taken from those patients.

**Shah**: Or known as mobilization.



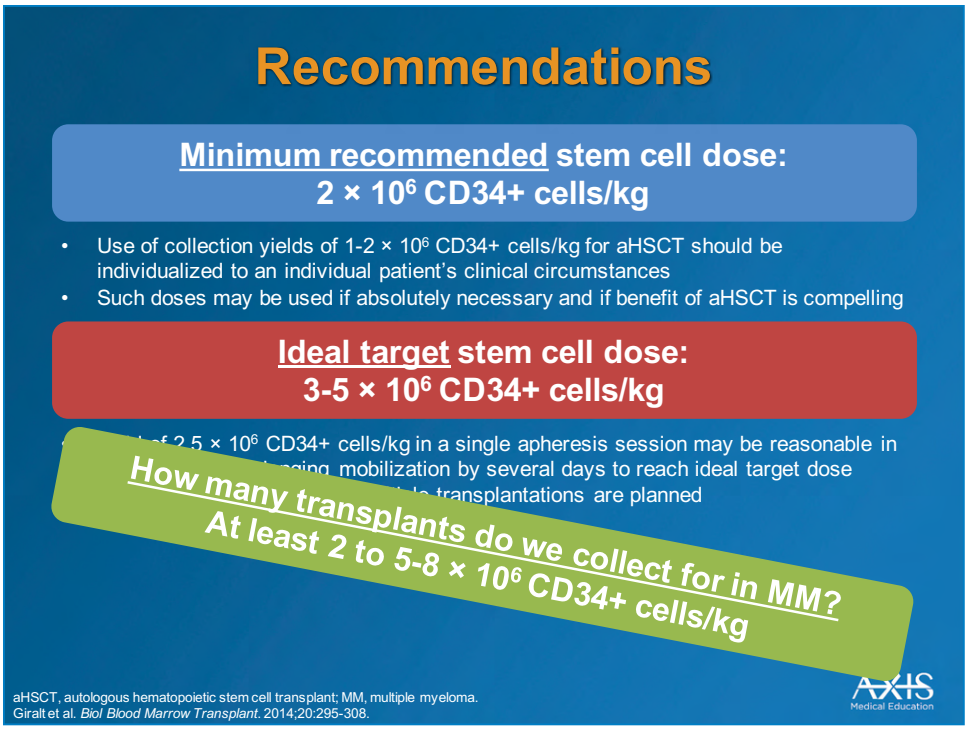

**Hari**: Mobilization. So the mobilization…here is a curve describing how many cells are needed for a transplant.

**Shah**: Right. And so we've generally thought – and we'll see this on the next slide – that you need at least 2 million stem cells or CD34+ cells, which we call stem cells, per kilogram. And you can get away with just that much. But, as you can see, there are some outcomes that are slightly improve with higher stem cell quantities. Really you don't need much more than 4.0 to 5.0. And as you can see, the minimum requirement is 2.0. We ideally target…I usually try to collect 5.0, 6.0 because we want to collect for two transplants, and that's something we're going to talk about in the next session also.

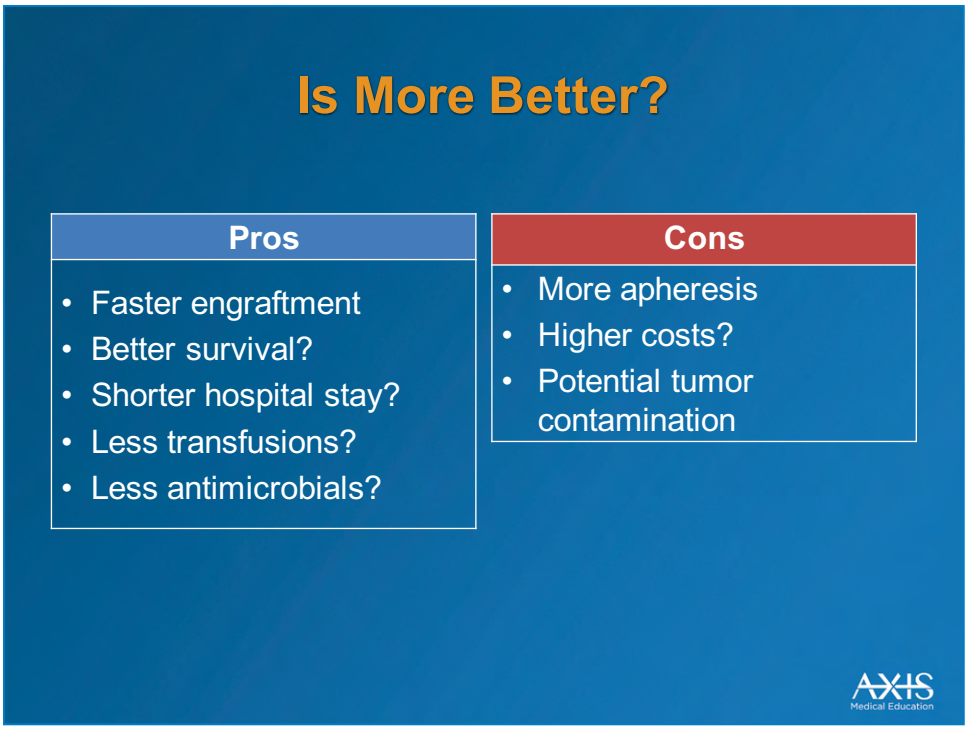



**Hari**: So these are the recommendations from the International Myeloma Working Group, and similar recommendations have come from the ASBMT, American Society of Blood and Marrow Transplantation, that the minimum is 2.0 ideal targets somewhere in that 5.0 range, just as you said. And for myeloma, though, we should offer patients the chance of having some stem cells in the bank and not use them all up at the beginning.

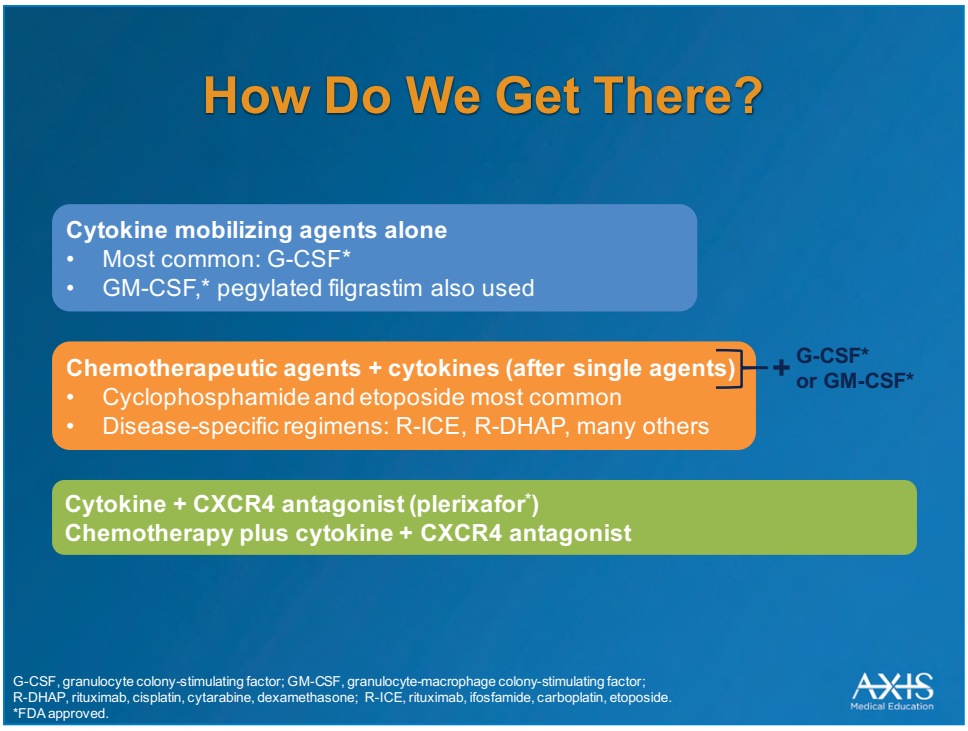
**Shah**: Right. I always collect for two, do you?




**Hari**: Absolutely. I think most academic centers that I know about, at least for two transplant. Sometimes if you get more, you can allocate them and do several bags so that you...and it turns out that if a patient has a significantly prolonged first remission from transplant, they are the people who are most likely to benefit from a second transplant at relapse, as we will discuss later.




So are more cells better? So again, to a point they are. Actually, I think to get more cells you have to put the patient through more and more sessions of mobilization or apheresis, and that would be the downside to getting it. But it would be better to get as many cells as possible in the first one or two days of mobilization.




And here are some of the mobilizing strategies.

**Shah**: So I think there's sort of three major tools we have to mobilize or what I call take stem cells out of the bone marrow and get them into the blood. And this makes it possible for patients to get their stem cells collected from a catheter instead of having to dig into the bone marrow, which was sort of the earliest way to do it. So the three tools we have are growth factors, so a granulocyte colony-stimulating factor or what we call G-CSF. And high doses of this not only increase your white blood cell count, but they sort of tell your stem cells to get out of your bone marrow and go to the blood. So that's one way. And with that alone, many times—actually often—we can mobilize patients and get enough stem cells. Some patients need a little bit more

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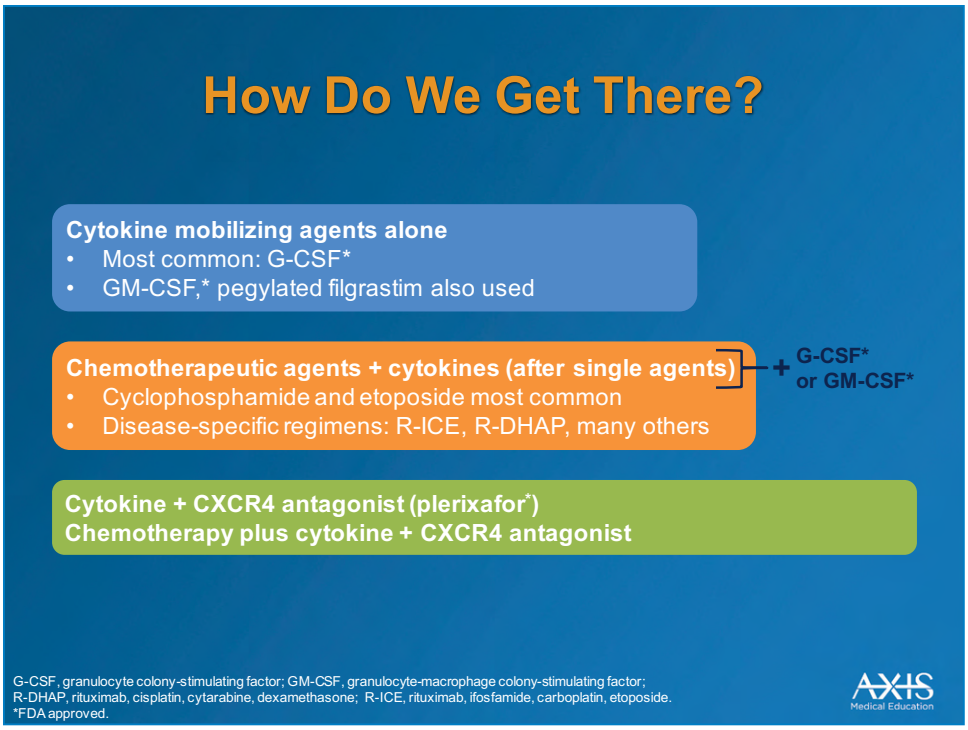


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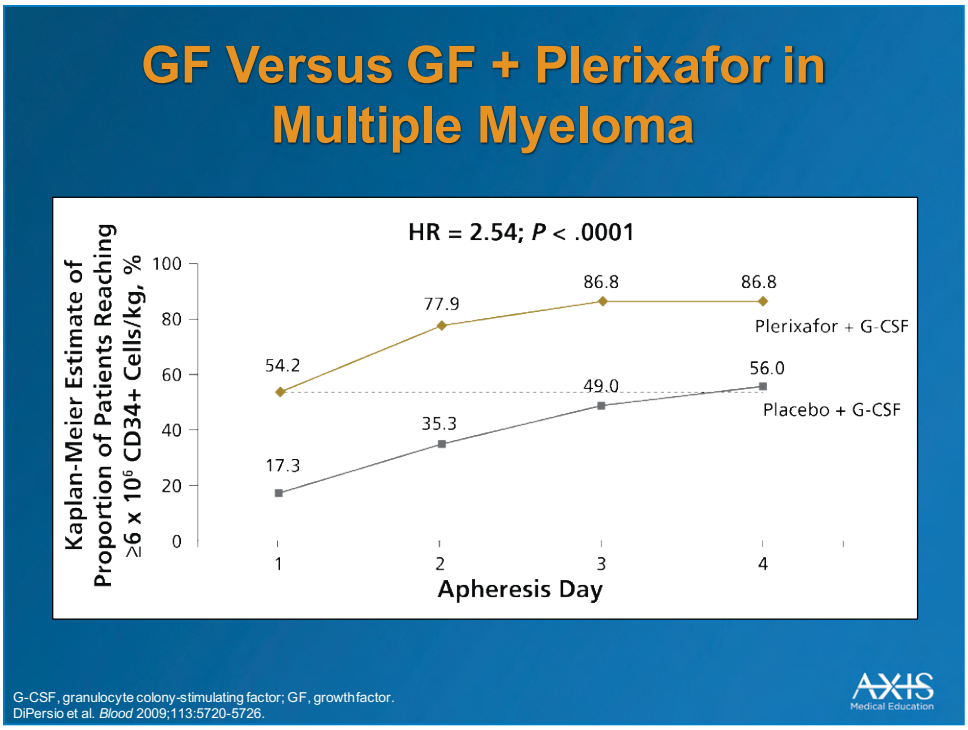
help, and for this we can sometimes use chemotherapy. And ironically enough, giving chemotherapy—which we would think drops your counts—actually allows for a more robust recovery with this growth factor, this G-CSF growth factor. And so that helps us when we think people might be a little bit difficult to collect.

And finally, most recently, we've been able to use a drug called plerixafor, which allows the cells that are stem cells to sort of "unvelcro" from the walls of the bone space and come out and be mobilized even better. And with that, we've had a really nice ability to collect people who we didn't ever think we'd be able to collect. And that's sort of now made this less of a barrier. I've really not had too many problems collecting.


**Hari**: I would completely agree with that. It's almost…very rare that you have a patient who's truly uncollectable. And there are pros and cons for each strategy. The simplest one I would say is just growth factors because actually there are generic growth factors, so the cost factors are significant. But again, that's probably like the middle path. And if you want to have more cells, obviously you would try to do either plerixafor or use chemotherapy plus growth factors. And there are some thought that there is antitumor effect of chemotherapy when you do chemotherapy plus growth factors, especially with cyclophosphamide. But, actually the data are not truly supportive of that. And I know some physicians who always try to use that because some of the earliest studies for transplant were done with cyclophosphamide mobilization, and in Europe they still use cyclophosphamide mobilization to a huge degree.

**Shah**: And they are in these randomized controlled trials that we were talking about as well.

**Hari**: Yes, so they truly think that they want to use for an antitumor effect, although we've never been able to show that, definitively that is.

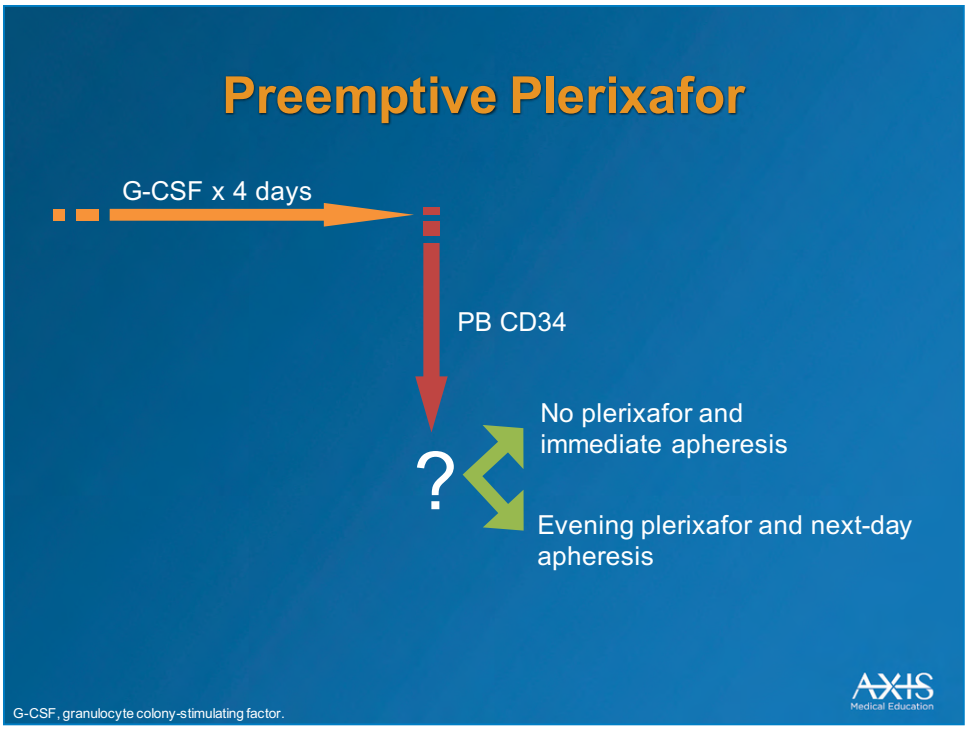



- Here again is the comparison between growth factors alone versus growth factors combined with plerixafor, the mobilizing agent that "unvelcros" the cells, as you very succinctly put it. Your ability to successfully collect patients with myeloma goes up. By Day 4, 87% of patients had that 6 million CD34s collected, which is actually a very robust good collection. Whereas if you just use G-CSF alone, it would be about 56%.

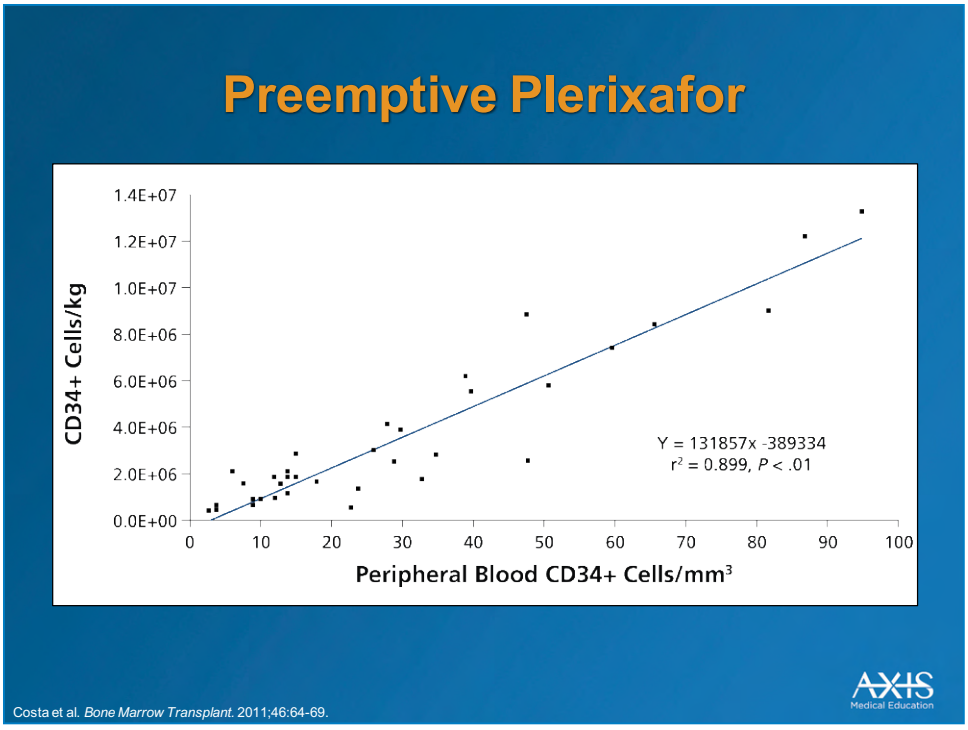
**Shah**: And I think this is one of the things we talk about related to cost, and we should consider this. Because although you may have a more expensive drug; for example, plerixafor, you have more days that you're subjecting a person to apheresis. And there are a lot of costs associated with that, not only monetary but time and physical. So the more sessions you have to have of apheresis that's a whole other nursing staff, a whole other time of the day for the patient, and whole other sort of organizational pathway that you have to do.

**Hari**: And the opportunity cost of being in that bed, which could be used for another patient.

**Shah**: Right, so you could maybe do things faster and have more patients be mobilized. So, I don't think all is lost just on the cost of drug alone, and something that each center has to consider when making their decisions about the pathway for mobilization.




**Hari**: So here is one way of doing it; it's just called preemptive plerixafor where you would give it to a patient based on a CD34 count. And there are a couple of different ways that people are using it because of the cost of the drug, as you mentioned.




