Greetings, and welcome to Optimizing Outcomes: Multiple Myeloma, web education program. It is now my pleasure to introduce your moderator Lizette Figueroa-Rivera. Thank you, Lizette, please begin.

Hello, everyone. On behalf of The Leukemia & Lymphoma Society, I'd like to welcome all of you and thank you all for joining us today.

LLS helps you navigate cancer treatment and ensures that you or your loved one has access to quality, affordable, and coordinated care.

Over the past 20 years, with so much advancement with treatments for multiple myeloma, not only has the median survival rate increased, but the increased understanding of myeloma biology has not only led to advances in diagnosis and prognosis, but has contributed to the development of targeted and immunotherapies.
LLS is the leading funder of visionary myeloma research and this investment has led to many approved therapies for patients in recent years. While progress has been made, our work continues. We have committed more than $31 million to myeloma research to find cures.

LLS supports a wide variety of grants, aimed specifically to investigating precursor states of myeloma, in order to learn how myeloma develops and progresses.

Please continue to inform us of what you need during this time and please continue to let us be there for you.

For this program we’d like to acknowledge and thank Genentech, Inc. and Biogen and Janssen Oncology for their support of this program.

Slide 3: FACULTY

It's my pleasure to introduce Dr. Benjamin Derman, Assistant Professor of Medicine at the University of Chicago in Chicago, Illinois. Dr. Derman, I’m privileged to turn the program over to you.

Slide 4: What's New in Multiple Myeloma?

Dr. Benjamin Derman:

Thank you so much. I am really pleased and happy to join everybody here, talking a little bit about myeloma. The title
of the talk is, Optimizing Outcomes: Multiple Myeloma, but I sort of summarize it a little bit differently, which is to really talk about what's new in myeloma? I mean, we could talk all day about everything from start to finish with myeloma or even beyond that, but what I really wanted to do was dive into a few different areas that I think are really new and exciting.

**Slide 5: Disclosures**

So with that, here are my disclosures.

**I declare advisory board fees Janssen and COTA, Inc.**

**I am an independent reviewer of a clinical trial for BMS.**

**I will be discussing off label and/or investigational use of therapies.**

**Slide 6: Objectives**

As far as thinking about what we’re going to talk about, I wanted to cover a couple of different areas. One is a hot topic right now, which is a precursor disease called smoldering myeloma and the question to answer there is, do we treat it or do we not, do we wait for myeloma to be diagnosed? And then, once patients are diagnosed with myeloma, should we be thinking about 4 drugs as opposed to 3 drugs, as is being done or has been done for several years? Does everyone need a stem cell transplant? Who can get it? What is MRD (minimal residual disease) and can we use it as a Decision Aid? And then focusing on what a lot of developments have been in, which is the relapsed/refractory space, this is myeloma that’s come back after a number of treatments and focusing on some of the newer treatments there.
Slide 7: Multiple Myeloma Diagnostic Criteria

Many of you may be familiar with this, but just for orientation purposes, myeloma really exists on a spectrum, at least how we currently define it. And we have on one end of the spectrum MGUS, which stands for monoclonal gammopathy of undetermined significance, and really what this is referring to is a low level of disease that is not really manifested in terms of organ disease or targeted involvement of the bones or the kidneys, so this is not somebody that we would typically start treatment for.

In between is something called smoldering myeloma. Smoldering myeloma is where a patient now has a reasonably high amount of disease that we can detect in the blood or the bone marrow or elsewhere, but they still don’t meet criteria for myeloma requiring treatment. Moving to the end of the spectrum, myeloma requiring treatment is patients who have either high blood calcium levels, kidney dysfunction, low blood counts, or bone disease. When I say renal insufficiency, that refers to low kidney function.

There are some newer criteria as well in the last 10 years or so, that say, well maybe if you don’t have this organ dysfunction, if you have just an extremely high amount of the disease, we would also consider treating that as though it’s myeloma.

Slide 8: Epidemiology of MGUS and SMM
So let’s talk a little bit about MGUS or smoldering myeloma. Most of the risk of developing smoldering myeloma is driven by its precursor, which is MGUS. And the risk increases with age, it’s more common in males, more common among African-Americans, or really anybody with African ancestry to be fair. And then also, it’s higher among patients who have first-degree relatives, about 2½ times the risk.

On the right, I’m showing you some different numbers that we’ve seen published through the Mayo Clinic study that was done many years ago. There is an amazing study going on in Iceland where they’re screening the entire adult population. They actually have 50% of all Icelandic adults above 40 years old who are screened for MGUS or smoldering myeloma. And what you can see is that MGUS has fairly high rates of prevalence among patients who are 80 years and older, but smoldering myeloma is obviously much lower than that. And what we’re hoping to see with that study over time is to see what happens to patients. And they’re doing some interesting studies to randomize patients to say, okay some of you are going to actually have intensive monitoring and some of you we’re not going to do that. And we want to see are there actually differences in the way that we approach patients from that regard. And what that’s hoping to understand is, does it make sense to actually screen all patients at some point for myeloma?

Right now the opinion is no, we shouldn’t be doing that. The PROMISE study is the closest thing to that, which is to say, what if you have a really high risk of developing myeloma at some point? Let’s say you have all these risk factors on the left side. And you can see here that the rates of the prevalence of MGUS is actually quite high when you select out for these higher risk patients. But still the question is, are we going to help patients live longer by screening, and that we don’t know. So these are the things that we’re going to learn from these studies.

When we talk about smoldering myeloma in particular, there is this thought that, not all smoldering myeloma patients are the same. Some have a higher risk of progression to myeloma and some may never develop myeloma, and that’s what’s very humbling. We can’t really figure out always who is going to develop myeloma, but we try.

### 2/20/20 Score

<table>
<thead>
<tr>
<th>Risk Factors for SMM Progression</th>
<th>Risk Category (No of risk factors)</th>
<th>Median Time to progression</th>
<th>Progression at 2 years</th>
</tr>
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<tbody>
<tr>
<td>BM plasma cells &gt; 20%</td>
<td>Low (0)</td>
<td>110 months</td>
<td>10%</td>
</tr>
<tr>
<td>M-protein &gt; 2 g/dL</td>
<td>Intermediate (1)</td>
<td>68 months</td>
<td>26%</td>
</tr>
<tr>
<td>sFLC ratio &gt; 20</td>
<td>High (2-3)</td>
<td>29 months</td>
<td>47%</td>
</tr>
</tbody>
</table>

One of the risk scores is this 2/20/20 score. So the 2 comes from an M-protein or an M-spike greater than 2, the 20s come from a bone marrow plasma cell percentage greater than 20% and a serum-free light chain ratio greater than 20. So if you have multiple high-risk features, that means that you are at a much higher risk of developing myeloma, somewhere around 29 months on average, which we call the median time to progression. And another way to think about it is that 47% of those patients will have developed myeloma by the 2-year mark.
Some have said, this study was done in 2018 and it was analyzing patients who were not being as closely monitored or we didn’t have advanced imaging, so maybe there were a population of patients that were higher risk for developing myeloma. But that remains to be seen.

Slide 10: IMWG Logistic Regression Score

There is a newer study that was looking at even making it more granular and you can split patients up even more into these different scores. And we don’t know for sure if that’s really going to be any better, but these are things that we use in clinic.

Slide 11: PANGEA Model: Another Way to Assess SMM

We also have something called the PANGEA Model, which came out recently, and this is what’s interesting. So, if you take a patient with these characteristics, a bone marrow percentage of plasma cells or myeloma cells of 25%, you have a free light-chain ratio of 30, which is above that 20 threshold, and you have an M-spike of 2.3, these are the abnormal proteins that are made by the myeloma. The 2/20/20 score that I mentioned predicts that the average time to progression to myeloma is 29 months. When you use the second score I just showed, they also predict that about half of patients are going to progress to myeloma at the 2-year mark, so 24 months. So it’s pretty similar. But then, you use this newer criteria called the PANGEA Model, which factors in a couple of different things, and here you see that the average time to progression to myeloma is actually 10 years. That’s a very different number than the 2 to 3 years that we’re looking at with the other score, so what gives?
I think what we’re learning from this is that the truth is, these models are all just guesses, they’re all just estimates, and we can’t just look at one value and say this is your risk, this is your fate, this is your destination, this is your destiny. I think what we have to do is really take a really concerted view of watching patients closely and not committing them to necessarily doing treatment.

