

Dr. Mario Sznol, The Cancer Drug Development Process June 8, 2008 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 is a medical oncologist specializing in pain and palliative care. He also serves as the Director of the Connecticut Challenge Survivorship Clinic. If you would like to join the discussion, you can contact the doctors directly at canceranswers@yale.edu or 1-888-234-4YCC. This evening Ken Miller welcomes Dr. Mario Sznol. Dr. Sznol is Associate Professor of Medicine in Medical Oncology, and he is here to talk about the process of drug development and clinical trials. Miller Mario, you joined the faculty here at Yale 3 or 4 years ago after a very long career in oncology, and also in the pharmaceutical industry. Can you tell us a little bit about your background in medicine? Sznol I started working for the part of the National Cancer Institute involved in drug development and I spent 12 years with them. After that I went to a small biotech company and directed their development of a very novel agent and then returned to Yale. I had a long experience with drug development in the government and in the industry. Miller Having been in all those different environments, can you give us an overview of the process of drug development, which people often refer to as bench to bedside? Sznol It is a very long process. It starts first with the discovery of something that has anticancer activity. There are two ways to find an agent that has anticancer activity. One is to take chemical compounds and basically screen them against cancer cell lines that are growing in test tubes, and something that actually has activity you take forward in further development. The more exciting approach over the past 10 years has been the ability to define the mechanisms that drive cancer progression, the exact molecular mechanisms, and then screen chemical agents against specific targets to see if any of them have anticancer activity. The latter approach allows you to define agents with very specific mechanisms of action and we think those agents are more likely to work in the clinic than the ones that are discovered empirically. Once you have an agent that has anticancer activity, there is a very long process to turn that chemical into a drug that you can give to patients. Subsequent to that, there is a very long process of clinical testing to actually develop the data that will eventually allow you to say the drug actually works in patients. Miller Thinking about drug development, I have heard it referred to like a funnel. A bunch of new possibilities come into the top of the funnel and at the bottom comes out a small number. Can you tell us a little bit about that, how many drugs are looked at originally for every one drug that is a good one? Sznol I am not sure that I can give you an exact number, but I can tell you that it is many, many drugs leading to a very few that are ultimately approved at the end. We tend to use the number that somewhere around 10% of drugs that enter clinical trials in cancer will ultimately make it for approval by the Food and Drug Administration. Many drugs fail in the initial processes of clinical testing, either because they are toxic, or because they just do not have the right activity. Miller Patients often ask why it takes so long for a new

treatment to become available. Why is that? Sznol First of all, often we just hear that a gene is active in cancer, or that a gene drives the cancer, and from just understanding the biology of developing a drug against that target can take a very long time, but it is also very important to remember that just taking a chemical entity and making a drug, in other words putting it into a vial and making sure that it is safe, being able to manufacture the drug, and then testing it in the clinic, can take years and years. For example, it can take a year just to find out the right dose and schedule for a drug, and it can take 3 to 5 years to do the final clinical trial that determines whether a drug works or not in patients. If you are thinking about the initial discovery of the drug in the test tube to final data in a randomized clinical trial that shows that it works, that could be a process of 7 to 10 years. Miller Which is a very long time and all those safety nets are in place to assure that it is the best drug for the patient? Sznol Absolutely. You do not want to have a drug on the market that does not work or has unpredictable toxicity. Even if it has toxicity, you have to understand how to manage that toxicity so you can give it safely. Of course, you want to know ultimately that a drug works, and to know that a drug works can take a very long time, but particularly the safety issues, you need a lot of information and you need to treat a lot of patients to know how to manage the drug well. Miller What role does the government play in cancer drug development? Sznol The government plays many roles in development. First of all, it funds much of the basic research and much of the clinical research required to take an agent from the bench to the bedside. The government does its own drug development, so not only does it fund it, but it also has a drug development arm. The National Cancer Institute, for example, has a group that is very much like groups that are present in pharmaceutical companies that develop drugs. Finally, the government is involved in the regulation of both clinical research and ultimately drug approval. Miller There has been a lot of publicity on fast track approval. How does that differ? People talk about the FDA having a fast track, what does that mean? Sznol http://www.yalecancercenter.org/podcast/Answers_Jun-08-08.mp3 into mp3 file Sznol All that really means is that the FDA commits to reviewing an application for approval in a somewhat more compressed time manner, but it does not really speed the process of drug development as much as what might be thought in the community. You still have to do the phase I trials, you still have to do the phase II trials, and you still have to do the phase III trials. It is only once you gather all of that information that the fast track process really kicks in. Miller Interesting. So all the work still has to be done, but it sounds like then the final review is quicker? Sznol It can be faster. Yes. Miller Can you review with us what is phase I, II, and III? Sznol Remember that when a drug comes into the clinic, there is no information. We do not know what dose to give, we do not know what schedule to give. So, we have to start at a very low dose and escalate the dose slowly. The first dose that you want to give to patients has to be low by definition so that it is safe, and then you escalate the dose in small groups of patients until you find what is called the maximum tolerated dose. That is a phase I trial, where you actually determine a tolerable