One is just in time where you would use it only if the patient is starting to fail a collection or preemptive and you measure the CD34 count on the day before mobilization; here is data for that. You see that once patients get to about 20 CD34 cells per $mm^3$ in the peripheral blood your collectable goes up above 2 million. So it's essentially a good cutoff. And if you're less than 10, most people would add plerixafor at that point.

**Shah**: Absolutely. Because you don't want to subject the patient to additional days of G-CSF, which is not going to be successful, right? So then you're losing time. And so you want to make sure that you do something...an educated guess basically, which is what preemptive plerixafor is. And with that, as you can see, you're able to actually nicely increase the yield that you're

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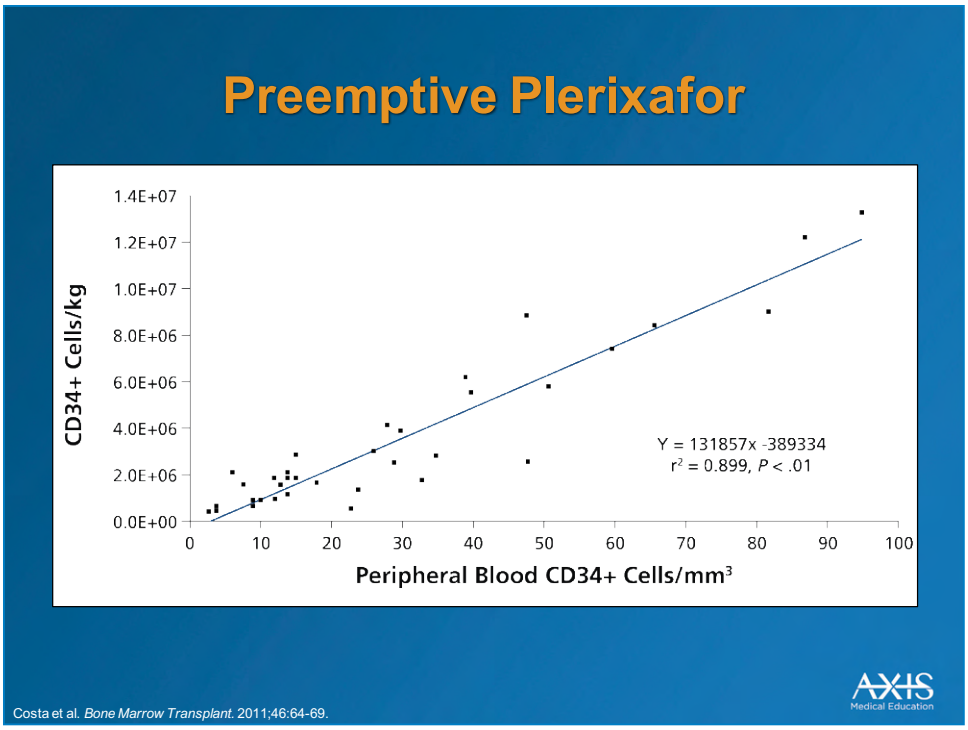


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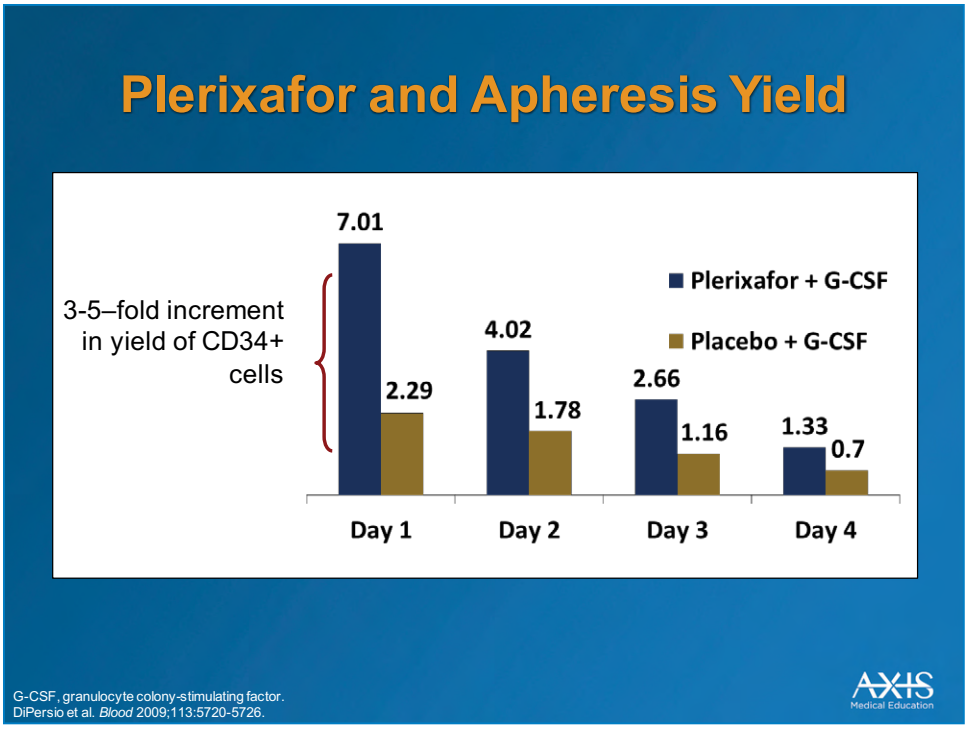
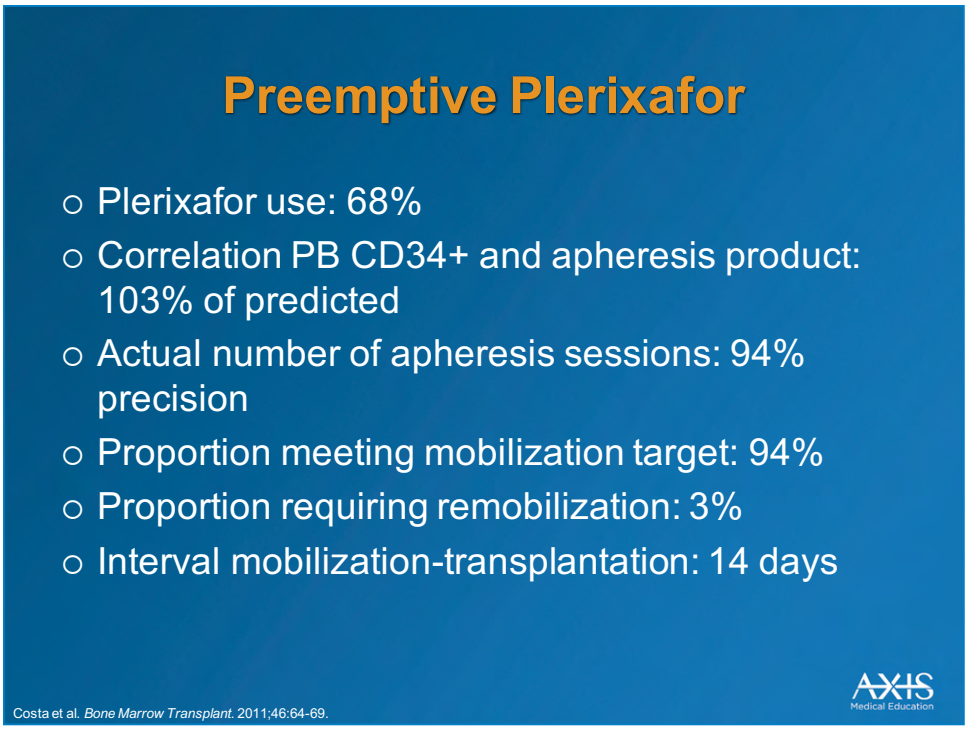
going to get of the stem cells, which I think is really important because you want to be able to do the transplant. I mean that's why the patient came to you. So, you don't want to have failed a collection.

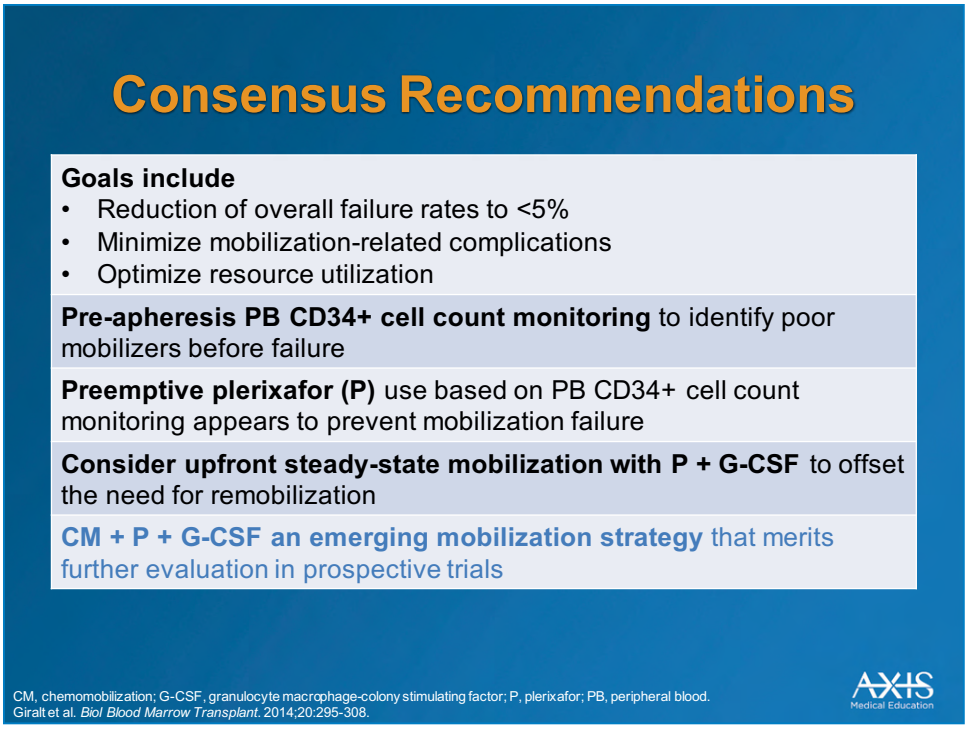



- **Hari**: Yes. And here, again, is data for the plerixafor improves the yield by three to five folds, which is huge, and it can mean the difference between five, six days on the machine versus one or two days on the machine.

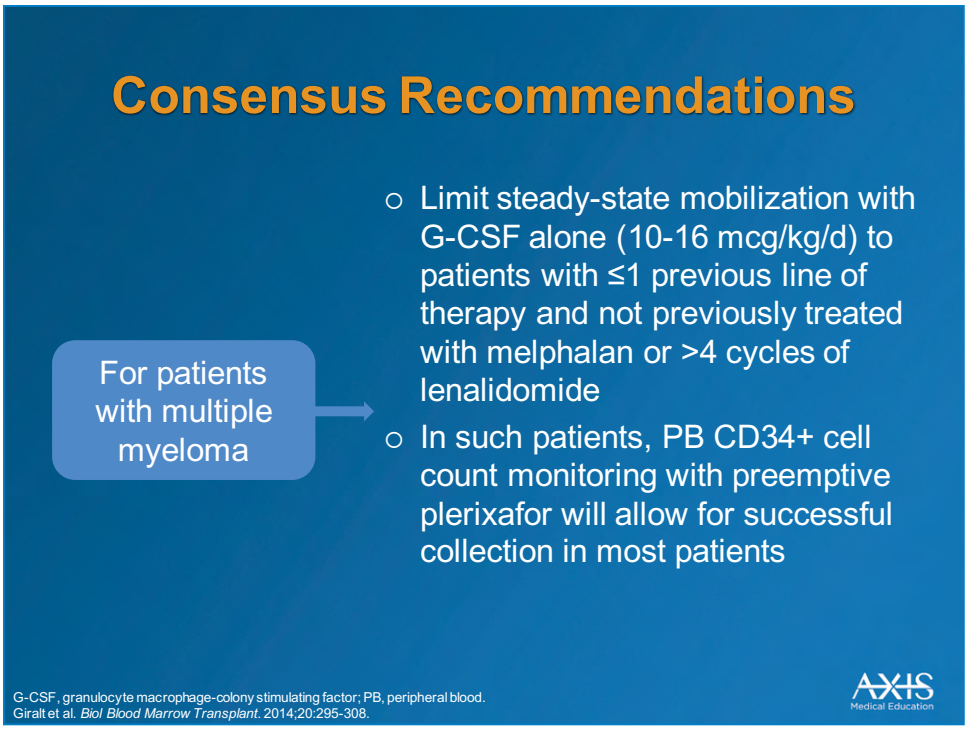
**Shah**: And it can make the difference between one or two transplants.



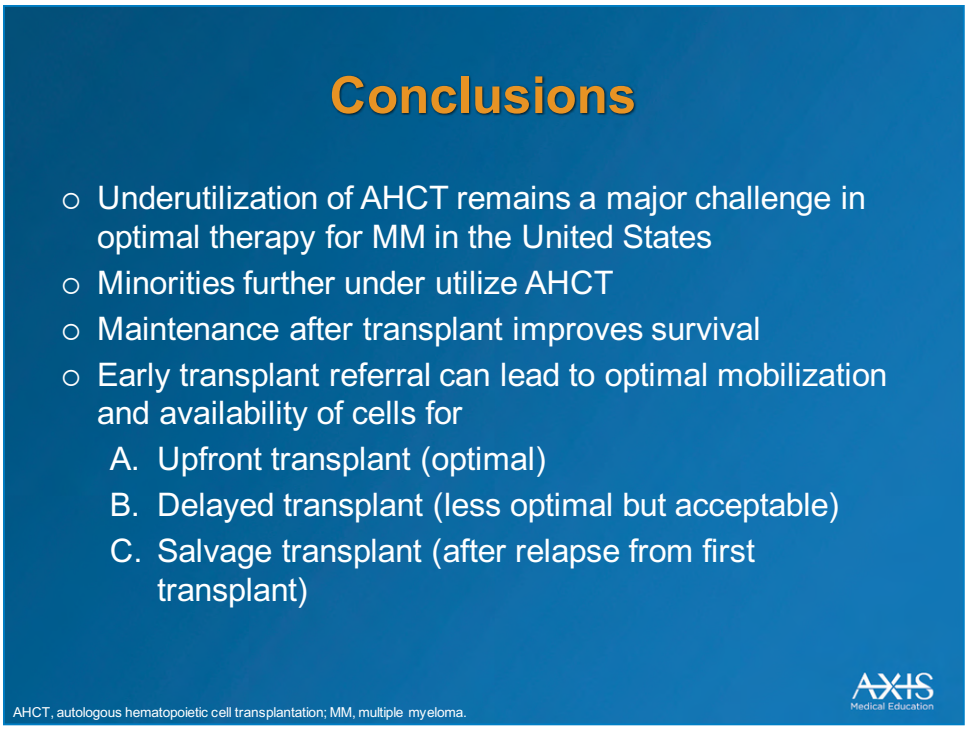

**Hari**: Exactly, yeah. And so here is some data from Dr. Costa's study on preemptive plerixafor. So he actually showed very nicely that the peripheral blood CD34 count and the CD34 count in the mobilized product were exactly correlated. And the number of apheresis sessions could be predicted to almost 94% precision. And the proportion meeting the mobilization target was also 94%. So mobilization is becoming not a huge barrier to transplant with the availability of these drugs and our fine-tuning how we use this.



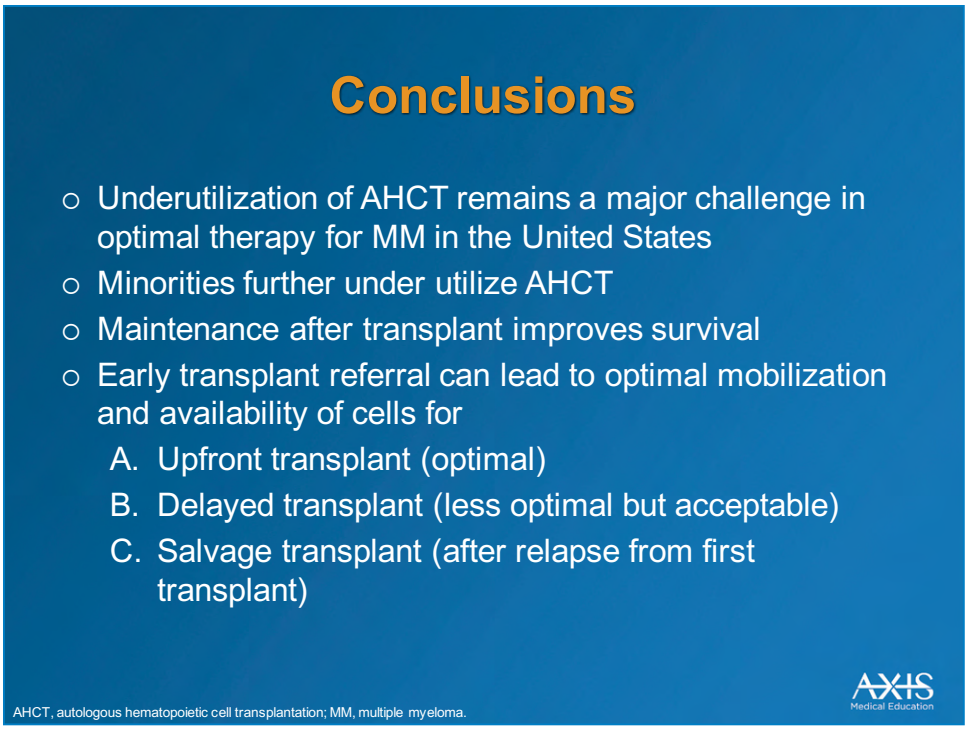

**Hari**: And here are the consensus recommendations again from the American Society of BMT. The goals are to reduce the overall failure to less than 5%, which we've done; and minimize the complications, which means minimize the number of sessions; and optimize resource utilization, which you very clearly pointed out.




**Hari**: And then, again, for patients with myeloma, these are the consensus recommendations to still limit the steady-state mobilization with G-CSF to people who have just less than one line of therapy, not people multiply treated. And if you're multiply treated, consider using plerixafor earlier upfront.




**Hari**: So I think we've had a really good discussion about some of these major points. That underutilization of transplant—despite overwhelming evidence to the benefit—is a major challenge in the United States, and it's a challenge for our patients, it's a challenge for our referring physicians, it's a challenge for us where we cannot get this effective therapy into the community to the people who need it the most. And I want to leave the viewers with this: that early transplant referral is critical in getting patients to transplant. And then, if that cannot happen, collecting stem cells and holding it for transplant at relapse; and for the patients who have undergone an early transplant, if they get a significant benefit from it at relapse, maybe use the cells again. So there is significant advantages to an early transplant referral, and *(cont'd on next page)*

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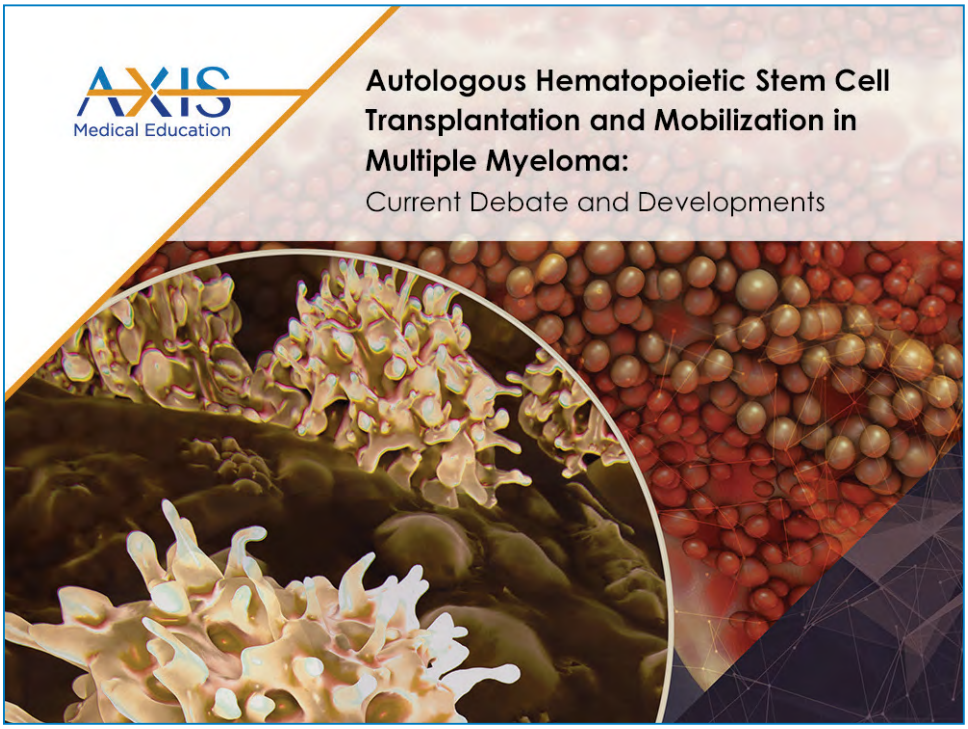
I think we should emphasize that to the referring population of physicians and also the patients with myeloma.

