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00:00:00.076 --> 00:00:21.769 Announcer Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital. Welcome to Yale Cancer Answers with the director of the Yale Cancer Center, Doctor Eric Winer. Yale Cancer Answers features conversations with oncologists and specialists who are on the forefront of the battle to fight cancer. Here's Doctor Winer.

00:00:21.846 --> 00:00:59.846 Eric Winer Tonight, I'm joined by Doctor Ion Krop. Doctor Krop is a professor of medicine at Yale School of Medicine. And perhaps, for tonight's discussion, the most important role that he plays here is that he is the associate director for clinical research in the Cancer Center and directs our clinical trials office. He himself is a practicing breast medical oncologist, but he oversees all of the clinical trials that we do here at the cancer center.

00:00:59.846 --> 00:01:12.384 Eric Winer And we wanted to talk about cancer clinical trials, what it's like to participate in the trial, why trials are so important. So Ian, welcome it's good to have you here tonight.

00:01:12.461 --> 00:01:15.153 Ian Krop Good to be here. Thank you for inviting me.

00:01:15.230 --> 00:01:32.615 Eric Winer First, maybe you could just tell us a little bit about your background before we get into talking about clinical trials. You yourself have have conducted clinical trials and you've done that in addition to being a practicing oncologist.

00:01:32.615 --> 00:02:08.115 Ian Krop Yeah. So I've been a breast medical oncologist for over 25 years. And throughout that time I combined seeing patients in clinic with also trying to develop new drugs for patients with breast cancer. And as we will talk about the way we develop drugs, is really absolutely dependent on clinical trials, because that's how we evaluate new drugs and determine whether they're going to be beneficial for patients.

00:02:08.115 --> 00:02:19.153 Ian Krop So I've led a large number of trials over the years testing new drugs for for patients with various forms of breast cancer.

00:02:19.230 --> 00:02:29.000 Eric Winer I would imagine sometimes you also test old drugs to try to figure out how to use them better as well. It's not just about new drugs, correct?

00:02:29.038 --> 00:02:53.692 Ian Krop It's it's not only testing new drugs in different situations, but also combinations of drugs that we for which we have our laboratory scientists, colleagues have identified as potentially beneficial to combine drugs that we hadn't done before. And that's a question that we ask using clinical trials as well.

00:02:53.769 --> 00:03:23.038 Eric Winer So before we get into talking about what it's like for a patient to be on a clinical trial and perhaps why someone might want to be on a clinical trial, maybe we can just talk a little bit about the

structure of different clinical trials. So there are phases of clinical trials. And maybe you could talk a little bit about what first phase one clinical trials are like.

00:03:23.115 --> 00:04:13.000 Ian Krop Yeah. So I mean I think it's it's I think most people would appreciate that when a new drug is developed by scientists and laboratories, that there's a long process between that point and when it shows up on a pharmacist shelf, and it's a series of first studies before it even gets to clinical trials done in laboratories and in animal models, to show that the drug is doing what we want in terms of inside cancer cells, and that it's safe in animals, and then it's tested in humans first in a type of trial called a phase one trial, which has several purposes.

00:04:13.038 --> 00:04:40.000 Ian Krop One is to figure out what the right dose of the drug is to use in patients. Another is to make sure that it's safe to use in patients. And what are the side effects. And to all of our drugs have side effects. And then a third is to get a preliminary evidence that the drug is actually helping shrink cancers and control cancers.

00:04:40.076 --> 00:05:31.346 Ian Krop And these are small studies really focused on safety and figuring out the right dose. Often these studies will be in 30 patients, 40 patients. And that's the first stage of trials are done relatively quickly. Once a drug has been shown to be safe and there's a dose that's been identified, and it looks like there might be some evidence that it's actually working against cancers, it moves to phase two trials, which are larger studies, often 80, 100 patients, maybe a little bit more, which is really now focused on showing that the drug is effective against cancer cells, effective against cancers and people, and just confirming that it's still safe even when we're now looking at a

00:05:31.346 --> 00:06:11.615 Ian Krop larger number of patients. And if the drug looks promising, phase two, that it is showing some benefit in at least some of the patients and it's confirmed to be safe, it then moves on to the largest type of trial, which is called a phase three trial, which are often randomized trials comparing the new drug against what is the current standard of care drug, what is currently being FDA approved, and what is using, what is being used in patients in the in the clinic, with a goal of demonstrating that the new drug is actually not only effective, but it's actually more effective than the current standard.

