WNPR CT Public Radio voice Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital. Welcome to Yale Cancer Answers. The director of the Yale Cancer Center, Dr. Eric Winer. Yale Cancer Answers features conversations with oncologists and specialists who are on the forefront of the battle to fight cancer. Here's Dr. Winer. Dr. Winer: 00;00;33;05 - 00;01;04;15 Tonight, we have a special show for you talking about the advancements made in cancer research over the past year, maybe the past year or two. And we're going to talk about how those research, how those advances actually take place, what's behind them with new therapies and diagnostic tools and research discoveries changing the landscape of oncology. It seemed like a perfect time to have my colleague, Dr. Patricia La Russo, who's an expert, maybe the leading expert in cancer drug development in the United States. Dr. Winer: 00;01;05;12 - 00;01;48;27 Dr. LoRusso is the associate center director for Experimental Therapeutics at the Yale Cancer Center. She's also past president of the American Association for Cancer Research, a very, very large organization that represents cancer researchers, both clinicians and basic researchers and people from all walks of research and from all over the world. And as President, Pat very much promoted the needs of clinical investigators and the importance of clinical trials. She's dedicated her career to advancing cancer treatments and improving patient outcomes. So, Pat, welcome to Yale Cancer Answers. Thanks so much for being here with us today. Dr. LoRusso: Thank you so much, Eric, for having me. Absolute pleasure. Dr. Winer: So I'm going to start off a little bit with the personal, because I know you have a personal story as to what prompted you to go into cancer. And maybe we can just talk a little bit about that. What made you as a 20 year old, want to go into cancer research? Dr. LoRusso: 00;02;17;07 - 00;03;01;22 Yeah, in fact, it was actually earlier than the age of 20. When I was young, I was a kid. Both of my parents had died of cancer. And so being a child whose parents have died, especially in those days, just similar, actually, to today, a patient dying of cancer is not necessarily an easy thing to watch, especially if they're a loved one in the Secret Life afterwards of what's next. And having an unknown of what's next can be challenging as well. And so I guess I can say that cancer became my enemy very early in my life. You know, nobody loves you like your parents. Dr. LoRusso: 00;03;02;24 - 00;03;36;04 There's nobody that takes care of you like your parents. And that void can be very significant. So I knew early on that I wanted to go into cancer research somehow, someway, and that I wanted to fight the enemy. Dr. Winer: 00;03;37;19 - 00;04;05;28 Well, and I think it's important for our listeners to know that you are not only a cancer researcher, also a cancer doctor. Over the course of the past three plus decades, you've taken care of countless patients, but you've also been involved in the development of just an incredible number of anti-cancer drugs that have changed the face of the disease for many, many people with cancer. So you grew up in the Midwest and you did much of your initial training and then your early, early and mid faculty work in Michigan, is that right? Dr. LoRusso: Absolutely. Dr. Winer: 00;04;06;23 - 00;04;45;21 How is it that in in the very early days when you knew you wanted to do cancer research, that you got into cancer drug development? Dr. LoRusso: Wow. So I

think much of it was that, first of all, we didn't you know, there were no drugs to treat many of these diseases we call cancer. Back when I was young, when I was a teenager and young adults. My mother died of a disease that's known as just which is gastrointestinal stromal tumor, which back then we had nothing for now patients. Dr. LoRusso: 00;05;12;15 - 00;05;39;08 But just in that many, many, many years as a chronic disease. My father died of lung cancer. There was nothing that we had a heavy smoker. There was nothing that we really had to treat him. Nothing. Now, depending on the subtype, there are many different treatments for the treatment of lung cancer patients. Many times can live several years when they have advanced lung cancer even longer than that. Sometimes for some people, absolutely decades plus some people are in 2025 can be cured of advanced lung cancer. Dr. Winer: 00;05;39;13 - 00;06;07;06 And of course, just to be clear for our listeners, there are patients with earlier stage lung cancer who are cured with surgery and sometimes radiation and sometimes now drug