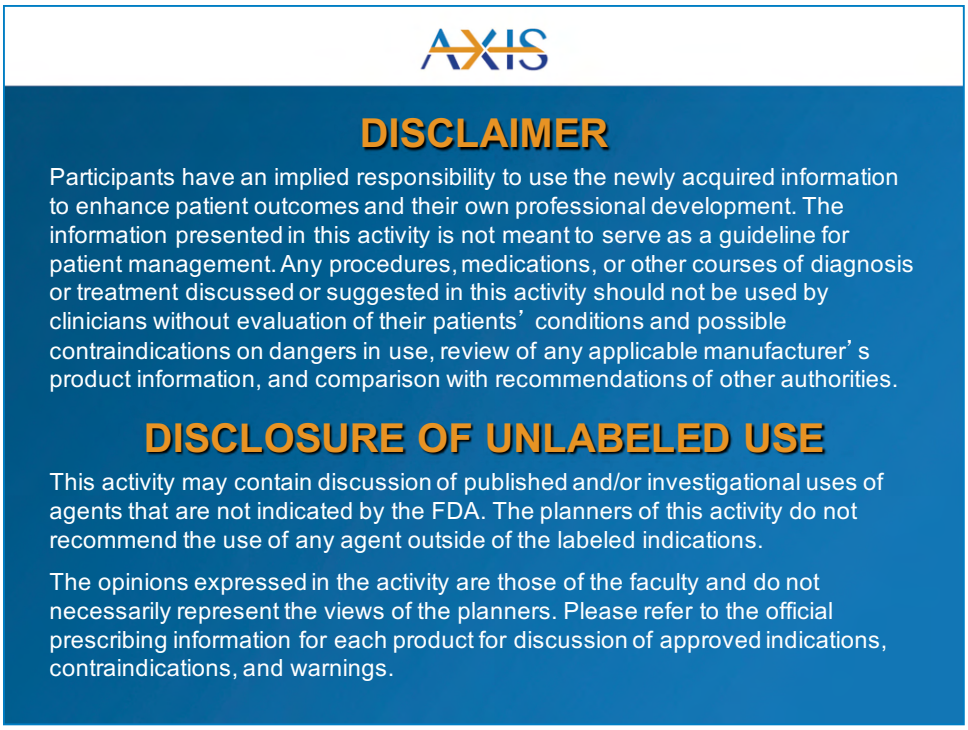
**Shah**: Of course, right.

**Hari**: We'll have a second segment of this activity where we'll continue our discussion with topics around induction, maintenance, and some of the changes that are happening with conditioning regimens for multiple myeloma and some cases.

## SEGMENT 2



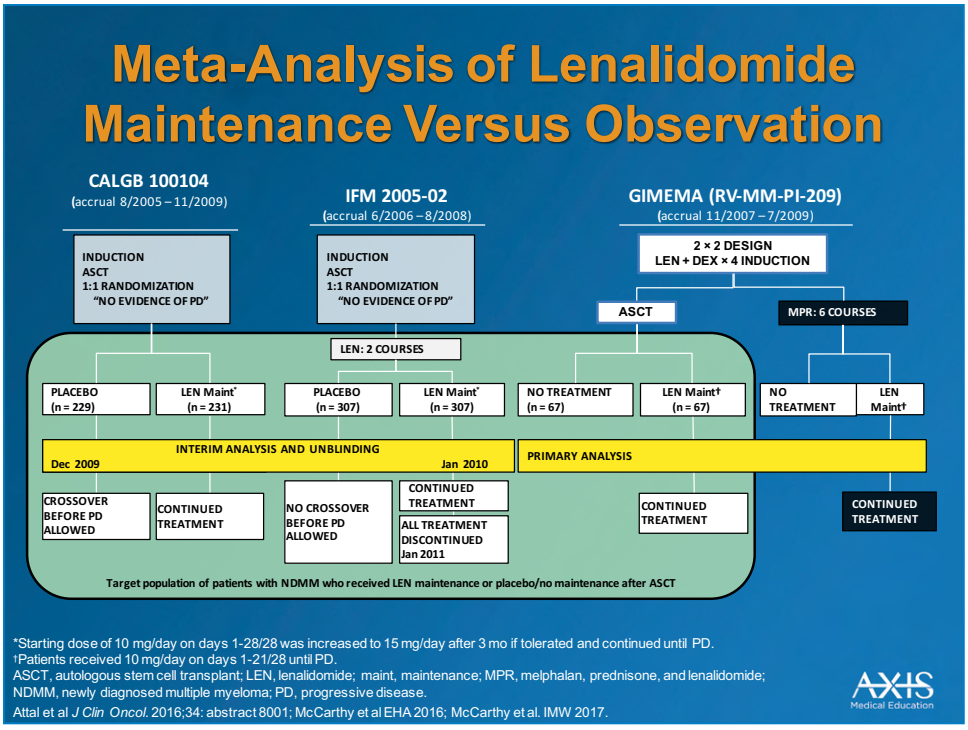

**Parameswaran Hari, MD**: Hello. Welcome to the CME-certified activity entitled *Autologous Hematopoietic Stem Cell Transplantation and Mobilization in Multiple Myeloma: Current Debate and Developments.* This is part two. I am Dr. Parameswaran Hari, Professor of Hematology at the Medical College of Wisconsin. And with me, Dr. Nina Shah, Associate Professor of Medicine at the University of California, San Francisco. Today, in this second part, we'll be discussing the most recent clinical data on autologous hematopoietic stem cell transplantation and also induction maintenance treatments in multiple myeloma and provide evidence-based updates on expert insights on this topic.





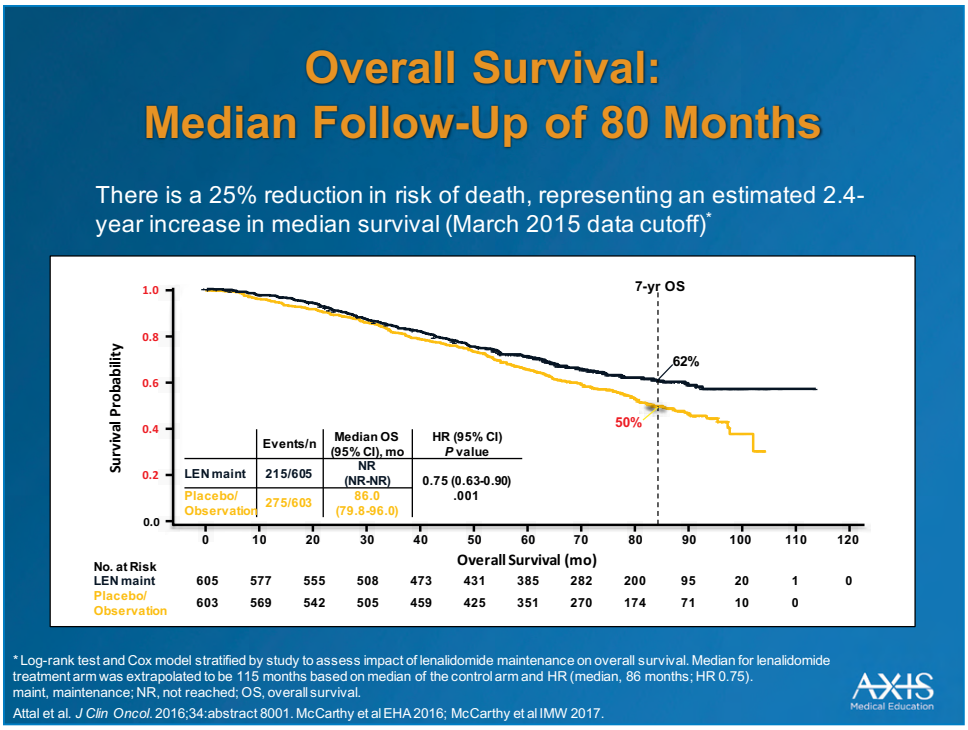
- Here are our disclaimers and disclosures.


So let's talk about maintenance. So we talked about the transplant paradigm and how we use transplant. And as we discussed a little bit in part one, maintenance seems to be an important component to extend the benefits of transplant much more than we've been able to do in the past.




And here is this meta-analysis, which is probably the most powerful evidence we have because it correlates all the three trials that have been done in this setting.

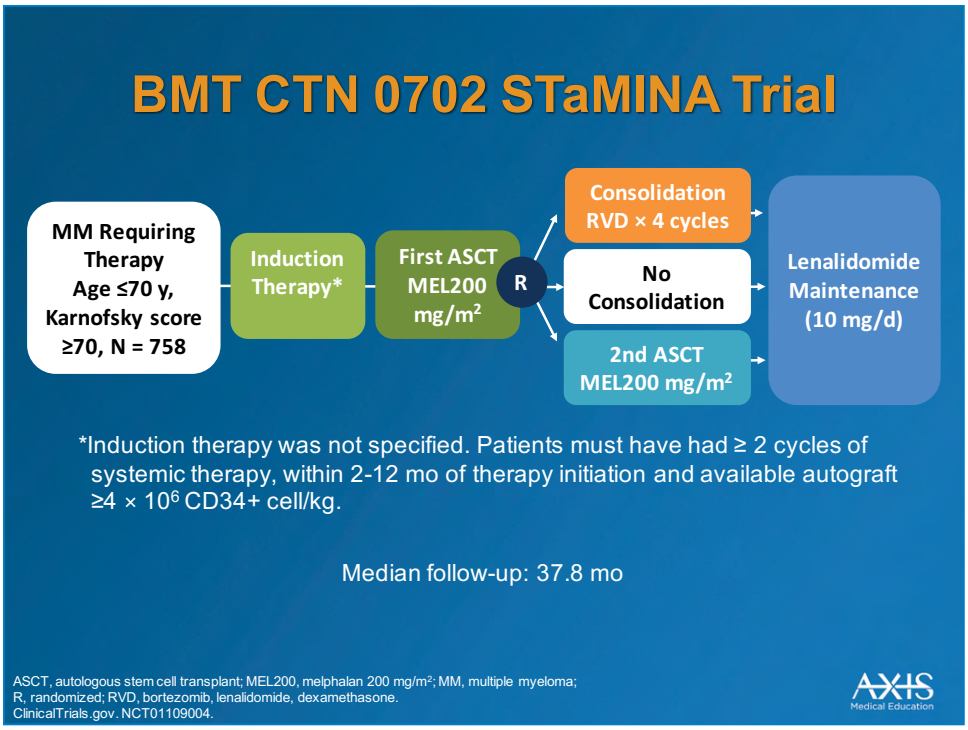
**Nina Shah, MD**: Yes, I think this was first presented at ASCO in 2016, and I was really floored by both the analysis and the ultimate results that it showed because it's hard to put a lot of trials together. But basically, this takes three randomized trials that had been conducted and collapses the data, so that we can all understand it easier. And the critical thing about this meta-analysis is it looks at trials looking at lenalidomide maintenance—those people that got it or didn't—and also it's in the era of novel therapeutics.




And as you can see on the next slide, when they did this meta-analysis, they were able to show that there was an actual increase in overall survival, which you can see on the curves. So they were able to show that patients who got lenalidomide maintenance, as they were randomized to get, actually were able to have longer survival. And what's really nice about these curves is you can see that top on stretching out where almost the median is just being hit so far out, 10 years out.

**Hari**: Right. Seven years later, 62%, which is an amazing number and was not even thought possible when these studies were actually started.

**Shah**: Right. No one knew it was going to be this way. So that's really sealed I think the fate of maintenance. And I think further what sealed it is updated results or new results from the BMT CTN 0702 trial. Want to talk about the design of that?




**Hari**: Yes. Actually this is a very important study—one of the largest transplant studies in the US—and this was 750 plus patients with newly diagnosed multiple myeloma, age less than 70. And the question really being asked was now we have transplant followed by lenalidomide maintenance as the paradigm; can we improve upon that with additional therapy? So that's the question. And we already know that transplant with lenalidomide maintenance is the standard, and it improves overall survival to the first decade of life after myeloma.

So here, after transplant, patients could follow three paths: lenalidomide maintenance would be the standard path. Initially when the trial was returned, it was returned for 3 years of maintenance, but now patients have the option of staying on it until progression. And then, a second arm was consolidation with the RVD regimen, which is bortezomib, lenalidomide, and dexamethasone, for four cycles, which takes about 12 weeks to complete. Thereafter patients go on lenalidomide maintenance.

And the third arm was a second autologous transplant or tandem transplantation. Because we have a lot of data from Europe suggesting that tandem transplantation is better than a single transplantation. So this was a very standard study. And induction therapy was not mandated to be anything in particular, but the significant chunk of these patients—more than 50%, in fact—got RVD or bortezomib/lenalidomide/dexamethasone as induction therapy, which is a key difference from European studies.

## BMT CTN0702 STaMINA Trial Results

| Result | Post-Induction + ASCT-1 Followed by: | | |
|---|---|---|---|
| | R Maint only n = 257 | RVD→R n = 254 | Double ASCT→R n = 247 |
| Median PFS, mo | 52.2 | 56.7 | 56.5 |
| Median OS, mo | 83.4 | 85.7 | 82.0 |
| High-risk patients, n | 59 | 65 | 57 |
| Median PFS, mo | 40.2 | 48.3 | 42.2 |
| Median OS, mo | 79.5 | 77.5 | 79.3 |

**No significant difference between the study arms**

ASCT, autologous stem cell transplant; Maint, maintenance; OS, overall survival; PFS, progression-free survival; R, lenalidomide; RVD, bortezomib, lenalidomide, dexamethasone.
Stadtmauer et al, 2016; ClinicalTrials.gov. NCT01109004.

AXIS Medical Education

So here are the results. And, as you can see, essentially the bottom line is that you could not beat simple lenalidomide (len) maintenance following transplant with at least these two strategies—tandem transplantation or consolidation before len maintenance after transplant—we're not able to overcome the advantage we have gained from len maintenance alone. So, for the time being, len maintenance remains the standard after an autologous.

## Current ASBMT Guidelines: Summary of Recommendations for the Role of Stem Cell Transplantation for Multiple Myeloma

**Recommendations for high-dose chemotherapy (HDC) with autologous hematopoietic stem cell transplantation (auto-HCT):**

1. HDC and auto-HCT as consolidative therapy in the up-front setting (Grade A)
2. Consideration of a first auto-HCT for patients with refractory disease (Grade C).
3. Age should not be used as a selection factor (Grade C).
4. Clinical trial options are strongly advised for patients with high risk cytogenetics, particularly del17p or t(4:14) (Grade C).
5. Melphalan 200 mg/m$^2$ is the standard regimen for MM conditioning regimen (Grade A).
6. There is insufficient prospective evidence to support tandem auto-HCT as the standard of care for all myeloma patients but can be considered in patients with less than a VGPR (Grade D) after a first auto-HCT in the context of a clinical trial.

ASBMT, American Society for Blood and Marrow Transplantation; VGPR, very good partial response.
Shah et al. *Biol Blood Marrow Transplant*. 2015;21:1155-1166.

AXIS Medical Education

**Shah**: And so we kind of wanted to move on to some of the guidelines. A couple of years ago the ASBMT (or the American Society of Blood and Marrow Transplant) published some practice guidelines that helped us—and practitioners around the US—to look for guidelines about when to refer for transplant, really what the role is of transplant for patients. And we tried to grade our evidence on A through D with A being the best. And we tried to use studies that had looked at randomized controlled trials and maybe outcomes with survival for grade A evidence. And based on that, we've been able to make multiple recommendations. The first is whether or not to use transplant. And so we do, as a grade A recommendation based on the studies we've talked about at length in the first part, recommend

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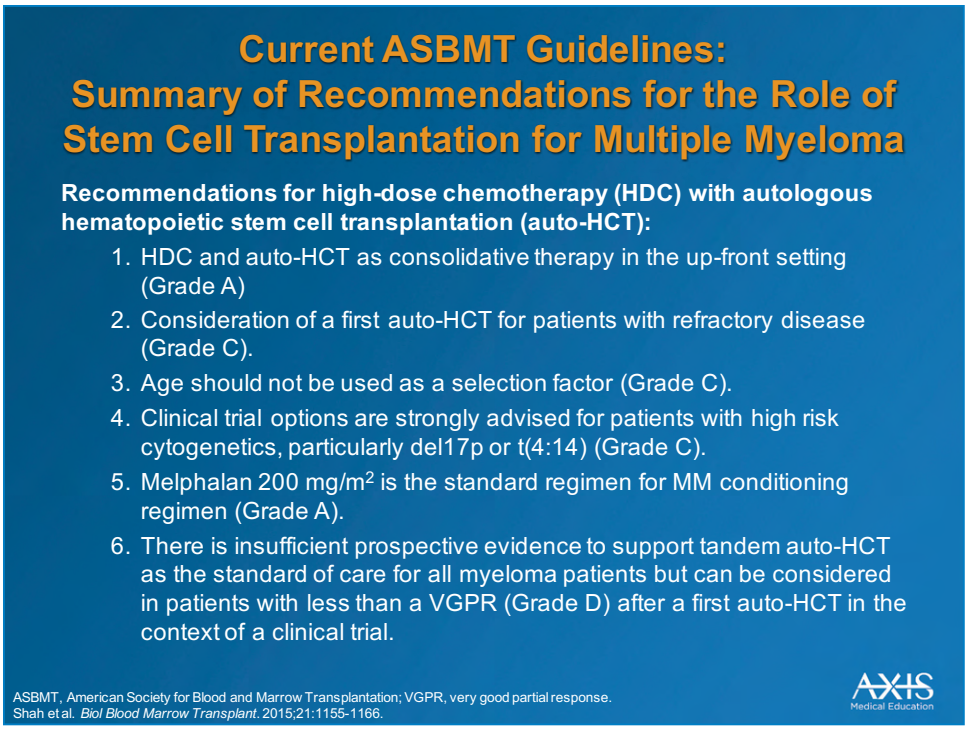


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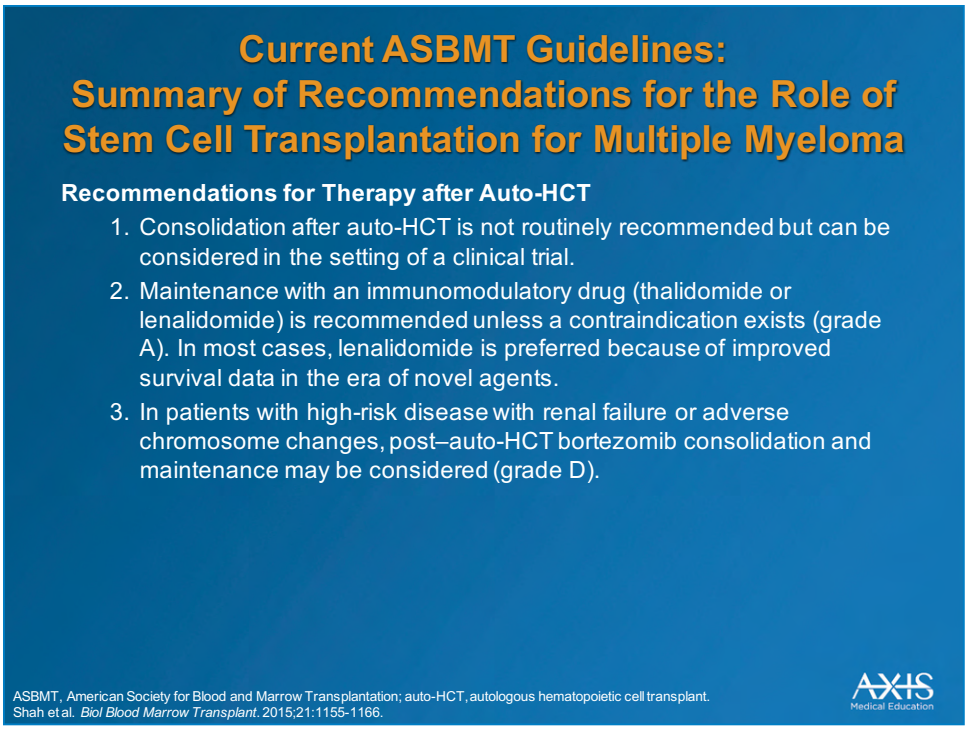
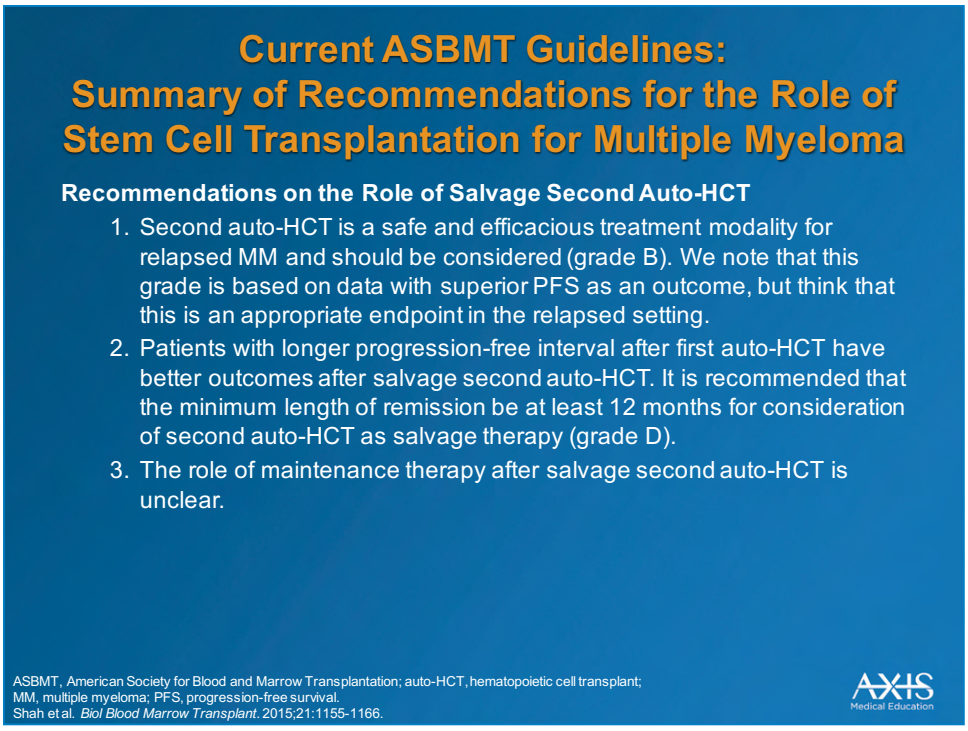
consolidation upfront autologous transplant after induction therapy, whatever the choice is. That's a grade A.

