Welcome to Yale Cancer Answers with your host doctor Anees Chagpar. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, it's a conversation about experimental therapeutics with Doctor Pat LoRusso.

Pat, maybe we can start off by you telling us a little bit more about what exactly is experimental therapeutics. It sounds so obscure and intellectual and scientific and strange. It sounds so obscure and intellectual and scientific and strange.

I think it is somewhat intellectual, and so I hope that I'll be able to explain to you what all that means. So with every cancer drug that we have, we treat patients for, every cancer drug that we have, we treat patients for,
drug that’s commercially available, it has to go through a series of testing not only in the lab to identify its activity, not only in other animal species, to make sure that it is safe to administer to humans, which are called toxicology studies, but then it has to go through a series of tests in humans first to make sure that the drug is safe to give, and then to find out how active it is, either alone or in combination with other agents.

So Phase one clinical trials are essentially trials whereby a new drug is tested for the first time in humans. Although the primary objective of a phase one trial is actually to make sure that the drug is safe to give to humans. We are also looking for a lot of other endpoints as well.

What kind of activity does it have against specific tumor types? How is the exposure of the drug in man relative to what we saw previously in various animal species and to assure that we have the utmost safety in these trials. Obviously all trials have to be approved.
the Food and Drug Administration before they can be initiated in humans, and that is the same thing with a phase one or first in human study. But what they do is based on animal trials previously done with the agent and toxicology studies that are also previously done. The FDA works with the sponsor or the drug company to identify a safe starting dose. A dose where we can feel quite assured that giving that dose will be safe to humans and to identify what the most relevant dose will be to go into subsequent phase two and three trials and then hopefully to go into FDA approvals for standard of care treatment. We do various escalation steps along the way to identify a safe dose that can be subsequently brought into a phase two efficacy or a phase two comparative efficacy study which may take anywhere from 3 to 10 or 12 escalation steps. So that we’re gradually increasing the dose to the point where we identify what a safe dose is that can be subsequently advanced to other phases of clinical trial development.
So this is really important work, because this is how we get the drugs into the clinics that actually provide the cures that all of us want for cancer. But it really starts very much in the lab, so help me to understand and help our listeners to understand what goes into getting a drug even into phase one because as you describe it Phase one clinical trials maybe seem really scary to a lot of patients. I mean this concept of being first in man. Many people are thinking why would I want to be the first ones for you to experiment and see what is safe and what is tolerable and what is efficacious? So let’s take a step back before that and kind of lay the groundwork for me in terms of what goes on before that. How do we get to the point of a phase one trial where you’re presenting data to the FDA? First a drug is developed in the lab based on a scientific principle or a scientific concept. So I think the best way to describe it would be to use an example.
primarily non small cell lung cancer and colorectal cancer, but other tumors as well, there is a mutation called KRAS G12C. And that mutation in large part drives that tumor and makes it extremely aggressive. It’s taken many, many, many years for chemists to develop a drug that can target or inhibit that mutation from continuing to allow the tumor to multiply and divide. So that drug probably took about 20 years conservatively of chemists working on trying to figure out how to target that mutation, which was extremely difficult because of the way that mutation is pocketed in the DNA of the tumor. Once they identify a compound that can bind to that mutation or attack that mutation, then they have to test it in animal models, tumors in animals that have that mutation to see whether or not the drug is going to work against those tumors inhibiting those tumors from growing, preventing those tumors in animals from metastasizing or going beyond where the tumor was originally implanted.
and identify that the drug is active, then we have to take it into toxicology studies where we test the drug in different animal species to make sure that we can safely give that drug to the animals without causing side effects or harms, and we usually have to do that in two or three different animal species, depending on what the drug is. But back in the olden days I call it when I first started doing clinical drug development, during development of drugs in humans, we didn’t have the scientific basis that we have today and today there’s a lot of science that is driving new drug discoveries in the lab, especially with targeted drugs because of the fact that unveiling the human genome several years ago allowed us to better understand the differences between the DNA and RNA. In tumors versus the DNA and RNA in the normal human and what we had to go after in those tumors to prevent them from growing and hopefully from preventing them eventually from even coming about in patients that may be high risk,
such as in prevention, but no matter where the drug ends up treating advanced stage patients, patients that have cancer that’s metastasized, or patients that have had cancer, but we’ve removed the tumor. And we want to prevent the cancer from coming back. Every drug that’s given to humans in a general oncology office has to at first be tested in early phase clinical trials and back in the olden days. You know, we tested a lot of drugs based on just these high throughput screens in mouse models without a lot of science, there was science there, but today, in 2021 the science has advanced much more that we are even selecting out certain tumor types. Patients that have certain types of cancers based on the science. Because we know even in phase one trials that we may have a greater chance of response and benefit if we only treat patients with those tumors. Going back to the KRAS G12C mutation that I was talking about a few minutes ago, we only included in those phase one trials
patients that we knew whose tumors had that mutation and in non small cell lung cancer in a phase one trial we were seeing close to 70-75% tumor response and in colon cancer, in patients who had colon cancer that had the KRAS G12 C mutation, we were seeing responses about 40 to 50% and many of those patients had a lot of prior treatments either immunotherapy, chemotherapy, or both and yet despite having all those different cancers be treatments because their cancers had that one mutation, there was significant benefit as early as in the Phase one clinical trial. So even though these trials are primarily toxicity finding studies and finding the recommended phase two dose many times in these trials, if we have a specific target that we’re targeting and we can identify patients whose tumors have that target, there is a potential therapeutic benefit for those patients either in terms of their tumors shrinking or staying stable for a prolonged period of time, even at some of the lower doses, because as I said,
we have to start low and go high, and with the initial drug that targeted KRAS G12C, responses were seen regardless of what the dose was, which is extremely encouraging and that drug is moving forward hopefully to FDA approval. So I think that there’s a few things there that you said that are so important to highlight, one of which is that our ability now to to figure out what the exact mutations are and to develop drugs that will target those mutations really not only benefits patients in terms of lack of side effects and potential better efficacy of a drug that targets a particular tumor, but it also really encourages patients to participate in clinical trials because you know that that drug, at least in animal models, has been shown to be efficacious against that particular mutation, and at least in animal models, doesn’t have high toxicity. And so Pat, when you’re designing a phase one trial and thinking about the patients who are eligible,
I think the other thing that was really critical that you said was not only how you target the population to those patients who could potentially benefit from this, for example, those who have a specific mutation. But also those for whom standard of care may be falling short where there may not be other options who have been through a number of series of different regiments and have come to exhaust standard of care options tell us more about how you go about designing a phase one trial in terms of who’s eligible and how many patients you need to have on that trial to get the information that you need before you can open this up to wider clinical trials?