therapy as well. But in the advanced stages, lung cancer was virtually always life threatening and life threatening in a short period of time in the past. And that has really changed. Dr. LoRusso: 00;06;07;27 - 00;07;34;18 Oh, absolutely. And so I knew that when, you know, it was always a focus of mine to try to work on treating the disease, because when I was young and I saw what happened personally, there was no treatment. So I did grow up in Detroit. I grew up in the inner city of Detroit. I eventually went into medicine and I then went back and trained in Detroit. I did my fellowship training in the inner city at Wayne State University, and I was very, very fortunate that there were two people there in particular that became my mentors. One did preclinical drug development, and I worked with Tom Corbett in his lab. Dr. Winer: 00;07;34;18 - 00;08;09;28 And of course, I think people know what clinical drug development is. That's that that's all the testing of new drugs from early stage testing to later stage testing that occurs in people and pre-clinical development is all the work that happens from the most basic of labs actually developing the drug itself and then testing it in initially in in the laboratory, in petri dishes and ultimately in animals generally before it actually is tested in people. Maybe you can walk us through the the process by which a drug is developed. Dr. LoRusso: 00;08;09;28 - 00;09;07;04 Yeah, I'll just focus primarily on the clinical end of drug development. And we've pre-clinical for another speaker. So once the drug is identified as being active preclinical, then it has to go through certain tests which are called toxicology tests, to confirm at least preclinical in animals that it is safe. It then goes into humans. The first step in humans is phase one. It's the first time the drug is called a first in human study, where, although we always treat patients in clinical trials with the therapeutic intent, which means we put patients on trials in hopes that they will have a clinical benefit, their tumor will shrink, their symptoms will get better. We still have to understand the safety of the drug in humans, and that's a phase one trial, a first in human trial. Dr. Winer: 00;09;07;21 - 00;09;48;21 And so just to be even clear, the scientific purpose of that trial is often to define the safety and the appropriate doses of the drug or the doses that can be given safely to people. But the clinical purpose, of course, is to make someone better, and what's been

very interesting over the years is that, you know, 25 years ago when we gave these Phase one drugs to people, they hardly ever worked. And now, because we're so much better at predicting which drugs work against which tumors, that that's not what you see any longer. You you actually very frequently have patients getting better. Dr. LoRusso: 00;09;49;02 - 00;10;19;06 150%. So when I first started, for every 100 drugs that went into the clinic, maybe 5% of them worked less than 5% sometimes, which were very, very poor statistics. Now, in 2025, although patients when their first exposure is to the concept of going on a phase one trial, are nervous and frightened, thinking that they're going to be with many times they say, I don't want to be a guinea pig. Oftentimes in 2025, because the way that the drugs are being developed based more on the knowledge of the biology of the specific cancer, they may get a better benefit from being on a phase one trial than actually getting what's known as standard of care off the shelf medication that your physician can just prescribe for you. Dr. Winer: 00;10;20;06 - 00;10;48;27 The paradigm has been amazing because of research that is largely done in academic centers like Yale Cancer Center that have helped us understand the biology of the disease so that we could develop drugs focusing on the biology. So, for example, in pancreatic cancer, where in fact we've made relatively little progress until really until the present time, I mean, we have hope that there's going to be a lot of progress in the near future. But it's very often that there is a mutation in RAS and all of or many of the new and promising drugs are drugs that in fact specifically target that mutation. Dr. LoRusso: 00;11;48;25 - 00;12;24;21 Absolutely. So RAS is one of the it's some molecular or genetic alteration within the tumor that we can now target and inhibit. So hopefully we can prevent the disease from growing and make it go away or shrink. I just recently had a patient as an example of metastatic pancreatic cancer, had failed chemotherapy. The first round of the first treatments