dose and schedule. Then, the drug goes into phase II trials, which is activity testing. You want to know whether the drug has activity and whether it causes tumors to shrink, or you use other measures such as improvement in symptoms, but even then it is not absolutely clear that activity translates into benefit, for benefit you need to do a phase III trial. Phase III trials are randomized trials either adding the drug to standard therapy, or comparing the drug to standard therapy. It is in those randomized trials where you really determine the two measures of benefit, which for patients is an improvement in symptoms or increase in their lifespan. Miller The other thing that we hear very frequently from patients and in the press is that new medicines cost so much money, especially some of these new targeted drugs. Why are they so costly? Sznol The process of drug development is just enormously expensive. I will give you an example. A patient who goes into a phase III trial, the final phase of drug testing, it can cost the company up to \$50,000 per patient to enroll the patient, collect the data and pay for all the other necessary tests that need to be done in order to develop the data that ultimately is submitted for registration. So, if you think about a clinical trial or phase III clinical trial, at the last stage there might be 1000 patients; a \$25 million to \$50 million investment just at this stage. We estimate that it may cost \$75 million to \$100 million to get a drug from test tube all the way to registration at the FDA, and you are not only paying for the development of that drug, you are also paying for all the costs of developing the other drugs that failed in the clinic. Sznol http://www.yalecancercenter.org/podcast/Answers_Jun-08-08.mp3 Miller In your career, have there been drugs that you worked with from the bench that made it all the way to practice, or close to it? Sznol Very few of us have had the privilege of working with a drug from the test tube all the way to registration. I have been involved in the registration process. For example, the drug interleukin-2, I was very involved with the clinical development and the registration of that agent, but I cannot say that I was involved from the very beginning to the very end for any drug and there are very few people who can claim that. Miller It also sounds like it is a very, very long process in someone's career. Many people hear about medical breakthroughs on the news and then they go to their doctor and they bring the article with them and then the doctor says that therapy is not available yet. Any advice for patients who are in that situation, they go to their community doctor and they are not able to get the drug on the market. Are clinical trials useful to participate in, in that situation? Sznol It really depends on what the breakthrough is. If the breakthrough is that the drug cures cancer in a mouse, I can assure you that that would be many, many years before that drug would be available to patients. If the drug is already in the clinic, they may be able to access it through a clinical trial. Sometimes, for example, if the information comes from a late stage clinical trial then that drug might actually be available through compassionate use programs that are usually setup at major cancer centers. It depends, but the best thing to do would be to check with an expert in the disease and to see if that drug is currently available for treatment of patients. Miller You mentioned compassionate use, what does that mean? Sznol

