Demystifying Clinical Trials:

What You Need to Know

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Jessica Jablon: Welcome everyone. Thank you so much for joining today's webinar, Demystifying Clinical Trials: What You Need to Know with Dr. Richard Finn. I'm Jessica Jablon. I'm the director of the West Region of Sharsheret.

We want to begin by thanking our sponsors, Eisai, Gilead Oncology, and Lilly, who have made today's webinar possible. A few housekeeping items to start us off. Today's webinar is being recorded and will be posted on Sharsheret's website along with a transcript. Participants' faces and names will not be in the recording. If you would like to remain private, you have the option to turn off your video and rename yourself or you can call into the webinar. We also have closed captioning available, so to display live captions on the bottom bar, click on captions and then click on, "Show captions."

You may have noticed that you were muted upon entering the Zoom. Please stay muted during the call. We will hold a Q&A at the end of the presentation. If you have any questions, please type them into the chat box and we will get to as many as we can during the Q&A.

I want to remind you that Sharsheret is a not for-profit cancer support and education organization and does not provide any medical advice or perform any medical procedures. Our full medical disclosure is being put into the chat. And as you know, Sharsheret is constantly offering webinars on a variety of topics. You can find our upcoming webinars and the link to our library of past webinars in the chat. Our next series of yoga webinars started today. You can join Sharsheret next Thursday, December 11th to relax and feel rejuvenated through movement during our tranquil Thursdays. And the registration link for that is also in the chat.

If you're facing a breast or ovarian cancer diagnosis, you don't have to face it alone. Sharsheret is here for you and your loved ones. Sharsheret provides emotional support, mental health counseling, and other programs designed to help navigate you through the cancer experience. All are completely free and confidential. And our contact information is going into the chat now.

Now, before we welcome Dr. Finn, I would like to introduce Gail, who will be sharing her personal story today.

Gail: Thank you. And I am joining this meeting from Columbus, Ohio, where I'm a patient at the James Cancer Hospital and Research Institute at Ohio State. My experience with the clinical trial may not be similar to what you have heard or experienced yourself, but I will just tell you what I have experienced in the last few months.

To give you a little bit of background, I was diagnosed with Stage 4 ovarian cancer in August of 2021. At that point, I didn't know if I was going to be seeing the end of the year, but here I am three and a half years later and I'm doing quite well. At that time of my diagnosis, I was told that the type of ovarian

cancer I had, that there was a high rate of recurrence so that the goal was not to expect to be cancer-free after treatment. The goal was to keep the tumors quiet and keep them at bay. And so, that's the fight that we've been fighting for the past couple of years.

I've had some recurrences. The most recent one was in August of this year. And at that point, my doctor told me that I did qualify for a clinical trial. One of the first things I asked was, "Do I keep my hair?" Because I was so tired of not having any hair. And she said yes, that I could keep my hair with this new drug that they were testing. And so, selfishly, I suppose that was one of the reasons I joined.

The other reason I joined was that I felt that, if I was going to be on this cancer journey, I wanted something good to come out of it. I wanted something to the greater good to come out of it. It was really important to me, and I felt very fulfilled in terms of contributing to the research and hopefully a new treatment or hopefully finding a cure for the disease.

So as I said, this has been my experience.

The first thing that I had to go through was to qualify for the clinical trial. And this was a battery of tests. It included blood work, EKGs, interestingly enough, an eye exam, a physical exam. Everything was very specific, very detailed, and the parameters were very strict to ensure the integrity of the research. I had to sign two different contracts. One was 21 pages, one was 12 pages long. Fortunately, it was pretty easy reading, but what that did was detail my responsibilities, the company's responsibilities, and what the research was. It also talked about information about the drug, side effects, and also included reasons that the trial could end. And that was, first of all, number one, if I wanted to leave the trial. Secondly, if the drug was found that it was not working for me. And lastly, if my doctor decided it was in my best interest that I leave the trial.

So, once I was accepted, that took a few days, probably about a week or so. I had a team assigned to me and they included three medical personnel. The first one was the day-to-day contact person who did all the scheduling. There were so many follow-up tests and phone calls and, "How are you feeling?" And just a lot of calendars to maintain. Secondly, there was a nurse practitioner that I saw every three weeks before I had an infusion. And she answered any medical issues that I had. And then lastly, there was the overall research study doctor who oversaw my experience.

So, on August 11th of this year, I started, knowing that the infusion days were going to be quite long. And then the days immediately following the infusion were really filled with follow-ups, follow-up blood work, EKGs, and everything. All blood work, all EKGs, everything was immediately sent to the company, Eli Lilly, for their research.

So, the infusion day itself would start with a visit to the nurse practitioner who looked at the most recent blood work and would clear me for the infusion. Then I would go to an area where the infusion itself would take place. It would be four to five hours. And then they asked me to stay for six hours for observation. It was quite a long day, but I will say again, that there was so much support staff, so much support in general. You could have visitors. It was a private room. There was food, television. I was laughing. It was like a spa day just going for this. And again, felt very supported all the way through it.