And interestingly enough, a lot of the other opinions surrounding transplant are not due to randomized controlled trials because they're hard to do but a lot of retrospective studies and actually expert opinion. So, we also thought that although the evidence isn't as strong, that you should consider a transplant even if you have relapse or refractory disease; it's still an option. And that age should not be considered a selection factor. And for high-risk patients, which we haven't talked about too much, that you should always consider clinical trials because we don't know how these patients do the best, although we think transplant is a part of it. We also talked about melphalan 200 being the standard of care, and we'll talk about some novel formulations of it.




**Hari**: And here again are some of the other recommendations for further therapy. As you saw, post-transplant consolidation with either a second transplant or other agents such as RVD are not recommended. And especially we have confirmation with that from the StaMINA study. And immunomodulatory drug, lenalidomide, is the standard of care maintenance and FDA approved now in the United States for this. And patients with high-risk disease such as translocation of (4;14), (14;20), (14;16), etc. And all those with kidney failure, post-transplant bortezomib may be considered, and the evidence for that is a little bit less than the evidence for lenalidomide, most phase 2 studies.




**Hari**: So here are some of the data on the role of a salvage second auto-transplant. Here again, there is only one randomized study in that setting, which we haven't touched upon, but was a study from the UK which suggested that a second salvage/second transplant was beneficial in people who relapsed more than 18 months after their first auto-transplant. And based on that, the ASBMT recommendations recommend that as a safe and efficacious modality for people who had an especially longer remission after their first transplant. And as we said before, if you collect cells for more than one transplant, they're better utilized in a salvage second transplant setting than as a tandem upfront transplant based on the StaMINA study results that we just showed. And the role of maintenance

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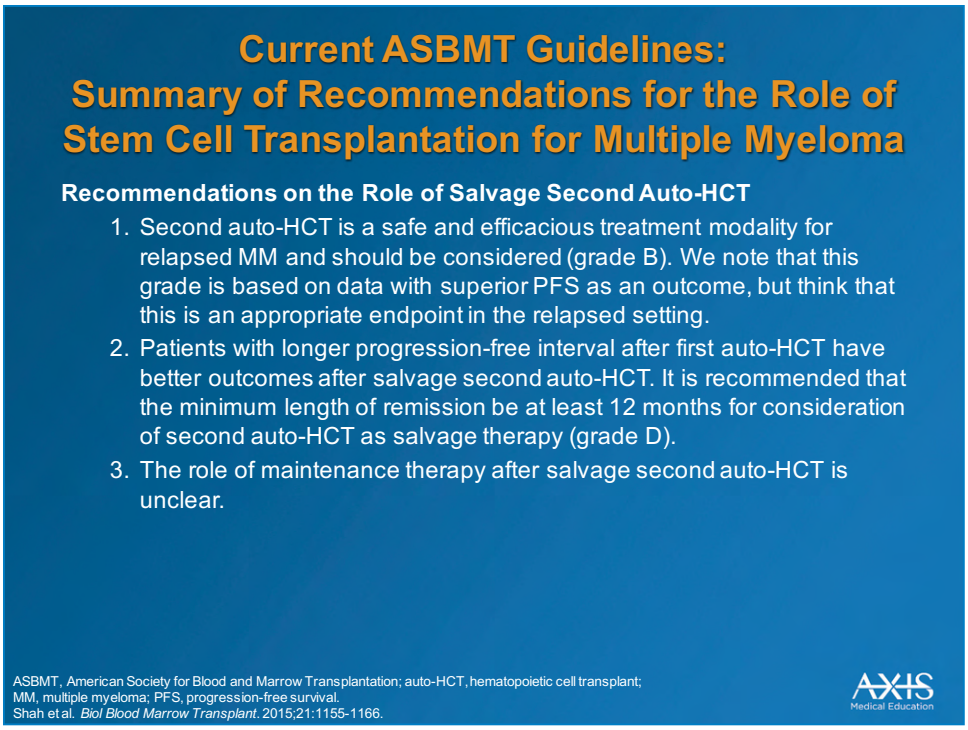


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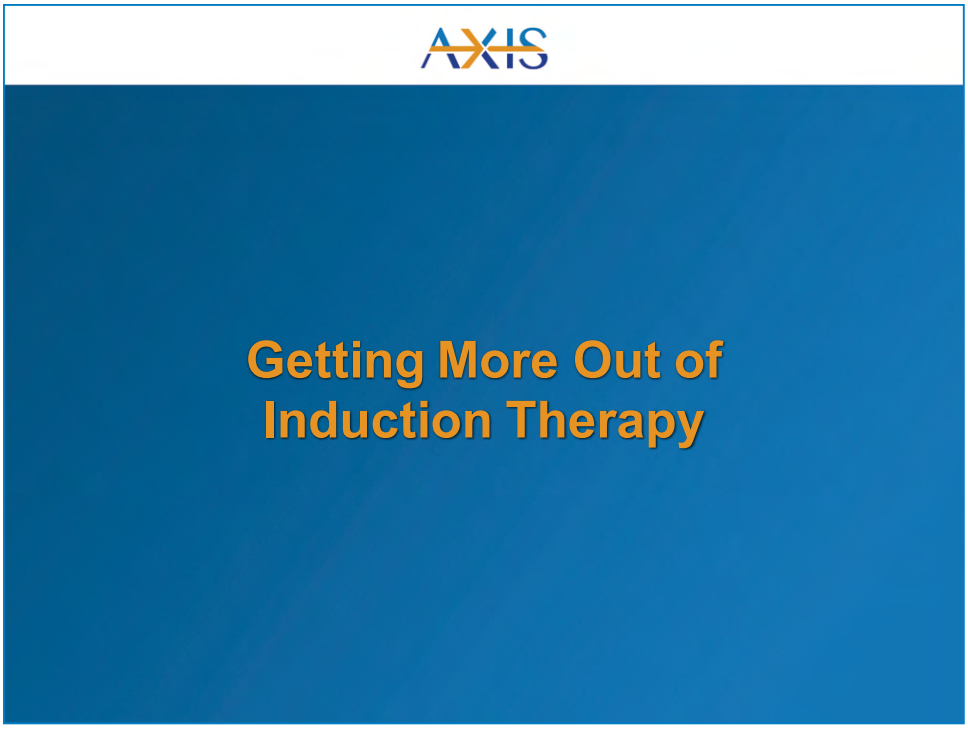
therapy after salvage at this point is unclear.

**Shah**: We don't know, and hopefully we'll have clinical trials to answer that, but it's good to consider.




- So, let's now talk about going back to induction, which is the treatment before transplant, and can we improve it. The big question is we have shown what is state-of-the-art right, but what is coming and what are the data for improving each component of this paradigm?

**Shah**: Right, how can we get even better?

## Questions in Induction

- Does induction matter if transplant is planned?
  - 3 drugs or 2 drugs for induction
  - Which 3 drugs – steroids + proteasome inhibitors + immunomodulatory drug vs others
  - Can we do better with induction?

AXIS Medical Education

**Hari**: How can we get better? How do we go to the next level in myeloma? So the big question is if a transplant is planned does induction matter? And I don't think we have a clear answer for that because the studies have generally looked at transplant versus no transplant and things like that. But we have some answers on the question of three drugs and induction versus two drugs and induction. And if you choose three drugs, which are the three drugs that are ideal? Is it a proteosome inhibitor, IMiD, and dexamethasone? Or it an alkylator such as cyclophosphamide with a proteosome inhibitor or an IMiD with dexamethasone?

## SWOG S0777: VRd Versus Rd

**Newly diagnosed MM (transplant eligible and non-eligible patients)**

**VRd** Q 21 days x 8 cycles **vs** **Rd** Q 28 days x 6 cycles → **Rd maintenance**

| Survival | VRd (n = 242) | Rd (n = 229) | HR | *P* |
|---|---|---|---|---|
| Median PFS, mo | 43 | 30 | 0.712 (0.560 - 0.906) | .0018* |
| Median OS, mo | 75 | 64 | 0.709 (0.516 - 0.973) | .025† |

*one-sided p value; †two-sided p value.
ISS, International Scoring System; Len, lenalidomide; MM, multiple myeloma; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide, dexamethasone; VRd, bortezomib, lenalidomide, dexamethasone.
Durie et al. *Blood* 2015;126:25; Durie et al. *Lancet* 2017;389:519-527.

AXIS Medical Education

So some of the data are here. So this is the SWOG study, and I think you are associated with that.

**Shah**: This is, I think, one of the most important studies in myeloma because all of us had really thought combination of the three drugs probably would be better, but we really needed to prove that. And I think this really helped us to prove that. So in this trial, patients were randomized to receive either three drugs with bortezomib and lenalidomide and dexamethasone or two drugs with just lenalidomide and dexamethasone. And this went on for eight or six cycles just to keep the time consistent between the two, and then they went on to maintenance. So you can see it wasn't with transplant necessarily. And here there was a clear advantage for three over two drugs both for the progression-free survival

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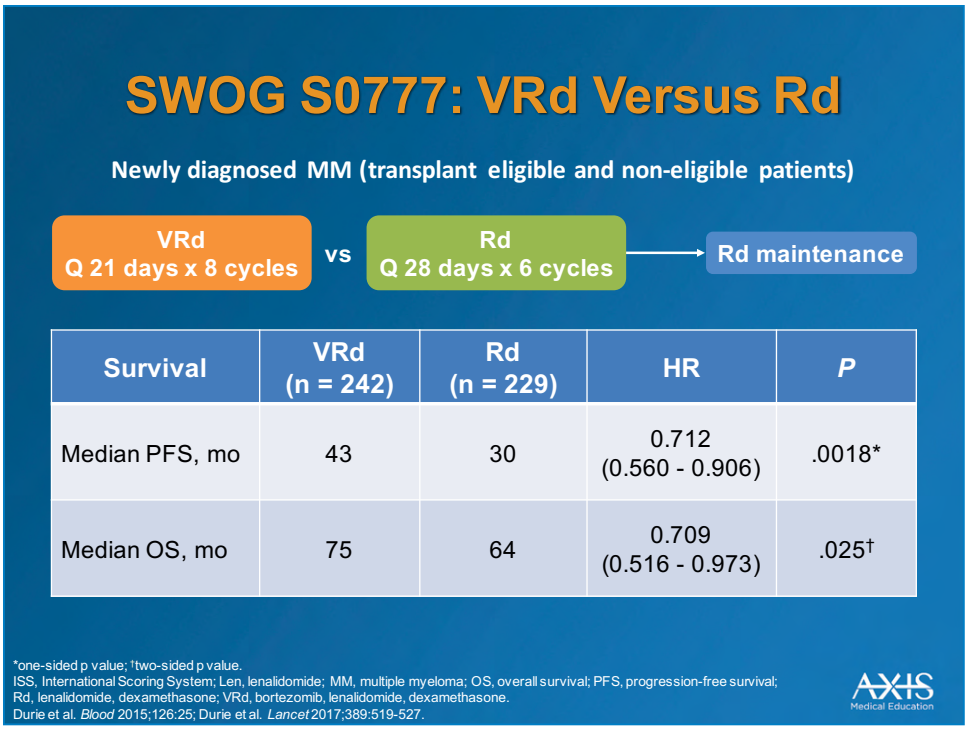


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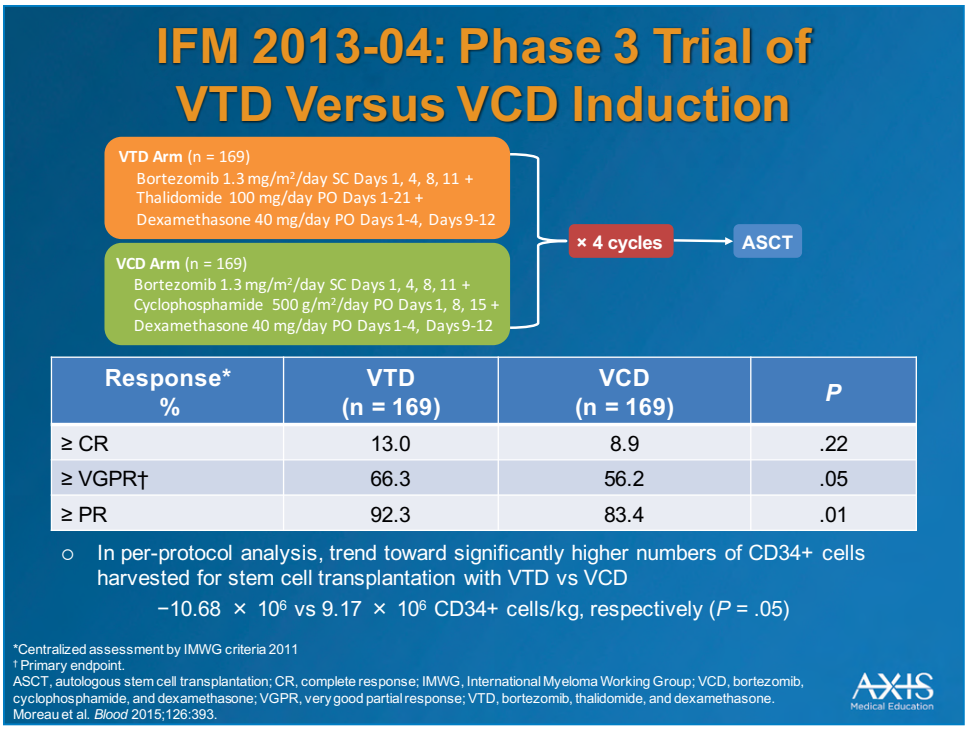
and the overall survival. And for me, this really sealed it that I should—when possible—be recommending three drugs to my patients rather than two.

**Hari**: Absolutely. I think that this study clearly proves that in this day and age for newly diagnosed myeloma the combination of a proteosome inhibitor, lenalidomide, and dexamethasone—which is the VRd regimen—is probably the best way to go upfront if whoever can tolerate that.

**Shah**: Right, exactly, which you always have to consider that.




**Hari**: So here is a study from the French myeloma group, or IFM, and they asked a slightly different question. When you choose three drugs, which are the three drugs? A proteosome inhibitor with an IMiD and dexamethasone, or the RVd combination; in France, they prefer to use thalidomide instead of lenalidomide, so that's a very similar combination called the VTD, which stands for bortezomib, thalidomide, and dexamethasone versus substituting the thalidomide for cyclophosphamide, which is an alkylator, a cheaper drug, and has some advantage in terms of cost. So, the question was four cycles of VTD versus four cycles of VCD—here we call it CyBorD. In patients who are eligible for transplant and going to transplant, what sort of responses can be obtained from these two different regimens? That was the question.

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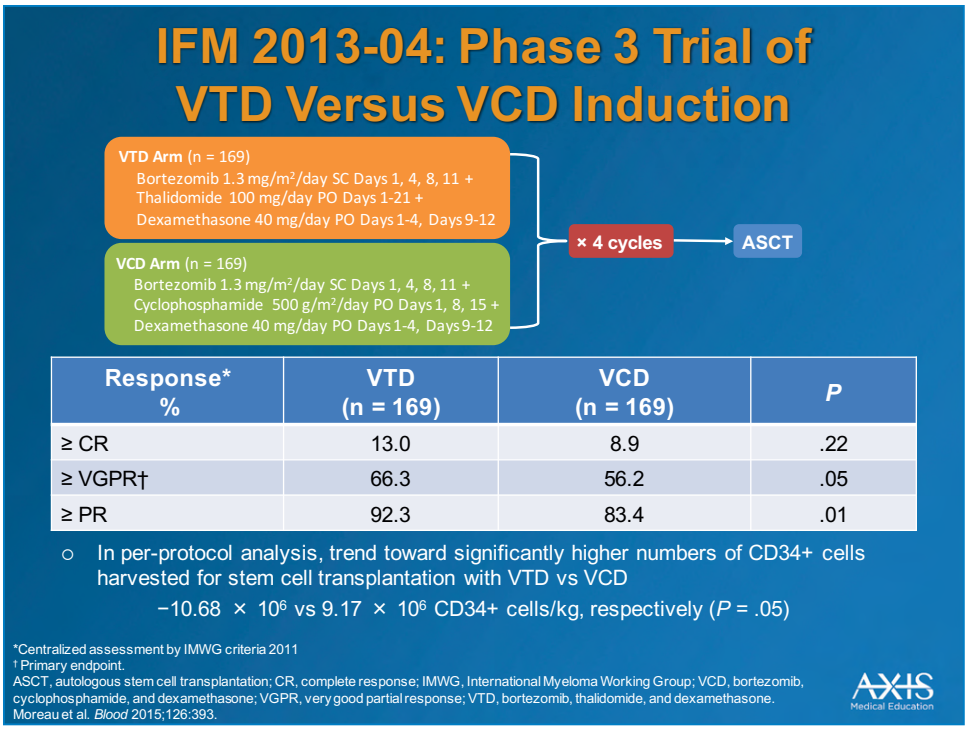


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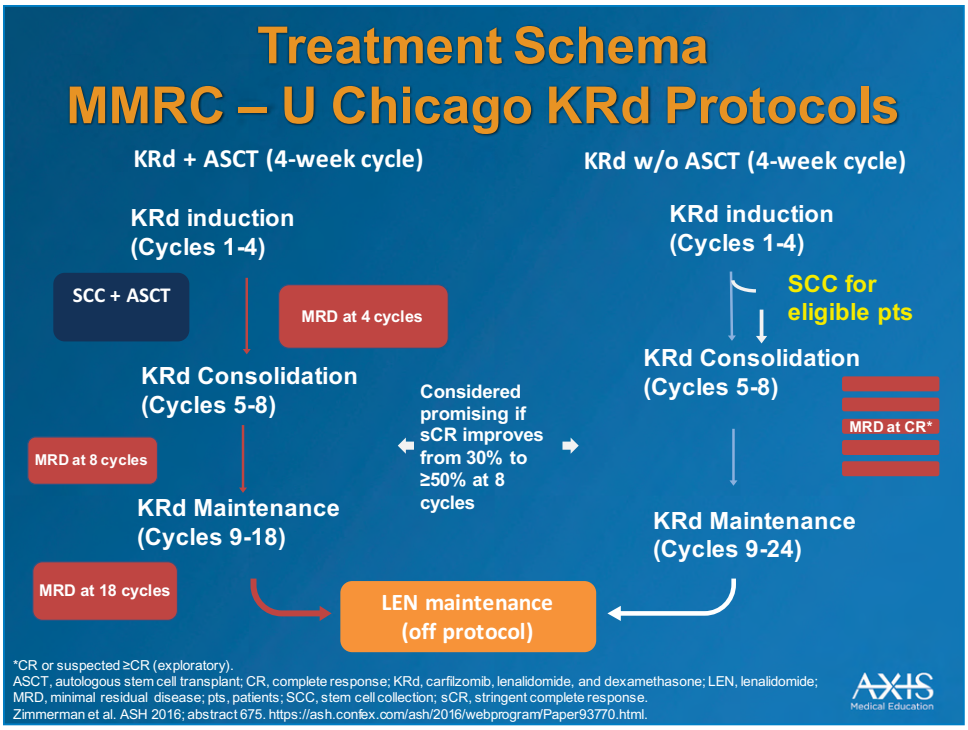
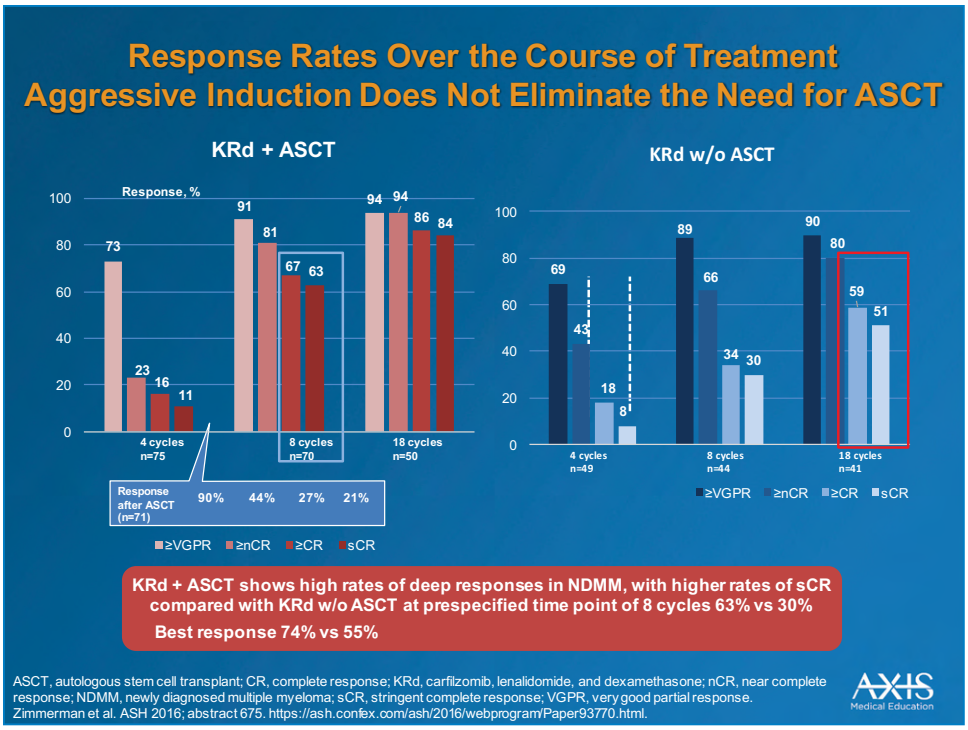
**Shah**: So you can see here that the response rates—when you look at greater than very good partial response—favored the thalidomide arm, so that would be bortezomib and thalidomide and dexamethasone, over the bortezomib, cyclophosphamide, dexamethasone. And although there were some more neuropathy with the thalidomide-containing regimen, it was thought that perhaps the combination of the proteosome inhibitor and the IMiD—or the immunomodulatory drug—and dexamethasone is better for response depth than the proteosome inhibitor and cyclophosphamide alkylator. And that I think that's one of the reasons that a lot of us, even in the States, kind of taking this data and adapting it to our own practices would choose lenalidomide-based therapy with lenalidomide, bortezomib, dexamethasone.

**Hari**: Yes, again, if you are going for a transplant, there are data suggesting that if you get to more than/better than VGPR (very good partial response) status before transplant your outcomes post-transplant are better. So we should try to get as many patients into that regimen, in an as efficacious amount as possible. And if the combination of IMiD/proteasome inhibitor is the combination to go for in that setting with that objective in mind. So I think most of us feel validated in our approach with using the VRd regimen.

**Shah**: Yes, with good data behind it.



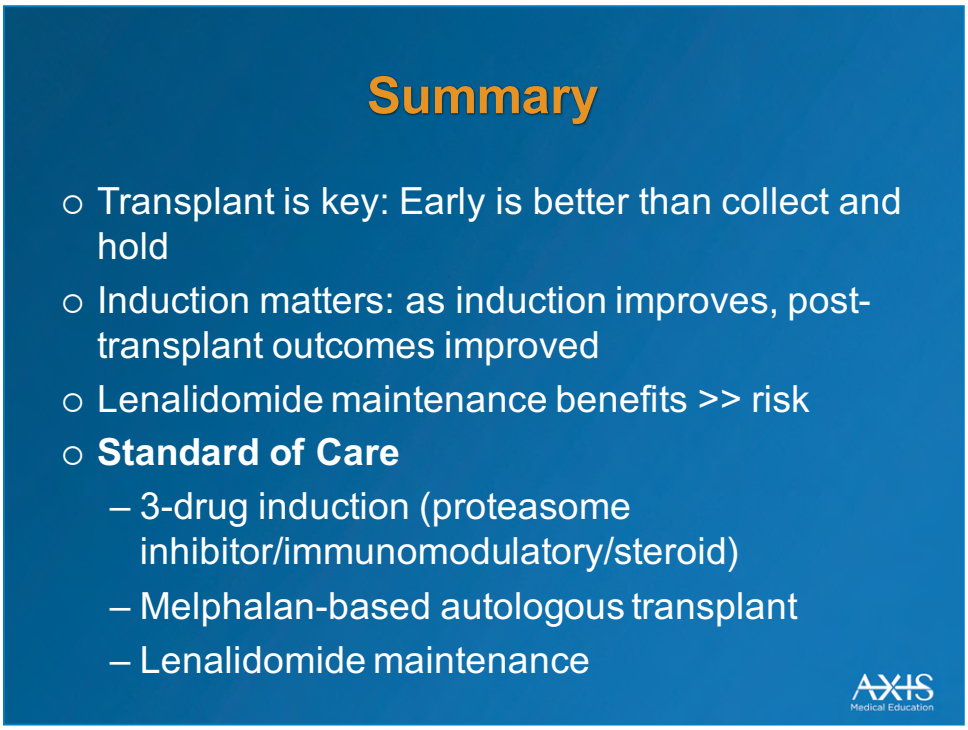

**Hari**: And here is a study which tries to go to a second-generation proteosome inhibitor. Improving on induction can we get better? So here the goal, again, was not the VGPR status, it was the status of minimal residual disease negativity. So I think we are moving away from a cruder form of a response assessment to a more sophisticated form of response assessment too. This was done through the MMRC in the University of Chicago. And these were two parallel studies actually done some time apart. So not clearly parallel but two studies. One of which used the KRd regimen, which is carfilzomib/lenalidomide/dexamethasone, the second-generation proteosome inhibitor with a transplant or without a transplant. And they're very similar. They used KRd induction, transplant, consolidation with KRd, and then KRd maintenance followed by LEN maintenance off protocol.




So these are the transplant results. And in fact, eight cycles you can see that about 67% and 63% of patients are in a stringent CR or a complete remission. And correspondingly, the number for eight cycles in the without transplant arm are in the 30%. After 18 cycles and including a transplant, it goes up to about 85%, which is unheard of. And without transplant, that's still in the 50 to 60% range.

**Shah**: Also unheard of.

**Hari**: Which is very good, yes, exactly. But again, two points—you can achieve these deep remissions, and transplant makes it better for at least 20% more patients. And you don't know who these patients are, so that's where you end up offering the transplant to everyone.




**Hari**: So in summary, I think we both agree that transplant is key, as we said in the first part of this. Collection and holding early is also another option. Induction matters: as we have shown, as induction improves, overall outcomes improve, even in the setting of transplant. And lenalidomide maintenance is with significant benefit despite its risk of venous thromboembolism; cytopenia, which is low blood counts; and also a small increase in the risk of second primary cancers. So the standard, at this point, is three-drug induction, ideally using a proteosome inhibitor, immunomodulator, and dexamethasone followed by a melphalan-based autologous transplant, and then lenalidomide maintenance.

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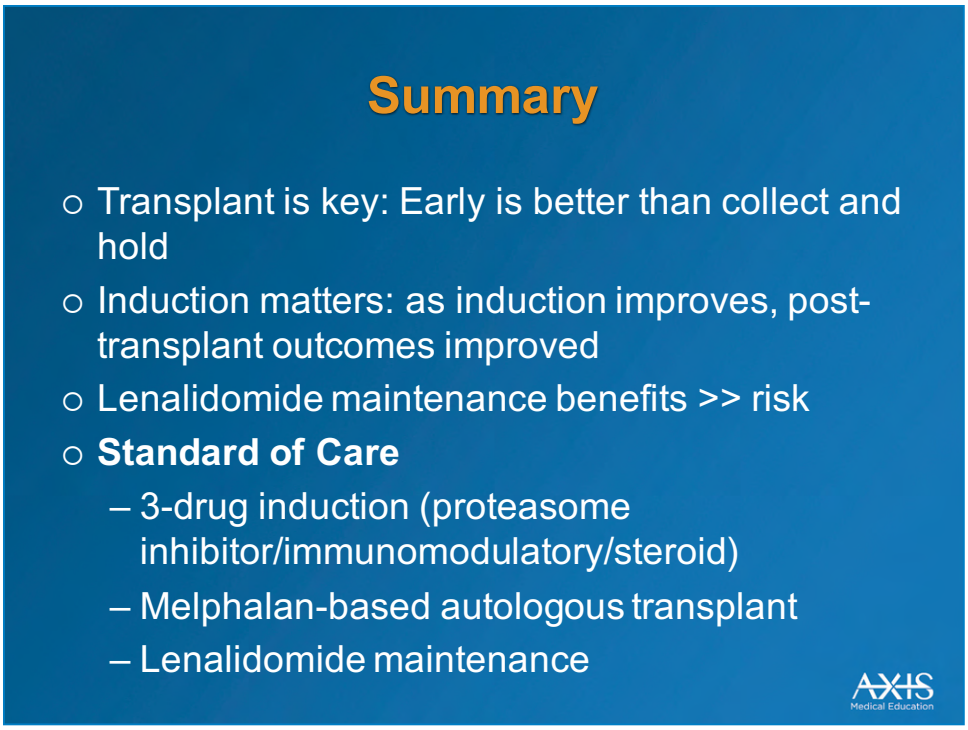


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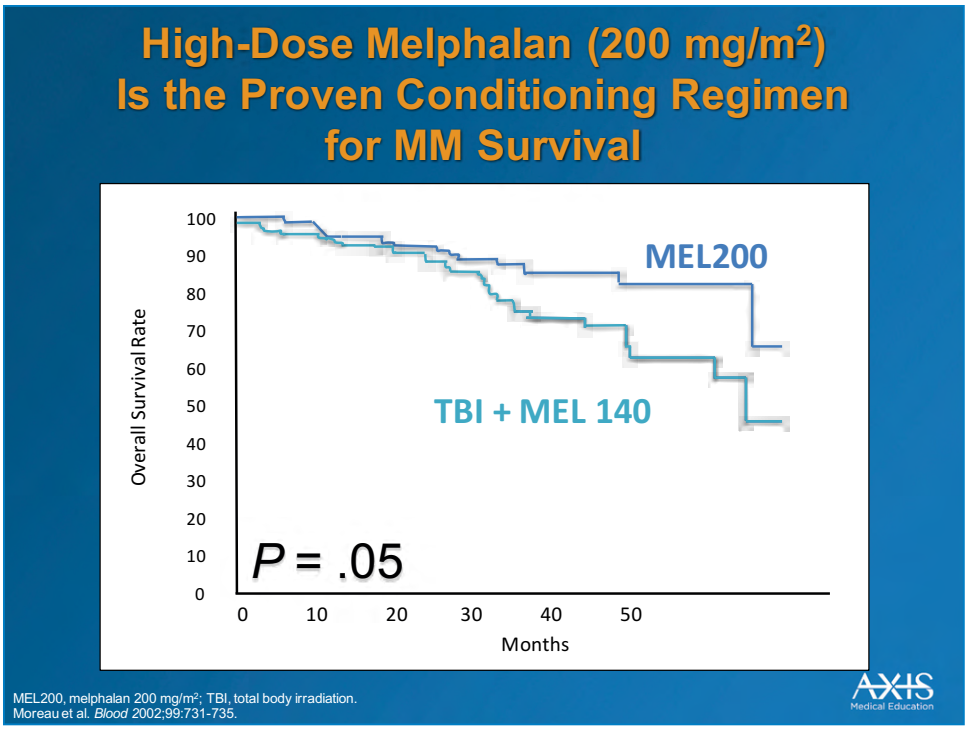
**Shah**: Right, which I think a lot of us would agree with. And I'm glad that we've all come together sort of after years and years of debate, and most of us are doing this I think.

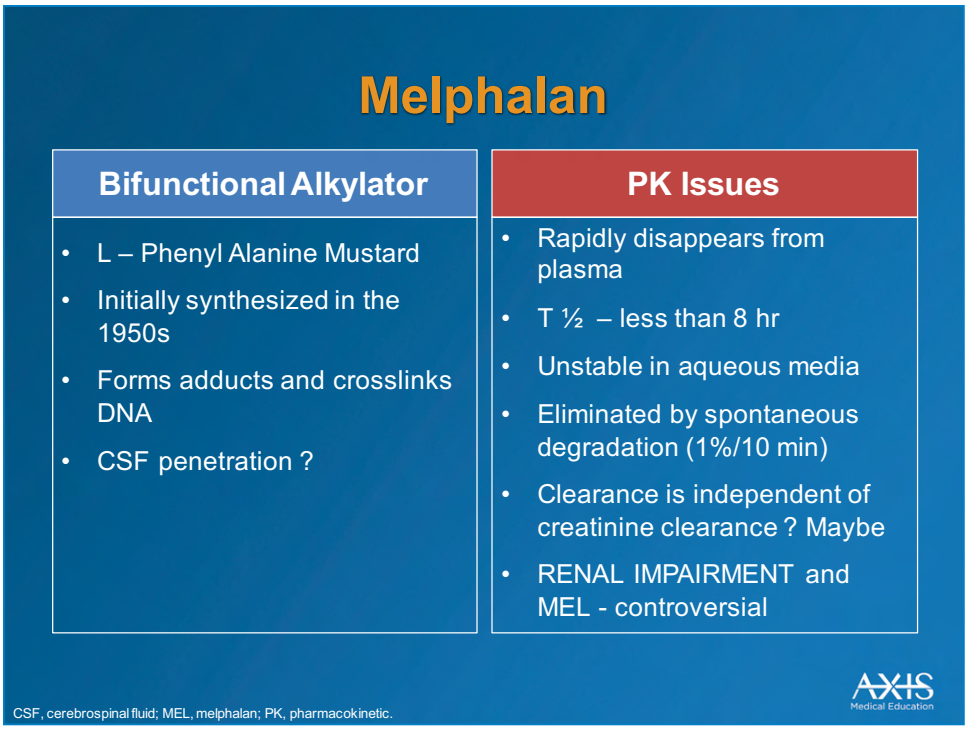
**Hari**: It is the modern version of total therapy.

**Shah**: Yes, it's the modern total therapy.


**Hari**: In the next part, we should discuss the often forgotten but very important conditioning regimen in transplant. So conditioning regimens have not changed a lot.




- This was a study done in 2002, which compared, at that time, the question was should we use total body radiation because myeloma is a very radio-sensitive tumor with melphalan, or should you just give melphalan alone? And the study was pretty conclusive in that MEL 200 is the standard, and addition of total body radiation with MEL 140 was not up to par. Overall survival was just barely statistically significantly better for MEL 200, but the toxicities were significantly higher for...so melphalan 200 became the standard. And that has been the standard now for almost 2 decades.




- But then, melphalan is a very, very old drug, and we have major issues with melphalan. And there has been renewed interest in making this better either with the addition of new agents to the melphalan or improving the melphalan itself to be more potent. So here are some of the issues.

  **Shah**: So the melphalan that we've traditionally used is actually very unstable. And to make a long story short, it becomes reconstituted and then has to be immediately given. And this is a problem because not every hospital can immediately run from their pharmacy and give the melphalan to the patient. And the most important thing about melphalan is getting it into the patient because we know it's the density of the drug that makes a difference for these myeloma cells. So it starts to lose its effect even within the first 10 minutes.

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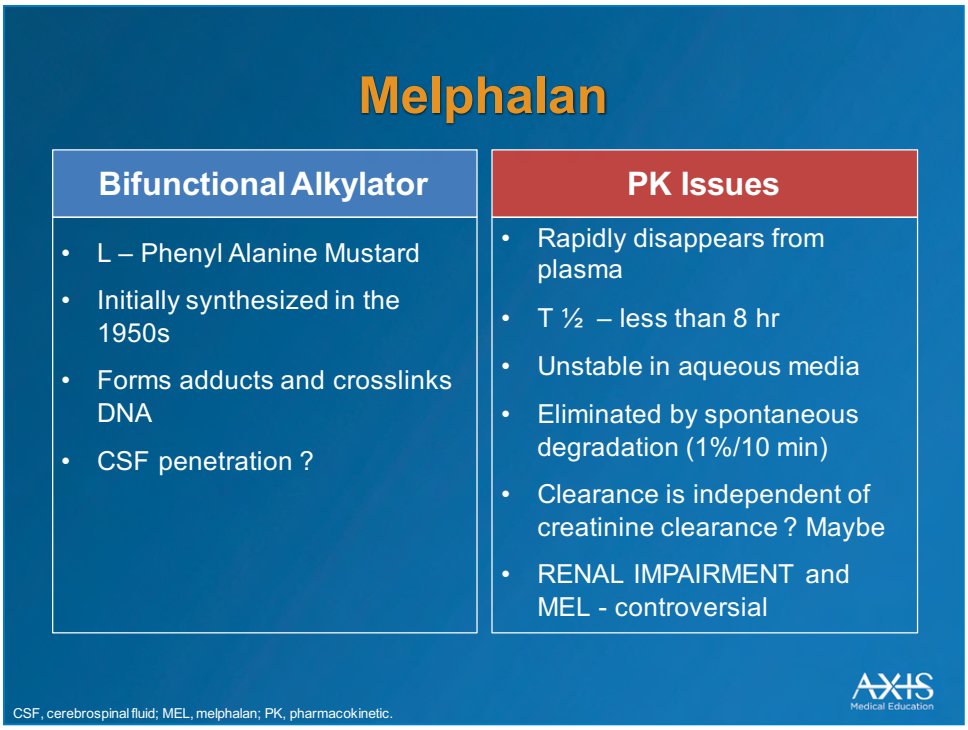


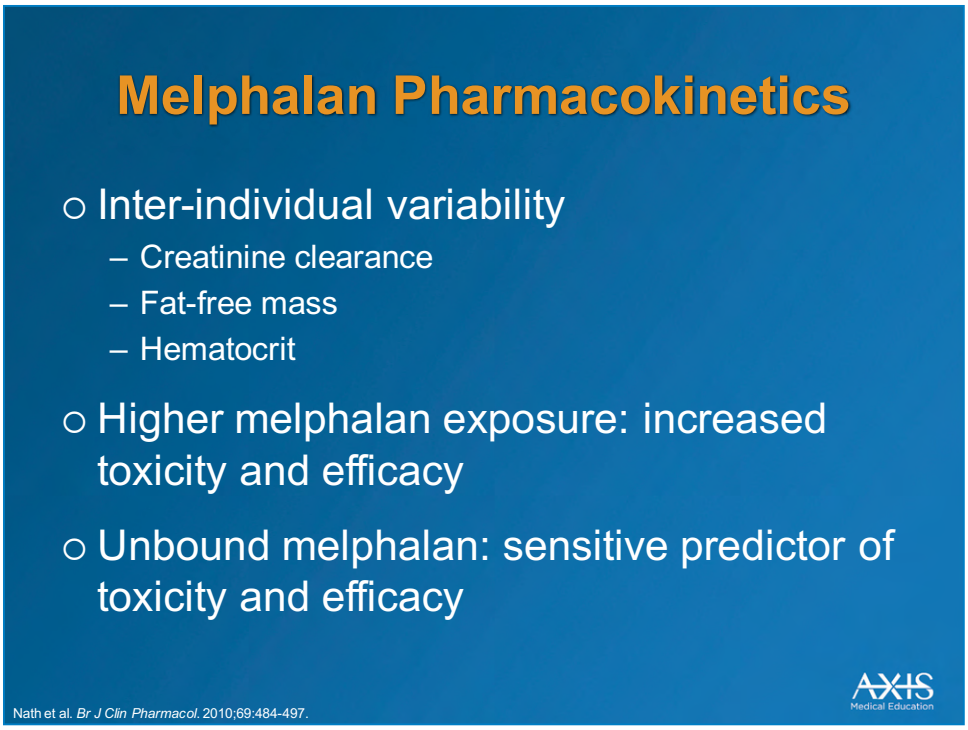


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So, we wanted to make sure that we could actually overcome this. And because of this, a new formulation of melphalan has been developed because we want to make sure that patients are able to get it, get it on time, and that they're able to get the effective nature of the melphalan infused and that it doesn't just dissolve away and is ineffective.

**Hari**: So to get a predictable concentration of melphalan in the patient and a predictable AUC (area under the curve) and $C_{max}$, a new formulation of melphalan was developed which eliminates propylene glycol, which is usually added as an additive traditionally. It's very difficult to get melphalan into solution, so they used to mix it with propylene glycol to get into the solution. So the new melphalan is called propylene glycol-free melphalan or it uses an agent called Captisol to get melphalan solubilized. So it's either called Captisol-enabled melphalan, CE melphalan, or PG-free melphalan, propylene glycol-free melphalan.

# Special Issues With Melphalan

## Administration

- When reconstituted, Melphalan rapidly hydrolyzes ~1% every 10 minutes
- Manufacturer recommendations:
  - Dilute dose in NS to ≤ 0.45 mg/mL and infuse over at least 15 minutes
  - Complete the infusion within 60 minutes of reconstitution of the vial
- BMT programs should verify that infusions have ended before the Melphalan expiration time/date

## Stability

- Highly unstable in solution
- 10% per loss of activity/hr
- Propylene Glycol
  - Additive to MEL
  - Toxic in the ICU setting when given as continuous infusion
  - Rate of PG infusion exceeds FDA guidelines when MEL bolus given currently

BMT, bone marrow transplantation; ICU, intensive care unit; MEL, melphalan; NS, normal saline; PG, propylene glycol.
Melphalan hydrochloride prescribing information.

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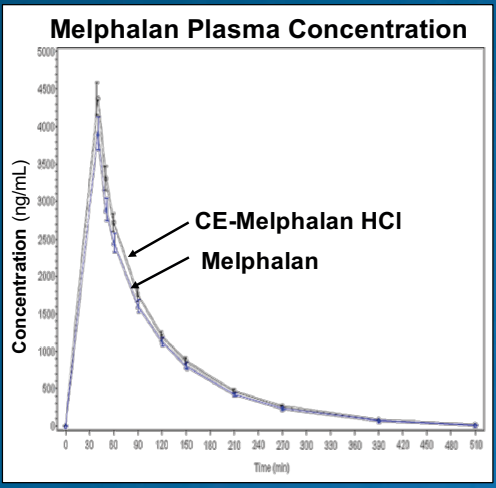
# CE-Melphalan (Propylene Glycol-free): Phase 2a Pharmacokinetic Study




**Bioequivalence demonstrated**
- Cmax: 112%
- AUC 0-t: 110%
- AUC-inf: 110%

**Successful myeloablation** (Day +3)
**Successful engraftment** (Day +11)

*No additional toxicities:*

**Treatment-emergent AEs** (100%)
- Common AEs: nausea, vomiting, hypokalemia, fatigue, decreased appetite, dizziness, and thrombocytopenia

**Treatment-emergent SAEs** (29%)
- Febrile neutropenia, mucosal inflammation, sepsis and extreme fatigue

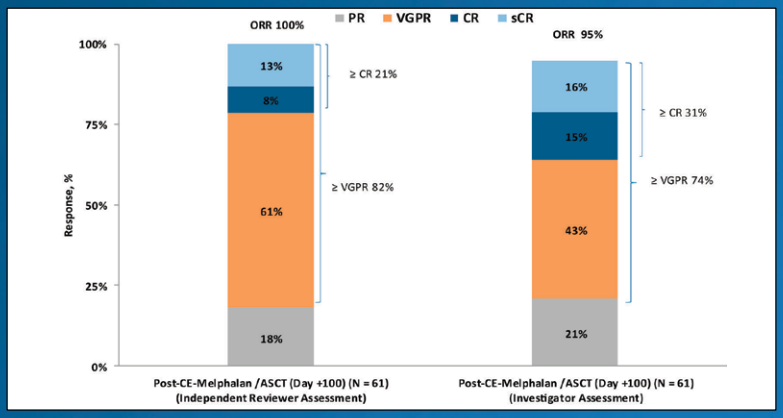
AEs, adverse events; AUC, area under the curve; CE, captisol-enabled; SAEs, serious adverse events.
Aljitawi et al. *Bone Marrow Transplant.* 2014;49:1042-1045.

AXIS Medical Education

- This was a pharmacokinetic study, which compared CE melphalan with regular melphalan at 100 mg/m$^2$ dose. And it was shown that just by the use of CE melphalan—without any other optimization—you could get 10% more higher levels of melphalan into the patient. And melphalan has a dose response curve in myeloma—we know that from many studies, for example, MEL 140 is less effective than MEL 200—and because of that, we believe that we have a safer product which has a better ability to achieve the dose response effect in myeloma. And it's much more stable, which eliminates a lot of the logistic issues with melphalan administration.

## Propylene Glycol-free Melphalan: New IV Formulation for Patients Undergoing ASCT

- Patients received 200 mg/m$^2$ of IV melphalan as 2 doses of 100 mg/m$^2$ each on days −3 and −2 followed by a day of rest before ASCT was performed on day 0
  - Patients were evaluated for safety and response through day +100




ASCT, autologous stem cell transplantation; CR, complete response; ORR, objective response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.
Hari et al. *Biol Blood Marrow Transplant*. 2015;21:2100-2105.

AXIS Medical Education

- Here is the data from a phase 2 study that was performed with CE melphalan, which showed that deep responses could be achieved with a more then VGPR response in almost 75% of patients undergoing this using an independent reviewer assessment.

## Propylene Glycol-free Melphalan: New IV Formulation for Patients Undergoing ASCT

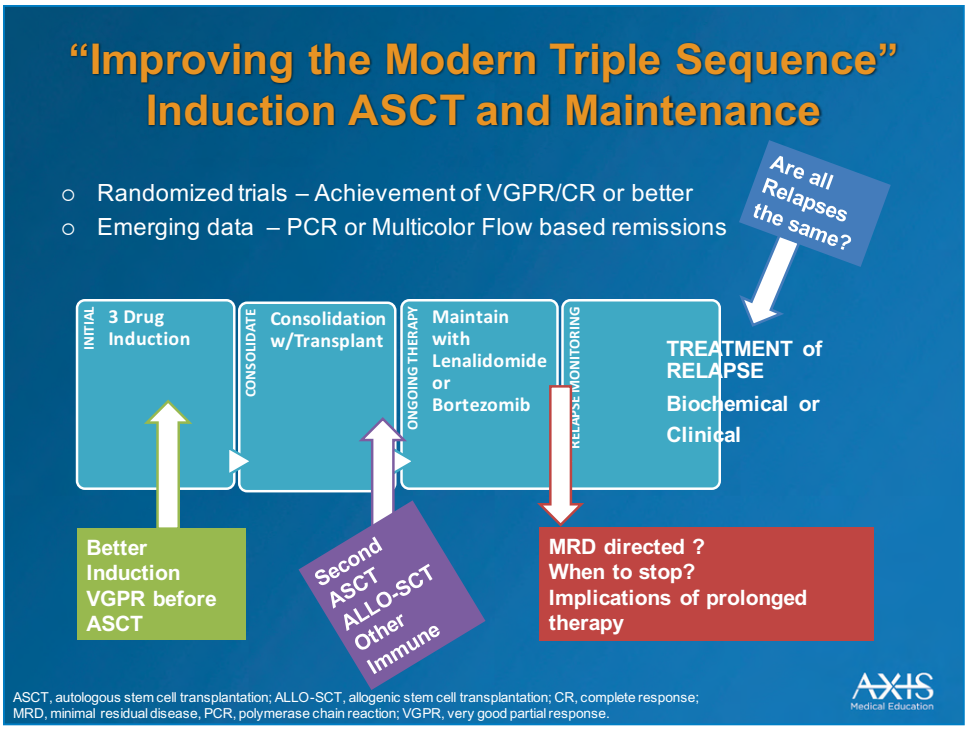
| MM Response Assessment* | Value |
|---|---|
| Overall response (sCR, CR, VGPR, or PR) | 61 (100%) |
| sCR | 8 (13%) |
| CR | 5 (8%) |
| VGPR | 37 (61%) |
| PR | 11 (18%) |
| Stable disease | 0 (0%) |
| Progressive disease | 0 (0%) |

*Independent Reviewer Assessment of response at day +100 after ASCT
- Myeloablation (day 5) and engraftment (day 13) were achieved with no mortality (day 100)
- Low grade 3 mucositis and stomatitis incidence
- No grade 4 mucositis or stomatitis

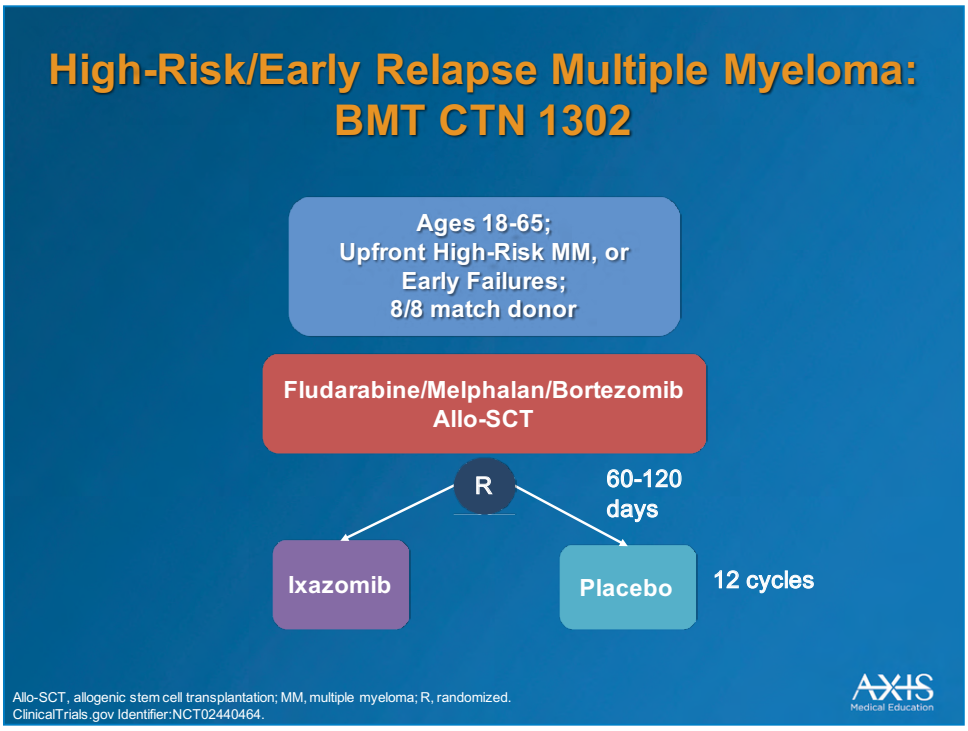
ASCT, autologous stem cell transplantation; CR, complete response; MM, multiple myeloma; ORR, objective response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.
Hari et al. *Biol Blood Marrow Transplant*. 2015;21:2100-2105.

AXIS Medical Education

- **Shah**: Right, and so it looks like even with independent reviewers the outcomes were essentially as you would have predicted for regular melphalan with very good overall response rate, 100%, and a better than VGPR response of 61%, which is great.




**Hari**: Absolutely. So again, coming back to the modern triple sequence, which is induction/transplant/maintenance, each component can be improved. We talked about three-drug induction as being the standard now, which may get better with the addition of antibodies. And then, agents to use to improve transplantation that new combinations or agents such as the new melphalan, which is the CE melphalan, or using an immune strategy along with transplant which we didn't talk much about. And then, maintenance primarily with lenalidomide and bortezomib in special situation.




**Shah**: So one of the things we wanted to talk about before was the high-risk patients and just briefly just touch upon this. We have an ongoing trial that looks at allogeneic transplant. So remember I was saying that we don't routinely recommend allogeneic transplant for upfront myeloma, but they are sort of a special group with these high-risk patients. They are harder to treat, we know that their duration of response is less, and once they relapse it's very hard to catch up with them. So we wanted to see if there's something else—besides just chemotherapy—we could do for them. And one of the things was an allotransplant. Because remember that an allotransplant not only gives chemotherapy but also allows for an immune-mediated effect because of a donor T cell. And so, for patients that have

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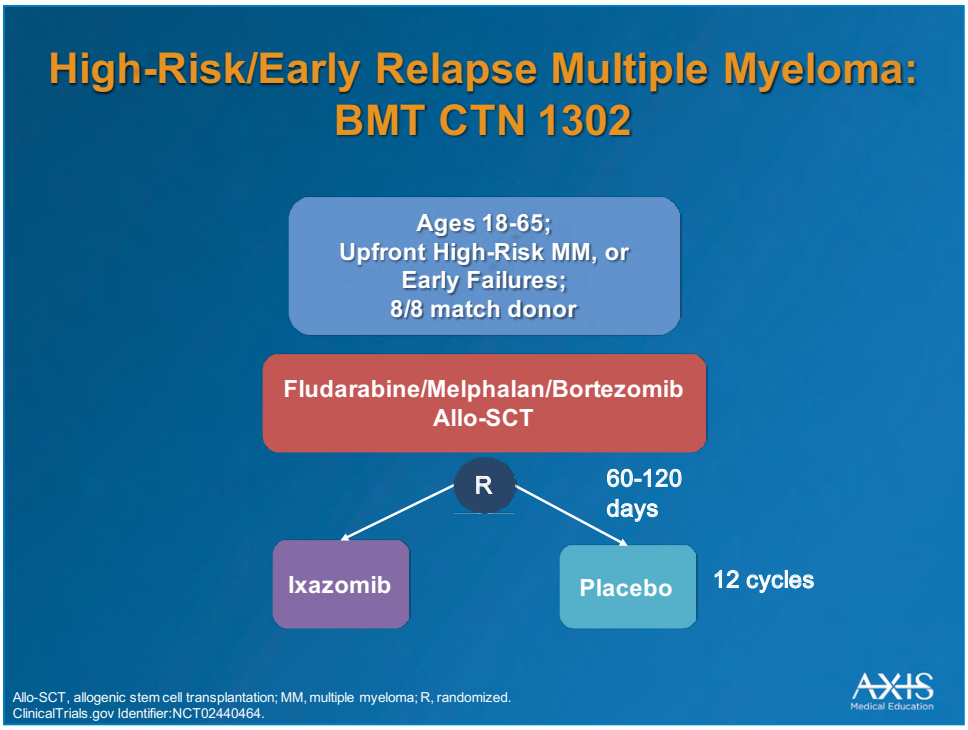


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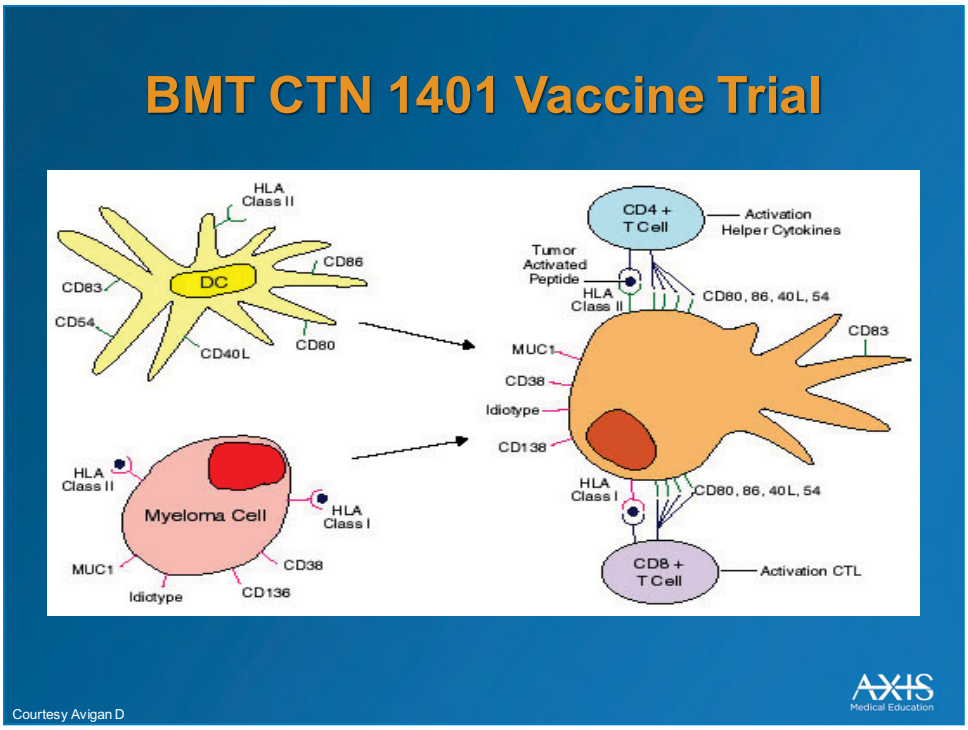
high-risk disease, they're eligible for the ongoing BMT CTN 1302 trial. And this looks at patients who are transplant eligible with high-risk disease and gives them chemotherapy with fludarabine and melphalan but also with bortezomib, which may be able to help them with their anti-myeloma effect, and then randomizes them to ixazomib versus placebo.

**Hari**: So this is an important study in that the patient population that we are using for the study is very specific—patients with well-defined, high-risk myeloma such as plasma cell leukemia or genetically defined high-risk myeloma either by cytogenetics or gene-expression profiling. And importantly, people who do not get the expected benefit from an autotransplant. So people can go on this study if they relapsed to early...early relapse, which is independent of FISH and cytogenetics and whatever you may have thought the risk was upfront. When a person relapses too early after a standard autotransplant, it always portends a poor prognosis.




**Shah**: So one of the other things making things really interesting now is immunotherapy in myeloma. And it would be an entire other session for us to talk about that. But, I wanted to touch upon things that are available for patients now. One of them is this BMT CTN 1401 trial. And the interesting thing about that is it's using a patient's own myeloma cells to make a vaccine. And so, patients that are newly diagnosed with myeloma we're collecting their tumor and then putting it in the freezer. And after they get their transplant, randomizing them to get vaccine or not vaccine. And those patients that get vaccine will have their tumor fused with their own immune cells, as a vaccine, and have that injected three times during their already planned maintenance therapy with lenalidomide.

And one of the great things about this trial is not only that it's being conducted in multiple centers—which are making their own vaccine—but it's taking advantage of transplant itself, which is a really nice immunologic time to try to put in more immunotherapies. If you can imagine that you're giving this high-dose chemotherapy and patient's immune systems are sort of reset, this is a good time to develop the immune system towards being against their own myeloma, which I think is one of the waves of the future.

**Hari**: I think it's a great trial, and it's a personalized vaccine. So this is a proof of a personalized study. Each patient is getting a vaccine that's unique to their myeloma, it's their own cells, their own

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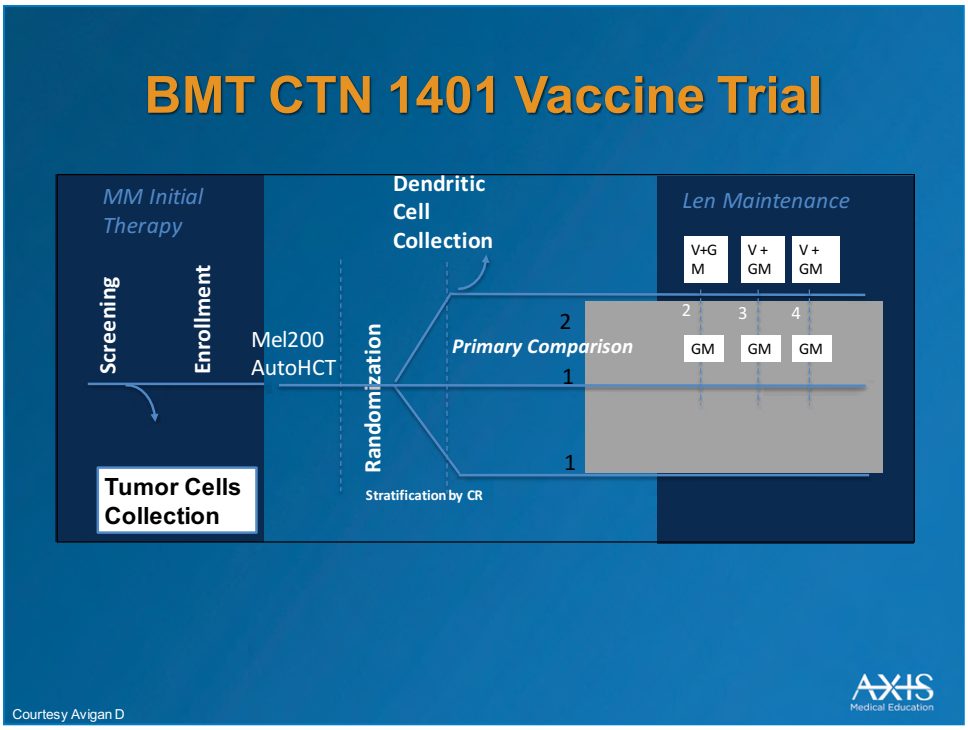


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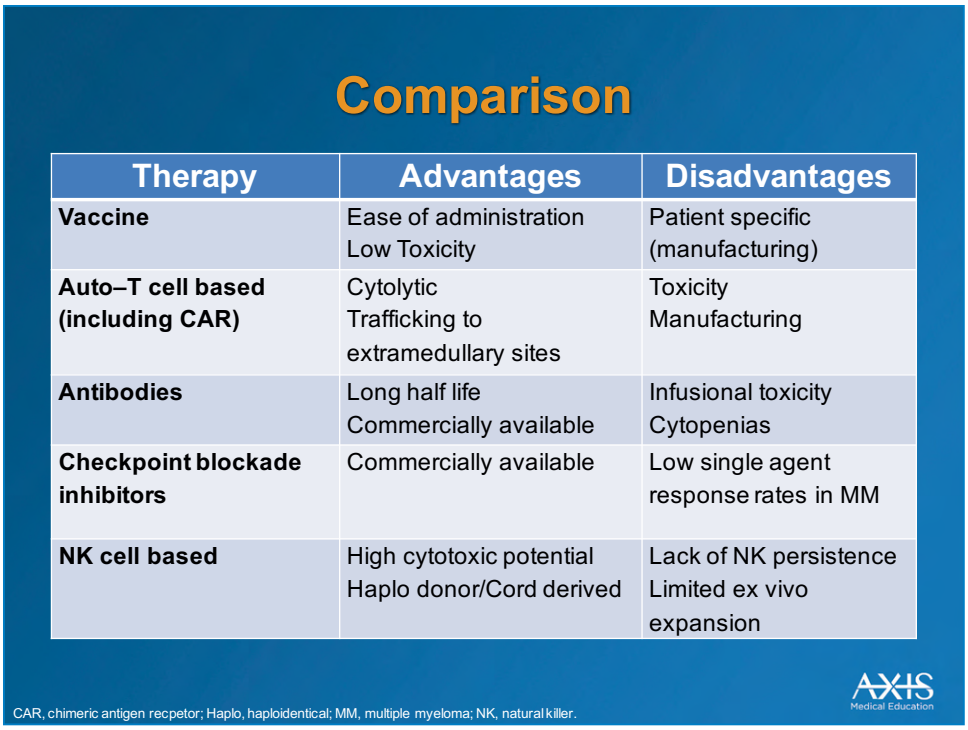
immune system. And as you mentioned, they reset the immune system after transplant at a time when their disease burden is very low, and at the time when the T cells for the immune cells are getting educated about their environment, the re-learning process, you're accelerating it against myeloma. So if this trial works out, it'll be, again, a game changer in myeloma.




**Shah**: I think so too. There is actually a lot of new immunotherapies coming out, and we just want to talk about a few of them. We talked about vaccine, which is now being actually studied in a randomized controlled trial, which is really exciting. But there are really many other immunotherapy options being developed in early phase. For example, chimeric antigen receptor T cells, which use T cells that are directed towards myeloma antigens, and recently there's been exciting data about that. Again, early but I think something that's coming along down the line. We talked about antibodies. So, for example, daratumumab, which has now gotten such great data in the relapse setting, we're trying to see if we can move it upfront in the trials that are ongoing to look at that.

And then something called checkpoint inhibitors, which are molecules that work to help T cells and NK cells work better; cells that may have been otherwise exhausted or tired and not able to function well, it sort of wakes them back up. And it's possible that patients with myeloma have a lot of these exhausted immune cells, rejuvenate these cells that could help fight against that patient's own myeloma without having to get another antibody or cell therapy. And then we also have some NK, or natural killer cell-based strategies which look at sort of an immune system's cell type that's usually used to fighting your own tumors that gets exhausted also, and if we could give new NK cells maybe that would help fight myeloma

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## Comparison

| Therapy | Advantages | Disadvantages |
|---|---|---|
| **Vaccine** | Ease of administration<br>Low Toxicity | Patient specific (manufacturing) |
| **Auto–T cell based (including CAR)** | Cytolytic<br>Trafficking to extramedullary sites | Toxicity<br>Manufacturing |
| **Antibodies** | Long half life<br>Commercially available | Infusional toxicity<br>Cytopenias |
| **Checkpoint blockade inhibitors** | Commercially available | Low single agent response rates in MM |
| **NK cell based** | High cytotoxic potential<br>Haplo donor/Cord derived | Lack of NK persistence<br>Limited ex vivo expansion |

CAR, chimeric antigen recpetor; Haplo, haploidentical; MM, multiple myeloma; NK, natural killer.

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better. All of these are so exciting, and we're not sure exactly where to use them yet, some of them upfront, some of them during transplant, but we're really hoping to have more clinical trials to look at that.

## Conclusion

- We can still improve on outcomes for MM patients
- Melphalan is the transplant chemotherapy of choice
  - CE-melphalan allows for more flexible administration
- The transplant phase may be an ideal time to implement some immunotherapies, including vaccines, T cells, NK cells and checkpoint inhibitors
- High risk patients should be considered for clinical trials

- And so there are a lot of discussion points that we can make about this session. I think the most important one that you made is that although we've had some proof of principle that transplant can improve outcomes, and early transplant can be better than delayed transplant so far, we're still looking to further improve upon this. What can we do before the transplant, what can we do with the melphalan that we give, and what can we do afterwards to make it better in addition to maintenance. We think that melphalan, the drug itself, is still a great drug for transplant, and thankfully we've been able to make it more stable and more accessible to patients. But the transplant phase itself might be this ideal time to implement these new immunotherapies, as you mentioned, when the cells are growing and being

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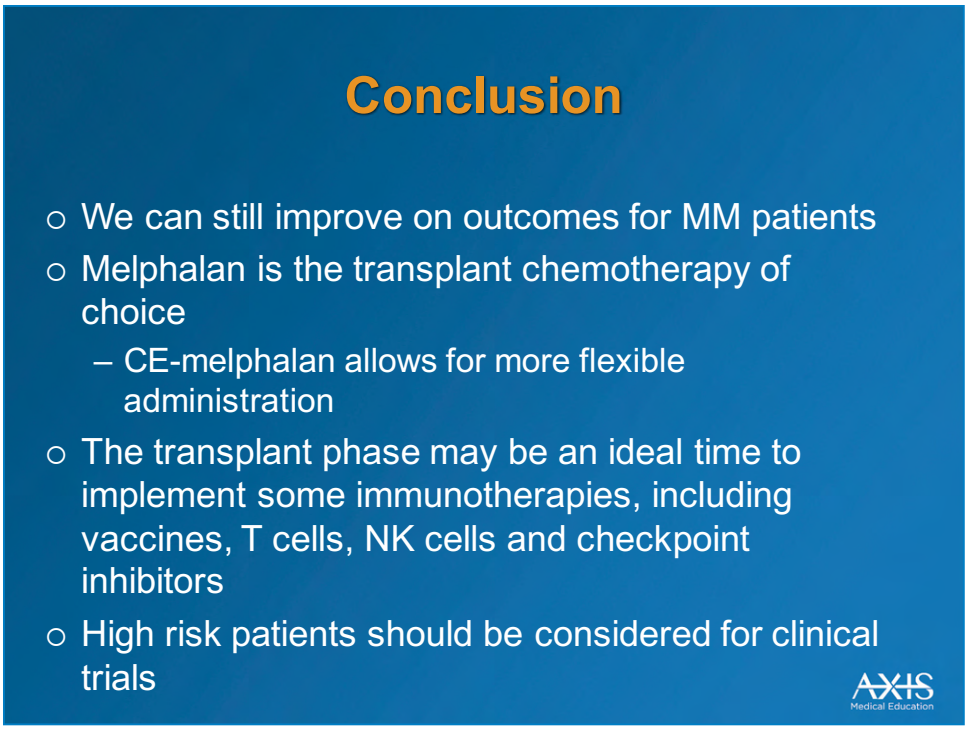


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reeducated; can we push them towards fighting against their own myeloma?

**Hari**: Ultimately, myeloma being a disease of your own immune system's inability to recognize the growing myeloma, too, and it's exhausted. And if we said that, we might be achieving a balance where the immune system might keep it in check.


**Hari**: And then I think we should have a couple of cases just to demonstrate what we've discussed. So let me ask you a question. I saw this patient probably 4 years ago who was a gentleman who worked in a hospital and he's a runner and he gets his annual physical, and he was about to retire and enjoy life in the Upper Peninsula of Michigan, which is like an idyllic setting. So he got his retirement physical and they noticed a high total protein of about 10, but the albumin was about 3.8. And one thing led to the other and before long he was seeing us with a paraprotein IgG-kappa of about 3 gm/dL. So we did a bone marrow biopsy and his bone marrow showed 35% plasma cells which were kappa light chain restricted, as expected, but did carry the high-risk marker translocation chromosomes for (4;14) in addition to some other standard risk markers. And he had an extensive search, including a bone survey and a whole-body CT scan, none of it showed any bone lesions. His complete blood count was normal and a CBC with no anemia. Creatinine was normal, calcium levels were normal. So at that point, what would you tell this patient?

**Shah**: Yes, this is a clear case of smoldering myeloma, right, so a myeloma that is there but may not be clinically significant, like we don't have any indicators that organ has been damaged. And what we used to do with these people is wait, wait, wait until something did happen. Thankfully, now we have a little bit more to guide us, and I think in this situation we could use those

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three options. So one, perhaps performing a whole-body MRI if that wasn't already done, because we know that having two or more lesions that you may not see on a survey but you can see on an MRI would push you to treat the patient.

I think bone marrows can be interesting in these patients, because it's important for these question mark cases to do probably two, a bilateral or a sequential one very early on, because if the patient has more than 60% involvement then you would want to treat them according to the new guidelines. And, finally, looking at the light chains, because the ratio is important, and if it's more than 100 then you can make a case to treat them, albeit they don't have clinically significant disease. And in this case, very interesting because they had a (4;14) right, that's always concerning. And I think probably in that case it's good to remember how many percentage of the cells had that and think about how important this is for their disease. And I think although they didn't make criteria to be treated, very close followup, closer than you might otherwise do.

**Hari**: Absolutely. Because of the high-risk marker and a vague, as you very rightly pointed out, a high light chain ratio, he actually did not meet more than 100, and at this time we didn't have these guidelines when he first met us. He was at about 90 with this light chain ratio, but almost there. So it's always a question if this is a biologic distinction or an arbitrary distinction met to treat. And the patient himself was not willing to get treated at that point because he was just about to retire and all that. But, unfortunately, within 2 years he actually progressed to active myeloma…

**Shah**: Right, which you would have predicted almost.

**Hari**: … which we could have almost predicted. He was at the high-risk end of smoldering myeloma. And, importantly, now we have clinical trials for patients in this setting.

So this patient actually went on to have active myeloma within 2 years, and then received upfront bortezomib/cyclophosphamide/dexamethasone regimen followed by an autologous transplant, and then he chose to receive bortezomib maintenance mainly because when we discussed the data for (4;14) myeloma and the use of immunomodulatory agents versus proteasome inhibitors in that setting, he liked the data about the proteasome inhibition, and he went ahead and had a proteasome inhibitor maintenance.

So he received bortezomib maintenance for 1 year and then stopped it, and then was followed for another 2 years. So a total of 3 years after the transplant he actually relapsed with the rising paraprotein now. And, again, no symptoms; it's almost as if the smoldering myeloma came back. And after following for a couple of times with the paraprotein going up, we recommended treatment. By this time more new drugs had come on the market, including carfilzomib. He had not seen lenalidomide so far, and he had not seen daratumumab, which was also available at that point. So at this point he chose to use the carfilzomib/lenalidomide combination and he's actually had a complete response to that at 3 months.

**Shah**: It's very effective, right?

**Hari**: It's very effective and based on the ASPIRE study, and at this point we are negotiating whether we should do a second transplant with his stored cells. And, again, he had a 3-year benefit from the first transplant…

**Shah**: So he makes the grade because even retrospective data, 36 months was even better.

**Hari**: Right, for a benefit from a second salvage autologous transplant. At relapse he was essentially not refractory to any of the drugs and he had already gotten about 3-1/2 years from his diagnosis to relapse, and that's very important. We have patients who relapse now who are not refractory to anything, because he had stopped bortezomib 2 years ago, and just on observation. And, again, it indicates to us the choices that we have for patients. So this patient hopefully will go on to have a second autologous transplant, and then he's planning on lenalidomide maintenance at that point.

**Shah**: Right, now he can do that. So do you want to talk about our person on dialysis maybe, because I actually recently had this patient who had had slightly a difficult to control myeloma but ultimately got cyclophosphamide and bortezomib and dexamethasone. Unfortunately, when the patient had presented, he had had light chain disease and had severe renal impairment to the point where he ended up being

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on hemodialysis. Even though he was given treatment with chemotherapy, his renal impairment did not reverse and he was still on dialysis when I saw him for transplant consultation. And as we talked about, patients with renal insufficiency and even dialysis should not be not considered for a transplant, they can be considered. And what we liked about his case was that he wanted to have something where he might have a longer-term outcome and he had the support and he was very interested in pursuing this. And his doctor was interested also, so he came to us relatively early in his course.

So we evaluated him, and I wanted to get your idea. Would you have also considered him for a transplant with a good performance status, etc., otherwise?

**Hari**: Yes. I think dialysis by itself should not be a contraindication for autologous stem cell transplant. We know that it's a limited time event, unlike an allogeneic stem cell transplant, there are no immune suppressive drugs, and dialysis being a hemodialysis is an effective intervention for these patients, as a renal replacement can be done effectively in the hospital. None of these patients are getting transplanted as an outpatient, obviously, and they all have to be admitted to the hospital. They do have a higher risk of mucositis, but most programs reduce the amount of melphalan we give them because it's a mucositis-inducing drug.

And many programs do 140, some programs actually ratchet it up a little bit more to 160 to 180 because of the dose-response curve of melphalan that we talked about. And I'm hoping for an era where we'll be doing melphalan with pharmacokinetics where we actually can measure the amount of melphalan in the person's body and how it's cleared, and then we know how much we gave to these patients.

But for the time being, there are… We just completed a CIBMTR study that was presented at ASH in 2016 where there was no mortality essentially for people that even severe or on dialysis undergoing transplant, and there was a significant proportion of patients who could come off of dialysis after transplant. So I think deep remissions and an early transplant probably can get even more patients off of dialysis, even if you achieve a complete light chain remission, his kidney might actually still have some scope of improvement.

**Shah**: Over time, right?

**Hari**: Over time, yes. We really should not use dialysis as a contraindication, and the benefits accrue. In the setting of myeloma, hemodialysis turns out to be a risk factor because of the difficulty in giving certain therapies, and mainly lack of efficacy; for example, you don't know the dose, it's clear.

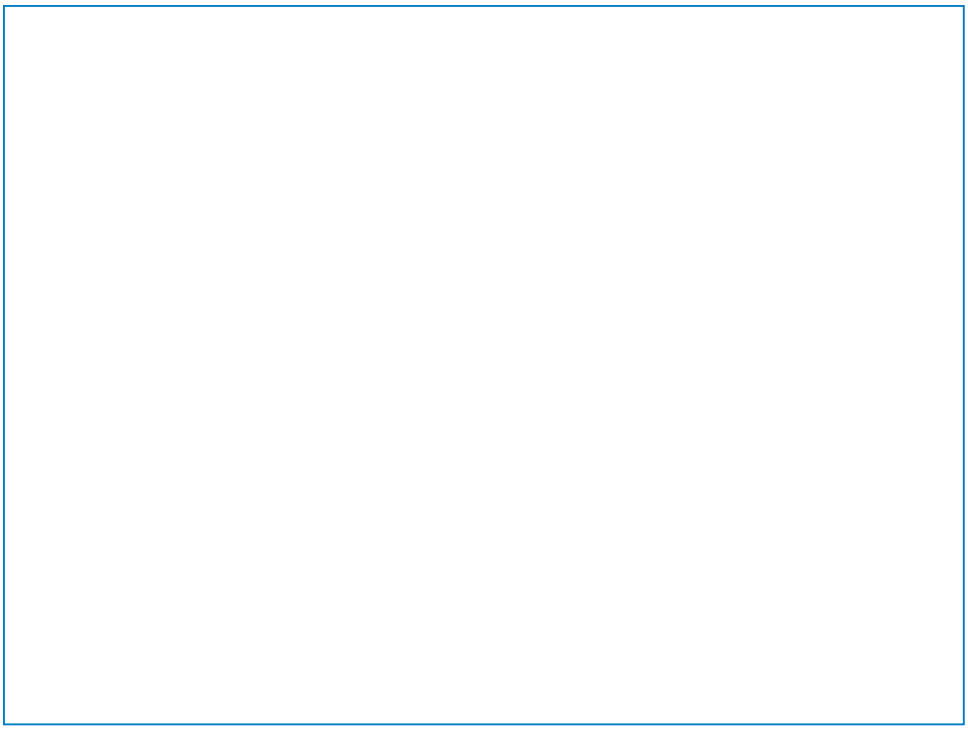
So I think we had a really good discussion here, and the key takeaways, as we mentioned, are the importance of transplant even in the era of drugs, the importance of maintenance after transplantation, and also the referral to transplant being a key step in a newly diagnosed person with myeloma of a transplantable age and comorbidity status.

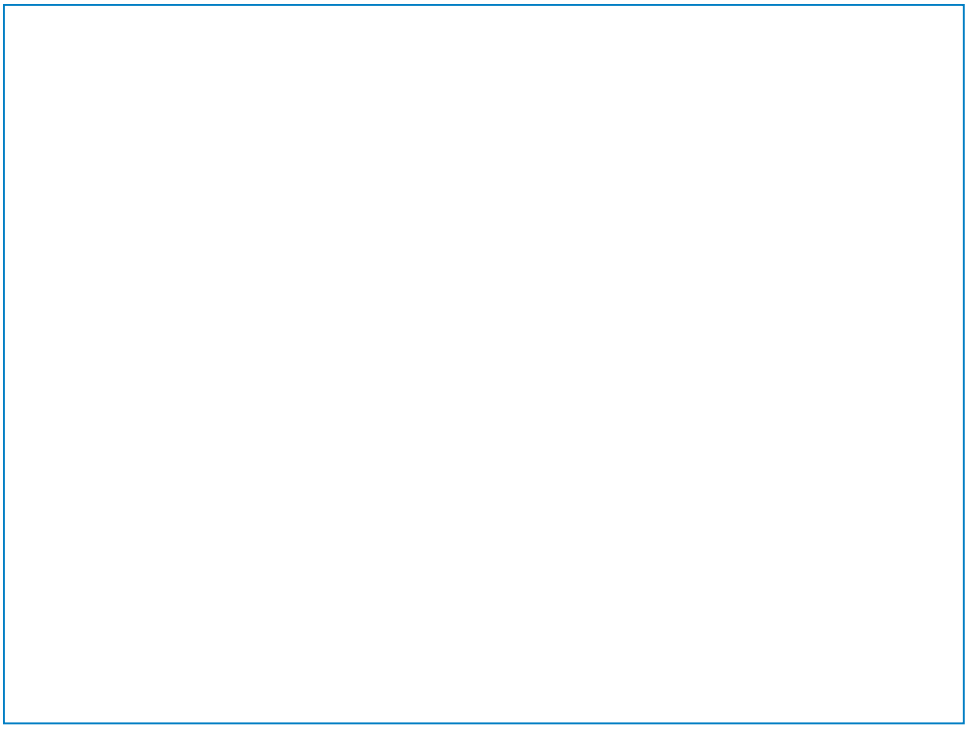
**Shah**: And everybody deserves an evaluation.

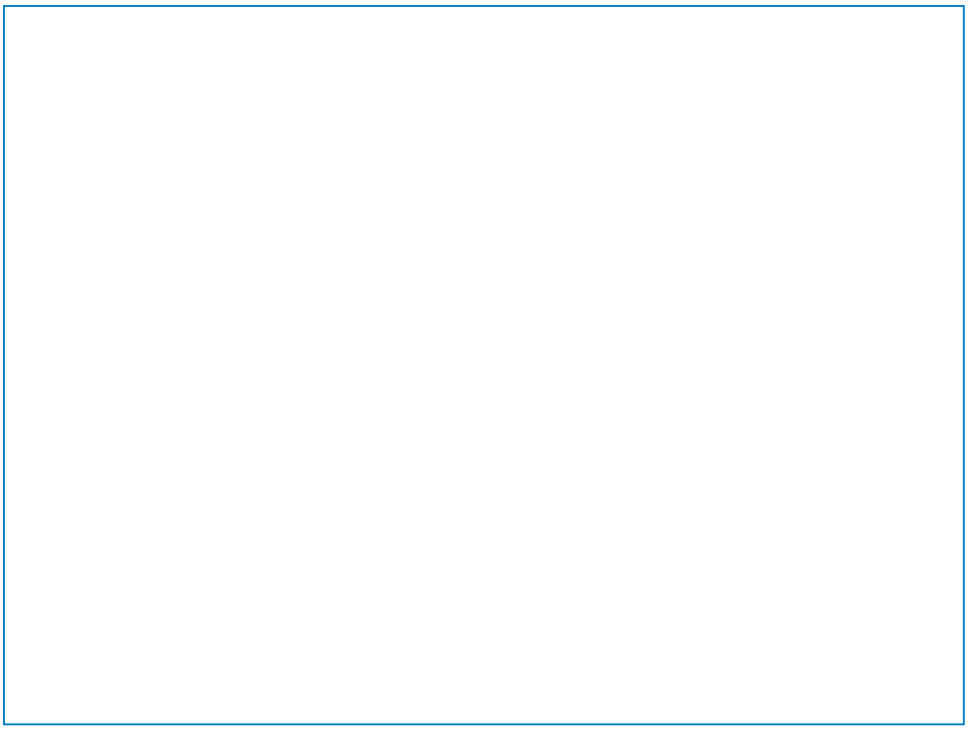
**Hari**: Everybody deserves an evaluation. I think that's one of the biggest things that we can offer a patient newly diagnosed with myeloma, a transplant evaluation.