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**Slide 12: Reasons to Consider Treating (High-Risk) Smoldering Myeloma**

- **Avoid end-organ damage from myeloma between visits**
- Two studies showed that Lenalidomide increased the time to death or progression (PFS) compared to observation.
- One study showed lenalidomide increased survival (caveat: included old definition of SMM)
- Might we cure patients if treating earlier?

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Okay, let’s talk about that for a second because I think that’s really the most important thing. People say here are the reasons that we should treat patients with high-risk smoldering myeloma. We want to avoid end-organ damage, we want to protect the kidneys, you want to protect the bones, we don’t want to see lots of high blood calcium levels. We have 2 clinical trials that already showed that when you give the drug lenalidomide [Revlimid®], it increases the time to death or progression compared to just watching patients. So the thought is, if you give treatment earlier, even if it’s low intensity, it may help patients prevent their myeloma from coming up sooner and it may even help them live longer.

When you look at lenalidomide in terms of overall survival, in terms of how long people live, there was 1 study that actually showed a benefit, although it was using older criteria so it makes the data a little bit less impressive.

And the last thing is, what if we actually can cure more patients if we treat earlier? The rule of thumb is generally that myeloma may not be a curable disease. I think we can cure some patients but we’re not curing all. And if we treat it earlier, maybe that will help.
Slide 13: Responses with Len and Progression in Observation Arm

So what are the reasons that maybe we should hold our role here, because I think there’s a lot to dive into here.

The first thing is that when you give just lenalidomide alone, the partial response, which means a 50% response to treatment, is only 50%. And only 4% are having what’s called a very good partial response, which means a 90% reduction. So I would argue, it’s not exactly what we’re looking for. If we’re talking about cure, you need to have 100% removal of the disease or eradication of the disease.

The other thing is, what about the number of people who had clinical progression in the observation arm? What we see here is that actually very few, only 3% of patients in the observation arm, had kidney disease or had some kind of kidney disease and we don’t know the severity, we don’t know that these patients went on to need dialysis. And only 12% had some bone disease or a mass of plasma cells, a mass of myeloma that showed up. So even if you combine these, that’s only 15% of patients who are being observed had a clinical progression, that I would argue is dangerous to a patient even in the worst-case scenario. And so that is, I think, a really important piece.

And then, what about quality of life? Well, actually what we found out is quality of life is not improved with lenalidomide. If you read the papers on this they’ll say lenalidomide did not worsen quality of life, but I would argue we’re taking patients who are completely asymptomatic and then we’re saying we didn’t make your life worse. But we didn’t make it better either. And I think that’s a struggle that I have when I’m talking to patients with high-risk smoldering myeloma is, I say, look I know I’m not going to make your life better, I could make it worse with treatment and this is with the least intensive treatment.
Slide 14: Reasons NOT TO Treat Smoldering Myeloma

So, I think those are some things that I take into consideration. My reasons not to treat smoldering myeloma is that, as I said, most patients who are being surveilled don’t get end-organ damage. And the other thing is that most patients don’t have a deep response to lenalidomide, only 50%. On top of that, we see that quality of life was not improved, I just showed you that. And the other thing is that newer, contemporary patients with smoldering myeloma, with better diagnostics at baseline, actually seem to have lower risk disease anyway. So this concept of high-risk smoldering myeloma, there’s not that many patients who are out there. And some of you may be even on this call, but the thing is that this is something that I think is still okay to watch.

So, the last thing I would say is that smoldering myeloma is actually still very similar genetically to myeloma. Most of the genetic changes in patients who have myeloma, they’re already there at smoldering myeloma. So the thought that we’re curing more patients, I don’t know that that’s true.

Slide 15: GEM-CESAR

So, if you really want to know the answer, this is an interesting study to look at, the GEM-CESAR trial. What this did is, it said we’re going to treat patients with high-risk smoldering myeloma as though they have myeloma. We’re going to go all in. We’re going to give a really good 3-drug regimen called KRd carfilzomib [Kyprolis®], lenalidomide, dexamethasone [various brands] as induction, which is the initial course of treatment to get the disease down.
we’re going to use a stem cell transplant, the patient’s own cells, called an autologous transplant, and then we’re going to give a little bit more treatment, and then we’re going to go on to what’s called maintenance therapy. So this is like what a normal myeloma patient might receive.

Slide 16: GEM-CESAR: MRD Status at 4 Years

And what we see is that even at 4 years after treatment only a little bit less than half of patients are free of even any microscopic disease, which we call MRD negativity. That’s the low level of cancer cells. And, when you look at the time to progression on the left, meaning the time to the disease coming back, only about 62% still were free of disease as far out as 70 months. So I don’t think that we’re curing more patients here when you compare it to normal, newly diagnosed myeloma.

Patients who were fortunate enough to get to a very deep level of response, which we call MRD negativity, the lack of any minimal residual disease, that is this blue line here, which you’re seeing, which shows that 93% of patients were free of progression at the 30-month mark, at about 2½ years. So again, that’s not surprising. We see that across clinical trials for multiple myeloma as well.

So, I don’t know if we’re really curing more patients. These numbers seem similar to the newly diagnosed space.

Slide 17: ASCENT
There was another study that we participated in called the ASCENT trial, which looked at an intensive 12 cycle or 1-year course of a 4-drug regimen without transplant, followed by maintenance therapy for a year and then things were discontinued.

**ASCENT: Responses**

- Median follow-up 26 months
- Response rate: 97%
- Complete response: 64%
- MRD negativity: 84% (n=73)
- 3-yr PFS rate: 89.9%
  (95% CI: 82.3%-98.3%)

Slide 18: ASCENT: Responses

And, the thing about this study is it’s still early but so far 97% of patients responded, that’s way better than that 50% that I mentioned. And not only that, but a large percentage of patients, 84%, had the deepest level of response and 90% of patients at the 3-year mark still have no evidence of disease. But the question is, what is going to happen to these patients in the long run? Are we actually going to cure more patients? And, we just don’t have the data on that yet.

Slide 19: A Tale of Three High-Risk SMM Patients

I had 3 patients on this study, for instance, and I give you their stats so to speak. These are anonymized but some had different levels of bone marrow disease and the amount of protein in their blood, but on the whole these were all relatively high amounts of disease to start with. These were all, in my opinion, if you were going to enroll somebody in a clinical trial, these were all very appropriate patients.
So the first patient achieved MRD negativity, they have no evidence of disease after the 2 years, which we’re calling end of therapy or EOT here. Then the second patient, they finished the 2 years, their best response was a 90% reduction in their disease but they eventually progressed and had to go on to a stem cell transplant. They’re doing well now, but the treatment course did not cure them. And then the third patient, something really odd happened, which is they fortunately had no evidence of disease after only 6 cycles but they kept telling me that they were so miserable being on treatment, they hated the idea of being on treatment because they were asymptomatic to start with, I made their life worse. So they withdrew and that was their preference.

And to me, these are the 3 things that can sometimes happen is, either you have an awesome response, and everything went well, or you have a great response but you’re not feeling well on it, or you just don’t benefit the way that we would hope. And I think those are the reasons that I’m very hesitant to be treating patients outside of a clinical trial.

Ongoing Studies in Smoldering Myeloma

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<tr>
<th>RANDOMIZED</th>
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<td>NCT04270409 (end. 7=330)</td>
<td>Isatuximab-Rd</td>
</tr>
<tr>
<td>DETTER-2MM (est. 2=288)</td>
<td>Daratumumab-Rd</td>
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<tr>
<td>AQUILA</td>
<td>Daratumumab Observation</td>
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<tr>
<td>NCT04776365</td>
<td>KRD/R</td>
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<td>Dar-VRD x 24</td>
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<tr>
<td>E-PRISM</td>
<td>ELO-Rd → ELO-R</td>
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<tr>
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<tr>
<td>NCT02960055</td>
<td>Isatuximab x 30</td>
</tr>
<tr>
<td>NCT02959577</td>
<td>Isomizam-Rd 9 ≥ 1 x 10 R x 15</td>
</tr>
<tr>
<td>NCT04776365</td>
<td>Iberamide</td>
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There are lots of clinical trials going on right now in smoldering myeloma. These are a number of them. Some are randomized, which is really the best way to really understand which is better. But notice that among these randomized trials, the control arm, which is supposed to be what we would do for patients normally, typically includes treatment. They don’t have observation. There’s only 1 study here that had observation as the control arm. And that worries me because we’re moving the goal post a little bit. I told you that my standard of care is observation but if all these other studies say that patients should get low intensity treatment as the control arm, then we’re not really understanding what is the benefit of treatment with multiple drugs over just observation. And I think that’s what we’re missing.

And then we have lots of non-randomized studies and these are helpful to understand ultimately how these treatments work, but we kind of know that they work. These are the same treatments that we use in newly diagnosed myeloma. The difference is that we don’t know if these benefit smoldering myeloma patients at all. And when you do a non-randomized study, we really have no clue how it would compare to observation, we’re just guessing.
Slide 21: Newly Diagnosed Multiple Myeloma

Alright, so that’s all about smoldering myeloma. But what I wanted to talk about now is, what do we do once patients actually are diagnosed with myeloma?

Slide 22: Myeloma Alphabet Soup

There is a dizzying array of treatments. This is not meant to be exhaustive but it’s alphabet soup. I’ve already shown you all these letters. I probably should show this slide even before that, but we group drugs into different categories. And we have the immunomodulatory IMiDs, which are some of our older drugs. Now, in the contemporary space we have proteasome inhibitors, such as bortezomib [Velcade®] and carfilzomib. And we have monoclonal antibodies, for instance daratumumab [Darzalex®]. I circled these 3 here, daratumumab, bortezomib, and lenalidomide, because those are 3 that I’m going to be talking about in just a moment. And, I’ve included some typical side effects that we might see for each of these.

But you can see to the right of it, these are the drugs that we’re typically using in the relapsed space and we’re going to get to some of these as well.
There was a study called the GRIFFIN trial, which looked to compare a 4-drug regimen to a 3-drug regimen. And so remember I was showing this to orient ourselves with the alphabet soup. The V stands for bortezomib, the R stands for lenalidomide, and the little D stands for dexamethasone or a steroid. And dara is short for daratumumab.

So in this study, the GRIFFIN trial, they randomized 207 patients to either get a 4-drug regimen or a 3-drug regimen, and the only difference was the inclusion of daratumumab. Then patients, after 4 cycles, would get a stem cell transplant followed by 2 additional cycles of the same treatment as before transplant, and then they would go on to what we call maintenance therapy, which many of you are probably familiar with. And again, the only difference between the arms was that in the blue arm, in the dara arm, they got daratumumab and lenalidomide, and in the red arm, the non-dara arm, they just got lenalidomide.

The main goal of the study was to see how many patients had no evidence of disease using traditional response criteria after transplant and a little bit of treatment after transplant. And they guessed that there would be a 15% difference. That’s what they thought would be needed to really say there’s probably a difference here in terms of the treatment.
And interestingly, while we’re still very encouraged by the results of the study and I’ll show you why, the difference in the stringent complete response, which is what they were looking at in the study, was only 10%. It was 42% for the 4-drug arm versus 32%. So when you think about a primary endpoint, which is the primary goal of the study, it actually was not met and this is a recent development. In the initial preliminary data that was presented, this data was actually shown to be significant. This regimen was shown to be better.

Slide 25: GRIFFIN: Progression-Free Survival Favors Dara-VRd

But one of the secondary endpoints that we look at, which is called progression-free survival is, I think, an important piece here.

PFS or progression-free survival means the time to progression or death. And this is different than overall survival, which is the time to somebody’s death. Now a lot of people will say PFS is not something we should be looking at because a patient cannot experience progression-free survival. They experience death, they experience quality of life changes, but progression, just because we delay the time to the tumor or the myeloma coming back, doesn’t mean that we made a patient’s life better or helped them live longer.

Now the problem with our trials in myeloma is that it’s not a problem, it’s a good thing that people live too long. So are we going to wait 10 years to figure out if a drug leads to better overall survival? And on top of that, as time goes on, all these newer treatments come along, so a patient who may not have gotten the better quote-unquote treatment, they can make up for it later with other treatments to get access to. So overall survival is actually a tricky endpoint in myeloma because patients are living so long, it takes us longer to get to see if there’s a difference, and you probably need a lot of patients, more than what we typically enroll in clinical trials, to be able to see that difference.

So a lot of the time we look at progression-free survival as what we call a surrogate, as a replacement for overall survival because it will tell us the answer sooner and I do have patients that would prefer to keep their disease away for longer. That is an important thing for them.

So while this wasn’t the main objective of the trial, and I’d argue it should have been, you can see that at 4 years more patients were alive without progression when they received the blue arm, which is the 4-drug regimen, over the 3-drug regimen. So 87% of patients were still alive without disease progression at 4 years, getting the 4-drug arm, as opposed to the 3 drugs, which was only 70%. And this is what we call statistically significant.

So even though this wasn’t the main objective of the trial, we do see a major difference there. And because of that, I have been often recommending this 4-drug regimen to most of my patients, regardless of their disease status or disease risk at baseline.
Now the other question that I get a lot and it’s coming up more and more is, what about transplant? Because the last study I showed you gave a transplant to everybody. So these were patients that were typically a little bit younger, more fit, they could withstand the rigors of 4 drugs and a transplant.

The DETERMINATION trial was a really important study that’s come out in the last year and this compared what we call early stem cell transplant versus a delayed approach. So in this study everyone got 3-drug treatment, called VRd, the triplet therapy, the same one that was compared in the last trial I showed you. But one arm of this study went on to get a stem cell transplant and the other arm did not. And they were advised or recommended to get a transplant if their disease came back a second time.

Now, I’ve included some stats here. Basically what it shows is that people who got a transplant had deeper responses, but what you really want to know and the primary endpoint was progression-free survival. So this number, this thing is coming back again.

And what we see here is that when you go out to 5 years and when you look at the averages, the patients who got a transplant kept their disease away for longer. So their progression-free survival was longer when you got a stem
cell transplant. On average you had about 5½ years with a stem cell transplant, as opposed to about 4 years with no transplant. The difference was 21 months to be exact.

The other thing that is notable though, is that so far when you look at the 5-year course, and even if you go out to 7 years, there’s no difference in the overall survival of patients regardless of which arm they were randomized to. What that means is that patients who got a transplant did the same as patients who did not upfront overall in terms of how long they lived.

Some people look at this data and they say, hold on, wait a second, you need to look at 10 years to really know what the impact of this transplant is. It’s simply too early to say whether there’s a difference in overall survival. But other people will look at this and say, I don’t know guys, those curves, that orange and blue curve, I mean you can’t even distinguish them, they’re completely overlapping.

So the thing to remember here is that this was not a trial of saying yes transplant or no transplant. This was transplant now or transplant maybe later. And, the maybe later is actually more like oftentimes not later because only 28% so far of the patients who did not get a transplant at the beginning went on to eventually receive it, so far.

Now the thought is that okay well, if those are the patients who did progress, you are making up the difference by doing a transplant later. So my takeaway from the data is that for most patients, if I think that maybe their circumstances in life are such that a transplant doesn’t make sense now, but I think they can get one later, I am okay with that.

**Slide 28: Patients with 2+ High-risk Features Need Better Therapies**

But there are a couple of circumstances where I don’t think that’s a good idea and one of those is patients who have high-risk disease features. And this is based on the chromosomal abnormalities or cytogenetic abnormalities, as we call them, and what you see here in this chart when you look at the PFS, the high-risk patients who did not get a transplant had an average time of disease progression of about a year and a half, whereas it was 55 months, which is almost 5 years, 4½ years or so when they got a transplant. That’s a really big difference. And what that tells me is that patients who have high-risk disease, they need to do something more than just 8 cycles of triplet therapy and maintenance. So that’s often what I am communicating to patients.

But there’s another group of ultra high-risk patients who have 2 or more high-risk abnormalities and these patients, regardless of what we can offer them, they are simply not doing great.

In the GRIFFIN study, only 50% of those patients were still alive and free of progression at 3 years, and it’s the same with a number of really high intensity therapies, even higher intensity than what I’ve showed you. So what that tells
me is, transplant may be beneficial but I don’t know that it’s adding much over just more intensified 4-drug therapy or prolonged 3-drug therapy. I think we still have a long way to go in terms of benefiting these patients.

Key Takeaways from GRIFFIN and DETERMINATION

- Quadruplet therapy appears to be associated with improved PFS over triplet therapy, regardless of disease risk.
- Transplant may still carry benefit for the right patient, especially those with high-risk disease.
- Patients with 2 or more high risk cytogenetic abnormalities need better therapies!

Slide 29: Key Takeaways from GRIFFIN and DETERMINATION

So my takeaways from these 2 trials are that, number one, the 4-drug therapy is associated with improved progression-free survival regardless of disease risk and that transplant may still carry benefits for the right patient with the right time, especially those who have high-risk disease, and we need to do better for patients who have 2 or more high-risk cytogenetic abnormalities.

Slide 30: MRD = Measurable Residual Disease

MRD, I’ve mentioned it a little bit, which is measurable residual disease or minimal residual disease. It refers to the low level of cancer cells that may be left over after treatment. I think of it like jumping into a pool. And the pool has different depths. On one end of the pool it might be 4-feet deep and on the other end of the pool it might be 12 feet. And if you’re swimming in this pool looking for a coin that I may or may not have thrown in the pool, I’m going to tell you look before you jump in, I have this coin and it’s going to represent the myeloma disease. I’m going to throw it in the pool or I may put it in my pocket. And I’m going to ask you to go and find it. And, you can look in the 4-foot end, the 6-foot part, the 8-foot part, the 10-foot part, you’re really good, you’re a good diver, you can look at all of those parts and if you still don’t see the coin you can be relatively certain that maybe I haven’t thrown that coin in there. Maybe there’s no disease that’s left over.
But, what if the coin is in the 12-foot end, which is the deepest part of this pool that I show you here, this 10 to the minus 7th (10^{-7}) here. And the issue is that when you’re talking about looking, this is beyond the level that we can search for. It’s almost like a little bit of an existential question, like is there disease present that I just can’t find, it’s below the limits of our testing, or is there really no disease there, did we really cure the patient?

**Slide 31: MRD is a Powerful Prognostic Tool**

And this is an interesting concept. How can we use MRD to guide our decision-making? Because right now most of what we know about MRD is to say it’s a really powerful prognostic tool. It can tell us if patients are going to likely progress sooner or potentially even live longer. Here we’re seeing that it doesn’t matter the disease setting, whether it’s newly diagnosed or relapsed/refractory, whether you got a transplant or not, MRD is super helpful in terms of deciding or predicting who is going to necessarily live longer. So that would argue that MRD negativity may be a worthy goal, like we want to get to the absence of residual disease.

**Slide 32: MRD2STOP: Can MRD-Negativity Guide Discontinuation of Therapy?**

There are some studies and this is one of our studies that we’re leading at the University of Chicago, looking to see if a patient has reached MRD negativity. You can’t find anything at the 10-foot end of the pool, which we call 10 to minus 6th (10^{-6}), which means you look at millions of cells and you still can’t find any myeloma. What we decided to do is, we said okay, we’re going to discontinue treatment, we’re going to discontinue maintenance therapy that patients are on,
all those people who are on the DETERMINATION trial, who are on Revlimid®, I have a patient who’s on cycle 128 of Revlimid, can we stop treatment for those patients? And then we actively surveil, we actively observe these patients to see what is going to happen to their disease. And so far when you look a year out after stopping treatment, 84% of those patients still have not a single shred of disease that’s detectable. And so far, we’ve seen about 13% of the patients on this study who have had even a microscopic amount of disease present, there’s much fewer who have actually developed disease progression, fewer than 10%. But of course our goal would be that none of these patients should ever develop disease progression. So we’re actually looking at deeper levels potentially to see if maybe we can get to the 12-foot end of the pool to say we found the coin at the 12-foot end, we shouldn’t stop treatment, that’s a bad idea.

So, we’re still working on this study and following patients and we should have hopefully more data on that.

Slide 33: MASTER Trial: MRD Response-Adapted Treatment

The other study that’s been presented is what’s called the MASTER trial. Many of you may be familiar with this, it’s been very popular among patients because it was a very aggressive treatment de-escalation using MRD testing. So for patients who at some point had 2 consecutive MRD negative tests, they were able to undergo discontinuation of everything. So some patients only got treatment for maybe 8 to 12 months and then they stopped all treatment. And what they found here is that 71% of patients were able to, at some point stop treatment, but as time went on, only about 50% of the total patients remained off of treatment without evidence of disease. Some had progressed, some developed microscopic disease that doesn’t require restarting treatment but certainly means that their disease may come back at some point.

And again, we saw the same findings that patients who have none or only one high-risk mutation, they do very well, but patients who have 2 or more, this is probably not the plan for those patients.

But again, this is really encouraging because it means we might be able to use MRD to guide decision-making.
Slide 34: First...Some Terminology

Okay, we’re going to make a hard right turn or maybe a left turn here. These studies are looking at what happens when patients do really, really well. Ultimately, we know that most patients, maybe two-thirds, are ultimately going to have their disease progress and they’re going to go through multiple lines of treatment. So we have to figure out what to do for them. And I want to discuss a little bit of terminology here in the relapsed/refractory space.

So we have something called triple-class refractory disease, which means that a patient is resistant to an immunomodulatory IMiD, which I’ve included in a little reference below, a proteasome inhibitor and an anti-CD38 monoclonal antibody. And then we can go even further and call patients penta-refractory, which means they’re resistant to 5 different drugs, 2 from the first 2 classes and then an anti-CD38. And we also count lines of therapy. A line of therapy means a course of treatment. And the only thing where it gets confusing is that patients who get a transplant, everything before and after the transplant all gets grouped into one line.

Slide 35: Relapsed/Refractory Multiple Myeloma

And why is this important?
Recent FDA Approvals

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idecabtagene Vicleucel</td>
<td>BCMA-directed CAR T-cell Therapy</td>
<td></td>
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<tr>
<td>(ABECMA)</td>
<td></td>
<td></td>
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<tr>
<td>Ciltacabtagene</td>
<td>BCMA-directed CAR T-cell Therapy</td>
<td>4+ prior lines of therapy (triple-class exposed)</td>
</tr>
<tr>
<td>Autoleucel (CARVYKTI)</td>
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<tr>
<td>Tecristamab</td>
<td>BCMA-directed bispecific antibody</td>
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<tr>
<td>(TECVAYLI)</td>
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<tr>
<td>Elraptamab</td>
<td>BCMA-directed bispecific antibody</td>
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<td>(ELREXPIO)</td>
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<tr>
<td>Talquetamab</td>
<td>GPRC5D-directed bispecific antibody</td>
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<tr>
<td>(TALVEY)</td>
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Slide 36: Recent FDA Approvals

Well, when we’re talking about relapsed/refractory myeloma, we have 5 new drug approvals in the last couple of years that are all involving immunotherapies. These are novel tailored treatments for myeloma. Many of them are targeting something called B-cell maturation antigen (BCMA) and 2 of them are CAR T-cell therapies, and 3 of them are called bispecific antibodies. We’ll get into what those are.

But all of them have the exact same indication, which is a patient must have 4 prior lines of therapy and they must be triple-class exposed. Triple-class, remember, is one IMiD, one proteasome inhibitor, and one anti-CD38 monoclonal antibody. So patients have to go through these therapies.

What’s getting crazy in myeloma now is that I just showed you that first study, the GRIFFIN trial, where patients got 4 drugs, 3 of which were from each one of the classes, even at the beginning. So it’s possible that some patients, even after one line of treatment, might already be triple-class exposed which limits our future options. And so while it might have helped their disease remain in control for a while, when they eventually progressed, they might be in a bind because they might want to be getting to CAR T-cell or bispecific antibody therapies earlier than what the FDA is currently allowing us to do. So this is a challenge. And hopefully will change in the near future.

Slide 37: CAR T-Cell Therapy Process

Key Toxicities:
- Cytokine Release Syndrome
- Neurotoxicity
- Macrophage Activation Syndrome
Let’s talk about CAR T. So CAR T-cell therapy will remind some of you about the stem cell therapy process but there are some key differences. In the clinic, what we’re doing is we’re actually collecting a patient’s T-cells. These are part of the immune system. They should, in normal circumstances, identify and potentially even kill foreign cells or cancer cells. That’s part of immune surveillance. But obviously they’re not doing that in this case.

So we take these T-cells and we send them off to a lab, a manufacturing facility, and what happens is a special virus is used to insert these genes that cause the T-cells to essentially make special receptors that we call chimeric antigen receptors that then get expressed on the surface of the T-cell. And in this case, what you’re doing is you’re training the T-cell to identify a target on the surface of the cancer cell of interest, in this case myeloma, and then it goes and starts destroying these cells very quickly and very aggressively.

And so, we have to look out for key side effects from these treatments. Most of this is from the inflammation that is caused by the tumor killing. So it’s doing a good thing, but we have to watch out for the side effects from it. So we call it cytokine release syndrome (CRS), which is this inflammatory syndrome that occurs. We have neurotoxicity affecting the brain and then we have this hyperactivation of inflammation called HLH or macrophage activation syndrome, which are sort of related processes.