never really responded that different chemotherapy treatments never really responded. But her tumor had what we call an MTAP loss, a genetic change that was actually a signature. And after just 16 months and 16 weeks of treatment, her pancreatic cancer, which is extensive and in the liver, has shrunk by 42%. She's not having many symptoms. She feels wonderful. Developing a drug to target it. The biology of the disease in hopes that we can make it go away. Dr. Winer: 00;13;07;18 - 00;13;40;26 Wow. It's great. Well, listen, we're going to have to take just a very brief break. And we've been talking to Pat LoRusso, who is the associate director for experimental therapeutics at the Yale Cancer Center, leading drug developer in in oncology. And we she will rejoin us in just a minute or so, and we'll continue our conversation. WNPR CT Public Radio voice 00;13;40;26 - 00;14;34;13 - Unknown: Funding for Yale Cancer Answers comes from Smilow Cancer Hospital, where a team of specialists provide genetic testing to inform patients of their cancer risk. Learn more about Milo's Genetics and Prevention program at Smilow Cancer Hospital. Dot org. Breast cancer is one of the most common cancers in women. In Connecticut alone, approximately 3500 women will be diagnosed with breast cancer this year. But there is hope thanks to earlier detection, noninvasive treatments and the development of novel therapies to fight breast cancer. Women should schedule a baseline

mammogram beginning at age 40 or earlier if they have risk factors associated with the disease, With screening, early detection and a healthy lifestyle, breast cancer can be defeated. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center and its Milo Cancer Hospital to make innovative new treatments available to patients. Digital breast tumor synthesis, or 3D mammography, is also transforming breast cancer screening by significantly reducing unnecessary procedures while picking up more cancers. More information is available at Yale Cancer Center dot org. You're listening to Connecticut Public Radio. Dr. Winer: 00;15;31;29 - 00;15;54;03 Good evening again. This is Eric Winer for Yale Cancer Answers. We're talking tonight with Pat LoRusso, a medical oncologist and a drug developer who has a long and illustrious history of developing many, many different cancer therapies over the past three plus decades. So we started talking a little bit about the process of drug development in people. And we were talking about first in human studies and phase one studies. And of course, I know that that's what you have largely focused your career on. Dr. Winer: 00;15;54;03 - 00;16;19;12 But if you could just very briefly go over the next steps, Phase two and Phase three study, since most of the time it takes a Phase three study to get a drug approved by the Food and Drug Administration. Dr. LoRusso: 00;16;19;17 - 00;17;12;12 Yes, you're absolutely right, Eric. So a phase two trial is as follows. Obviously, a phase one trial. Phase one trials have to be done for safety. Once we identify that the drug is safe and we identify in the phase one trial what the right doses and what the right schedule of giving the drug is. Then we go into phase two and phase two. We select out specific types of tumor. Previously, it used to be breast cancer, lung cancer, colon cancer. Now, in 2025, we're obviously still treating those types of cancers in phase two, but it may be more specific than once we identify whether or not that drug has any benefit in those patients. Dr. LoRusso: 00;17;12;24 - 00;17;56;27 Oftentimes will then go to phase three, where we test that treatment against what is currently standard of care or what people will currently get if they have that disease and are just going to their regular cancer doctor who would give them a specific treatment based on previous studies. So phase three is where we test that new treatment either by itself or in combination with standard treatment compared to standard treatment to make sure that it is better than standard treatment and hopefully also safer for and standard treatments. Dr. Winer: 00;17;56;27 - 00;18;42;22 And I think a good way to think about this, at least from a patient standpoint, is that in a Phase three trial we're typically testing the best available standard therapy against something that a lot of pretty smart people have thought about a great deal and hope that it's better than standard treatment. And of course, all of these trials go through extensive both scientific review and what's often called human subjects review. You know, and it's pretty rare in any trial for there to be placebos, unless, of course, it's an active drug plus a placebo versus another active drug plus a placebo so that people can tell whether they're getting drug A or drug B, because it is important that oftentimes that neither doctors nor patients know the exact treatment they get, although there are studies where people, of course, do know the treat-