Many times, as you know, when a drug is being developed data is generated that shows that it actually works, or at least a very strong suggestion that the drug works, but it takes time even from that information to final registration approval and marketing by the FDA. So, the FDA has a process in which drug companies can provide the drug through a clinical trial mechanism essentially to patients who would not be able to get the drug otherwise, so it looks like a clinical trial, but in fact it is a treatment protocol. Miller So in a sense it is trying to make the drug available a little bit quicker for people that have problems. Sznol That is exactly right. It is being made available for treatment as though the drug works, but it is not commercially available so it is being made available through a compassionate use clinical trial. 12:12 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Jun-08-08.mp3 process. Under those circumstances, the eligibility criteria is much looser, so many more patients can get access to the drug than might be able to get the drug in a clinical trial. Miller Are those drugs provided free of charge in that setting? Sznol Almost always they are provided free of charge. Miller There are different settings and you have talked a little bit already about where drug development is taking place, there is the federal government, there are pharmaceutical companies and academic medical centers. What are some of the differences in the drug development process in those settings? Sznol Well the government and industry develop drugs in very similar way. Academic centers do not actually do drug development, they participate in drug development. Drug development is the entire process of taking a molecule from the very beginning to the very end, whereas academic centers are involved in drug discovery and they are involved in individual clinical trials, but they usually are not involved with the entire process from beginning to end. Miller It sounds like that portion of it is almost a Herculean effort with many different people involved in different laboratories. Is that fair to say? Sznol Yes, the collaborations between industry and academics are very strong and they need each other in order to develop drugs successfully. It is very important to have drug companies involved in this process because they are the ones who oversee and are actually invested in the success of that drug. After all, if they were not involved, who would be available to manufacture or produce the drug, put it in a vial and make it available in the market place so that the patients have access? They are very important in the process. Miller Well we would like to remind you that you can e-mail your questions to us at canceranswers@yale.edu. We are going to take a short break for a medical minute. Please stay tuned to learn more information about drug development with Dr. Mario Sznol from the Yale Cancer Center. 14:28 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Jun-08-08.mp3 early detection, and a healthy lifestyle are the most important factors 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 now 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 public radio. Miller Welcome back to Yale Cancer Center

Answers. This is Dr. Ken Miller and I am here today with Dr. Mario Sznol from the Yale Cancer Center discussing clinical trials and drug development. Mario, we have been talking a little bit about clinical trials. Why are they important to patients and why they are important to medicine in general?Sznol First of all, without clinic trials we wouldn't make any advances in clinical medicine. In cancer the truth is we do okay, but for the most part our treatments in advanced cancer are not very effective, so we need clinical trials in order to find better treatments for patients. For individual patients, often times standard treatments are not optimal. They may get some benefit from it but they may not be cured. A clinic trial may offer them a chance to have even a better outcome in that setting.Miller You are very active in clinical trials here at Yale. From the work that you are doing, what is an example of a clinical trial that you are excited about here?Sznol As an example, we are going to be bringing a drug into clinical trials. We did not discover it, but we are going to be collaborating with a pharmaceutical company on an agent that works specifically in the tumor microenvironment to block the tumors defenses against immune responses. Essentially it will help enhance the immune response to attack and kill tumors. Now that drug is in early clinical testing, so this will be a phase I trial in which we will look at escalating doses and prolonged treatments schedules. In that clinic study, we will study the immune responses of patients and we will observe for antitumor responses. We are very excited about this drug because both from a biological perspective and a clinical perspective, the animal model data it is a very active agent.Miller It sounds like a fascinating trial to be able to look at how the immune system might help defend against cancer. It actually brings up the topic that I look as modern approaches to clinical trials. How does your approach differ from what would have been done 15 years ago?Sznol Because we now understand the mechanisms of these drugs, or at least have a better understanding of the mechanisms of these drugs, there is a great deal more emphasis on early clinical studies, and in lay clinical studies, to obtain blood and tissue from patients and to verify17:27into mp3 file http://www.yalecancercenter.org/podcast/Answers_Jun-08-08.mp3 that whatever effects we were seeing in the test tube and animal models actually occurs in patients. If we do this early in the clinical developmental process, we do not know for sure that the drug works, but we know the drug at least has the right biological activity and it gives us encouragement to proceed and do the larger phase II and phase III clinical trials. Sometimes if a drug does not work when we do these biological studies, we understand why the drug didn't work and then we can go back to the lab and develop better drugs for patients.Miller So you are saying, in a sense, you know what the target is, and what are you going after, but if you find very early on that this drug does not hit the target, you might be able to build a better drug?Sznol Absolutely, sometimes it does not hit the target for simple reasons, you do not get the right blood levels, we find out that it has metabolized incorrectly or sometimes we find that maybe that target is not as important in humans as we thought it might be. There is another very interesting use for markers, which is to select the patients that may respond. Remember, even for a single disease, breast