00:06:11.615 --> 00:06:21.346 Ian Krop And if that trial does confirm that it's better than the current standard, then that typically would lead to FDA approval and then widespread availability.

00:06:21.500 --> 00:06:50.461 Eric Winer Let's take a step back, though, and focus on those earliest phase trials for a minute. The phase one trials. So that's where a drug that may not have been given to very many people, in fact, there's always got to be somebody who's number one, who's the first person to receive a drug, typically at a pretty low dose because we start low and go a little higher.

00:06:50.538 --> 00:07:25.500 Eric Winer Phase one trials have changed over the years. It used to be 20, 30 years ago, that phase one trials were really the last thing people ever thought about, because it was pretty unlikely that any patient would get a big benefit from a phase one trial that wasn't in any way selected specifically for their cancer. But phase one trials have changed since then, and there are more and more phase one trials that I think we're hopeful about in terms of having a real impact on a patient's cancer.

00:07:25.538 --> 00:07:27.730 Eric Winer Can you talk a little bit about that?

00:07:27.846 --> 00:08:00.115 Ian Krop Yeah, no, it's a really important point, and it's probably worth taking a further step back and describing the kind of drugs that we are testing in clinical trials these days. You know, as you said, 25 or 30 years ago when I started doing clinical trials, pretty much all of our trials up until that point had been testing chemotherapies, chemotherapies or drugs that generally are targeting cancer cells that are growing quickly.

00:08:00.115 --> 00:08:23.538 Ian Krop They're designed to kill cells that are growing quickly, and cancers tend to grow more quickly than normal cells. And so that's how chemotherapy can be beneficial. The problem is, is that there are other normal cells in the body that also grow relatively quickly, including blood cells and the cells that line your your GI tract, your colon, your hair cells.

00:08:23.576 --> 00:08:39.269 Ian Krop And so those cells often can be damaged by chemotherapy, which is one of the main reasons why chemotherapy causes side effects. Nowadays, we rarely are testing new chemotherapies. We feel like.

00:08:39.461 --> 00:09:04.000 Eric Winer And this was if I if I can just jump in for a second. This was often patients who had received multiple different kinds of chemotherapy. There were no getting yet another kind of chemotherapy. And while there was some hope that it would work, and occasionally they these drugs would work. I think the hope at that time was was certainly far different from the way it is today.

00:09:04.192 --> 00:09:11.038 Eric Winer So today we're not looking at these chemotherapy drugs in phase one trials for the most part.

00:09:11.115 --> 00:09:21.615 Ian Krop Right. And yes, that's one of the reasons why, as you said, phase one trials were kind of a last resort and very.

00:09:21.692 --> 00:10:00.384 Ian Krop Very, very frequently not very effective, both because the drugs were, were not were not very selective and because the patients cancers at that point had already developed resistance to other chemotherapies. The reason why things are different now is because what virtually all clinical trials are these days are looking at what we call targeted therapies, drugs that are specifically designed to block pathways that are driving the cancer cells, that are that for which the cancer cell is dependent upon.

00:10:00.384 --> 00:10:28.423 Ian Krop So it's something that's really critical for the cancer cell to grow. And if we block that particular pathway, then we

can often have pretty dramatic benefits in terms of stopping the cancer cells from growing and killing the cancer cells. And what makes these particularly unique is that these targets are often only in the cancer cells. So our scientists colleagues often are working very hard to identify things.

00:10:28.461 --> 00:10:54.384 Ian Krop These pathways that are only important for cancer cells and not important in normal cells. So we get that. What's why we call it targeted therapies. Because these are therapies that are specifically going after things that are important for cancer cells and not important for normal cells or less important for normal cells. So we tend to see much larger benefits than we did in the past.

00:10:54.384 --> 00:11:12.038 Ian Krop And often in these phase one trials, these are the first time the patient's cancer has been attacked in this way, so it's less likely to have been developed. Resistance already because of the prior therapies. We're not looking at the same targets.

00:11:12.115 --> 00:11:45.653 Eric Winer And and oftentimes by using techniques like genomic evaluation of the cancer, where we look at many, many different genes within a patient's individual cancer, we can identify pathways that may be upregulated where there may be specific genes that lead to the the manufacturing of proteins that could be problematic for the patient, good for the cancer that we can then potentially block with these drugs.