And then, what would follow is the day after the day after that, the day after, probably about four or five days after that, I would have to go back for follow-up blood work and EKGs mainly. So, I had infusion every three weeks. And after cycle three, which was nine weeks into the study, I had CTs that showed that the drug was working, that the tumors were stable or shrinking. So, the research team was very excited.

The thing that was not so exciting is that I had some side effects that were really getting worse and worse. Fatigue, a lot of fatigue, and I developed some digestive issues, constipation, diarrhea was always a battle. Between the two, I developed some taste changes and that affected appetite. I had experienced some weight loss. And so, after cycle four, I really was left with the decision, do I continue with this test drug that was working and working really well? Or do I take a step back, find out what other options there were? And it became a quality of life issue for me. Do I want to struggle through the side effects that the test drug was causing?

And so, I did talk to, again, a couple of doctors about what options there were if I went back on a more traditional chemo treatment. And the answer was yes, there were options to go that route. So, after meeting with my family and talking about things, I decided to leave the study and I'm at peace with that. The side effects from the study are residing and I've had two treatments now in the more traditional chemo and it's working well. So, I'm really at peace with it.

But it was really nice to hear that the study team that I worked with for the trial was really supportive. And they emphasized that I should not consider the whole experience a failure, that my participation did provide them some really valuable research and research information that they could continue to use. So, for that reason, I'm really glad that I did it. I was told that I might qualify for another one and I'd be happy to do that. But again, I think just for the greater good, it was nice to know even now that I did something that would participate more than just myself.

For now, I am back doing well on the more traditional chemotherapy and continue to look forward and hopefully continue this cancer journey and live my life.

So, that's my story.

Jessica Jablon: Thank you so much, Gail, for sharing your personal experience with us. Your story really shows us that it's possible to maintain a sense of control while participating in a clinical trial and that, while everybody's experience is different, the impact you're making for yourself and for others is truly remarkable. So, thank you and thank you for being here today.

Gail: Of course.

Jessica Jablon: Now I'm going to introduce Dr. Richard Finn.

Dr. Finn is a professor of medicine at the Geffen School of Medicine at UCLA in the Department of Medicine Division of Hematology-Oncology. He was an undergraduate at UCLA where he was involved with early laboratory studies investigating the HER2 oncogene and the development of monoclonal antibodies to this target in breast cancer with Dr. Dennis Slamon. He participated in the preclinical studies that defined the clinical candidate that eventually humanized and became the FDA-approved agent, Herceptin. He went on to medical school at USC, returned to UCLA for his clinical training in internal medicine, and then hematology-oncology. And he currently splits his time between patient care and directing the translational research laboratory in the Division of Hematology-Oncology.

His research interests are focused in the development of targeted therapeutics for solid tumors across histologies to support the larger efforts of the department. His personal interests lying the development of these targeted agents in hepatobiliary and breast cancers. He has two half days dedicated to patient care, one of which is a leader in the multidisciplinary hepatobiliary cancer system program at UCLA where he's involved with clinical studies aimed at bringing novel therapeutics into the treatment of patients with these malignancies. Dr. Finn has also spoken at Sharsheret events in Los Angeles. And he even ran the New York City Marathon as part of Team Sharsheret a couple of years ago.

So very excited to have you here, Dr. Finn. I will turn it over to you.

Dr. Richard Finn: Thank you very much for that very nice introduction and thank you very much to Sharsheret for inviting me and Gail for sharing your story. It's very inspiring for all of us when we see patients because participating in clinical trials is voluntary. And obviously, you do it because you want some benefit for yourself but also for others. And you made that very clear. And no drugs would be around unless people participate in clinical trials.

And I am going to share some slides here and we'll give a short overview on drug development. Can you guys see my slides?

Jessica Jablon: Yes, we can see them. Yes.

Dr. Richard Finn: Okay, great. So, in a lot of topics, introduction is the ABCs of the topic, but in reality, with clinical trials, we're talking about the Phase I, II, and IIIs.

And every drug that is available today goes through clinical development. There's no way around it. If people like Gail did not participate in studies, we would not have any drugs. Clinical trials are done for several reasons, but ultimately for regulatory approval for the FDA or the EMA in Europe or other regulatory agents to say this drug can be sold. And by getting that stamp, we're showing that this drug is effective and safe at what it does.

Now, going backwards though, there is a lot of compounds that industry and now academia produce, whether they're small molecules, whether they're antibodies, or other types of drugs, that all go through a series of testing to get to regulatory approval. And the failure rate is very high, right? You can see on this slide from anywhere from five to 10,000 compounds that start in a chemical laboratory and biology laboratory that then enter preclinical phase where they're trying to optimize the drug for giving it to people, understanding how it's metabolized, how well it interacts with or kills tumor cells versus normal cells, and then goes into clinical development. And we'll talk more about these phases and eventually regulatory approval. Probably at least a decade or more.