Right, so first of all, there are a limited number of patients that go on the phase one trials because we’re really looking for potential side effects of the drug to make sure that the drug is safe to give to patients. So we slowly increase the dose will
treat one to three patients and we’ll have to get them through at least three to six weeks of treatment before we then can increase the dose and add another one to three patients as an example. And so I wanted to pick up all of the things that we look at in terms of Phase one, clinical trials and how we actually get these drugs to market right after we take a short break for a medical minute. Please stay tuned to learn more with my guest Doctor Pat LoRusso. Support for Yale Cancer Answers comes from AstraZeneca, working to eliminate cancer as a cause of death. Learn more at astrazeneca-us.com. This is a medical minute about smoking cessation. There are many obstacles to face when quitting smoking as smoking involves the potent drug nicotine. But it’s a very important lifestyle change, especially for patients undergoing cancer treatment. Quitting smoking has been shown to positively impact response to treatments decrease the likelihood that patients will develop second malignancies.
and increase rates of survival.

Tobacco treatment programs are currently being offered at federally designated Comprehensive cancer centers and operate on the principles of the US Public Health Service Clinical Practice guidelines.

All treatment components are evidence based and therefore all patients are treated with FDA approved first line medications for smoking cessation as well as smoking cessation counseling that stresses appropriate coping skills. More information is available at yalecancercenter.org.