00:11:45.730 --> 00:12:10.038 Ian Krop We know that cancers often have many mutations in the DNA of the cancer. These are basically mistakes or changes in the DNA that make that cancer cell different than the normal cell. And these mutations are often one of the things that are driving these cancers. And we now have a large number of drugs that target those specific mutations.

00:12:10.038 --> 00:12:44.730 Ian Krop So if we, you know, as normal part of cancer care these days, we typically take the DNA from a cancer, from a person's cancer sequence, the DNA. Identify which particular mutations are driving that cancer. And those can be vulnerabilities that we can target with one of these drugs. Selective for the particular mutation. It really is a much more personalized approach to care than in the old days when we would just use chemotherapy, which was not selected at all for that particular person's cancer.

00:12:44.730 --> 00:13:14.576 Eric Winer So it sounds like today, unlike 20 or 30 years ago, that there are patients who might consider a phase one trial of a new targeted therapy that is believed to be particularly important for their cancer, based on a detailed assessment of their cancer. And they might do that not necessarily after having had 5 or 6 different therapies, but earlier on in their course of treatment.

00:13:14.653 --> 00:13:40.500 Ian Krop Yeah. And again, for for two reasons. One is that these drugs tend to be much more effective, and they're based on much stronger scientific rationale than, than just chemotherapy. So they tend to be more effective than previous types of treatments. And again because they're

selective for the particular driver of that cancer, which is not likely to be found in normal cells, they tend to have less side effects.

00:13:40.500 --> 00:13:59.192 Ian Krop So I think it's a you know, it tends to be a much better balance of effectiveness, meaning benefit with much lower risk due to side effects. So for that reason, it makes sense to use them earlier in a patient treatment course than in the past.

00:13:59.269 --> 00:14:23.307 Eric Winer Yeah. So oftentimes in taking care of patients, we think about many different types of trials at different points in time. But but the possibility of considering a phase one trial earlier rather than later is something that has really become pretty common at large medical centers. We're going to have to take a very brief break. We'll be back in just a minute.

00:14:23.461 --> 00:14:43.576 Announcer Funding for Yale Cancer Answers comes from Smilow Cancer Hospital, where the early onset cancer program provides care and support for patients from 18 to 45 years old. Their mission is to reduce the burden of cancer and improve patients quality of life. Smilow-Cancer.Hospital.org.

00:14:43.653 --> 00:15:14.269 Announcer There are over 16.9 million cancer survivors in the US and over 240,000 here in Connecticut. Completing treatment for cancer is a very exciting milestone, but cancer and its treatment can be a life changing experience. The return to normal activities and relationships may be difficult, and cancer survivors may face other long term side effects of cancer, including heart problems, osteoporosis, fertility issues, and an increased risk of second cancers.

00:15:14.307 --> 00:15:43.346 Announcer Resources for cancer survivors are available at federally designated comprehensive cancer centers, such as the Yale Cancer Center and Smilow Cancer Hospital, to keep cancer survivors well and focused on healthy living, the Smile Cancer Hospital Survivorship Clinic focuses on providing guidance and direction to empower survivors to take steps to maximize their health, quality of life, and longevity. More information is available at YaleCancerCenter.org.

00:15:43.423 --> 00:15:46.346 Announcer You're listening to Connecticut Public Radio.

00:15:46.423 --> 00:16:15.615 Eric Winer Welcome back to the second half of Yale Cancer Answers I'm Eric Winer, director of the Yale Cancer Center. And I'm joined by Ian Krop, who leads our clinical trials effort. So I we've been talking for the most part about early phase clinical trials. And you touched on phase three trials, which are often looking at a new drug and comparing it to the standard of care or a new combination and comparing it to the standard of care.

00:16:15.692 --> 00:16:24.423 Eric Winer Are these drugs all active drugs, or do we sometimes use placebos here? It's a question patients often ask, right?

00:16:24.461 --> 00:16:55.500 Ian Krop It is a question patients often ask. And there is a role for placebo in in many types of clinical trials and oncology. We we typically don't use placebos. With one major exception. We have almost never do a trial in which patients would only get placebo. Yeah. So typically the only time we typically use placebo would be in a trial where we're trying to test whether adding a new drug to a standard to the current standard of care would be beneficial.

00:16:55.500 --> 00:17:23.192 Ian Krop And so in that situation, patients would be randomized to either the standard, the current standard of care by itself, which is what they would be getting if they weren't on a trial versus the standard of care, plus the new drug. And in the people who were randomized to the standard of care alone, they would also get a placebo so that it could be compared directly to the to the combination with the targeted drug.