And if we go back earlier to what we call here target identification, right? So, chemotherapy in cancer medicine is largely an old way of treating patients. And when I say chemotherapy, I mean systemic chemotherapy, the Taxols, the platinums, the doxorubicins, these types of drugs. Really, they are very toxic, and the art of oncology is giving them safely and making them tolerable but also having them treat cancer.

There's been a lot of understanding from biology over the decades. And now we have been able to identify certain proteins that drive cancer growth or support cancer growth. And this has led to the development of a whole new age of cancer therapy, which are really new targets for treatment. And so, now a lot of our effort is to develop drugs that target specific proteins or genes even or mechanisms. And this has led to small molecules that target various proteins or antibodies, now even immunotherapy.

And there is a lot of risk in drug development inherently because you might have the best target for treatment, develop a great drug to inhibit that, but then you can run into problems anywhere along the way. Maybe the drug isn't well-tolerated; maybe it isn't soluble and it's hard to deliver, can't give it to patients because it doesn't get into their system well; funding issues, a small company developing a drug takes money, and if they run out of money, then something won't move forward. So, there's risk along the way.

And ultimately, the goal is to get the drug approved to show that we are helping people.

So, there are different types of studies. Many of you will either be approached by a doctor to say, "I think a clinical trial is right for you," or you're going to get on the clinicaltrials.gov website and look for a clinical trial. You're going to enter your diagnosis, and many studies will pop up and they're going to be descriptive. They're going to describe the studies.

There are essentially three main phases, Phase I, II, III. There's also something called Phase 0. Phase 0 is even a study where we don't even potentially expect a benefit for patients. This is a study where maybe we'll do a biopsy of a tumor, patients get a drug, and then we get a biopsy sometime later just to see how the body reacts to the drug, how the tumor reacts to the drug. And these are also often incorporated around a surgical procedure. Someone might be planning to have a lumpectomy for a local breast cancer and maybe they'll get a drug for a few weeks while waiting for their surgery. And the doctors will collect blood and a piece of the biopsy and surgical tissue to see what this drug is actually doing to the tumor, a very unique opportunity because usually we only know how drugs work based on laboratory studies or in mice. And this type of study allows us to study a drug actually in people and can very much inform how the best way is to use these drugs.

But in reality, most drugs go through a more traditional Phase I, II, III setting. And Phase I are typically studies taking patients. And it might not necessarily be a specific cancer. Sometimes they're taking various cancers or different subtypes of cancer. It depends really on the molecule being studied. If they know it's going to work in breast cancer, then it might be a Phase I breast cancer focus study or even a HER2+ focus study. It really depends on the mechanism of the drug. And these type of studies are trying to figure out the best way to dose the drug, the safety of a molecule, how frequent to give it, and looking for a signal of some fact that it's working, right?

Remember, every new drug has to go through Phase I testing. And Phase I test studies are not to be automatically classified as, "I have nothing else to do." Sometimes Phase I studies take newly diagnosed patients in the frontline setting. And they might be looking at a combination of a standard drug with a new drug. And as long as someone's getting the standard drug, they can go ahead and give it to patients who are newly diagnosed or in first line need of treatment.

But many times, Phase I studies don't have a lot of track record in the clinic and patients are watched very closely. Often these studies take a lot of time for patients because we're monitoring the blood levels. They might need to come to clinic several days a week or there's a different schedule for everybody for every study. But the idea is really to understand how best to give this drug safely.

So, when a drug graduates from Phase I, typically it goes to Phase II. Sometimes there'll be something called a Phase 1B study and that's built into a Phase I. And

its idea is the same as the Phase II. And that is to establish more data on how well the drug works or the regimen works, and then also to build on safety data.

As we go from Phase I to Phase II to Phase III, the size of studies gets much larger. Typically, a Phase I study can be fairly small, 20 patients, 50 patients in general, enough to get a sense of what the right dose is for the disease that's being studied. As we go to Phase II, we're looking for larger numbers to better understand, will we see activity and more safety data. Still, there can be pharmacodynamic or pharmacokinetic, I use those terms above in the Phase 0 discussion, but these are ways for us to better understand what the drug is doing in people and how it's affecting their organs.

So, as we go from Phase I to Phase II to Phase III, as the studies get bigger, there's more complexity and there's more cost, right? A Phase III study to get a new drug approved typically is at least $100 million, if not more. And in the context of breast cancer, when you think about adjuvant breast cancer, early-stage breast cancer, there was just a press release. And this presentation is very timely because I think next week is the San Antonio Breast Cancer Conference, the largest breast cancer meeting of the year. And there'll be a lot of clinical data there. And recently there was a press release of a new antiestrogen compound from Genentech and Roche in early-stage breast cancer, but it was several thousand patients. And the cost of that type of study is well over $100 million. So, as drugs progress in their lifespan, also the investment becomes greater because by the time you get to Phase III, you are betting a lot that this drug, which started 10 years ago in the laboratory is going to make it to FDA approval.