ments they're getting, but they're not just getting a sugar pill. Dr. LoRusso: 00;18;42;22 - 00;19;07;13 Correct. Maybe five, six, ten years ago, a placebo arm might be given all by itself a sugar pill all by itself versus a new drug. But in 2025, that is extremely rare. Dr. Winer: 00;19;07;20 - 00;19;27;19 Yeah. No, it's only, you know, you have, I guess, one way of thinking about it is imagine there are two different drugs you're testing against each other. One is blue and one is yellow, and you can't change that. And so there then might also be a yellow placebo to go with the blue pill and a blue placebo to go with the yellow pill so that neither the doctors nor the patients know necessarily what they're getting. But we know that they're getting an active drug. Dr. LoRusso: 00;19;27;19 - 00;19;53;05 Exactly. Exactly. And those are control. Those are called blinded studies so that there is no bias. And and then there are times when we simply can't blind the study because there are different side effects with the two treatments. And even if we tried to blind it, that both doctors and patients would immediately figure it out. And in those situations, we don't even try. Dr. Winer: 00;19;54;10 - 00;20;30;00 Absolutely. So, for instance, if they're in the investigational drug that you're studying causes rashes, but the standard treatment doesn't cause rash, even if you try to blind it, the standard treatment won't give you a rash. So you pretty much can at least guess what you're getting. If you're getting the rash. Yeah. And I think sometimes people don't realize how important clinical trials are, because the only way we move the field forward is by conducting these clinical trials. It's not by guesswork. Dr. LoRusso: 00;20;30;00 - 00;21;28;10 And, you know, patients will say to me, and I'm sure they say this to you, they say, well, you know what? What's your experience with this particular drug? And my answer is always, you know, my experience is based on, you know, a dozen patients, two dozen patients. And one tends to be biased in the patients you remember in terms of how they did. You tend to remember the last, best and last worst anecdote you have. Whereas what we really rely on are the results from the studies. Dr. Winer: 00;21;28;10 - 00;21;55;28 Exactly. And, you know, when patients come to me because I do phase one trials, they're often very concerned. And I tell them every drug that your doctor has already given you or is planning to give you has had to go through phase one, phase two and phase three trials in order to then become approved for commercial use. Dr. LoRusso: 00;21;55;28 - 00;22;37;21 So are there ever times when something goes through a phase two trial and it's just such a home run that there's an approval based on that Phase two trial? Occasionally that does happen. It can happen. And it's called an accelerated approval. That can either happen with a limited phase three or a phase two that shown overwhelming therapeutic benefit. But oftentimes with accelerated approval, the FDA will want you to do a definitive trial in phase three anyway, just to confirm that what was identified in a very limited number of patients holds true in a larger patient population. Dr. Winer: 00;22;37;21 - 00;23;09;27 But for example, if we had a phase two trial in pancreatic cancer and 90% of the patients had dramatic shrinkage of their tumor, I would imagine that that could go for an accelerated approval if, in fact, this study were conducted in a rigorous manner. Dr. LoRusso: 00;23;10;07 - 00;23;38;12 Yes, that has been

some of the changes that have been made at the FDA through the Oncology Center of Excellence, allowing scenarios such as that, because the FDA is there for patient safety and patient benefit. If they saw something similar to that, they would definitely want to advance forward for the good of the patients that have the disease because, you know, we want to make these things happen as quickly as possible. Dr. Winer: 00;23;39;02 - 00;23;52;00 So let me shift gears a little bit. And as the past president of the American Association of Cancer Research and just as a very thoughtful oncologist, can you comment on some of the biggest breakthroughs that you've seen over the past couple of years? Dr. LoRusso: 