00:17:23.192 --> 00:17:34.807 Ian Krop So again, in that case, everybody on the trial gets the current standard of care that they would get if they weren't on a trial. But some fraction of the patients would also get the new drug.

00:17:34.846 --> 00:18:13.230 Eric Winer I just thought of one where we used a placebo in recent years as the only drug, and that was the aspirin trial in breast cancer, where after completing breast cancer therapy, patients were randomly assigned to receive either an aspirin once a day or a placebo to see if aspirin could possibly prevent recurrence. And in fact, not only were there placebos for aspirin, but if there needed to be a dose reduction because of side effects, they had baby aspirins and baby aspirin placebos.

00:18:13.423 --> 00:18:38.692 Eric Winer The study, of course, showed that aspirin had no benefit. But that was a situation where, because the standard was no therapy or no additional therapy, that I think patients were pretty comfortable with the idea of a placebo. But it is it is pretty unusual. So what's it like for a patient to be on a trial as opposed to getting standard treatment?

00:18:38.730 --> 00:19:02.461 Ian Krop Yeah. No, it's a it's a good question because it's not something that I think people just through normal channels would really have much experience with clinical trials. You know, I think first you have to talk about how patients get involved with a clinical trial. And I think the the oncology field in particular feel that a clinical trial is really part of standard care.

00:19:02.538 --> 00:19:30.615 Ian Krop It's not some kind of complete alternative thing that that only occasional patients might be interested in. It's really part of standard of care. And that's because the development of new, new, better drugs is happening so quickly in oncology that there's just a number of trials always available. When a patient gets involved in a clinical trial, it's often when you're discussing with your oncologist what is the next treatment step or what is the first treatment step.

00:19:30.769 --> 00:20:04.846 Ian Krop And so we often would talk to patients

about the standard of care as one option, and then a clinical trial as another option. There might be multiple standard of care options and multiple clinical trial options. And then if after hearing about a clinical trial, why it might be a good option for them, patients would if they are interested, we would talk to them in more detail, go over something called the informed consent document, which is a very detailed document which explains why the trial is being done.

00:20:04.884 --> 00:20:28.846 Ian Krop What are the potential benefits of the trial? What are the potential risks and what is involved in the trial in terms of the number of visits and procedures that would be involved? And if the patient, after going over that and discussing it with the physician and discussing it with their family, decide that they would like to participate in the trial, we first confirm that they're eligible.

00:20:29.000 --> 00:20:59.769 Ian Krop That often may entail some laboratory tests or some of these DNA tests that we had just mentioned, and they would sign the informed consent and and then start the trial. And once on the trial, the treatment is really or the the process is not much different than receiving a standard of care drug. They would either be getting the the pills if it's an oral treatment or going into infusions.

00:20:59.769 --> 00:21:26.192 Ian Krop If it was an IV treatment, just like they would a standard of care. There may be some extra visits involved. There certainly would be extra people involved on the care team monitoring patients. So there's there's there's more support for patients on a clinical trial. But from a day to day standpoint, it's really not much different once they're on the trial than if they were on a standard of care treatment.

00:21:26.192 --> 00:21:49.115 Ian Krop It is important to point out that being on a trial is completely voluntary. We always make sure people know that there's what the alternative standard of care treatments are. And once you start a clinical trial, you are always able to decide that you want to stop at any time. And that would not affect your subsequent treatment or anything else.

00:21:49.230 --> 00:21:53.538 Ian Krop We would then offer whatever the standard of treatment was at that particular moment.

00:21:53.576 --> 00:22:22.230 Eric Winer And I think sometimes people don't realize that if for any reason their doctor thinks that they're not doing well with the trial, either because their cancer isn't responding to it or because they're having particularly severe side effects, that the first priority is always the patient. It's not getting some answer from the trial. And in fact, if someone has to stop treatment, that's an answer in and of itself.

00:22:22.307 --> 00:22:34.576 Eric Winer So I don't think people have to worry that somehow they're going to lose control of, of, of their life or that anyone is in charge other than their doctor.

00:22:34.653 --> 00:23:01.269 Ian Krop Correct. So either the doctor would decide that you would recommend that they stop the therapy, or the patients

themselves can decide to stop the therapy. But, but but clinical trial therapy, just like standard of care therapy, is often only given for as long as it's benefiting patients. And if it stops being beneficial, then you would stop the clinical trial therapy and move on to other types of treatment.