And we'll talk about some of the endpoints and things like that. But at a high level, this is the goal of these various stages.

Now, again, as you type in and look for clinical trials on the internet or from your doctor, there's several things that we keep in mind on different types of studies.

So, some studies are single arm, and some are randomized. What does that mean? A single arm study means everybody gets the same treatment. And typically Phase II and Phase II studies are single arm. We're evaluating a regimen for safety and efficacy. As we get more advanced, Phase II where we're looking for regulatory approval, these by and large have to be randomized where you're taking a standard and comparing it to something new. And that means some patients will get Treatment A, some will get Treatment B. As compared with single arm, everybody's getting the same treatment.

And then there's single center versus multi-center. If you're at an academic institution, there might be a study that's only available at your site. These are often studies that are developed by the institution itself and may or may not have pharmaceutical industry support, but because of the size of the study and the budget to pay for this study, it will only be done at your center. This is

versus multicenter studies. Multi-center studies occur at all phases, Phase I, II, III. Multi-center studies are more complex because patients are being treated at various sites and you need to coordinate and collect all the data and investigators need to be able to talk to each other to know if someone's having a side effect at Institution A. Maybe I need to be aware about that, be aware of that at my institution. And often larger studies are multi-center because you need more patients and sometimes relying on one center to provide a hundred patients can be difficult.

And then there's open label versus blinded. So, an open label study means everybody knows what you're getting. The investigator knows, the patient knows, the sponsor knows. And typically, Phase I and Phase II studies are open label. Even some Phase III studies are open label. If you're comparing an IV treatment, an intravenous treatment, versus an oral treatment, that's hard to blind because some people are getting something in their vein and some people are getting a pill. So, even Phase III studies might be open label.

Blinded means no one knows what you're getting except for a database housed somewhere where the data is stored. Blinded studies are the highest level of evidence because there's no bias. There can be no bias because no one knows what you're getting. When things are open label, single-center, single-arm, there's a lot of unawareness bias. If I know you're getting a drug that I think works, my interpretation of things might be a little different than if I didn't know. That's a fact. And the way we try to overcome that is to use blinded studies, randomized studies.

And some studies are placebo-controlled, and some are not.

Now, I hear from patients, I don't want to be a guinea pig when they hear clinical research from the beginning. But research is very highly regulated and every drug we have goes through clinical development. And patients are not treated and they should not be. And I think the regulatory structure is set up. And those of us in clinical research and clinical medicine view clinical research and clinical trials as often the best option for patients because you get access to something that's new, something that's promising. And we would not do a placebo-controlled study if it was not ethical.

So, we might have a new drug that we're adding to hormone therapy. And the only way we'll know that combination is really better is if we compare that combination to hormone therapy alone. And when we do those studies, we might have a placebo pill for that new treatment. So, everybody gets standard treatment. Everybody's going to get hormone therapy. Some will get the new drug; some will just get a sugar pill. Now, that's not being a guinea pig because everybody's getting standard treatment and we can't tell you that the new treatment is better than the standard treatment until we do this experiment.

Clinical trials are experiments, just like in the lab, except we're in the clinic. And to get good data, you need to design a good clinical trial. And just because a

placebo is involved, it should not be interpreted as a negative because typically in placebo studies, everybody gets some standard treatment. It's whether or not the new treatment helps.

So, how do we interpret clinical trials? There's something called the endpoint. The primary endpoint is what we're trying to determine from the research. Then there's what's called secondary endpoints, which are things that we're also trying to learn from the clinical study. So, in clinical research, the ultimate thing we want to do is to improve clinical benefit, make patients better. And the gold standard is really to help people live longer.

But there are also some endpoints in certain situations that are also very important and can inform how a drug is helping people. One is something called the objective response rate. Patients see their doctor and you want to know, am I responding? How do we know that? Typically, it's by imaging, a CT scan, an MRI done at certain frequency, all of that usually dictated in the context of a clinical trial. And a tumor might be shrinking on a CT scan, but that does not necessarily mean they have an objective response.

And I don't want to get too nuanced here, but there are certain criteria that we use in trials. In order for someone to be considered a responder, their tumor has to shrink 30% from baseline. So, your tumor might shrink 28%, which is great, but by a clinical trial criteria, you'd be considered to have stable disease. So, when you read a press release or a clinical trial report and it says the objective response rate is 30%, that means 30% of patients had their tumors shrink by more than 30%. But you can still get a clinical benefit if your tumor doesn't grow, if it shrinks a little bit. And progression is defined as an increase of 20%. These are somewhat arbitrary, but those are the rules in clinical research.

Another common endpoint we use is something called progression-free survival. Progression-free survival is the time from when you start treatment until you progress, progression by the objective response rate or if someone were to pass during the course of the study. And PFS is used very frequently in breast cancer trials often as a primary endpoint. And the reason for that, if we look at hormone-positive breast cancer or even HER2+ breast cancer, women with this disease can live fortunately several years. Median survival for advanced disease is now five or six years. So, if a clinical trial's only goal was to improve overall survival, it would take five years to get a readout or even longer. So, sometimes we use progression-free survival as a surrogate for overall survival, meaning PFS patients progress and go on to other treatments but progression-free survival is sometimes a primary endpoint.

Time to progression, also something based on radiology, how long it takes from when you start the drug until it starts to grow. It's just based on radiology and not on how patients feel or their clinical course, unlike PFS.

Toxicity, very important. You might have the best drug for a disease, but if it makes the patients feel so sick and horrible, it's going to be hard to make that a

useful tool for us. Toxicity, often we evaluate as something called adverse events. You'll see that term in clinical research material. And we grade that anywhere from Grade 1 to 5. Grade 1 is typically minor. Grade 5 is very serious and can lead to death and then things in between. And that's how we score side effects for patients.

And very important is measuring quality of life. That is often a secondary endpoint. And again, this is often measured by surveys. Patients are now given like an iPad and at every visit they'll answer questions about how they feel, their symptoms. And there are validated assays to measure patient's quality of life. This is an area that now is maybe being assessed. Some people are using an Apple Watch or such wearable technologies that people can wear all the time. And that can give a readout of their activity level when they're not in the office and other measurements. But it's an important part of what we do.

So, I thought, what are the advantages and disadvantages of participating in a clinical trial?

Well, access to new and promising drugs. And I'll be very honest; some trials are more exciting than others. Some trials have a new approach to treating cancer or to a new pathway that is very exciting. Some trials that are just developing a new cytotoxic chemotherapy might be harder to get excited about. Still, it might be important. There's always a scientific rationale, but most patients have nothing to lose to going on a clinical trial as far as treatment for their disease. Clinical trials give patients more options. Standard of care options are always available, but clinical trials come and go. Slots come and go. Where you are in your disease course come and go. Some studies are only for frontline or second line, third line. So, some trials, if you start a certain treatment, you might no longer be eligible for that trial.

And patients on trial are watched very closely. I mean, even in standard of care, patients are watched closely, but because of the regulatory environment and our concern with experimental drugs, patients are watched even more closely in clinical trials. And that's one of the cons. It can be a little inconvenient because patients, you need to make more visits. There isn't as much leeway of when you can get treated or get imaged. All of that is dictated by the protocol.

And Gail talked about this. When you go in to start for a trial, they'll tell you you need to be here every Monday at 10:00. Maybe you need to have blood drawn on Tuesday at a certain time. And especially if you don't live near the site, clinical trials can only be done at certain places. At UCLA and many centers now, there's a network that participates in clinical trials. We have satellites. LA is very dense. Manhattan is very dense. Chicago, very hard to get downtown to see your doctor. But there are mechanisms that now clinical trials are open in community sites, so patients don't need to drive all the way to the main center to be part of a clinical trial. Otherwise, that could be inconvenient.

And obviously, there's a great reward in helping others. To say you participated in a trial and helped generate data that went on to a practice changing drug is very important. And I think Gail commented on that.

And the cons, as I mentioned, inconvenience. There's a lot more restriction on your time as part of a clinical trial and there is unknowns. Certainly in Phase I studies, the true side effect profile might not be fully established. And while we have a sense of what might happen and expectations, until you give it to people, there's still some unknowns and that carries some risk and there's unknown benefit. A lot of patients who participate in Phase I studies do it recognizing that there isn't a lot of data to say this drug is going to help you. We have a reason to think it might help. It targets a certain pathway. We think it's important for cancer, but I can't tell you versus a drug that's FDA approved that it works in 30% of people, the average survival is X, the toxicities are A, B, C.

So, what are the steps?

And again, Gail highlighted this. Clinical research is voluntary. The first thing you should receive is a patient bill of rights, which tells you you can change your mind at any time. Nothing is binding. You're an individual. You have liberty. You decide what's best for you. Now, if you know, I'm not going to want to do this study, you should just be honest. You're not hurting anybody's feelings. Doctors will still take care of you. It's totally voluntary.

The first thing you do is you sign the consent. Consent is a process where you say, "I understand. Everything's been explained. And I agree to start pursuing this study." You'll get a copy of everything you sign because again, sometimes screening documents now, consent documents, are 50 pages. Some of them can be very complex and you can't really read that in the office in five minutes. So, sometimes you can take it home and come back and consent. Consent most often is done in person, but you get a copy of everything you sign.

You then go into screening. Screening is where the clinical trial dictates what needs to be done to qualify for the study. There's baseline labs, baseline imaging. A lot of studies need an EKG, maybe an echocardiogram, whatever it may be, maybe a new biopsy.