00;23;52;03 - 00;24;10;29 Yes. Yeah, I can. So there are very, there are specific classes of drugs that I'm very excited about. One of them is called Antibody Drug Conjugates. Many people earlier on called them magic bullets where there's a drug but attached to it is another drug. Dr. LoRusso: 00;24;11;18 - 00;24;43;12 So the drug is typically a monoclonal antibody, a drug that will target either a certain receptor or certain target of the tumor. Attached to it is another drug, and it delivers that drug to the tumor. And what it does is it can enhance the treatment of the disease, but it also can not only be more directive in how it delivers the medicine, but it can also change how the medicine is exposed to the tumor, giving it a greater duration of exposure. Dr. LoRusso: 00;24;43;13 - 00;25;11;24 There have been several antibody drug conjugates that have come out recently FDA approved, and they've been extremely exciting and fought and have been Dothan as one drug for bladder cancer. There have been drugs for breast cancer, now lung cancer. They're getting even more sophisticated that there may be two targets that the drug is going after with this new drug or one target with two different drugs that it's trying to deliver to the tumor. Dr. LoRusso: 00;25;12;13 - 00;25;49;03 Also targeted therapies for getting better targeted therapies that, you know, before ten years ago, we could not progress. Now I'm bringing that up because that was a target that you talked about previously. Dr. Winer: 00;25;50;05 - 00;26;24;14 And just, you know, maybe you could describe what a targeted therapy is. Dr. LoRusso: 00;26;25;06 - 00;26;50;23 Yes, a targeted therapy is a treatment that is given to a certain tumor that expresses a certain abnormality or has a certain receptor on the membrane of the tumor on the on the outside of the tumor for which we want to go after to prevent that tumor from being able to divide and grow. And there has been, you know, obviously cloning the human genome many years ago, back around 2000, kind of began to lead the revolution of targeted therapy. Dr. LoRusso: 00;26;50;23 - 00;27;27;28 We also call it personalized therapy, because instead of just giving a patient anything, because it's been shown to work in the past, we give them a drug that's specifically targeting their tumor based on certain abnormalities that we find within the tumor. Dr. Winer: 00;27;29;17 - 00;27;55;03 And we often think about, for example, chemotherapy as being a bomb that you drop on the tumor and pretty nonspecific. It just destroys everything in its wake. Whereas many of these targeted therapies—and by the way, of course, we still use chemotherapy, we sometimes use chemotherapy in combination with targeted therapy. And it's not all such terrible treatment. But targeted therapies fundamentally are far more specific than chemotherapy. Dr.

LoRusso: 00;27;55;05 - 00;28;23;29 Correct. And another thing about cytotoxic therapies is those antibody drug conjugates that I was talking to, those quote unquote magic bullets. Oftentimes what they're delivering is cytotoxic therapy and they're trying to deliver it directly to the tumor. Dr. Winer: 00;28;25;13 - 00;28;50;22 Yeah. So in our last minute or a little bit less, can you just look into the future and tell me where you think we're going to be in terms of cancer treatment in 10 to 15 years? Dr. LoRusso: 00;28;50;22 - 00;28;50;29 Well, I can dream about the future based on current science. I believe that in 10 to 15 years, many of the diseases that we call cancer—and I say that more than once now because there are many different types of cancer and even a specific cancer like breast cancer has many different types—we're going to understand those subtypes to such a greater degree and develop drugs for them such that I think even if you're diagnosed with advanced cancer, which currently most of the advanced cancers cannot be cured and they're what lead to your demise, I think in 10 to 15 years, even if we can't cure those diseases with the novel treatments that are being developed and the better understanding of the disease, cancer may convert to a chronic illness such as diabetes. WNPR voice: 00;28;51;07 - 00;28;59;03 Dr. Patricia LoRusso is the Amy and Joseph Perella, Professor of Medicine and Medical Oncology at the Yale School of Medicine. If you have questions, the address is CancerAnswers@Yale.edu. Past editions of the program are available in audio and written form at YaleCancerCenter.org. We hope you'll join us next time to learn more about the fight against cancer. Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital.