MMRF Patient Webinar Series – *Clinical Studies*

May 5, 2023

Transcript

Mary DeRome (MMRF): Hello and welcome to the Patient Webinar series brought to you by the Multiple Myeloma Research Foundation. I'm Mary DeRome, Senior Director of Medical Communications and Education at the MMRF.

We have with us today two myeloma experts who will be discussing clinical studies and how they benefit patients with multiple myeloma or its precursor conditions such as monoclonal gammopathy of undetermined significance (MGUS) or smoldering multiple myeloma. You will learn about the different types of studies as well as their importance and clinical benefits. Dr. Elizabeth O'Donnell is the director of Early Detection and Prevention at the Dana-Farber Cancer Institute and an associate professor of medicine at Harvard Medical School. She specializes in plasma cell disorders with a particular interest in lifestyle, medicine, and patient and caregiver quality of life. Dr. Andrew Yee is an assistant professor of medicine at Harvard Medical School and is on staff at the Center for Multiple Myeloma at the Massachusetts General Hospital Cancer Center in Boston, Massachusetts. Let's get started with our first speaker, Dr. Yee.

Andrew Yee, MD: Thank you, Mary. And I'd like to thank the MMRF and the industry sponsors for helping to make this patient webinar available. I'm really excited today to talk about clinical studies, because they're an important part of what we do and they're an important part of how we advance the field. I know Dr. O'Donnell will help amplify some of these points as well.

The goal of the clinical trial is to make progress against multiple myeloma. It's really through clinical trials that we develop treatments and strategies that have the power to transform patients' lives, improving the quality of life as well as the length of life.

It's through clinical trials that we develop new therapies and look at ways to combine these therapies. And through clinical trials, we also better understand how multiple myeloma works, how the disease emerges, why patients do well, and areas where we can improve on these treatments.

I think, the more we understand the disease, the better we can develop newer therapies. It's really with clinical trials that the survival of multiple myeloma has really been transformed and nearly doubled in the past several years. We've had so many new drugs that have been approved since 2003, and a lot of these approvals have happened in the past eight years or so.

All these advances develop so rapidly. It's really a very exciting time for us to be able to offer all these therapies for patients. I think about what we can offer a patient now, and it is so much different compared with what we could offer five years ago.

That's really a result of the new drugs that are being studied in these trials, as well as understanding the biology of myeloma better. These are drugs that are probably familiar to patients as well as to caregivers. They include immunomodulatory drugs, proteasome inhibitors, and monoclonal antibodies, which really have served as the backbone of myeloma treatment.

But some of the most exciting developments have been in cellular therapies, such as chimeric antigen receptor (CAR) T cells, as well as therapies like bispecific antibodies, which target B-cell maturation antigen (BCMA). These represent some of the latest advances in the field. With these newer therapies, the survival has really improved significantly over the years. A lot of these advances have really accelerated in the past eight years or so; drugs approved in that time frame are being used right now in the clinic.

So, what are the steps of how we develop a drug? There's one pathway where a researcher is in the laboratory, they identify a target, and then, after bench work, they test it in animals to see if there's activity. And then, based on that, we do clinical trials to assess the efficacy and the safety profile of the drug.

This illustrates a very linear pathway to drug development. But I recognize that sometimes luck plays an important role. And there's an expression: chance favors the prepared mind.

I think about the story behind thalidomide, lenalidomide, pomalidomide, and how several insights led to these drugs being developed into multiple myeloma therapies. It's really been a game changer for multiple myeloma care. So, there are different facets of this process; drugs can be rationally designed, and luck can also play an important role.

But at the end of the day, you need to take an idea and you have to validate it, first in animal models and then in humans. The reality is that there are lots of great ideas, but you really have to see if these treatments work in people. There are a lot of variables that can't fully be accounted for in animal models. So, there's a lot of time and effort that goes into designing clinical studies, which are highly regulated by the FDA and guided by ethical standards.

When we design a study with all those factors in mind, we have to be very thoughtful to maximize patient safety as well as to make sure that when patients go on the study that that we have information that can be useful for current patients and future patients.

Some basic things that we have to think about include how many patients will be in the study, the protocol, and the regimen. There's a lot of thought that goes into all the different steps to make sure that patients are well cared for in the study.

These studies have to pass muster with the FDA, the Institutional Review Board, and the scientific review committee. So, there are multiple steps before an idea gets translated into a clinical trial with patients.

