

Welcome to Yale Cancer Center Answers with Drs. Ed Chu and Ken Miller. I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and Dr. Miller specializes in pain and palliative care. If you would like to join the discussion you can contact the doctors directly at canceranswers@yale.edu or by phone at 1-888-234-4YCC. This evening Dr. Ed Chu speaks with Dr. Louis Denis, Director of Clinical Research at Pfizer Oncology.

Denis I trained in medical oncology in Belgium. As you can hear, English is not my first language. I moved to the States in 1998, and first was at the Cancer Therapy and Research Center in San Antonio and then joined Pfizer in 2001. I joined Pfizer when its drug development group in oncology was still in its infancy. I was able to join them at a time when some of the early products were being developed.

Chu Are you involved with a particular project or do you help oversee a number of different cancer drugs being developed at Pfizer?

Denis We largely work in teams and project teams. They have one or more product in its development. Over the years I have worked on a number of products, specifically ones in early development, and more recently in late stage development.

Chu It is interesting because when we think of Pfizer, we typically think of a company that focuses on drugs that treat high blood pressure, cardiovascular disease, and CNS diseases, but Pfizer has become a major player in the field of oncology.

Denis That is correct. When I joined we had a very interesting pipeline, but outside we were not well known for our cancer research. More recently, with the merger with Pharmacia and the development of that pipeline, we have become a partner in the industry of moving some of those products forward.

Chu About how much of Pfizer's portfolio is committed specifically for cancer treatment?

Denis Over the last few years there has been an explosion in the investments and commitment of Pfizer in oncology. Approximately 20% of our research and development budget, which is approximately seven billion dollars, is committed to the development of new cancer drugs.

Chu That is a pretty significant investment on Pfizer's part.

Denis It is a very significant investment and we are very hopeful that we can

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deliver better medicines for cancer patients in the future.

- Chu For our listeners out there, you are based on the Eastern part of Connecticut, is that right?
- Denis Pfizer has its R&D headquarters in Groton, New London here in Connecticut. Regarding oncology with the acquisition and mergers of other companies, the oncology group is based here in Connecticut, in La Jolla, CA and in Milan, Italy.
- Chu It is obviously local here in Connecticut, but it is also a global pharmaceutical company.
- Denis We are definitely a global pharmaceutical company.
- Chu Before coming to Pfizer you said that you were at the Cancer Therapy and Research Center at San Antonio Texas. The CTRC is also known as the institute for drug development and it has been viewed as one of the leading preeminent cancer drug development centers in the country. How was your experience when you were there in San Antonio?
- Denis When I trained in medical oncology it became evident that you are only as good as the drugs you are using to treat patients. For this reason my focus quickly shifted to clinical cancer research and I went to work at a center in the Netherlands, in Rotterdam, which was well known for its early cancer drug development and from there had the opportunity to work with indeed some of the best mentors in the States for early cancer drug development.
- Chu Namely Dr. Daniel Von Hoff, Dr. Eric Rowinsky and Dr. Anthony Tolcher.
- Denis They were all present there and were a pleasure to work with. They have been great mentors to me both from a technical prospective and as a reflection of patient care.
- Chu It is curious because one wouldn't think of San Antonio as being a hot bed for cancer drug development, yet at that time, and still today, any interesting new compound that was being developed usually found its way through San Antonio.
- Denis It was quite a fascinating period indeed. Many new targeted agents, developed as alternatives to the more toxic chemotherapy agents, were being developed and San Antonio, having a focus on phase 1 drug

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development, grew significantly in the number of projects and trials they were able to manage. The key leadership of Dr. Von Hoff, Dr. Eric Rowinsky and subsequently Dr. Anthony Tolcher, has really helped put them on the map of cancer drug development.

Chu You mentioned targeted therapy a little while ago, can you explain what target therapy means.

Denis When we say targeted therapy we mean the treatment of cancer by specifically focusing on one or more drug targets. These are proteins, or other elements in the cancer cell pathway, that help it survive. By targeting those specific proteins, we can affect and affectively kill cancer cells without being too toxic to the normal cells in the body.

Chu So in essence, we are trying to develop magic bullets?

Denis In essence, yes.

Chu This is hopefully much safer for the patients who are taking these medicines.

Denis That is of course what we are aiming for, more effective drugs that are better tolerated.

Chu Being in San Antonio, and now in your current role at Pfizer, you have seen the entire spectrum of cancer drug development. A lot of people do not appreciate how long it takes to actually bring a drug from the laboratory all the way into clinical trials and then eventually into everyday practice. Can you please explain a little bit about how that process works?

Denis I will be happy too. First of all one must understand the biology, which is critical in identifying which target we would focus on in affectively being able to treat cancer. There are many potential targets out there and we have to make a selection of which targets are, what we call, drugable, and which targets can indeed be affected with some of the new and future medication. Secondly our chemists, who are extraordinary in their development of new molecules that are able to selectively affect those targets, work on a new compound; that takes at least 4- 6 years, sometimes even longer just to identify a molecule, or molecules, that can be affective against a certain target. Subsequently, those new molecules, or a medicine in an early phase, will have to be tested for safety and efficacy in early clinical models. They are not yet tested in patients, but in cell cultures or animal models, which are needed to test the efficacy of the drugs. After all that information is gathered and closely scrutinized, we will go, with a

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large package of information, to the health authorities and FDA, and request the opportunity to test these agents in patients.

Chu How would you describe the relationship between your company, Pfizer, and regulatory agencies such as the National Cancer Institute, NIH, and the FDA?

Denis In essence that relationship is viewed by us as a partnership. The reason for this is, of course they have their primary objectives of regulatory action, and we have our focus in bringing new and better medicines forward; at the end of the day we both want the same thing and want to develop better drugs for patients. Partnership is the essence.

Chu It is interesting because a lot of times we hear in the news and in the media that relationship as being portrayed as adversarial with a lot of friction and tension between the pharmaceutical industry and FDA, but it sounds like your view is very different from that.

Denis The perception and the way that we work with the health authorities is always one that we need to come to consensus on. Of course we sometimes have settings where we have different views and a consensus has to be driven, but that is part of a healthy debate and healthy learning. The health authorities have their experience not just having been exposed to products from Pfizer, but from other pharmaceutical companies as well. Due to this they might have insights which we, even with our extensive package, might not have. On the other hand, by working for so many years on a specific drug and having the topmost scientists in our labs working on these products, there is definitely a significant level of experience within industry on those specific compounds. There is an opportunity for healthy debate, but at the end of the day we need to come to a consensus.

Chu How would you compare the experience, with respect to the drug development process and the decisions that are made in moving forward with a particular agent, that you had when you were in San Antonio, which obviously is viewed as a topnotch academic center, and at Pfizer,?

Denis First and foremost, the early drug development which was the focus in San Antonio has a number of aspects. The institute for drug development focuses on more discovery and laboratory based research, so we have that integration and then trying to translate that to the clinic. The opportunity, which Pfizer and the industry offers, is to follow a specific drug from its inception to the clinic in the further stages of development and potentially to a successful approval in being able to utilize it for patient care.

- Chu Obviously the drug development process at Pfizer is a much more involved, lengthy and broader process.
- Denis I think the drug development process itself is a lengthy process. Pfizer provided the opportunity to put that all within one organization where you move along with the product. There are different challenges and different stages of development, but it is a very exciting place to be as we feel that we are helping progress within cancer research.
- Chu We would like to remind you to e-mail your questions to canceranswers@yale.edu or call 1-888-234-4YCC. We are going to take a short break for medical minute. Please stay tuned to learn more information about the process of cancer drug development with Dr. Louis Denis from Pfizer Oncology.

Medical Minute

Breast cancer is the second most common cancer in women. About three thousand women in Connecticut will be diagnosed with breast cancer this year. But earlier detection, non-invasive treatments and new therapies are providing more options for breast cancer patients and more women are able to live with breast cancer than ever before. Beginning at age 40 every woman should schedule an annual mammogram. You should start even sooner if you have risk factors associated with breast cancer. Screening, early detection, and a healthy lifestyle are the most important thing in defeating breast cancer. Clinical trials are currently underway at federally designated comprehensive cancer centers such as the Yale Cancer Center to make new treatments, not yet approved by the Food and Drug Administration, available to patients. This has been a medical minute and you will find more information at www.yalecancercenter.org. You are listening to the WNPR Health Forum from Connecticut Health Radio.

- Chu Can we give the listeners out there a sense of types of clinical trials that are involved as we try to develop a new agent in the clinical setting.
- Denis Let me start with why a clinical trial. It is key to understand that when we develop these agents, we need accurate and scientifically rigid data to make decisions with continuing to develop the drug. There are always questions to be asked, which we call hypothesis, and they need to be addressed in the setting of a well-designed clinical trial. Once a drug comes into the clinic, the initial focus, of course, is safety. What is the safety profile of this drug? What is the tolerability? What are the potential side effects? Within that first trial, which we call the phase I trial, our overall aim is too objectively, and in a well-defined fashion,

describe and characterize the safety profile of an agent. While we do that, in steps we escalate the dose of the drug until we reach a dose what we would call a maximum tolerated dose, or a recommended dose. At that moment we would have a dose that could be used for further trials. Historically, those initial trials were solely focused on safety and not as much on other components. Currently, with the understanding and improved knowledge of the biology, we are focusing on biomarkers, and other parameters such as specific imaging techniques to understand if any of those are actually hitting the target as we earlier discussed.

- Chu That is a key issue because what we would like to do is get away from empiric therapy, and hopefully develop therapies that are hitting specific targets.
- Denis That is absolutely correct and when we include some of those biomarkers in the early stages of development, we gain more and more confidence in bringing the drug to subsequent and larger trials.
- Chu In phase I studies, do you tend to focus on a particular disease, or do you include patients who have a wide range of cancer types?
- Denis Many times we do realize that these drugs that we bring to the clinic for testing do not have a proven efficacy profile or a proven safety profile, so these are truly experimental agents. We gain more and better insight with the improved methods and models that we have. Before going into the clinic, we have a good understanding of the safety profile of these agents. But still these are truly experimental agents. So many times these drugs are being administered to patients who have previously received standard treatments. We offer the opportunity then to participate in such a trial to patients with all tumor types.
- Chu If a drug successfully goes through a phase I trial and it is found to be safe and there is a hint that it may be active in particular types of cancer, what is the next stage of clinical trials?
- Denis Within that first setting, sometimes, we have hints of activity. This is happening more and more because we better understand the biology. Sometimes we target patients once we have reached a dose that we deem safe and potentially effective. Subsequently, we move to a phase 2 trial where we ask the question, is this drug effective in some specific tumor types? Now it could be a specific tumor type or even within a certain type of cancer. There are several subsets of cancer types which express a specific target, and as such we conduct a number of those trials,

and just to emphasize these trials are not conducted by Pfizer, they are conducted by investigators like yourself in close partnership with the pharmaceutical industry, and then test those drugs in a phase called phase 2 trial for efficacy.

Chu It is a very important point to emphasize to our listeners that you work very closely with academic cancer centers throughout the country and that highlights the close interactions and collaborations that need to take place between industry, academic centers, and ultimately with the National Cancer Institute and the FDA.

Denis That is absolutely correct. We have a focus on quality of clinical trials and work with key investigators such as yourself, Dr. Chu, who have extensive experience in patient care and management and can help lead the development process of some of these agents. Much of the credit really has to go to the investigators and particularly the patients participating.

Chu Absolutely, and we go from phase 2 to phase 3. Tell us a little bit about what phase 3 studies are all about.

Denis We are at the stage where we have successfully passed phase 1 and in some of the phase 2 trials we have evidence of activity. At the moment when some critical evidence of activity has been demonstrated, we like to refer to this as proof of concept, which then could be a trigger to confirm the efficacy in larger clinical trials, the so called phase 3 clinical trials, These clinical trials are really conducted to almost definitively answer the question, does the use of this drug help improve the outcome of the patient? The health authorities rely on these types of well-conducted clinical trials to answer the question of whether such a drug could be considered for approval and then used on patients.