And once you pass screening, then you start the study. You get enrolled is the technical term and you would start. Every institution is different. Every study's different. Depending on how many tests need to be done, how soon you can get this test done, screening hopefully should not be more than two to three weeks. I don't think most patients should view that as a delay, waiting two weeks or three weeks. Even if you saw a doctor on Monday, it takes a week or two to start treatment in most places because you got to get insurance approval and things like that. So, that wait for most patients of two to three weeks to get on a study should not be a hindrance. If patients are really that sick that they need to start ASAP, then they're probably not good candidates for a study. But most patients that go into screening will proceed into participation.

There's a lot of staff involved in clinical research. The person who's responsible for the study at your institution is called the principal investigator. But sometimes the principal investigator goes on vacation. Maybe they're not in clinic that day, they go to a meeting, so there's sub-investigators, usually also physicians who are involved in the study. They also put patients on study as well as cover for each other.

Then there's a whole staff that you may or may not meet. Coordinators are the people in the clinic who are helping collect data from you, who you're calling and scheduling your appointments, asking about how you're feeling, making phone calls during the week, really coordinating all the aspects of your participation. There's a data manager, someone who's behind the scene, who's recording results of your blood work and CAT scans and physical exam, somebody to collect the data. There's usually a scheduler who works with the coordinator to get your CT scans on time and your infusions. We have typically research assistants who are helping the coordinator manage biopsies or collecting blood, shipping things. For a lot of studies, we need to ship imaging, transfer things. And then regulatory, making sure that we're doing things in compliance with the FDA and with the sponsor.

So, I'm going to walk you through an example. I mean, this is a story that I was integrally involved with that actually I've been very blessed. It has had a fairly big impact.

And if we go back to the early 2000s, we got this molecule, PD-0332991 from Pfizer. It was a collaboration with UCLA, me and Dennis Slamon and others. And this was a drug that was designed to block proteins in cancer called CDK4/6, cyclin-dependent kinases. And these proteins regulate how cells grow, how fast they divide. And since cell division is important in cancer, it was felt to be maybe a way to treat patients. In the early 2000s, the Nobel Prize actually went to the scientists who developed or understood the CDK pathway and cell division pathway. But how we target it and who will benefit, we don't know at the time.

And we did this preclinical. So, this was a preclinical study. This drug was created in the late '90s and kind of sat on the shelf for a long time. PD is for Park Davis, which eventually was bought by Wyeth, which was eventually bought by Pfizer. So, this drug was passed along. And it was the first in class of a new class that inhibits CDK4/6. And we showed in the laboratory. And here, the small bars of the cell lines that are sensitive, the high bars are those that are resistant in the lab. And the most sensitive cell lines were hormone receptor-positive breast cancer cell lines. So for the first time, we showed that a CDK4/6 inhibitor in the lab might work only in this ER+ group. These red and yellow ones are triple negative breast cancers. The dark blue are the HER2, which also might be sensitive. But needless to say, we showed in the lab that this worked in the hormone receptor-positive breast cancer models preferably and it also worked in combination with hormone therapy in the lab.

So, this led to a Phase I-II study. And also this study was a global study. It was open-label. At first, the Phase I component, patients got what now is known as Palbociclib, but at the time it was still PD-0332991. This study was launched around 2009. And this study initially looked at the combination of letrozole, an aromatase inhibitor, a standard treatment for hormone-positive breast cancer in common donation with Palbociclib, for one, to make sure it was safe. And then we looked at early efficacy.

And you can see here, we're looking at progression-free survival over time. And patients in blue got the combination. In red, they got letrozole alone. This was open label. Everybody knew what they got. And we showed that patients who got Palbociclib, we have essentially doubled the time it took their tumor to progress. Now, this was relatively small, 80 patients per arm, but this was quite a large benefit never seen before in hormone-positive breast cancer.

And the FDA, based on this study, gave Palbociclib accelerated approval. Accelerated approval is a mechanism where the FDA says there's reason to believe that this drug really helps people. It's safe and there's a high unmet need, the unmet need here being advanced ER-positive breast cancer, very common disease, the most common type of breast cancer, and in need of new treatments.

However, accelerated approval requires a confirmatory study. And that became this Phase III study, which we published in 2016 in the New England Journal of Medicine. And this study was much larger. This study took over 600 patients, right? You see 444 got the combination, 222 got the letrozole. This study was blinded and placebo controlled. So, everybody got letrozole but only some got Palbociclib and some got letrozole alone. This is the highest level way to know if a drug really works. And this really demonstrated exactly the same data that we saw in the Phase II study. And this led to full approval in 2017 and eventually global approval of this regimen.

And since that time, many of you may know, there's several other CDK inhibitors approved. There's Ribociclib and Abemaciclib. Several studies were done, which were very similar in their design. And all of them had very similar results. When you look at the magnitude of benefit on progression-free survival here, that was the primary endpoint. Some of these studies have shown an improvement in overall survival, specifically Ribociclib. Palbociclib and Abemaciclib had a trend, but it did not reach statistical significance. Needless to say though, the studies were not designed to show an improvement in OS, but really PFS.