There are several types of clinical trials: phase one, phase two and phase three. The purpose of a phase one study is to make sure that the drug is safe and to establish what dose to use in future studies, because sometimes the phase one study is the first time the drug has been studied in a human. Typically, in a phase one study, they start at a very low dose, and then there's gradual dose escalation while they monitor for side effects and potential toxicities.

This dose escalation is a very methodical process, again, to maximize patient safety. The phase one study is generally how we confirm the safety of the drug. And as part of that, we can start to see some early evidence of therapeutic activity.

A phase two study generally buildings on the findings from the phase one study. After the phase one study, the team generally feels comfortable with the dose to use, so the phase two study usually involves a larger number of patients. The phase two study is designed to ask: does the treatment work? What is the efficacy of this drug in multiple myeloma at this dose?

For example, the study design for teclistamab (Tecvayli), which is an anti-BCMA bispecific antibody that was recently approved at the end of last year. That study evaluated the dosing of teclistamab. Finally, they reached the right dose, and then the drug was studied in a phase two study, which led to its approval.

Dr. O'Donnell led the study of RVD (lenalidomide [Revlimid], bortezomib [Velcade], and dexamethasone) lite. In her phase two study, she studied a modified dosing schedule for older, transplant-ineligible patients. It was with her study that we established the efficacy of RVD at that specific dose. And now, it's established as a standard of practice for transplant-ineligible patients.

In the phase three study, there's usually a randomization component, where patients are randomized to two or more arms, and that's to compare the efficacy of one arm versus another arm. Generally, we have one arm that represents the standard practice, the treatment that you would receive if you were not participating in the clinical trial. And then there's an experimental arm, which is investigating, a newer therapy that hasn't been fully tested yet.

One thing that comes up when people talk about clinical trials is that they wonder if they are going to get a sugar pill. In oncology trials, generally speaking, all the arms have an active component. The agent in the control arm reflects the standard practice, which is what you would be getting if you were not participating in a trial. The other arm is the experimental arm.

I should also mention that sometimes these clinical trials evaluating combinations of drugs that are already FDA approved. And the purpose of these clinical trials is to establish how the combination works. That is, does the combination add to the efficacy of the individual components? A lot of the therapies that we use in multiple myeloma involve these multidrug combinations.

The IKEMA study was a phase three study that compared the validated combination of carfilzomib (Kyprolis) and dexamethasone versus the experimental arm, which included the addition of isatuximab (Sarclisa) to carfilzomib and dexamethasone. This randomized study led to the approval of this three-drug combination of isatuximab, carfilzomib, and dexamethasone.

The DETERMINATION study was a randomized study that looked at autologous stem cell transplant as part of initial therapy versus as a deferred strategy at time of relapse.

In both of these phase three studies, there was a control arm. But in both studies, the control arm was an established standard practice that we would offer as part of routine practice.

One of the major movements forward is looking at actionable alterations in multiple myeloma, to be able to personalize the care of multiple myeloma. That is, to be able to look at the genetic underpinnings of the disease and to be able to say, “We should pick drug combination A versus drug combination B.”

So, the clinical trials that MMRF is taking an active lead in are designed to better validate that strategy. And one of the approaches is the MyDRUG umbrella study, which is looking at patients who have relapsed disease. And then, there's a comprehensive effort to do sequencing, to be able to identify the genetic alterations that are associated with a patient's disease and, based on that genetic alteration, to pick a regimen tailored to that genetic alteration. That's a landmark study that's ongoing.

There's another type of study design called the basket study, where all the patients have the same alteration, for example, a *BRAF* mutation or a high tumor-mutational burden, but they might have different disease types. So, some of the patients in a basket trial may have myeloma, melanoma, lymphoma, or some other disease types. Because a lot of cancers can be defined by the mutation that's driving the disease.

Other types of studies are really important for further rounding out the picture. We have longitudinal studies and registry studies that help to see the long-term outcome of these patients. They gather a group of patients and then follow them long term to see how this disease evolves over time. You need these studies to gather the information in a structured manner to make it as understandable as possible. And then they're expanded access programs where you have treatments that are on the verge of approval. We make it available as part of expanded access so patients can have access while the treatment is working its way through the FDA.

Thank you for giving me a chance to provide an overview of clinical studies. Now I'll turn it over to Mary.