Chu Typically, how long does the process take, starting with the very first phase 1 study to the completion and analysis of the randomized phase 3 trial?

Denis That can be a very significant period of time, 10-12 years is what we are experiencing at this moment. We are heavily focused in accelerating the process. The science is improving significantly. We have a better understanding on how to apply the information that we gain from our trials. What we see now more and more is that while we learn, we improve the process. Historically it had been phase 1 followed by phase 2 followed by phase 3. Now, we conduct what we call a phase 1 early trial, but with the biomarkers and with an early evidence of imaging, we already can get

some hints of efficacy in those very early studies. Subsequently, if we have sufficient confidence, trial design could indeed morph into what we call phase 2-3 trials where we try to accelerate asking the question, getting the early evidence of activity, and then rapidly moving into the confirmatory part of such a trial. There are some hurdles around it because we continue to learn, and by merging the stages of development, you do not really have the opportunity to fully apply the learning of your earlier trials. That is where judgment comes in and we need to determine if we should move ahead aggressively or do the tried and tested way of stage development.

Chu I would think that cancer patients desperately want to see the whole process accelerated so that they have access to newer, and hopefully more effective, safer therapies. I am just curious, how does the FDA view this process of trying to accelerate drug development?

Denis From our prospective it is clear that the FDA has been focusing on accelerating the process. In the oncology setting particularly, there is the opportunity of obtaining what is called an accelerated approval. There are very stringent criteria for such an accelerated approval, but if a drug is indeed developed and shown to contribute significantly to the patient population in heavy need of new medications, the process allows it to become available. From the clinical research prospective, we continue to conduct subsequent trials to continue to get more and more information to confirm those initial findings. It is very important to stress that the drug development process does not really end with the approval. Following approval, there is continued monitoring both from the industry and from the FDA.

Chu In particular they look at whether or not there are new or different side effects that may be coming out.

Denis Absolutely, there are always surprises, but there are also settings where more and more data confirms the improved safety profile that one of these drugs could have.

Chu One question that is always asked of me is why are these drugs so expensive to the patients? Obviously the cynical view is that the pharmaceutical industry is trying to make huge profits, but it sounds like the whole process takes so long and requires so many different steps, that it is not hard to imagine that this is also a very costly endeavor.

Denis It is a very costly endeavor and we would like to point out that overall the cost of drugs is only 10% of the total of healthcare cost. What we are

really trying to do is to develop better treatments overall. Due to the importance of doing scientific and stringent clinical research, heavy investments have to be made in designing the right trials, executing the right trials and gathering the data; that is indeed a very costly process. What drives up the cost mostly, however, is the fact that many of these drugs which we develop do not even make it to the clinic. I have recently experienced where Pfizer invested largely in the development of a new immunologic agent. Phase 2 trials conducted suggested improvement of survival for those patients. We conducted two large phase 3 trials on a global scale and were very committed and excited, unfortunately the results did not work out and those are costs that have to be taken into account.

Chu Roughly, how much would it take to get one drug through the entire process and approved by the FDA, can you give some ballpark figure?

Denis I do not have a ballpark figure available. I have heard the cost of 1 billion raised but it might even be higher.

Chu What is the chance of a drug actually starting from phase 1 and getting approval?

Denis It has been improving. I would say 1/40 would be low and it might even be less.

Chu It is tough odds. I have heard 1/20, 1/40. Louis, I want to thank you so much for being our guest today and hopefully we will have you back on a future show to hear more about what is going on at Pfizer Oncology. Until next week, this is Dr. Ed Chu from the Yale Cancer Center wishing you a safe and healthy week.

If you have questions, comments, or would like to subscribe to our podcast, go to www.yalecancercenter.org where you will also find transcripts of past broadcasts in written form. Next week, Ken Miller speaks with Dr. Robert Udelsman about thyroid cancer.