And this is just an example of how we see side effects presented in the medical literature. This is looking at adverse events or side effects in more than 20% of patients. This comes from the Palbociclib studies. And when it says all causality, that's either from the treatment, the disease, regardless. It's just who had side effects. And the most common thing with these drugs, as percent, has been low blood counts, some low grade infections. Things that we're more concerned

about are high grade, Grade 3, Grade 4, and there's a whole system on how this is scored.

So, in conclusion, clinical trials are critical for improving patient care. We would have no drugs without them. And there are several different types of trials to be aware of, the phase and conduct, the endpoints, the risk and benefits. And at the end of the day, you need to ask your doctor if a trial is right for you. And it's often the best option. And it's not only to be thought of as, "Oh my gosh, I have no other options. I need to go to a clinical trial." That's not the case. At every phase and question, a clinical trial may be the best thing. The doctor might say, "Well, you don't need a clinical trial." And that might be because we have good treatments available. But that doesn't mean that there might not be a trial available that might offer you some benefit.

So, I'll stop there and I guess take your questions.

Jessica Jablon: Oh, well, thank you. Going to add myself there to the spotlight. Dr. Finn, thank you so much for breaking that down so clearly. I learned so much from you about clinical trials that I didn't know before. And I'm sure that everybody on the webinar feels the same way. We did get some questions in advance and I know that you answered a lot of them already, which is great. And if you have any others that you'd like to add in the chat, go ahead. We only have time for a few, but we'll get to what we can.

You did answer part of this question, which is, it always necessary to travel in order to participate in a clinical trial?

Dr. Richard Finn: Yeah, it depends. I mean, some trials are open. People think of clinical trials as being associated with large academic centers. And that is true. That's why they exist.

But many trials now are available in community sites. I know in Southern California, even in one community, some community practices might offer trials and the one down the block does not. So you do not need to travel far. And I can't say that generally for everywhere in the country, but more and more, the NCI as well as clinical trial networks are trying to access patients where they are. And they're not all at the site of an academic center. And it's just not practical and feasible for patients to travel so far. Again, Los Angeles, someone might be five miles away, but that's a 45-minute drive and that's taxing on people. So, if you can get something closer to home, that would be a great option.

Jessica Jablon: Someone had asked, how can we, I guess, deal with educational barriers in cultural or language to help keep people more informed?

Dr. Richard Finn: Yeah, that's a good question. I mean, one thing, again, I think it goes to the stigma that clinical trials have that if you're in a research study, you don't have anything else available or it's the end of the road. And that's across cultures.

There's also a certain distrust of research. If industry is involved, pharmaceutical companies, that build some distrust that it's all business. They just want to make money. And I think educational efforts like this, interacting with your doctor, I mean, you do need to trust your doctor at some point. You need to be comfortable with them and have some faith that they're doing what's best for you.

Consent forms have to be done in a patient's native language. We have an effort at our institution that when we open a study to have it available, all the educational documents and the consent documents already in the common languages that we might see in Los Angeles. We have a large Asian population, obviously a large Spanish-speaking population. So, we try to have those materials available for them so they can understand in their own language. Having language competent people available, sometimes centers will have coordinators that speak different languages. It's a big asset to help communicate, having translation services.

But there is a stigma to clinical research, I think. I find that, especially when you meet someone for the first time. It's one thing you have a relationship with somebody and there's some trust there. But when someone comes in for an opinion and the first thing you say is a clinical trial, people get nervous. And I have a friend at the National Cancer Institute, and he said they don't have that there because if you're going to the NCI, you're going for a trial. Whereas you go to a community office or even you might not associate UCLA, the U part, with research. So, I think having that front and center and making patients aware that research is important in various languages is a way to counter some of that.

Jessica Jablon: Somebody in the chat asked, why can it be significant to improve PFS if OS doesn't improve? And could it mean less treatment during that PFS period and thus a better quality of life?

Dr. Richard Finn: That's an excellent question and somewhat complicated to answer. So, the question is, is progression-free survival a validated endpoint for overall survival? Meaning, if you improve PFS, does that automatically mean you're going to improve OS? And there's a lot of nuance there because in order to improve OS, that takes a long period of time.

In pancreatic cancer, studies don't look at PFS because OS unfortunately is not that long. And the difference between progression-free survival and OS is very short. However, in breast cancer, fortunately, patients are doing better and better. And to wait for an overall survival readout, it can take years. And that is why PFS is often used. And since OS is not the primary endpoint, it's not what the study was designed to answer, it can be liable to various artifacts because OS is not just a product of what you get in the first line. You get something upfront, then there's treatment A, B, C, D that you can get after. And breast cancer, hormone positive-breast cancer, there's eight or nine different therapies that patients can go on.

So, what we do in the frontline, it can be very hard to prove how that affects things years later. Hopefully that helps a little bit.

And I see the question about ovarian cancer, same thing. Patients now with ovarian cancer in the frontline are living longer and longer. There's more things to offer them. But a study in frontline might offer PFS. But a study in third line or fourth line, they might rely just on overall survival, again, because overall survival isn't measured in years.

Jessica Jablon: One last question for you for this part of our webinar. What about insurance with regards to clinical trials?

Dr. Richard Finn: Excellent, excellent question. So, there is an impression for some that, just because you go on a clinical trial, everything's paid for. Not always the case. Typically, clinical trials will pay for the part of the care that's not covered by insurance, meaning any intervention that's required for the study, they will pay for.

And the other thing is I work at UCLA. You need to have some insurance. It could be Medicare, Medi-Cal, private insurance. That's fine, but you need to have some insurance in order to be treated because not everything will be covered by a clinical study.

For example, a study might say, "We want CT scans every six weeks." And we might say, "Well, that's not standard of care. Standard of care is a CT every three months or every 12 weeks." So, the study will pay for every other scan. They'll pay for the six-week scan, the 12-week scan will go to insurance, and then the 18-week scan will go back to the study, something like that. Or if you need a special blood draw or a special procedure that isn't usually done, then the study would have to pay.

But typically, you still need to have some coverage for standard of care things.

And some of the challenge, some patients have an HMO. They're in a system that controls everything and they don't always let patients go out of the system for a clinical trial. And that is something that can be challenging for patients. They might come for an opinion and pay for it out of pocket and say, "What do you have to offer?" And we might say, "Well, this is standard, but we have this really exciting trial." Patient might say, "Well, I want to be in the trial," but if their insurance doesn't let them leave the system, that could be a problem for participation because the study doesn't automatically pay for everything.

Jessica Jablon: Thank you. Well, thank you so much, Dr. Finn, for sharing your expertise with us today.

Dr. Richard Finn: Sure.

Jessica Jablon: I also want to thank Gail for sharing her story with us. As we begin to wrap up, I just want to remind everyone that if you're a member of our Embrace program, someone who is facing advanced breast cancer, we invite you to stay on the Zoom for a more intimate breakout session with Dr. Finn immediately following this webinar.

We want to thank our sponsors again, ASY, Gilead Oncology, and Lilly, whose support made today's webinar possible. And as we wrap up, please take a moment to fill out a brief evaluation survey that's being put into the chat. It really does inform our future programming.

A reminder, our Tranquil Thursday's yoga webinar series is happening now on next Thursday. The registration link for that is in the chat. I know Dr. Finn had mentioned San Antonio Breast Cancer Symposium. We'll be doing a webinar on that in January, so definitely keep the lookout in your inbox.

Please remember Sharsheret is here for you and your loved ones. We provide emotional support, mental health counseling, and other programs designed to help navigate you through the cancer experience. All are completely free and confidential. And our contact information is in the chat box. I'm going to ask that my colleague puts the evaluation link into the chat box one more time. Please fill it out if you can.

Thank you so much, everybody, for joining us today. We hope to see you online soon.

About Sharsheret

Sharsheret, Hebrew for “chain”, is an international non-profit organization, that improves the lives of Jewish women and families living with, or at increased genetic risk for, breast or ovarian cancer through personalized support and saves lives through educational outreach.

With regional offices in the Midwest, Northeast, Southeast, West, and Israel, Sharsheret serves 275,000 women, families, health care professionals, community leaders, and students. Sharsheret creates a safe community for women facing breast cancer and ovarian cancer and their families at every stage of life and at every stage of cancer - from before diagnosis, during treatment and into the survivorship years. While our expertise is focused on young women and Jewish families, approximately 25% of those we serve are not Jewish. All Sharsheret programs serve all women and men.

As a premier organization for psychosocial support, Sharsheret works closely with the Centers for Disease Control and Prevention (CDC) and participates in psychosocial research studies and evaluations with major cancer centers, including Georgetown University Lombardi Comprehensive Cancer Center. Sharsheret is accredited by the Better Business Bureau and has earned a 4-star rating from Charity Navigator for four consecutive years.

Sharsheret offers the following national programs:

The Link Program

Peer Support Network, connecting women newly diagnosed or at high risk of developing breast cancer one-on-one with others who share similar diagnoses and experiences

- Embrace™, supporting women living with advanced breast cancer
- Genetics for Life®, addressing hereditary breast and ovarian cancer
- Thriving Again®, providing individualized support, education, and survivorship plans for young breast cancer survivors
- Busy Box®, for young parents facing breast cancer
- Best Face Forward®, addressing the cosmetic side effects of treatment
- Family Focus®, providing resources and support for caregivers and family members
- Ovarian Cancer Program, tailored resources and support for young Jewish women and families facing ovarian cancer
- Sharsheret Supports™, developing local support groups and programs

Education and Outreach Programs

- Health Care Symposia, on issues unique to younger women facing breast cancer
- Sharsheret on Campus, outreach and education to students on campus
- Sharsheret Educational Resource Booklet Series, culturally-relevant publications for Jewish women and their families and healthcare Professionals

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