00:23:01.307 --> 00:23:30.653 Eric Winer You know, I've often wondered whether patients realize how important trials are for moving the field forward, and that people who choose to participate in trials should actually feel good about the fact that they've done it. Because not only are they getting what we believe to be is very effective therapy for themselves, but they're helping make progress for future generations of patients.

00:23:30.730 --> 00:24:01.384 Ian Krop Absolutely. You know, I do think it's truly a win win type of situation. The patients often benefit because, as you said, they're getting, you know, the latest state of the art type of treatment. And they're providing benefit for patients who develop cancer in the future because that's how any all of the new drugs that have been developed and have have, you know, all the many breakthroughs that we've seen in cancer are all developed through clinical trials.

00:24:01.384 --> 00:24:22.692 Ian Krop And if we didn't have clinical trials, we wouldn't have any any new drugs. And so, you know, when we ask patients about their experience on clinical trials, that is one of the things that they're that often they cite is the the good feeling they got knowing that they're helping not just themselves, but, you know, other patients who are going to be developing cancer in the future.

00:24:22.884 --> 00:24:59.461 Eric Winer It is fair to say that our progress would be a tiny, tiny fraction of what it is without clinical trials, because it is how we change the standard of care, how we make things better. Now, trials can be sponsored by the government sometimes, although that's not the majority of trials. Sometimes an individual institution can sponsor a trial. And sometimes, and I should say frequently, large clinical trials are sponsored by the pharmaceutical industry.

00:24:59.461 --> 00:25:30.000 Eric Winer And that is largely because they're so incredibly expensive to conduct. I mean, a large clinical trial can cost tens and even hundreds of millions of dollars. So for those large trials that are conducted by industry, oftentimes we get an answer and the drug gets approved. But it seems like we don't always know just how to use those drugs in clinical practice.

00:25:30.000 --> 00:25:32.538 Eric Winer How do we deal with that?

00:25:32.615 --> 00:26:01.192 Ian Krop Yeah. So I think the first priority is to establish the drug is better than the current standard of care, that it is an advance. And that is the main goal of one of these large phase three trials. But once we've shown that, then there's the question of are there particular types of cancers or particular patients who benefit more from this therapy versus a different therapy?

00:26:01.269 --> 00:26:38.846 Ian Krop And that's often a harder question to answer, and one that is often less of a priority for our industry colleagues, the pharma and biotech companies, because they're trying to just keep developing drugs as fast as possible. That's something that that we in academic centers like Yale are doing somewhat smaller clinical trials, but looking at specific characteristics of cancers that may make them more likely or less likely to respond to a given treatment so that we in the future.

00:26:39.000 --> 00:26:55.423 Ian Krop The goal is to be able to personalize a treatments a patient's treatment so that it specifically effective against that person's treatment, and we can use the drug in that person versus not in a person who's not likely to benefit.

00:26:55.500 --> 00:27:28.269 Eric Winer And then sometimes, you know, a drug may be shown to be beneficial as the first treatment. But, you know, it may turn out that there's no reason that it shouldn't be given as the second treatment or the third treatment, because it has some number of side effects and, and maybe effective there as well. So, you know, I think that what often happens is that a trial that answers a question leads to other questions.

00:27:28.269 --> 00:27:33.115 Eric Winer And it's important that we ask those in a rigorous way to.

00:27:33.192 --> 00:27:56.615 Ian Krop Right. And what that means, though, in the big picture, is that we have to do a lot more clinical trials. You know, back when we were testing 5 or 6 different chemotherapy drugs, and we would test those in all patients with lung cancer or all patients with any kind of cancer, which is some of the early cancer trials were done.

00:27:56.653 --> 00:28:26.153 Ian Krop We only needed a few clinical trials now because there are the therapies are very targeted. We have to have many more trials for each of the different targets. And each of those different targets can be present in different types of cancer. And as you mentioned, if we're trying to understand the best way to sequence the drugs and to identify which patients are most likely to benefit, as you can imagine, it just takes a huge number of trials.

00:28:26.192 --> 00:28:38.538 Eric Winer Well, I want to thank you for joining us. I've been speaking with Doctor Ian Krop Thank you so much for going through all these complex explanations with us tonight.

00:28:38.615 --> 00:28:57.692 Announcer If you have questions, the address is CancerAnswers@Yale.edu and 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.