An Address From Dr. Richard Pazdur: How the Changing Landscape of Oncology Drug Development and Approval Will Affect Advanced Practice

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INTRODUCER Good afternoon and welcome back. My name is Jack Gentile. I am the Chairman of Harborside, the conference organizer for this meeting, as well as the publishers of *JADPRO*, the *Journal of the Advanced Practitioner in Oncology.* I am also very proud to be a founding member of the Board of Directors of APSHO. The time I have spent with advanced practitioners in oncology has been one of the highlights of my career. I have been the beneficiary of your hard work, your skill, your humanity, both as a publisher and a patient. I am delighted to be joining you here today. One of the other highlights of my career has been the time I have spent working with the keynote speaker, Dr. Richard Pazdur. The title of Dr. Pazdur's lecture is "How the Changing Landscape of Oncology Drug Approval Will Affect Advanced Practice." I have known Rick and his wife Mary for 20-plus years, going back to his days right here in Houston at MD Anderson. And while Dr. Pazdur really needs no introduction, I am going to embarrass him and give him one anyway. Dr. Pazdur is the Director of the US Food and Drug Administration's Oncology Center of Excellence. He also continues to serve as the Director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research. In these dual roles, he has led the charge for safe, thoughtful, and accelerated reviews for new therapies and cancer. At a time of rapid advancement in drug development, Dr. Pazdur has been right there in the forefront. Prior to joining the FDA, Dr. Pazdur

was a professor of medicine at the University of Texas MD Anderson Cancer Center. He is a proud son of Chicago. He is a graduate of Northwestern University, the Loyola Stritch School of Medicine, and clinical training programs at Rush Presbyterian and The University of Chicago. Dr. Pazdur has published hundreds of articles, handbooks, and textbooks—few of which I am very happy to say were with me. He has won many awards and has appeared on many noteworthy lists of who's who, including his 2015 listing in *Fortune Magazine's* 50 Most Powerful People in the World, But most importantly, he has made a profound difference in the lives of countless patients with cancer. He is a clinician, a researcher, a regulator, a teacher, and a leader. He is one of my heroes and, luckily for me, one of my friends. Please join me in welcoming Dr. Pazdur.

RICHARD PAZDUR Thank you, Jack, for the very warm introduction. The title of my lecture is listed on this slide and it is "How the Changing Landscape of Oncology Drug Development and Approval Will Affect Advanced Practitioners." What is the most important word on this slide? Change. My late wife always commented when I asked her the question, "Who likes change?" and she would say the only person that likes change is a baby with a wet diaper, but we all have to face change. Change comes from societal expectations of government, for example, the FDA, of the medical profession, of the nursing profession, of advanced practitioners. It is the result of scientific changes that affect us all and how drugs are developed, how therapies are developed. Before I begin my talk, I would like each one of you to think about the

changes you all have experienced in the field of oncology over your careers. One of the advantages I have compared to some of you in the audience is gray hair, so I have a perspective that dates back to 1979 when I began in medical oncology. Let me just share with you what oncology was like in 1979, and I realize that many of you may not have even been born in 1979. For CML, the only therapy that we had was hydroxyurea and busulfan. The only therapy that we had for the treatment of melanoma was DTIC. In colon cancer, the only drug that we had was 5-FU. Renal cell—the only drug we had, probably many of you won't even recognize it, was a hormonal therapy called megestrol acetate, which was a progestational agent. The landscape of oncology has changed dramatically throughout the entire years that I have been involved with it. And for each one of us that is sitting in the audience, we should ask ourselves where will we be in the next 40 years and what will our therapies look like, what will our diseases look like? Because, in addition to these therapies that we have developed, the diseases have also changed, and we no longer just speak of lung cancer as a single entity, but we refer to it as EGFR-positive mutational status lung cancer, or ALK-positive lung cancer, BRAF-positive lung cancer, so the diseases themselves have changed, and I think it is important for us to realize that.

Here are some of the learning objectives of this talk, and I hope you will find it an interesting talk as I will try to explain what we do at the FDA and how, as a government agency, we have to be responsive not only to the scientific changes but also to societal expectations. The FDA is a governmental agency,

and hence we have to be receptive to the needs of the American public. I have no financial conflicts of interest.