When we look at the construct of the CAR T-cell therapies first, what you see here is that there is this T-cell receptor in blue and it’s trying to bind to a tumor antigen which is being expressed, this is basically a protein that’s being expressed by the target cell. So on the right you can see what a modified CAR T-cell looks like, it’s kind of like the most efficient form of the T-cell receptor, so that it binds tightly and quickly to the target of interest on the myeloma cell here, in this case BCMA. Once it binds, it triggers everything down the line here to then activate this T-cell to initiate its killing mode.

### KarMMA-3: Ide-cel vs Standard of Care

<table>
<thead>
<tr>
<th></th>
<th>Ide-cel (n=225)</th>
<th>SOC (n=129)</th>
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<tr>
<td>Median times of</td>
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<td></td>
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<td>therapy</td>
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<td>3</td>
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<tr>
<td>Extranodal</td>
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<td>24%</td>
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<td>Disease</td>
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<tr>
<td>HR Cyrogeneitcs</td>
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<td>46%</td>
</tr>
<tr>
<td>Toxicity</td>
<td>66%</td>
<td>67%</td>
</tr>
<tr>
<td>Penta-refractory</td>
<td>6%</td>
<td>4%</td>
</tr>
</tbody>
</table>

SOC regimen (n=129):
- 43 Dara-Pd
- 30 Ixva-Pd
- 30 Ixva-Rd
- 22 Ixva-Pd
- 7 Dara-Vd

Duration of Response:
- **Idel-cel**: 14.8 months
- **SOC**: 9.7 months

**Slide 38: KarMMA-3: Ide-cel vs Standard of Care**

So, there are a couple of different products that have been investigated. The first was something called idecabetagene vicelucel or ABECMA®. And the KarMMA-3 study was the randomized Phase 3 trial that showed it is way better than standard of care. I’m not going to get into right now whether the standards of care here were really actual standards of care, but the bottom line to take away is that patients with 2 to 4 prior lines of therapy in this study really only had about a 4½ month benefit in terms of progression-free survival, whereas patients who got CAR T therapy in this case went about a year to a little bit over a year before their disease came back.

Among the people who responded, which about 73% of people responded, it was about 15 months before the disease came back, which we call the duration of response. So this is a key benchmark to look at.
Slide 39: BCMA-Directed CAR T-cell Therapy

When you look at the side effects, what you can see is that there was higher rates of low blood counts somewhat, but infections weren’t much higher. There was of course a very high rate of cytokine release syndrome, that inflammatory syndrome, but most of it was pretty easily managed, what we call Grade 1 to 2. Grades 3 and 4 are the much more severe forms.

Slide 40: KarMMA-3: Ide-cel Toxicity

And then as far as neurologic changes, they were present in about 15%. So not a nothing. This is a real treatment with important side effects.

And, there were a higher number of deaths on the CAR T arm due to side effects from the treatment. Whereas more people who did not get CAR T died because their disease relapsed. So you’re trading some things off here. I might be able to control my disease better but it might kill me because of these important side effects.

So, these are important things that we have to be thinking about.
Slide 41: CARTITUDE-1: Ciltacabtagene Autoleucel (CARVYKTI)

There was another study done, a couple of studies done, using a different product called ciltacabtagene autoleucel, which is a mouthful. The brand name is CARVYKTI™ and the trial was called CARTITUDE-1. And this data was just recently reported at one of the conferences over the summer in terms of the final numbers. And amazingly, 98% of patients responded. And not just that, but in this first group of 97 patients who were treated, the average or median time, in this case to progression or death was 35 months, which means that almost 3 years on average were patients benefiting from this treatment. And this is a one-and-done treatment similar to the ABECMA treatment. You get this treatment, there is no maintenance therapy, patients are continuing onward because it's a living drug, it's living inside of the patient, so we don't give additional therapy afterward. So, this is really, really important.

Ciltacel Side Effects

- Low blood counts are common
- Cytokine Release Syndrome (CRS): 92%
- Second Cancers: 23% (10% hematologic malignancies)
- Neurologic changes: 20.6% total (10% severe)
  - ICANS: 16%
  - Parkinsonism: 5 patients (5%), median onset 43 days
    - Resolution in only 50%
  - Mitigation strategies
    - Reduce tumor burden prior to infusion (optimize bridging)
    - Early aggressive CRS/ICANS management
    - Bell's palsy

Slide 42: Ciltacel Side Effects

There’re also some important side effects that we should mention too. A lot of them are the same as what we saw with idecel or ABECMA. We have cytokine release syndrome, low blood counts. We did see a pretty high signal for second cancers in this group. We don’t think that it’s specifically related to this product, but we can’t be certain. These are patients who’ve gotten stem cell transplant and Revlimid and lots of other things, so it’s hard to know.

And then as far as the neurologic changes, one interesting piece that we learned from this is that there was this late onset of neurologic changes that were more similar to like Parkinson's disease. And this is very troubling, having seen it myself, while it’s rare, it doesn’t always resolve in all patients. And so, that’s something that we have to be focusing on.
Slide 43: CARTITUDE-4: Cilta-Cel vs Standard of Care (DPd/VPd)

The Phase 3 study that was done, which is a randomized study against the standard of care, also showed that similar to ABECMA, that cilta-cel or CARVYKTI is better than the standard of care. And this was done even earlier with 1 to 3 prior lines of treatment.

Now I think the big takeaway for me is that this works extremely well, regardless of the setting that you use it. I don’t know that we’re going to find that cilta-cel works better when you give it earlier. The difference is that we might get it into more patients by that point, so that’s the key thing. So I’m very bullish on this and the FDA is going to be reviewing both products to see if they’re going to move it up from 4 prior lines to maybe 2 to 3 or maybe even 1 in some cases, prior lines of therapy. So that will be something really important to watch.

Bispecific Antibodies: Bridging CD3 on T-cells with...

Targets on myeloma cells: BCMA, GPRC5D, FcRH5

I want to leave enough time for questions, so I’m going to finish up talking about bispecific antibodies, which is this technology, this drug, that is going to bridge a patient’s natural T-cells and CD3 is a signal on the surface of almost all T-cells with the myeloma cell. So we already talked about BCMA, but there are other targets that we can use, such as GPRC5D and FcRH5.
Slide 45: MajesTEC-1: Teclistamab (BCMA x CD3)

The first drug to get approved in this space was a drug called teclistamab. Teclistamab is bridging BCMA and CD3 and in the pivotal trial that was looking at this, about 63% of patients responded to the treatment and the progression-free survival was about 11.3 months as a median. And among patients who responded, among those 63% of patients who responded, their duration of response was about a year and a half. So this is a very good option for patients. It’s off-the-shelf, we don’t have to wait for it, we don’t have to manufacture anything. The side effects in general are a bit lower than what we see with CAR T.

Slide 46: MagnetisMM-3: Elranatamab (BCMA x CD3)

We also have another drug that just recently got approved called elranatamab, which is the same mechanism. And about 61% of patients responded. It has a little bit less follow-up time but overall we see that at 15 months 51% of patients were still responding to the drug, so we’d assume that the progression-free survival is going to be a little bit after 15 months, so it’s very encouraging. We think that these are pretty similar. We’re still waiting to see if there’s any differences between the drugs.
Slide 47: BCMA-Directed BsAb’s: Infections are Common!

But one of the things that is similar across all the bispecific antibodies that are being studied, and I’ve included some investigational agents here as well, is that the overall survival, I mean the overall response rate is somewhere between 60% and 70% and the infection rates are pretty high. And they’re persistent. And that’s the thing that’s troubling. Whereas with CAR T therapy, oftentimes the infection risk is limited to the first few months, with bispecific antibodies it’s a persistent rate of infection because you’re continuing to give the drug almost every week in most cases.

So this is bad. We do not want people dying from infections. And these drugs were mostly studied during the era of COVID, even before vaccination, and many patients died because of COVID or other bad infections. And I’ve seen some weird infections with these drugs. So it’s something that we really have to keep in mind. Continuous treatment is not great. So what everybody’s trying to figure out is, can we actually reduce the frequency of these therapies?

Slide 48: MonumenTAL-1: Talquetamab (GPRC5D x CD3)

There’s another bispecific antibody called talquetamab, which is using a different target. So this could be used in patients who may progress after a drug that is going after BCMA or instead of completely. And the overall response rate was about 74% in this study. And, you can see that there were some differences. Some were given every week dosing, some were given every 2 weeks, which we call q2 weeks, q2W. And, you can see that they work pretty similarly. Maybe the every 2-week dosing may be better for patients. So this drug is out there. It’s approved already. And it’s something that we’re already thinking about.
The other encouraging piece to this is that when you look at patients who had prior treatments going after BCMA, for instance, they actually responded quite well. 63% of these patients who may have gotten CAR T or one of these other bispecific antibodies, they responded to this drug, which is very encouraging.