Welcome back to Yale Cancer Answers. This is doctor Anees Chagpar and I'm joined tonight by my guest doctor Pat LoRusso. We're talking about experimental therapeutics, and phase one clinical trials, and right before the break, Pat, we were talking about how you go about designing these phase one first in man clinical trials and we were talking about the fact that, you know, it seems to me to be a little less scary than it was in previous years.
Because drugs these days are so much more targeted and there is a lot of regulation and a lot of preclinical work in terms of animal studies, that goes into really making sure that these drugs are efficacious and not toxic, at least in a couple of animals species before it ever hits phase one clinical trials. But you were starting to tell us right before the break about how you design these phase one clinical trials. How many patients you involve, what your inclusion criteria are, the safeguards that you put around these trials. Because still, for some patients, this may seem really scary and often is used as a last resort, so can you talk a little bit about that? Oh yes, absolutely. And thank you for the opportunity to do so. So to begin with, In terms of finding the dose that we want to start with and how we’re going to escalate, that pretty much comes from the toxicology studies that we’ve done before we get into the clinic before we go in demand. But also exposure of the drug.
So what was the exposure that was needed in the various model systems that we used in order to see benefit to see the tumor regress either in the mouse models or in the in vitro Petri dishes? Because we know that we have to start safe. But we also want to make sure that we can get to an adequate exposure, because if we can’t get to an adequate exposure, we are concerned that we may not see the benefit and oftentimes there is a very large what we call therapeutic window, a window or a dose at which we started to see activity to a dose where we saw side effects in animals and the easier it is for us to identify how fast we’re going to increase our doses. Another thing is we look at the inclusion and exclusion criteria and in terms of toxicity, if we know that the drug preclinically in animals led to some type of a side effect, animals led to some type of a side effect, we have to select out our patients based on that, or do some additional tests to make sure we can hopefully safeguard patients and follow them closely so that they don’t have a side effect. But in terms of efficacy as well, it would not be in 2021 because we know so much more.
about the science and how the science is driving the tumor in humans, we want to select out patients that will have the greatest chance of benefit. So back 25 years ago when I started doing Phase one trials, we would do what we called all comer studies. All patients, regardless of the tumor, were allowed to go on phase one trials. Because we didn’t know enough about the science that was driving particular tumors. And nowadays in 2021 it’s not uncommon for us to design a trial that may only have two tumors, or maybe two tumors and a third arm of tumors that have a specific mutation an like the KRAS G12C story that I was telling you about. We knew that the primary tumors that we needed to go after were the lung tumors that were either lung cancer or colon cancer that harbored this KRAS G12C mutation. But there are other tumors that rarely harbor this mutation as well. Cholangiocarcinoma, you know various tumors and so we allowed a third arm or a third basket of tumors to be enrolled of those different tumors that might have that mutation.
Additionally, back in the olden days, we used to see patients that had failed everything, even drugs that really were not doing that much for them, but might have been FDA approved for commercial use. Nowadays we realize that may not be the best patients to put on these studies, especially seeing that we're targeting science. And we're not looking necessarily for patients now that have exhausted everything. But like for instance, we have a trial that only wants patients that have failed what we call frontline therapy for colon cancer or frontline therapy for pancreas cancer. Only one treatment for their metastatic disease, and then we want to bring them on the trial because we know that the farther out you go in terms of number of different treatments of a patient is given, many times there’s a significant decrease in the ability for that tumor to respond to a certain treatment, and so we’re requesting even in early phase once we’ve gotten to that dose that
we want to advance forward instead of just going right into a phase two, we may do what we call expansion cohorts. In that phase one trial and where we put only patients with colon cancer, or only patients with ovarian cancer. And only those that may harbor as an example, Because we want to move the drug through as quickly as possible, but as safely as possible so that we can hopefully advance that drug right into a phase three trial, which is a randomized trial looking at standard of care versus the new drug or standard of care versus standard of care. Plus the new drug together so that we can hopefully advance that drug to commercialization to make it accessible to all patients that could benefit from that drug as quickly as possible. Yeah, I think that’s so important right in thinking about the fact that even if you look at our standard chemotherapies, many of these are drugs that were developed back in the quote the good old days, which really aren’t targeted and now that we have these targeted therapies it may be patients who
have specific mutations.
To really look at clinical trials before they’ve exhausted all of their options.
So Pat, my next question is,
do you find that patients are still resistant to looking at clinical trials?
Do they have enough information about where to find these clinical trials and for the people who are listening on the radio today who may be thinking,