Mary DeRome (MMRF): Thank you, Dr. Yee. That was a great explanation of how clinical trials work. And I think it's really noteworthy, as you mentioned, that myeloma has made a lot of progress in the past few years.

Many, many clinical trials have been done and many, many new therapies have been approved. And that has only been through the volunteering of patients to join clinical studies, which is critically important to advance medicine in every field, but even more critical in myeloma, which has a lot of unmet need.

Now we're going to hear from Dr. Elizabeth O'Donnell on how to participate in a clinical study, what that means, and what the experience is like. Dr. O'Donnell?

Elizabeth O'Donnell, MD: Thank you very much. That was a great talk by Dr. Yee. I want to echo his sentiments that it's a privilege to be here today and to be participating in this discussion.

My part here is to talk a little bit about what it means, as a patient, to be part of a clinical trial and what does that really look like.

The question that a lot of patients ask is, "Aren't clinical trials for people who are running out of options?" You know, clinical trials are actually available in a variety of phases during a disease course. And when we think about myeloma as a disease, we recognize that patients have many lines of therapy over many, many years. And so, specific to multiple myeloma, no, these are not only for patients who are running out of options.

As Dr. Yee pointed out, some studies, like the DETERMINATION study and the RVD lite study, are done in patients who are newly diagnosed. Sometimes, we have trials for patients who've had 2 to 3 lines of therapy. And then there are studies that come later in the game where we're really trying to bring in new therapies where we may not have good options anymore.

I want to give a little personal background. I started my career in medicine over 20 years ago at Dana-Farber as a clinical research coordinator. It was my job to help the patients on studies. I was so inspired by the work that I saw being done and the importance of what was being done, that that's actually what motivated me to become an oncologist and to do clinical trials and clinical research.

These studies are available very broadly and may be available to you in an early stage, middle stage, or late stage. And one of the other things to know is that sometimes the drugs or the treatments that are offered for patients who have resistant disease (disease that's no longer responding to standard therapies) may be novel and may not

be available in other contexts. So, a clinical trial gives you the opportunity to potentially receive something that you may not otherwise be able to receive.

A question patients will often ask is, “If I go on to this clinical study, will I be cured?” Sometimes, participants in clinical trials are the first to receive therapy, so we don't have an answer to how well you will do with any therapy. And honestly, that's true even of our approved therapies. We do these studies so that we have general understandings of how effective therapies are and we can share that with our patients. But really, we can never truly say how well someone, an individual, will do with a different therapy. It's important to understand that when you're using something in a clinical trial, it may or may not be more effective than the standards of care.

When we're doing something like a phase three study, you know that you're getting an effective therapy. Those studies are often done to challenge the norm. For example, you have an approved, excellent therapy, and as in the case that Dr. Yee discussed, you're bringing in a third drug to see if you can make the efficacy of that two-drug combination even stronger.

Also, it's important to note that treatments may have side effects. These are exciting therapies, but you have to understand that, as you're getting a new drug or a new combination of drugs, there may be side effects. And those side effects can be different than the ones that we've experienced in the prior combinations. It's important that when you think about your role in participating in clinical trials, you recognize that not only may you get a benefit from participation, but what you're doing may contribute to other people getting a benefit down the road.

I think myeloma has been so fortunate over the past two decades to see so many new drugs become available. Just as of the last couple of years we now have bispecific T-cell engagers, like teclistamab, and CAR T cells. All of those amazing innovations came out of clinical research and clinical trials.

How does a patient know if they qualify to participate? Clinical trials have specific eligibility criteria. And the eligibility criteria are there for two reasons. One, to make sure that these trials are safe for the patients who are participating. And two, we need to have parameters so that we can use these trials to compare patients.

So, each study has specific requirements for patients to be eligible. That may mean how many lines of therapy they've had or which prior therapies they've had. There are other eligibility criteria that are specific to the participants, things like how well your kidneys are working, where your blood counts are, and so on. Patients may be excluded from clinical trials if they have another type of cancer that's active. And there are certain types of myeloma for which a patient may be excluded from a clinical trial: there's a very small percentage of patients who have something called nonsecretory or oligosecretory myeloma, where we don't have blood protein markers that we can measure to assess response.

So, we are somewhat bound by these eligibility criteria, but each study can have different requirements. So, it's worth going through the process. If you identify a trial, talk to the study team and see if you're eligible.