**Talquetamab Safety**

<table>
<thead>
<tr>
<th>AE (%)</th>
<th>0.4 mg/kg IC QW²</th>
<th>0.8 mg/kg IC QW²</th>
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<tbody>
<tr>
<td></td>
<td>Any Grade</td>
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<tr>
<td>CRS</td>
<td>113 (79.6)</td>
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<tr>
<td>Skin-related AE¹</td>
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<tr>
<td>Nail-related AE¹</td>
<td>74 (51.7)</td>
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<td>Dysesthesia¹</td>
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<tr>
<td>Rash-related AE¹</td>
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<td>Decreased appetite</td>
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<tr>
<td>Infections</td>
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<td>17%</td>
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**Slide 49: Talquetamab Safety**

As far as the side effects, infections seemed to be a little bit lower risk, especially serious infections. But one of the key things that we noticed is that skin changes, nail changes, and taste changes are a new side effect here that we don’t see elsewhere. And these were at pretty high rates. About half of patients had some form of this. They did not reach the point where they were so severe to disable patients, but there are cosmetic issues. Sometimes with the taste changes it can cause weight loss. So, 40% of patients had weight loss. These are things that we really have to pay close attention to.

**RedirecTT-1: Can Bispecific Antibodies Be Combined?**

- **Teclistamab**
  - Approved BCMAxCD3 BsAb
  - Response rate 63%

- **Talquetamab**
  - GPRC5D-directed BsAb
  - Response rate 74%

**Slide 50: RedirecTT-1: Can Bispecific Antibodies Be Combined?**

What about adding these drugs? If one is good and the other is good, can we combine them?
There is actually a recent study looking at combining 2 of these drugs together, teclistamab and talquetamab. And what the study found is that, you can increase the response rates as much as 95%. When you look at the amount of time that it keeps the disease away, it’s almost like you added them together. So I don’t know that adding the combined treatment is really better than just doing them sequentially, one and then another, but for the right patient this may make sense. We’re not doing this clinically yet, this is still in clinical trials.

The last bispecific I’ll talk about is a drug called cevostamab. Cevostamab is looking at a different target, FcRH5. We’re not seeing as good of overall response rates. This drug is still in development. We don’t have any FDA approval yet for this. But I mention it for completeness sake.
Slide 53: Bispecific Antibodies and CAR T-cell Therapy in Myeloma

What I’m going to end on here before I’m done is to say that, there’s reasons why we may choose one versus another in terms of bispecifics versus CAR T therapy. Bispecifics are quick, we can get them right away, they’re off-the-shelf, we don’t have to wait, we don’t have to wait for the manufacturing, there’s no additional chemotherapy, whereas with CAR T-cell therapy we give some doses of chemo beforehand to clear out the body’s T-cells. CAR T cells typically require a longer inpatient hospitalization than bispecifics do. The side effects are relatively similar but infections seem to be more persistent with bispecific antibodies. And then as far as dosing is concerned, you can see that we start every week with bispecifics and then they can go to every 2 weeks versus a one-and-done for CAR T therapy. These are both highly active types of treatments but the durability may favor things like cilta-cel as opposed to the others. And then as far as combinations, bispecifics certainly could be combined with other drugs, whereas CAR T we’re typically using it on its own.

Slide 54: Thank you!

So with that, I want to thank you very much. I want to make sure we have time for questions. And for the LLS folks, I didn’t know if you wanted to take it from here.
Lizette Figueroa-Rivera:  
Thank you so much Dr. Derman for such great information in regards to the advancements within the myeloma field.

Lizette Figueroa-Rivera:  
We will start with a question from Denise, our web audience. Doctor, you were just speaking about CAR T versus bispecifics. And Denise is asking, do you think CAR T and bispecifics will start being used instead of autotransplant?

Dr. Derman:  
That's a great question. Thanks for asking that, Denise. The short answer is yes. I do stem cell transplantation as part of my job, it’s not my only job, I’m not a transplanter as a profession, but it’s part of what we do. I think transplant will always have a role, but there are several studies that are currently in development and ongoing right now that are actually looking in a randomized fashion, whether CAR T therapy upfront might be better than a transplant. So, patients are getting some induction therapy to bring the disease burden down, as we call it, to actually get about close to a 90% reduction in disease, and then instead of using transplant, we’re going to use CAR T therapy instead. And we don’t know yet.

I think there’re a couple of advantages to using CAR T in this setting. One is that the side effects that we worry about, cytokine release syndrome and neurotoxicity, typically are more severe in patients who have a high disease amount coming in, or what we call disease burden. And that is not avoidable oftentimes. It’s an unavoidable situation when patients are relapsing because we’re using it because precisely they don’t have a lot of options. Whereas in the newly diagnosed setting, we’ve just reduced their disease by a significant percentage, so we think that the side effects will be less.

And then on top of that, melphalan [Alkeran® or Evomela™], which is the drug that we use in autologous stem cell transplant, which is what causes all the side effects, it’s a really rough drug. Not to mention that long-term side effects, including second cancers, is real. So might CAR T not only be easier to tolerate but also might prevent fewer long-term effects.

That’s why we really want to know what is the impact of CAR T on the future in terms of second cancers and the like.

With bispecifics, I think for patients who don’t want to go to a transplant, there’s going to have to be really carefully
designed studies. I think the infection risk to me is an important one. Transplant of course carries an important infection risk, but similar to CAR T, it’s usually a time-limited piece, whereas with bispecifics this is going to go on as long as you’re on them.

So, I think it’s going to take a long time to get this answer. Because patients do so well, these trials are going to take a long time to give that answer.

**Lizette Figueroa-Rivera:**

Thank you, Doctor. I have a question from Wilbur. Wilbur is asking what are the latest recommendations for treating neuropathies?

**Dr. Derman:**

That’s a great question, too, Wilbur. So neuropathy, just to make sure we’re on the same page, this is the numbness and tingling sensation that people can get in their fingers and toes. Some people who have a related condition, called amyloidosis sometimes it coincides with myeloma, they may have neuropathy even at the beginning. But oftentimes patients develop it on-treatment.

One of the key culprits is a drug called bortezomib or Velcade® is the brand name. And, about 75% of patients who get bortezomib seem to develop neuropathy. It can be reversible in some cases, but in other cases it is not and we don’t always know who is going to get it and we don’t know who is going to recover from it.

What we do know is that giving bortezomib once a week instead of twice a week makes a big difference in the incidence. Especially for older adults. And I guess I usually define that, no one get offended, we’re just saying older adults, anyone 70 or older, I tend to be very careful about the bortezomib dosing. You can reduce the dose, decrease the frequency.

But there are other drugs too, like pomalidomide [Pomalyst®] or even lenalidomide that seem to be associated with it.

So in terms of treatments, my first go-to is usually duloxetine, the brand name is Cymbalta®. This is actually more guideline-driven that should be our first drug that we try. Another common one I see is gabapentin [various brands]. Gabapentin is okay. I think the issue with gabapentin is that you start low and you can go very high with the dosing. It’s hard to know when to switch the dosing, is it working, or we’re just not on a high enough dose. So that’s one of the challenges I have with gabapentin.

Pregabalin [Lyrica®], which is a cousin of gabapentin, can be useful.

But those are right now some of the more obvious treatments that we’ll use.

But I would say, even using these in the clinic, it’s not 100% success rate in terms of treatment of the neuropathy. The main things you’ve got to do is decrease the frequency or the dosing or stop the drug completely, or use these other adjunctive treatments to see if you can help it.

**Lizette Figueroa-Rivera:**

Thank you. And you did mention age, so Sharon is asking, are all treatments available for all adults, no matter what the age?
Dr. Derman:

It’s a good question. With myeloma we’re lucky because we have a lot of therapies that are well tolerated regardless of the age. A lot of our standard, or I shouldn’t say standard, but conventional chemotherapies are exceedingly well tolerated.

I’ve given 4-drug therapy to patients who are in their late 70s or 80s even without an issue.