become involved in a clinical trial?Sznol That is a very difficult question and they need to have a very long discussion with their physician about all of the options; both standard treatments and investigational treatments. If their physician is not terribly familiar with clinical trials for that specific disease indication, it is worthwhile to get a second opinion with an expert in that disease who understands all the clinical trial options for that disease.Miller What is the process of informed consent? What does that mean and how does that translate to day-to-day practice?Sznol We have developed, over a very long period of time, a process in which patients are informed22:57into mp3 file http://www.yalecancercenter.org/podcast/Answers_Jun-08-08.mp3 completely of the risks and benefits and their rights within a clinical trial. It is incorporated into often a very long document that we provide the patients to read so that they know exactly what they are going to get, what kind of drug they are going to get, when they are supposed to be in the clinic, how much blood is going to be drawn, what the risks of the trial are, and their rights too, for example they can withdraw from the study at any time. The informed consent also informs them of all the confidentiality protections that are now in place for patients. It gives them phone numbers to contact for the physicians and also for the ethics review board at the institution where they can ask questions or make complaints if necessary.Miller It sounds like it is a pretty thorough document.Sznol Very thorough document and in fact one of the things that we are concerned about is that they have so much information that sometimes it is hard for the patients to go through at all.Miller Do you get a sense, in the United States, of what percentage of people with cancer are being treated on the protocol?Sznol Unfortunately, it is a very low number. It is probably less than 10% and some people have estimated as low as 2% or 3% of all patients with cancer go on clinical trials. That is a shame because clinical trials are often the best option for patients and it is the only way we are going to advance the field.Miller In terms of informed consent, there is a lot of discussion about risks and benefits. What are some of the risks associated with a clinical trial?Sznol The major risk is that you are getting an investigational agent, and therefore, the full side effect profile is not known. Even though there is information from animal models and from patients who received the drug before, there are always unexpected side effects that may occur. That is really the major risk.Miller And the benefits on the other side would be what?Sznol The benefits are unknown. That is why we are doing the clinical trial. We have an idea about what the benefits might be, but the fact is it is a clinical trial and that means we really do not understand the benefits. For many clinical trials, there may be no benefit at all.Miller What is some of the clinical research you are involved with now that you are excited about?Sznol In general, there are early phase clinical trials, so very novel drugs that are being tested in phase I25:18 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Jun-08-08.mp3 studies. Those are very good option for patients in which all standard options have been exhausted. There are also phase II trials in which we know something about the drug and the drug's range, from drugs that target blood vessels

to drugs that activate the immune system, to very novel drugs that blocks signaling pathways in cancer cells; a wide variety of mechanisms of action and very interesting new agents. Miller Can you give us an example of any one trial that again you are particularly excited about? Sznol I'll give you an example of two trials. One is at one end of the range, which is a compassionate use study of a new immune therapy called anti-CTLA4. This is a very powerful activator of the immune system, so powerful that it can sometimes cause side effects of turning the body's immune system against their own tissues, but we and others have seen some incredible responses. Unfortunately they are only in a small number of patients, but we've seen incredible responses in patients who would otherwise have been refractory to all other kinds of treatment. We are very excited about this agent. It is in very late stage clinical testing. At the other end of the spectrum, we are testing a very novel immunotoxin which is essentially an antibody that binds to the surface of tumor cells and attached to this antibody is a toxin. It is like a Trojan horse that enters inside specifically into melanoma cells. Once it is inside the cells, it releases the toxin and kills the melanoma cells from the inside. That is an early stage clinical trial but we are very excited about this kind of an agent. Miller On one hand it sounds like Star Wars and on the other end it sounds like these things may make a big difference for patients. Sznol We will certainly have to prove that, but yes. Miller Mario, I want to thank you. This has been a terrific program. This has given us, and myself as well, an improved understanding of what happens in drug development. I want to thank you very much for joining us on Yale Cancer Center Answers. Sznol Thanks for having me Ken. Miller From all of us here on the program and from the Yale Cancer Center, we want to wish all of 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, you will learn about the surgical treatment of esophageal cancer.