The financial considerations of participating in a clinical trial are variable, and it's a very important conversation to have with the study team to make sure that this is understood from the get-go. Sometimes drugs are provided at no cost as part of a study. But sometimes, if the drugs are part of a standard-of-care regimen, they will be billed to your insurance.

So, it's very important to ask if the study drugs will be free or billed to your insurance. Also, ask the study team if there are any additional stipends that can be provided. Some studies do include stipends for hotel stays, for travel, or for gas, which might help you mitigate the costs of coming somewhere for a study.

Be sure to ask about that. You can ask the coordinator for details. And many offices have financial counselors as well, just to make sure you're protected. Usually, anything that's standard of care whether you're on a study or not, such as blood labs once a month for myeloma, are an assumed cost that's billed to your insurance. But things that are over and above what is normal are often billed to the study.

Some patients wonder, "Will I be treated like a guinea pig?" The answer is no. The goal of this research is not to use people to try new things. It's to take work that's already been done in a preclinical setting and bring it safely to patients. Participation is always voluntary, and we are heavily monitored, both by codes of ethics and by institutional review boards that thoroughly review any clinical trial before it is activated within an institution, to make sure that it is well thought out and safe for patients. And studies are continually reviewed for safety and efficacy as they progress. There are significant safeguards in place to ensure patient safety and welfare on a clinical trial.

What are some of the benefits? You will continue to have your normal standard of care in terms of office visits and labs. But one of the things that I always highlight to patients is that a bonus of clinical trial participation is that you get a team. Medicine is a team sport to begin with, but clinical trials have specific roles, including research coordinators and specific nurses, and so participating in a clinical trial does give you a few more eyes on your care and a few more people to talk to when you have questions. Sometimes, I would say, being on a clinical trial is even a higher standard of care, just because of the amount of extra involvement you have. I think this is a critical point.

And I say to all of my patients that deciding to go on a clinical trial is always voluntary. We have standard-of-care drugs that can be offered, so you're never obligated to do a clinical trial. I will speak on behalf of my colleagues. Our number one priority is your welfare, your safety, and also your happiness. So, you're never obligated to do a clinical trial for your doctor. If you are on a clinical trial and you find that it's not working for you, it's okay to come off. That's okay. And that is part of the informed consent process, which allows you that freedom to choose.

The other question that could come up is, “What happens if it’s not working? Do I have to stay on the trial?” And the answer is no. In fact, most clinical trials are built just like any other therapy is, to assess your response and to make sure that if it's not working or if you have progressive disease, you come off and move on to your next therapy. You will not remain on a clinical trial if it's found to be not effective, and you will always be in charge of what goes into your body. You will always have the right to discontinue participation, and it will not impact your relationship with the team.

Like I said, we're all people who love what we do and really want what's best for you. Please, always know that.

If you're interested in clinical trials, the MMRF offers a phone number for their Patient Navigation Center. Many patients that I've spoken with have used it. It's an excellent resource. If you're looking for clinical trials, you can also visit the website and look at their clinical trial finder. You could also ask your own hematologist or oncologist about available trials. And there are also web pages available. Clinicaltrials.gov is a resource where you can see what might be feasible based on location, and you can also check with academic medical centers that are close to home.

You do need to be aware of the logistical considerations of a clinical trial. When you're treated locally or off a clinical trial, we sometimes have a little more latitude. The rules of clinical trials can be a little more strict in terms of when and where you have to be treated. So, as you think about reaching out for a clinical trial, make sure to consider whether that will be feasible for you. Talk to your doctor about eligibility. If you are thinking of going to an academic center or traveling for the clinical trial, it is probably best to talk to your hometown local oncologist first, just to understand if this is going to be the right study for you and whether it will be feasible.

Very often, patients will call in and we can have our research nurses or one of our study team members talk to you over the phone before you make the commitment to travel, to just see if what you're interested in you would actually be eligible for.

Part of the clinical trial is informed consent. We usually like to give the patients a consent form to review in detail. We don't sign on the same day. We want you to read through it. Come back with your questions. Answer those questions before we sign.

There are some questions that you should bring. Ask about how the study team works and how often you'll see the doctor or have to come to the cancer center. As I mentioned, clinical trials can have a more rigorous visit schedule. Sometimes, there can be additional visits for testing drug levels in your blood, over and above your treatment days. Just make sure that those are visits that you are able to realistically go to, as you think about embarking on this.