Transplant, I would say, while I typically take the opinion that there’s no age cutoff, that I would consider it for patients of most ages. Truly there is an age at which point maybe ‘the juice is not going to be worth the squeeze’. And sometimes the way I’ll talk about it with patients is to say, at least around transplant and the newly diagnosed setting, is to say in the best case scenario I can guarantee you that you are going to live 1, maybe even 2 years longer because you do this transplant. You have to accept that 3 to 4 months of that time is going to be spent recovering and feeling pretty ill and then there may be other issues that come down the line. So if it’s 1 year, is that going to be worth it? So you have 9 months of feeling well and 3 months of not. And a lot of patients will come to me in their later 70s, let’s say over 75, and say I’m not sure that it really makes sense for me. And on top of it, we have so many other good therapies that we don’t really need to employ that.

CAR T therapy is a trickier one because I’ve used it again in patients who are in their younger, lower 80s – later 70s, and to me it really comes down to, what is the functional status? We are lucky to have a geriatric assessment program in our University of Chicago clinics where I can rely on them to say, hey, tell me if you think that I’m crazy, tell me if you think this is going to be a good idea. They don’t say yes or no, but at least they say, here’s our experience telling us that this is going to be somebody who has a good chance of success or if it’s likely going to lead to complications.

Lizette Figueroa-Rivera:

We’ll go to our next question. Doctor, John is asking, is dexamethasone necessary during maintenance therapy 5 years post-diagnosis?

Dr. Derman:

Short answer is probably not. And I want to stress that these are often things that you probably need to discuss with your treating physician. Dexamethasone, so let’s talk about that for a second.

Prior to the newer age of therapy, patients were getting probably 3 to 4 times the doses of dexamethasone that we are giving now. So, the typical dose starting out for people under 75 will be about 40 milligrams a week of dexamethasone as opposed to maybe 20 milligrams for older adults. And, we were giving much more than that previously. And there was a very pivotal trial that showed that lower doses of dexamethasone actually improved survival. So whilst people will look at us and say, wow, 40 of dex, that’s a lot, and you may all feel that way who’ve received it, it’s much lower than what we used to give. Okay, so that’s the context there.

The other thing that I want to mention is that when a patient is on bortezomib and their disease progresses, when they’re on lenalidomide and their disease progresses, we say this disease is resistant to these drugs, we’re not going to really go back to them. We say the disease is resistant. But dexamethasone, we never say that about. Dexamethasone somehow seems to carry through with each regimen and part of this is because in the studies that have been done with single agent drugs, take isatuximab [Sarclisa®] for example, dexamethasone significantly increases the response rate, so there is some synergistic activity that dexamethasone adds.

But, I do think there is some diminishing returns at some point. Maybe it’s necessary when you’re first starting a regimen, but for somebody who’s in maintenance therapy, let’s say it’s lenalidomide, I actually don’t include dexamethasone at all. If some patient is needing the dexamethasone as a premedication, like I use with daratumumab, or as a premedication with like a carfilzomib or a bortezomib, I could see that. But we don’t think that you need it.
Another proof of this is that we ran a Phase 3 trial, where in maintenance, compared lenalidomide to a combination of lenalidomide and carfilzomib, called KRd. And we showed that KRd led to better progression-free survival, superior progression-free survival was associated with, compared to lenalidomide alone.

The Italian group did a study called the FORTE trial, and they did a similar randomization, but they only looked at carfilzomib with lenalidomide without dexamethasone versus lenalidomide. And the benefit still stood.

So I can’t compare them much else otherwise, but I can say that at least that’s encouraging that the dexamethasone does not need to be continued for the long-run. And some are even removing it, even after several cycles of regular treatment, not just maintenance.

Lizette Figueroa-Rivera:

Thank you. And Kathy is asking, are patients more symptomatic with the 4-drug regimen, and will there be more side effects if you’re taking 4 drugs versus less drugs?

Dr. Derman:

The safe answer is to say when you’re on more drugs, there’s going to be more side effects. That just makes sense.

I think one of the things that’s encouraging to me though about the 4-drug regimen, in this case dara-VRd, is that the drug that you’re adding is daratumumab and to me that’s the one that probably carries some of the fewest side effects.

There is a risk of infusion reactions on the first day, or injection reactions on the first day that you get it, afterwards that typically risk-reduces to near to zero. And then, infections is the other piece of it.

But to me, I find that it’s exceedingly well tolerated, even among older adults. In fact, the trial without bortezomib, which to me is the hardest one to tolerate among the drugs or at least causes the highest rate of neuropathy, when the MAIA trial, which looked at daratumumab, lenalidomide, dexamethasone, 40% of the patients were over 70 years old and they stayed on therapy. So that tells you that it’s a pretty easily tolerated drug if people aren’t coming off of treatment and staying on. And that’s been my experience.

So, oftentimes the drug that I’m wondering whether to include is actually the bortezomib. I like the lenalidomide, I like the daratumumab, it’s a convenient schedule, but the bortezomib is the one where I wonder how much patients can tolerate it.

Lizette Figueroa-Rivera:

Sure, thank you. And Brittany is asking, how are late effects being monitored with these newer therapies?

Dr. Derman:

Carefully. I don’t mean to be flippant, the issue is that we’re not seeing patients quite as frequently as they’re further out from CAR T, let’s say. So a lot of this comes from the clinical trials to be honest with you, the pharmaceutical companies have to do their due diligence. But there is also post-marketing surveillance. So, these things can get reported to the FDA and this is how we start to learn as a field about how these treatments come about.

The cynical piece is to say that when you’re using these drugs in very late lines of therapy, people aren’t necessarily living long enough to be able to see late effects. But I’m hoping that as we use these drugs a little bit earlier and patients live even longer, that’s when we can really gain an understanding, a better understanding of potential long-term effects.
In regard to the second hematologic malignancies or second blood cancers that developed in the study with cilta-cel, interestingly that has not been seen in the other studies with ide-cel, with the other CAR T products, nor has it been seen in the Phase 3 study. And actually, the Phase 3 studies are really the most important because what you can then say is, these are very similar patient populations, half of them got CAR T and half of them didn’t, and now I can see what’s happening to them in the long-run. That’s really the best way to look at these long-term effects.

In the DETERMINATION trial, patients who did not get a transplant, you’d think that their risk of second cancers was significantly lower but it actually wasn’t that much lower. The difference was that the types of blood cancers that patients got were different. More patients in the transplant arm got what’s called acute myeloid leukemia and it was still pretty low, it was about 3% to 3.5%. And about 2.5% of patients got a second blood cancer in the non-transplant arm and they were almost all acute lymphoblastic leukemia.

So these are different types of cancers. And this is not meant to scare anyone, these are still really rare events and people live longer getting these therapies than not. But, it’s really the randomized approach that gives us that signal.

Lizette Figueroa-Rivera:

Right. And you just mentioned earlier line treatments, so Helen was asking, when can new patients expect CAR T to be moved to an earlier treatment line?

Dr. Derman:

I will preempt this by disclosing that I don’t have any inside information and I don’t know anyone at the FDA. I’m just giving my personal opinion.

Ide-cel is going up for review with the newest data that I showed you later this year. And this is a review by the FDA. And I think the main question for the FDA is going to be, will they change from this current designation of 4 prior lines of therapy required before you can get ide-cel?

It’s very rare that I can get the drug approved off-label, so to speak, if I prescribe it earlier than a patient has gotten 4 prior lines of therapy. Cilta-cel is going to be up for review in early 2024, probably in the first quarter I would say. And so, things are not going to change until then. And, the studies that are ongoing looking at even earlier, we have to wait until those read out before we gain an understanding.

But in Europe for instance, they already approved CAR T for patients with 3 prior lines of therapy. So the different regulatory agencies looked at the same data and came to different conclusions. And maybe the FDA is being just very conservative with it.

But the other thing that I didn’t talk about, and I have an interest in and have written about, is the fact that these therapies are still kind of scarce. It’s not like you can just go anywhere and get your CAR T and move on. There’s a process. Each institution gets a certain number of slots and if you want one type of product versus another that might make the waiting time more, so all these things really have to be all taken into consideration.

Lizette Figueroa-Rivera:

Thank you. And to continue speaking about CAR T-cell therapy, Barbara was asking, is it possible to use donor T-cells and do you have similar graft-versus-host and graft-versus-myeloma effect as you do with possibly an allogeneic stem cell transplant?
Dr. Derman:

That is a super good question. And so the answer is, there are studies that have been ongoing, looking at taking other people’s T-cells that are healthy, super active T-cells, and you still have to genetically modify them. You still have to change them so that they can identify the myeloma cells.