how far do we keep going down the line thinking about the next line of therapy in the next line of therapy, all of which may be less effective versus trying a clinical trial.
And how do I get information about what clinical trials are out there that might be well suited to me in my tumor?
In the Connecticut area obviously you know Yale Cancer Center is an outstanding resource for clinical trials.
And you know, contacting somebody at Yale Cancer Center, if you have a GI cancer cancer of the colon or stomach,
contacting the GI team to see do they have trials available?
Or if you have metastatic disease, your cancer is spread outside of its primary source, contacting our team as an example, and if you contact Yale, they will get a hold of the right physician to be able to answer those questions. You can also go on cancerclinicaltrials.gov, a website that is sometimes very difficult to maneuver. You can ask your primary oncologist, but depending on how comfortable they feel in referring you, you're at the disposal and you're at the mercy of them sending you for a second opinion or sending you to a site that may have clinical trials that may not be available to them. Sometimes it’s very difficult for these patients to find these trials. Unfortunately, of all patients that are diagnosed and treated for cancer, less than 3% of them are ever put on a clinical trial, and there are certain communities of patients, the underrepresented minorities, those patients in rural communities that have the greatest impact of not being offered a clinical trial or not being able
0:25:35.528 –> 0:25:38.826 to get access to a clinical trial.
0:25:38.83 –> 0:25:40.261 So I mean,
0:25:40.261 –> 0:25:42.169 there are some organizations
0:25:42.169 –> 0:25:44.43 that you can contact
0:25:44.43 –> 0:25:47.622 that may help you find a trial
0:25:47.622 –> 0:25:50.42 or calling the NCI directly,
0:25:50.42 –> 0:25:52.91 but many times it’s difficult
0:25:52.91 –> 0:25:53.41 unfortunately,
0:25:53.41 –> 0:25:55.41 to even maneuver those
0:25:55.41 –> 0:25:56.91 avenues of information.
0:25:57.96 –> 0:26:00.27 So Pat, you mentioned underrepresented
0:26:00.27 –> 0:26:03.608 minorities and I just want to pick up
0:26:03.608 –> 0:26:05.841 on this just for a minute because
0:26:05.85 –> 0:26:09.042 for many patients who may be
0:26:09.042 –> 0:26:10.41 from underrepresented minorities
0:26:10.484 –> 0:26:12.308 African American patients,
0:26:12.31 –> 0:26:15.208 for example, they may be reluctant
0:26:15.208 –> 0:26:17.78 to participate in clinical trials
0:26:17.78 –> 0:26:20.15 given historical events
0:26:20.15 –> 0:26:23.25 that have happened in this country,
0:26:23.25 –> 0:26:26.806 which have been deplorable in terms of
0:26:26.806 –> 0:26:30.2 clinical research and how it was conducted,
0:26:30.2 –> 0:26:33.679 can you alleviate some of their fears
0:26:33.68 –> 0:26:36.998 and anxieties?
0:26:37 –> 0:26:39.81 Because of some of those
0:26:39.81 –> 0:26:42.058 previous events that occur,ed
0:26:42.06 –> 0:26:44.632 especially with minority populations,
0:26:44.632 –> 0:26:47.847 the Food and Drug Administration
0:26:47.847 –> 0:26:51.396 the FDA has put very strict rules
0:26:51.396 –> 0:26:53.915 and regulations in place that
0:26:53.915 –> 0:26:56.665 will prevent that from happening.
And in fact, there are many investigators, epidemiologists and scientists that are trying to understand why underrepresented minorities are not as well represented and the number one reason is because they are not offered a clinical trial. One of the other reasons is geographic and financial barriers. Those are two of the other reasons, but it isn’t because they’ve necessarily refused a clinical trial, the lack of being offered far outweighs their refusal. The geographic barriers far outweigh their refusal, and in fact there are very, very slim statistics of the last 17 FDA approved cancer drugs and less than 4% of all patients that were recruited were black, less than 4% of all patients recruited were Hispanic, and it’s important to have underrepresented minorities represent a significantly larger population of cancer patients. And we need to see if their tumors respond the same way their tumors.
tumors may have some genetic, or some germline mutation or differences and we need to understand that and how it impacts their tumors. I think that’s so important because at the end of the day, once all of these trials are done and these drugs are marketed as standard of care, these patients are going to receive these same therapies that may have been developed on a completely different population. So Pat very quickly in our last minute, I just want to get one last question in which is you mentioned financial barriers. Are clinical trials covered by insurance or do people have to pay out of pocket for these drugs? The drugs themselves, if they are investigational drugs, they do not have to pay for them. They will be given free of charge by the sponsors. Medicare coverage analysis covers a lot of the tests that are needed for clinical trials, but I think some of the greatest financial barriers are commuting back and forth to places some of the standard of care.
copays that are required, and hopefully we will be able to work towards getting a lot of those things funded through new initiatives that can help patients. Because the patients that need these studies the most sometime are patients that do have a problem gaining access to their copays or paying a babysitter so that they can go and participate in these clinical trials, or drive or pay for parking at the sites that they have to be treated. Doctor Pat LoRusso is a professor of medicine at the Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written. Farm at yalecancercenter.org. We hope you’ll join us next week to learn more about the fight against cancer here on Connecticut Public Radio.