You should ask whether you will need to undergo additional tests. There may be additional imaging, bone marrow biopsies, and lab tests. Be sure to ask about those.

Typically, the informed consent form includes the schedule of assessments and goes over the risks and benefits of those, as well.

You can ask what is currently known about the new drug or drug combination. Some clinical trials are for drugs that are already FDA approved, and we're just combining them. So, we often know a lot about the drugs, but we may not know the side effects when they are given together. And then, there are new drugs where we have preclinical data, data from experiments in cell lines and before they're actually first used in humans. Sometimes we start with lower doses so that we can learn about the safety profile to make sure we keep patients safe.

Ask what side effects to expect and what to do if there are side effects. We want to make sure you know whom to call and what your resources are, should there be any issues. Always check about vitamins or other medications. That's a standard part of clinical trials. It is important to bring up vitamins, because as we're evaluating new medications, vitamins are not always processed the same way, or we may not know as much about them as other FDA-approved drugs. So, make sure your study team is aware that you're taking them. They may ask you to stop taking those when you start a clinical trial.

You can ask if you can get treatment with your local doctor. I never say never, but typically, with clinical trials, because of the data collection and because of needing to follow the protocol recipe to ensure that the results can be analyzed, they often have to be done at the center that's running the trial.

Sometimes, centers have multiple sites, a main location and a satellite site that's in the community. So, sometimes there are community practices that can offer clinical trials. But do inquire about that, because very often these visits do have to be done where the clinical trial is being held.

And we already talked about it, but make sure to ask about insurance: how much will be covered and what will be covered.

To summarize, I think there's been nothing but incredible development in multiple myeloma, where survival rates have nearly doubled, and we expect to continue to see progress.

One thing that wasn't brought up today that I think is worth explaining is that when we have new therapies, the way they start is, just as Dr. Yee explained, first we find the dose and we expand the safety and then they have to slowly work their way forward. So, when new drugs are used, we have to make sure that they're safe and effective before we use them to replace drugs that we already know are effective, and then they have to be challenged head-to-head to prove their superiority.

This can take years. But we have these incredible therapies, and they are in development. And the future is so bright for myeloma as they move their way forward.

We've had so many drug approvals in the last two decades, and it is because of patients' participation in clinical trials and because of physicians and nurses and clinical coordinators who believe in this kind of work that we're here where we are.

It's a team effort. Clinical trials are available for all stages of myeloma. Inquire, no matter what stage you're at, whether you're newly diagnosed, or in your second or third line of therapy, or maybe looking for novel therapies. No one is expected to be a guinea pig. Our research and clinical trials are under very tight supervision and are held to very high standards and the most important thing, always, is open and clear communication between the physician, the team, and the patient.

We want to hear from you. We care about you. And this is truly a partnership. It's been a tremendous privilege and pleasure to be here to talk about something that I'm very passionate about. I know Dr. Yee is, too. So, thank you for your attention and we will be happy to take any further questions.

Mary DeRome (MMRF): Thank you so much, Doctor O'Donnell. That was a great presentation. Now we're going to have Dr. O'Donnell and Dr. Yee answer questions that have been submitted. And you can call the Patient Navigation Center at the MMRF to provide answers to questions that do not get answered today.

Dr. O'Donnell and Dr. Yee, we have a lot of questions from patients about trials for patients with precursor conditions, mostly smoldering myeloma. I know that this is a bit of a controversial topic right now in multiple myeloma, to treat or not to treat patients who have precursor conditions. I know this is a tough question to start with, but I think that, because we have so many questions, we should probably start there.

Here's a question from a patient: "I am newly diagnosed, have high-risk smoldering myeloma, and have received conflicting suggestions from three different medical centers regarding clinical trial versus observation as the best choice for me." We all know that the more people you ask, the more answers you're going to get right, especially in the field of myeloma. So, when is a clinical trial the best option for a patient with high-risk smoldering myeloma? Dr. O'Donnell, I'm going to start with you.

Elizabeth O'Donnell, MD: I would say that a clinical trial is always the best option for treatment of high-risk smoldering myeloma, because we're still learning. When we think about the recommendation for whether to treat high-risk smoldering myeloma or not, I think the one thing that we can all agree on, and Dr. Yee, feel free to disagree with me, is that the way to treat this is in the context of a clinical trial so that we can really start to understand who needs to be treated, if they need to be treated, and really try to get at this fundamental question of whether or not we should or should not be treating smoldering myeloma. Dr. Yee?