Well that’s easy enough because we’re already doing that for patients’ own cells. But the tricky part is what you said about the graft-versus-host disease. So this refers to the T-cells not recognizing the host. So they think that the patient’s cells are evil, are foreign, so they’re going to go and attack your organs and cause significant issues.

So how do you get around this? Well maybe you could do what we do for stem cell transplantation and only take T-cells from patients who are perfect, what we call HLA [human leukocyte antigen] matches, but that’s also problematic because you could still get graft-versus-host disease. So, what companies who are working on this have done is they’re coming up with novel strategies to basically remove the receptors that are responsible for graft-versus-host. But then what happens is you’re modifying these cells so much that you start to worry that whether these are really that healthy and can behave like normal T-cells. And I think that’s been the problem.

So there was a product called ALLO-715 that was published, it definitely works, it’s an active product with allogeneic T-cells, but the duration of response, the durability was just not there. And so I don’t know actually what’s going on as far as the development of that but there are some other products that I’ve been involved in as well that I can’t really speak on, but needless to say there’s a lot of work that needs to be done.

Lizette Figueroa-Rivera:

Yes, thank you. And Jeannie is asking, is there a way to proactively protect your kidneys?

Dr. Derman:

I mean as far as when patients are especially early on, hydration is super important. And this is because myeloma makes these proteins called antibodies and the antibody is a Y-shaped protein and on the end of the Y, at the flanker, are these things called light chains. So some patients with myeloma have a whole intact immunoglobulin with the heavy chain, which is the Y, and then the light chains on either side and we can measure that. Other patients have a high amount of just the light chain that’s produced and those are dangerous because they can clog up the kidneys. And one of the important things is hydration, you want to keep flushing the kidneys, so somewhere around 2 liters of water a day, which as somebody who’s still getting their first cup of coffee from the morning down, I can tell you it’s hard to take 2 liters of water, but you have to do that.

As time goes on, it’s probably a little less important to maintain that level of hydration to be honest with you, but that’s really the main thing.

And patients, you guys are getting your labs checked pretty frequently, so we know when there’s insults to the kidneys. I mean, if I got the flu and you checked my kidney function, you’d probably find that it was low during that time and then it recovered. That’s the way humans are; amazing regenerative capacity to improve.

But, I don’t know, I think that’s kind of how I see it.

Lizette Figueroa-Rivera:

Thank you. And Paula is asking, is it true that the time of being in remission lessens with each subsequent treatment?
Dr. Derman:

Well, I would say that was true. Meaning typically yes, each successive treatment that we give usually gives a shorter response. But now with CAR T therapies and bispecific antibodies I showed you that CAR T therapy, one product is 13 months, another one gives 35 months potentially before the disease comes back, that’s significant change from this 4½ months or something that we might expect from a treatment in that setting. So, I think that’s really important.

Bispecific antibodies are the same way. As they move further up, we want to use our most effective therapies earlier, that’s just how we like to do things. Maybe that will be true again, that the later line treatments are going to work less well, but right now we’re sort of in this strange period where all these immunotherapies can only be used later, but they’re extremely effective.

Lizette Figueroa-Rivera:

Right, thank you. And Susan is asking, what can be used for bone strength after 2 years of Zometa® infusions?

Dr. Derman:

Bones are affected by myeloma and it’s a little different than other cancers because the myeloma cells secrete other messengers that basically tell the bones to leach out calcium and this is what causes a lot of the time these bone lesions or lytic lesions as we say. So this makes patients at risk for fractures.

One of the things that you can use are 2 different classes of drugs, one called bisphosphonates and the other one is called denosumab, or should I say RANK [receptor activator of nuclear factor kappa-B] ligand inhibitors.

Bisphosphonates basically deposits this special type of mineral in the bone that makes it impossible to leach out, so it helps to prevent further resorption of the bone, further wearing down of the bone. It can, with time, help to strengthen the bone as does treatment in and of itself. Denosumab or this RANK ligand inhibitor actually works to protect and block the signals that tell the osteoclasts to leach bone away. So those are the 2 ways that they work.

They’re helpful. I mean they’ve shown in clinical trials to prevent fractures or reduce the risk of fractures. There was a study that was just recently done looking at 2 versus 4 years of the drug called zoledronic acid and they found that there were fewer skeletal-related events, in other words fractures, with 4 years.

But what I don’t know from that study is, what was the disease status of all the patients in that study? To me a patient who has really good disease control does not need to be on long-term bisphosphonate therapy or anti-resorptive therapy for their bones, in my opinion. And I don’t do that typically. I might be in the minority but I don’t think I am. I don’t look at it as a fixed duration. I mean 2 years is kind of the thing that we think about but I am less aggressive with those treatments because they do have some side effects and people often need dental work and it interferes with that sometimes. So I guess what I’m saying is there might be a reason why you would want to extend therapy beyond 2 years if the disease is not controlled and somebody has a history of bone disease, but otherwise I tend to sort of limit the amount of treatment that they get for that.

Lizette Figueroa-Rivera:

Thank you. And Cynthia is asking, if someone was looking for a new opinion with a new team of people, where would you recommend someone start? Is finding a myeloma specialist best and then allowing them to help build the team?
Dr. Derman:

Yeah, I’m biased, right? This is what I do, I live and breathe myeloma and I find it probably bewildering for general oncologists to be able to stay on top of all the latest evidence. But at the same time, for patients, they don’t want to wait for lab work to be done and to see me and to pay for the parking, and I recognize that the patient experience is not always amazing at academic centers 100% of the time.

So, my recommendation is, in general, I still think it’s great to have a person, a myeloma specialist who’s in your corner to be able to look over your treatment plan and say, yeah, this sounds great, or I would change this, or to say, hey, maybe this is the time for transplant or CAR T, and now you have access to that person. Because sometimes when the urgency is there to do something different when things are not going well, you want to be able to have that relationship with somebody to be able to get in. And sometimes as a new patient it can be hard. I mean sure, a lot of you have experienced that where it takes a long time to get in to see somebody.

So for instance with CAR T therapy, I much prefer to see patients where maybe they’re on their 4th line of therapy and they just started, but they haven’t progressed and I can talk to them about all the latest and greatest in CAR T, but say we’re not there yet for you but here’s what we need to do when the disease starts to progress. And that way everyone’s prepared, everyone knows what their role is going to be as time goes on.

And as far as building the team around you, I’m blessed, I work with wonderful advanced practice providers and PAs [physician assistants] who have been doing this for 7, 8 years, longer than I have in some cases, and know myeloma as well as I do, I would think. And so, that’s part of the team. And then, any other providers, radiation oncologists or surgeons or whatever, we have those connections, we know those people who are the go-to people for these things.

Lizette Figueroa-Rivera:

Thank you and I think that’s really important to know. And thank you Cynthia for your question, which was our final question today. And special thanks to you, Dr. Derman, for volunteering your time and your expertise with us.
You may also reach out to one of our Clinical Trial Nurse Navigators in our Clinical Trial Support Center by visiting LLS.org/Navigation or call an Information Specialist.

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**Slide 57: LLS EDUCATION & SUPPORT RESOURCES**

- **Online Chats**
  - Online Chats are free, live sessions, moderated by oncology social workers. To register for one of the chats below, or for more information, please visit [www.LLS.org/Chat](http://www.LLS.org/Chat)

- **Education Videos**
  - View our free education videos on disease, treatment, and survivorship. To view all patient videos, please visit [www.LLS.org/EducationVideos](http://www.LLS.org/EducationVideos)

- **Patient Podcast**
  - The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit [www.TheBloodline.org](http://www.TheBloodline.org)

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**Slide 58: LLS EDUCATION & SUPPORT RESOURCES**

The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancers: [www.LLS.org/Finances](http://www.LLS.org/Finances)

To order free materials: [www.LLS.org/Booklets](http://www.LLS.org/Booklets)

The Leukemia & Lymphoma Society offers financial assistance to help individuals with blood cancer. For more information you can visit our website at LLS.org/Finances, and The Leukemia & Lymphoma Society is also a proud partner with Dollar For, which is a national nonprofit organization that helps patients apply for hospital debt forgiveness and eliminate medical bills. Their services are completely free and you can visit LLS.org/DollarFor, which is Dollar For for more information.
Slide 59: THANK YOU

Again, we would like to acknowledge and thank Genentech, Inc. and Biogen and Janssen Oncology for their support of this program.

Dr. Derman, thank you again for volunteering your time with us today. And on behalf of The Leukemia & Lymphoma Society, thank you all for joining us.

Goodbye and we wish you well.

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