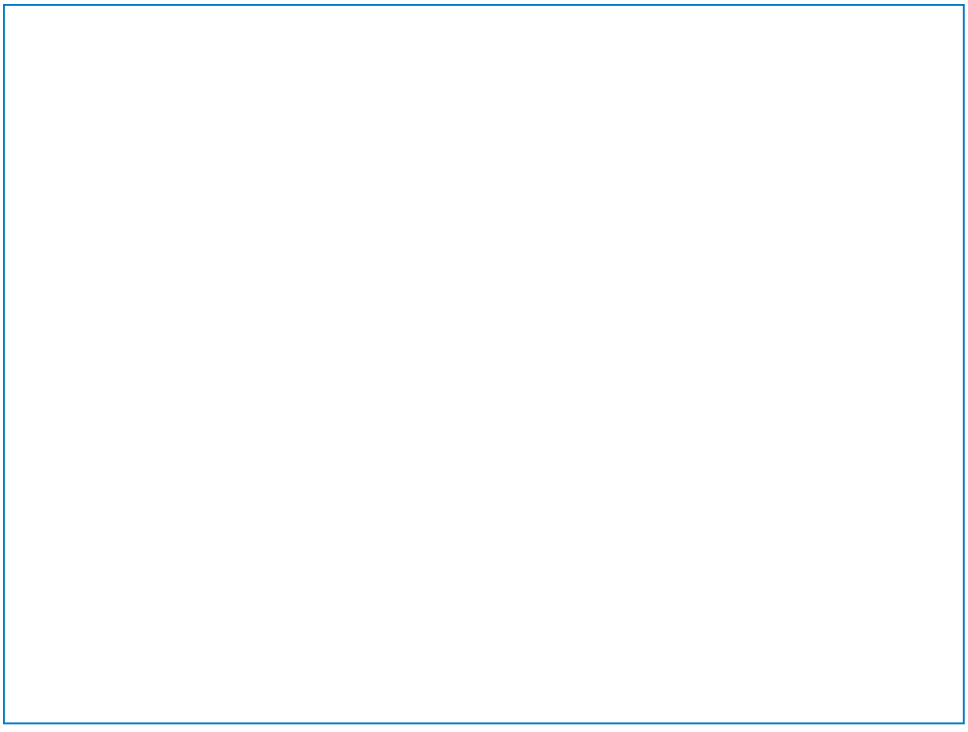
**Shah**: Great, completely agree.

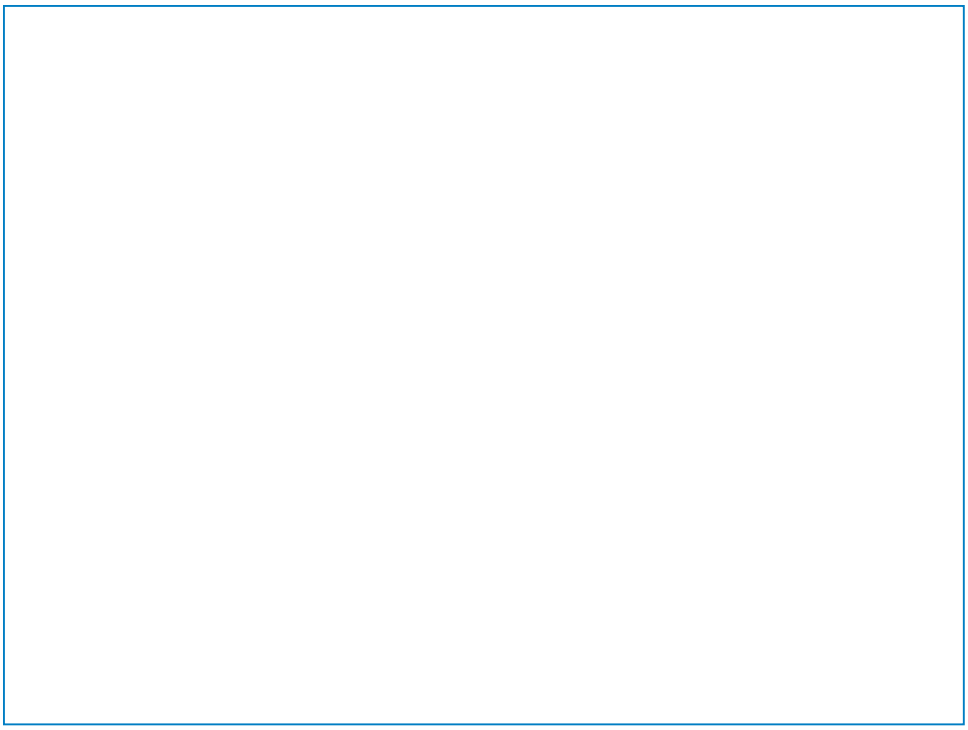
**Hari**: Thank you for your participation in this CME activity, we enjoyed talking to you.

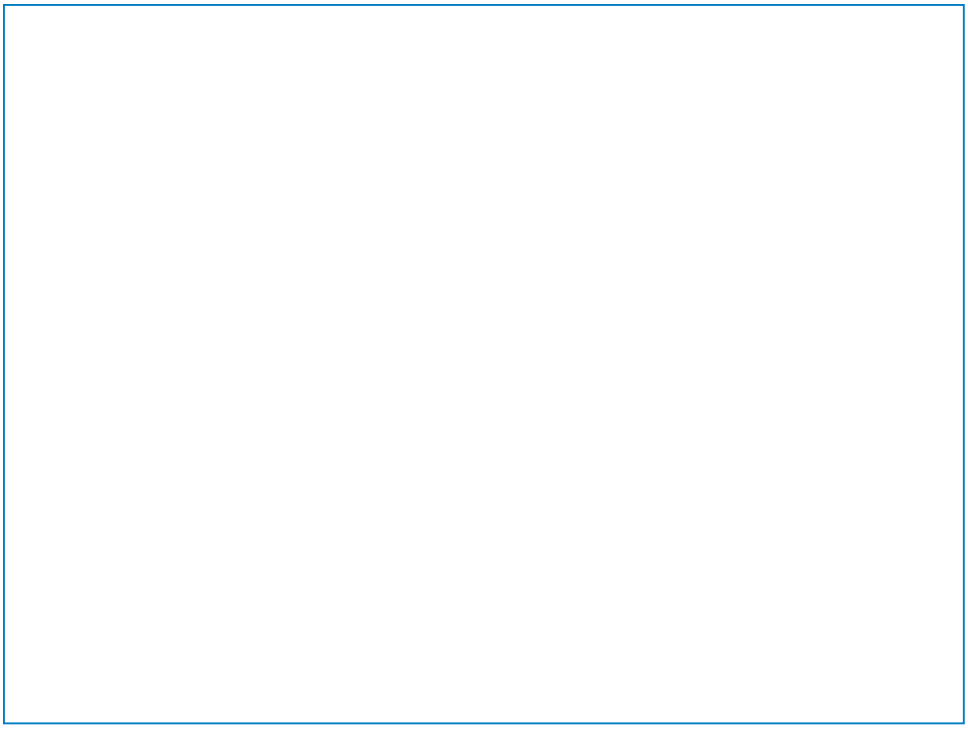


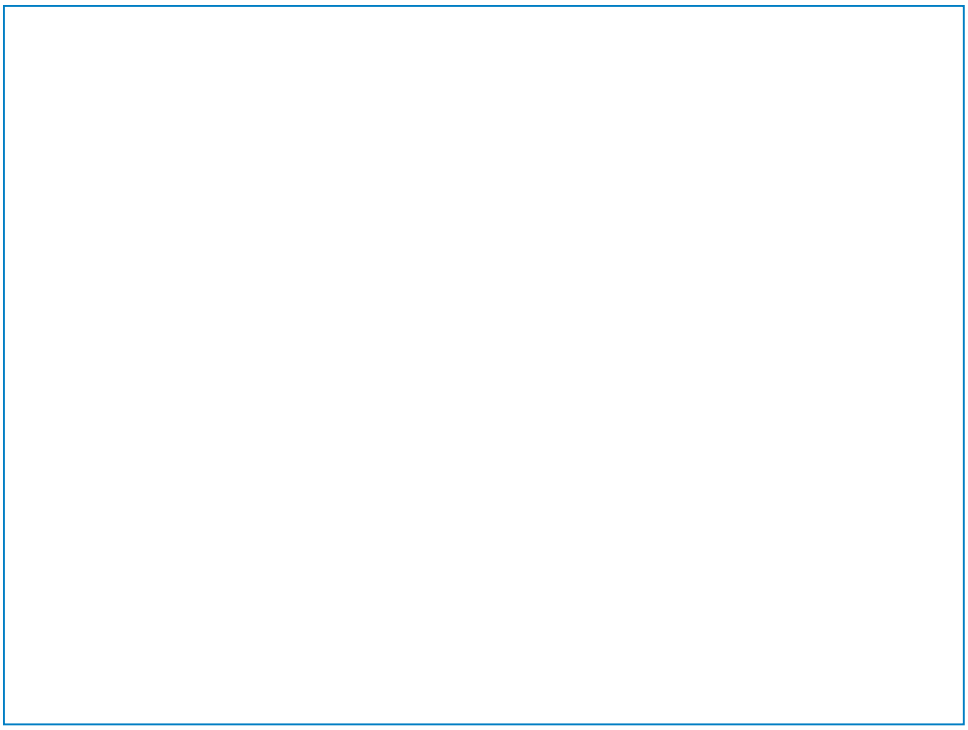


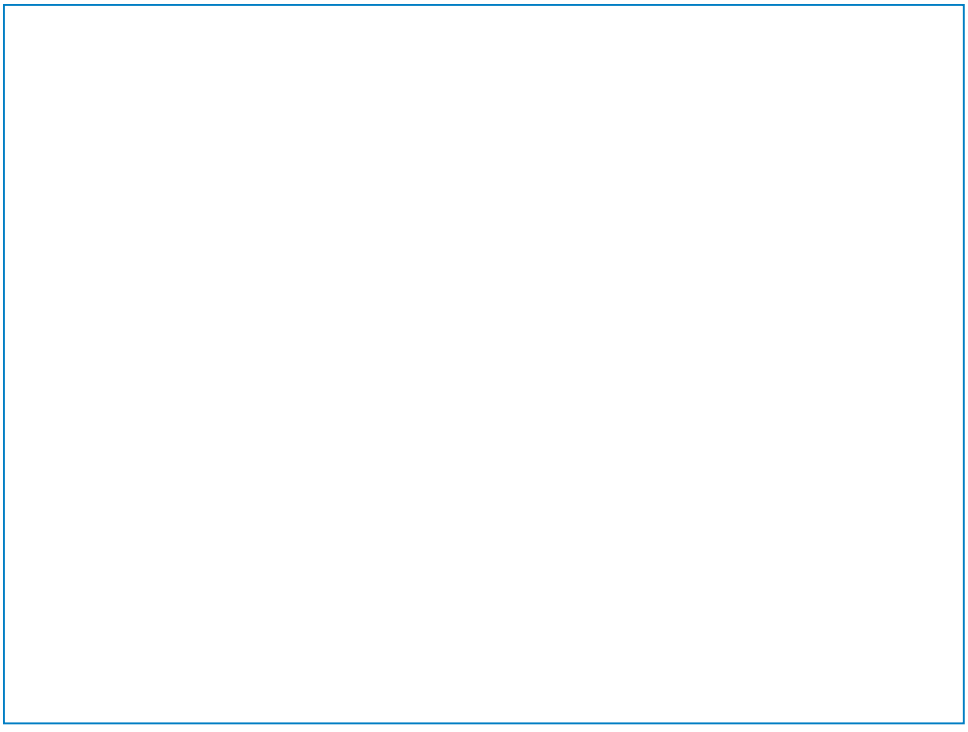


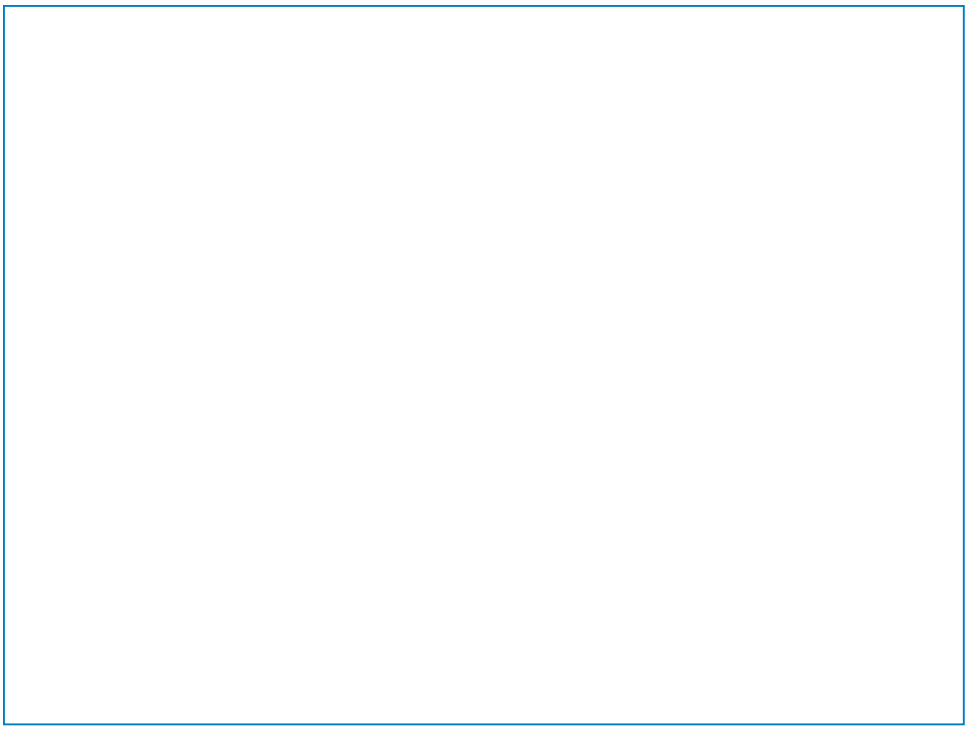


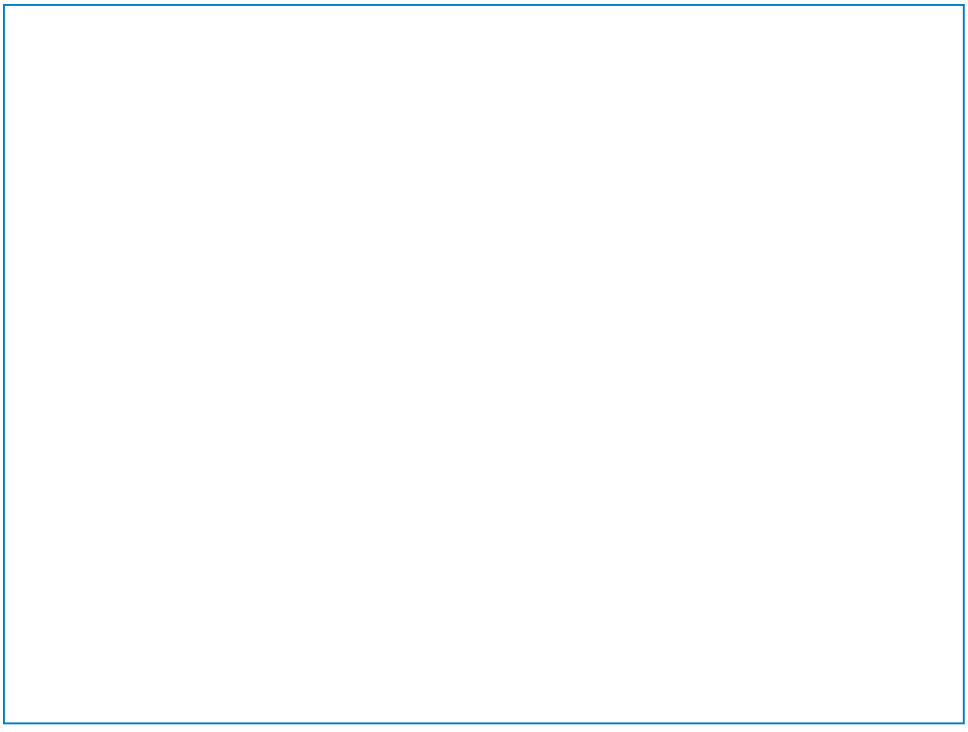


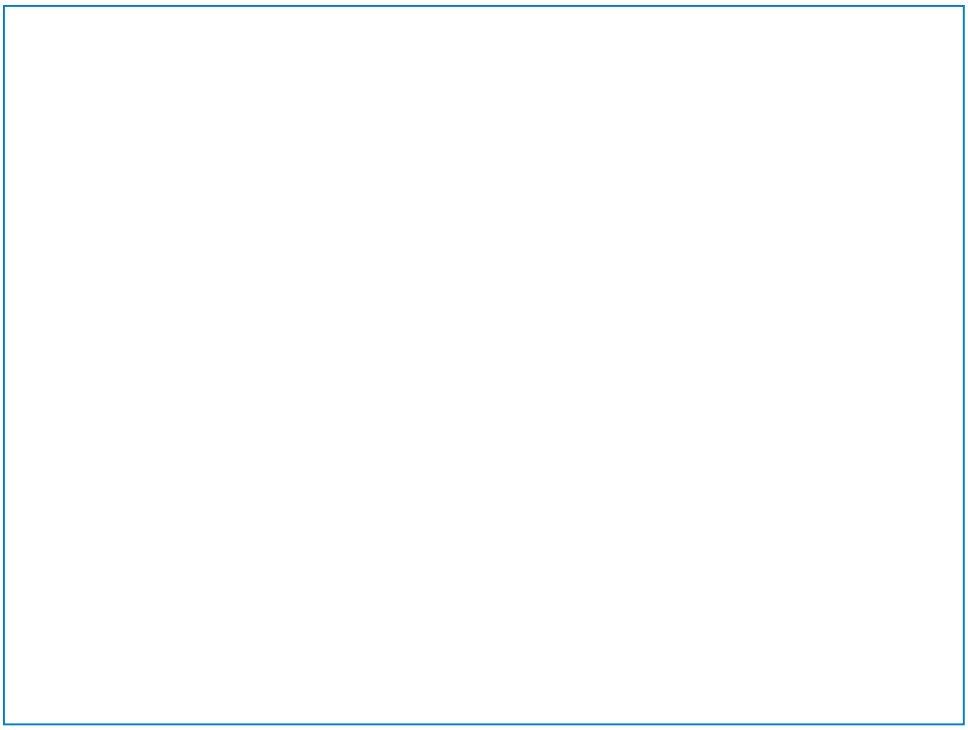


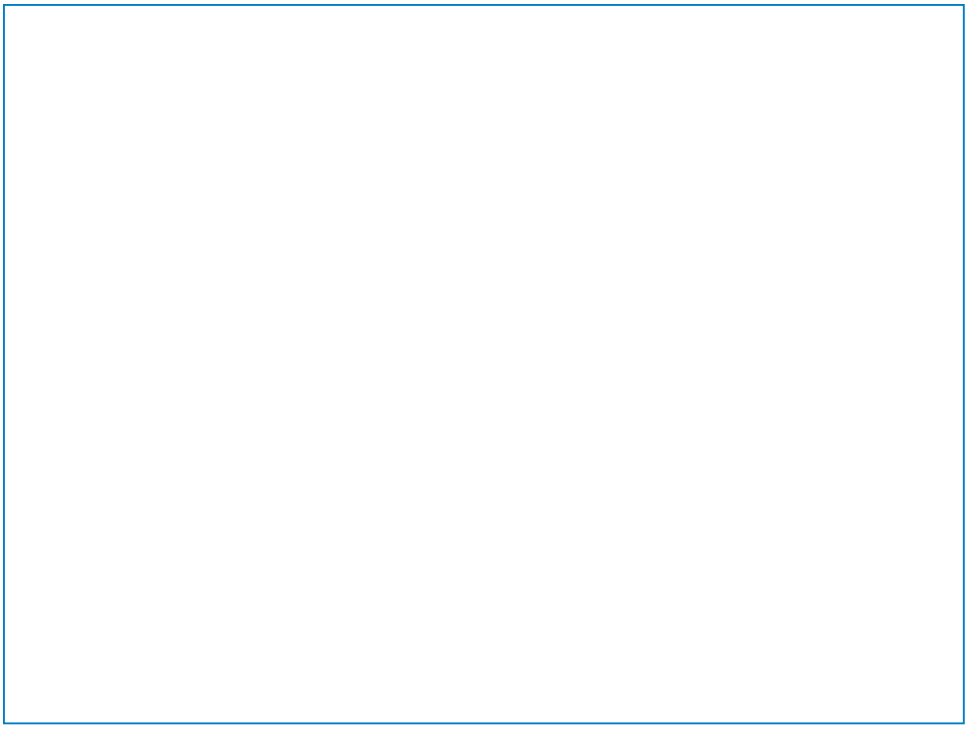












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