Andrew Yee, MD: Yes, I was going to echo exactly the same thing. I think the reason this patient's been getting three different answers is because it really is one of the least understood areas in the field. If we knew what the right answer was, everyone would

have said the same thing. And I completely agree with Dr. O'Donnell; for high-risk disease, I think the clinical trial is the best way to gain access to treatment.

Mary DeRome (MMRF): Okay. And we also had a patient ask about trials for patients who have MGUS. Dr. Yee, are there any of those in in the works or ongoing right now?

Andrew Yee, MD: I think there are some studies. The conversation here is an extension of the smoldering myeloma discussion. But for patients with MGUS, I think the risk of progression is even lower. The studies of MGUS include an observational study in Iceland. But in terms of treatment studies, that is something that is being looked into. I think if anybody's going to have the answer to that question, it would be Dr. O'Donnell.

Elizabeth O'Donnell, MD: I think, yes, there are studies being designed in high-risk MGUS and some of the lower-risk MGUS. Right now, most of the clinical trials for smoldering myeloma are in the high-risk population. But I do think there's an interest in potentially treating high-risk MGUS and low- and intermediate-risk smoldering myeloma.

There are some important distinctions here. There are some that would argue that MGUS and smoldering myeloma are really a continuous spectrum. And I think there's some truth to that. A lot of the research, not just in clinical trials, but also biological research, is trying to understand if we can better predict who is at risk of progression, because the reality in MGUS and smoldering myeloma is that not everybody will progress and not everybody will require therapy in their lifetime. So, there are opportunities within the MMRF and within different studies to gather bone marrow and blood specimens to try to better characterize these conditions and follow people longitudinally.

Not every clinical trial is therapeutic, though there are some therapeutic trials being designed. The other thing that we haven't touched on is that there is a world of clinical trials beyond drugs themselves. For people who have MGUS and smoldering myeloma, this is a great area in which to investigate lifestyle interventions. For example, there was a recent study of a vegetarian diet intervention in precursor disease. I think there are a lot more of these studies coming our way that not only assess if there are nonpharmacologic interventions, but also, when you do these interventions, do they have any effect or modify the disease at all?

It's a very exciting area of study right now, and it really speaks to how much progress we've made in myeloma that we're now moving the question forward to these earlier precursors. Now that we have better biological understanding and better therapies, we can start to ask the question of, if we do these treatments earlier, can we even get better results?

Mary DeRome (MMRF): That was really interesting. I saw that study about diet in precursor conditions and in multiple myeloma in general. There were some interesting data there.

A couple of people asked about different scenarios regarding financial concerns in clinical trials. For example, what happens if you need extra care because of side effects? Will the study pay for that? And if not, does insurance normally pay for this extra care? Dr. Yee?

Andrew Yee, MD: I think, generally, the insurance will cover the standard-of-care aspects of the clinical trial, and that would include taking care of the side effects or, if you had some complication from the treatment, it would, generally, cover that. I don't think there necessarily be a separate carve-out that a patient would be on the hook for.

In my experience, I really haven't had a situation where, for whatever reason, a patient had a problem and then the insurance company didn't cover that. I just haven't really encountered that. And I think Dr. O'Donnell probably feels the same, right?

Elizabeth O'Donnell, MD: Yes, I haven't either.

Mary DeRome (MMRF): Okay, great. Here's a question from a patient who's relapsed and heavily pretreated. The question is, "How do you line up participation in a trial before you need it?" When current treatment is working, the doctor does not usually consider trials. And when it stops working, we need to do something quickly, and a study is often not an option, based on the prework that has to be done or the inclusion and exclusion criteria.

What is the best way to think about lining up a new treatment like in the clinical trial for a patient who is sort of in this situation? Dr. O'Donnell, can you comment on that?

Elizabeth O'Donnell, MD: I often say that myeloma is like a chess match, where you have a certain number of pieces, and you have to think about how you're going to play them. Whenever I'm planning a line of therapy, I'm also planning the line after that. So, you can talk to your doctor and ask them what comes next.

When it comes to clinical trials I think there is a certain strategy, because you have to be thinking steps ahead. If you're not at an academic center, when you are refractory and you know that you have a limited number of effective combinations that you're aware of, that's the time to go to an academic center. If you're not already at one, have a consultation, see what the clinical trials options are, and stay in contact with that academic center so that they're aware of you.

Dr. Yee and I were both very involved in CAR T-cell therapy and getting to the point where we had approved therapies. That's a great example; we kept a list, and slots were limited. Patients put their names in, and, as slots became available, we were able to get them into the trial. Reaching out, seeing what's available, and keeping in contact can be very helpful so that if and when you do need that next line of therapy, it's ready to go.

Mary DeRome (MMRF): Great. That's good to know. Thank you. Here's something that we haven't heard about much. We have a patient who was in a clinical trial for a customized vaccine. They're asking if you have any comments on customized vaccine therapy.

Andrew Yee, MD: Not specifically. I know that's the next frontier, using vaccines to stimulate the immune system to treat myeloma or precursor states. Dr. O'Donnell and I have been involved in a vaccine-based trial for smoldering multiple myeloma. I think participating in a trial like that is great. I think if one is available and it's for your particular stage, it's great. I'm fully supportive of that.

I just want to emphasize again that the way we get these new therapies really involves the participation of patients. I do recognize that sometimes it is a lot to ask of a patient. You have to travel to a site to participate in a trial. And there's a time component, too. It's something that we don't take for granted. We definitely appreciate that.

Elizabeth O'Donnell, MD: I agree with Dr. Yee on that. And I think it's a really interesting area of study, particularly in the area of precursor disease.

Mary DeRome (MMRF): A patient has asked, "What is your opinion of iberdomide as an option for high-risk smoldering patients?" Do you have any comments on that, Dr. O'Donnell?

Elizabeth O'Donnell, MD: It's a drug that we're very excited about, but it's something that has to be studied. It's hard to say, in the absence of data.

Andrew Yee, MD: One thing to add is that we want patients to feel enthusiastic about participating in a clinical trial. We want them to be invested. I think that when patients are enthusiastic about participating, everything just goes a lot more smoothly.

These questions do come up a lot. We want something that patients feel comfortable with. We want patients to be informed, excited, and enthusiastic about participating.

Mary DeRome (MMRF): The next question is, "How can a patient join a clinical trial?" I would imagine this is the scenario where the patient is going to a doctor who has not mentioned the possibility of clinical trial yet. I think that this comes back to communication with your care team. Dr. Yee, would you agree with that? And, how would you counsel this patient if they came to you for a second opinion?

Andrew Yee, MD: I completely agree. Communication is 100% important here. And I think it's always appropriate to ask the team about the clinical trial options. That is, to ask if a clinical trial is something they would consider here. And I think it's always fine for patients, on their own, to seek out a physician who is involved with clinical trials, because I think if a physician doesn't mention clinical trials, it might be because they're not participating in a clinical trial.

Whenever I see a patient, I try to make a distinction between what we can do as part of a clinical trial and what we can do as standard practice. But I think asking your team is always appropriate. I think, as practitioners, we expect patients to ask these questions. We get asked those questions all the time. It's really very routine for a patient to ask a question or for a caregiver to ask a question.

Mary DeRome (MMRF): All right. This isn't exactly a question about clinical trials, but it's an interesting question. The patient asks, can you please ask the panelists what a CD34 reading of 2.93 from Harvest means. The ideal target, I gather, is five. Initial chemotherapy is finished, and I am waiting for first transplant. Maybe a clinical trial would be a better option than an initial transplant?"

Andrew Yee, MD: I think the 2.93 value is referring to the number of stem cells collected. I'm not a bone marrow transplant doctor. I think the goal is to collect approximately 2 or 3 million, and I think that the decision about the transplant would be based on whether they feel that the collection was adequate. Sometimes they try to collect more. Sometimes we try to collect enough for two stem cell transplants.

I think that question would be a good one for your treating team. In terms of whether or not a trial would be appropriate here, I think that that gets a little complicated, because when we talk about clinical trials for patients, we tend to divide them into different groups. And one group of trials would be for newly diagnosed patients, patients who haven't had any treatment. And then we have trials for if the initial treatment doesn't work anymore, a time of relapse.

But there are emerging trials that are looking at patients who don't achieve the best possible response after initial therapy. But at this time, if the treatment that you're on is working, the decision about whether or not to proceed with the stem cells is not necessarily a trial-related question.

Mary DeRome (MMRF): Dr. O'Donnell, if a patient withdraws from a study due to life events, or for whatever reason, will there potentially be animosity or a negative atmosphere with their provider? Could the provider see the patient's withdrawal as unethical and a lack of commitment and that they shouldn't have joined the trial in the first place?

Elizabeth O'Donnell, MD: No. You know, it depends on the duration of the study, too. Sometimes, studies go on for many, many years. That's a good outcome, in fact, when patients continue to derive response. Obviously, we would prefer that patients stay on, for the integrity of the data, but it is not held against you.

You know, life happens. Maybe you weren't working at the time because you were sick from your myeloma. And now you're well enough and you want to go back to work. It's going to impact things. There are a lot of good reasons why sometimes patients need to come off clinical trials.

I would say that if it's not going to be feasible or you don't think it's going to be the right thing for you, probably don't embark on it. But again, there are a lot of reasons why patients have to come off of trials. And at the end of the day, oncologists are generally nice people, and we just want what's best for our patients.

Mary DeRome (MMRF): Here's an interesting question: is there a source where a patient can get a status report on a trial? I know that if you go on clinicaltrials.gov, you can sometimes see the status of a trial, depending on whether or not they've reported some results. But if you were on a trial or if you wanted to go on a trial and you wanted to find out more about that trial, where would you get that information?

Andrew Yee, MD: I think this might be where the MMRF comes into play. The trial navigator would be a good resource. And then, clinicaltrials.gov provides information about the status of trials, but in terms of where the trial is, how many patients they've accrued, or preliminary results, that information not necessarily on clinicaltrials.gov. Sometimes you have to Google, sometimes you might have interim trial results that are presented at clinical oncology meetings (for example, the American Society of Hematology meeting or the International Myeloma Society meeting). And if you're on a trial, you also should ask the team taking care of you, who would have the more granular information about the status of the study.

Mary DeRome (MMRF): Okay. Dr. Yee, you mentioned this during your part of the presentation about receiving a sugar pill or a placebo during the course of a clinical trial. In general, as you did mention, that is not done, because it is not ethical to not treat patients who have cancer. Can you expand upon that a little?

Andrew Yee, MD: Sure. Generally, for oncology trials, because patients have a disease that needs to be treated, there isn't a treatment that would be a placebo. Now, having said that, when we do these trials, we try to be completely transparent about what the patient is receiving. So, if you're on arm A, you're getting the treatment that's assigned to arm A. It might be a situation where it's treatment A versus treatment A plus X, and it's possible that X could be a placebo. In that situation, all the patients are getting treatment A, and X could be an additional active drug or it could be a placebo.

I should provide some additional clarification. I'm thinking about maintenance therapies after autologous stem cell transplant. So, there was a point in time, years ago, where lenalidomide wasn't available. So, in some of the studies that looked at maintenance therapy after transplant, patients were randomized to lenalidomide versus standard of care, which was observation. And that observation could take the form of a sugar pill, but that would have been the standard practice at that time.

Mary DeRome (MMRF): So, basically, when you're in a trial, for the most part, especially in a phase three trial, the experimental treatment is being compared to the standard of care.

Andrew Yee, MD: Right. Exactly.

Mary DeRome (MMRF): That's basically what the phase three trials are. And in general, the trial treatment has to work better than the standard of care in order to achieve approval in a phase three trial.

Andrew Yee, MD: Absolutely.

Mary DeRome (MMRF): Dr. O'Donnell, just one last question for you. Would general oncologists who treat myeloma patients get offended by a clinical trial initiated by the patient?

Elizabeth O'Donnell, MD: Not at all. I can't speak for everybody, but my hat goes off to general oncologists. It is so hard to do everything so well. But I think anybody recognizes that there's only so much in the standard-of-care armamentarium. A good doctor always wants what's best for their patient. And I do not think patients should worry about their provider's feelings when it comes to these types of questions. Go for the clinical trial if it's appropriate.

Mary DeRome (MMRF): Again, I totally agree. And it comes down to the importance of communication between the patient and their doctor. If you're not getting satisfaction, with respect to communication, from the care team that you're currently seeing, then it might be time to seek out someone else that you feel comfortable with.

Andrew Yee, MD: Yes. We want patients to be happy with their care.

Elizabeth O'Donnell, MD: That's 100% right.

Mary DeRome (MMRF): Okay, that is all the time that we have today for questions. I'd like very much to thank Dr. Elizabeth O'Donnell and Dr. Andrew Yee for their time and also for their contributions to this presentation.