What is the FDA? First of all, some of you might think the FDA stands for Federal Drug Administration. No, it is the Food and Drug Administration. The FDA is responsible for the assurance of safe and effective medicines for the American public and for the security of those medications. For our purposes in oncology, we are talking about drugs and biological devices, medical devices, which include in vitro diagnostics, such as the diagnostics test to identify populations that may benefit from precision medicine, the food supply of the county and radiation products. The FDA is responsible for about $0.25 of every dollar spent by Americans, so the FDA is the regulatory agency for about one-fourth of the American economy.

There are many misconceptions about the FDA. First of all, we do not take cost into consideration. When we are meeting with sponsors and evaluating a drug for approval, we look at the science, the safety, and the efficacy of the product we are looking at. We do not look at what the drug will cost, nor do we have discussions with the companies that we regulate with regard to the eventual pricing of the drug or the product. We also don't regulate the practice of medicine. What the FDA does during our approval process is determine whether an application in front of us is safe and effective, and many times it may be used in the practice of medicine in off-label indications. That is something that the FDA does not regulate.

At the FDA, there are many centers, but the three most common centers that oncologists deal with are the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER)—they were involved with the most recent Carticel evaluation—and the Center for Devices and Radiological Health (CDRH), and as I mentioned, that center probably impacts the medical oncology mostly with regards to the approval of in vitro or companion diagnostics.

When I began my job at the FDA—and now I am going to begin my 18th year there—we had about 10 medical oncologists. To show you how rapidly the field of medical oncology has grown at the FDA, there are now over 80 medical oncologists that work at the FDA, and when I use the word medical oncologists I am also referring to about 15 or 20 pediatric oncologists that also work with us. At the time that I began at the FDA, everybody was a jack of all trades. Our reviewers did lung cancer, breast cancer, hematological malignancies, GI malignancies. The same reviewer would review the same application. It became quite apparent to me about 10 years ago that we really needed to change our structure at the FDA, so we did something very similar to what occurs in academic departments of oncology. We specialized in specific malignancies, so we have various divisions—they are listed there on the slide—with disease-specific teams ranging from breast cancer to melanoma sarcoma, to lymphomas. And also we have a group of people that work with us that look at the preclinical evaluation of these drugs, and they are toxicologists that come up with a starting dose of the drugs and the escalation schemes in phase 1 and early-phase

studies. Most recently—and this was created basically about a year ago now—with the advent of the last administration, the Moonshot program by Joe Biden, the FDA Center of Excellence, and I was honored by being named the Inaugural Director of the FDA Center of Excellence. What the FDA Center of Excellence does is work with all of the medical oncologists in the FDA to provide a comprehensive evaluation of drugs. We evaluate drugs for the prevention, screening, diagnosis, and treatment of cancer. We work with our colleagues in CDRH to develop companion diagnostics. We develop and promote the use of methods created through the science of precision medicine, and we also, most importantly, incorporate the view of the patient in making regulatory decisions. The FDA has spent a lot of time and interest over the past few years looking and trying to incorporate the patient's viewpoint in the approval process. This new center, which has begun over the last year or so, is aimed at really organizing medical oncology.

The way, as you saw, that the FDA was set up, was focusing on the products that the FDA regulates. For example, there was a center that regulates drugs, a center that regulates biologics, a center that regulates devices and that represents the industries that the FDA regulates. This is where I get into the topic of change. What we heard from the community, from patients, from the American public, is that they want an FDA that really represents how patients are treated. Patients go to a doctor, for example, for the treatment of cancer. They don't go necessarily to the doctor for the selection of a biologic therapy or the selection of a drug or the selection of a device, but really for a more comprehensive approach

to the treatment of their disease. The Center of Excellence was aimed at establishing that more comprehensive approach to evaluation of drugs and bringing in a patient focus.

When I began at the FDA in 1999, oncology was a very, very small area. Let me ask you this question, when you consider all of the drugs that are being developed in the United States, drugs that are for cardiovascular diseases, infectious diseases, psychiatric drugs, neurologies, pain medications, anesthesia agents, what percentage of drugs are the oncology drugs? It's about 40%. This represents a huge undertaking by the pharmaceutical industry in the developing of a specific discipline of drugs, or a specific class of drugs. It is the largest class of drugs that is presently being developed by the pharmaceutical industry. But oncology drugs are different from other drugs, and the field of oncology is much different than, for example, cardiology or psychology, etc. I have attempted to list here some of the differences that we have because they really impact us as to how we look at drugs at the FDA. First of all, oncology drugs are being used for the treatment of severe and life-threatening diseases. This is important to realize because there is an urgency; we have to approve drugs in a timely fashion because people's lives are at stake, and many times people want these drugs and we have various programs already established to allow patients to access unapproved drugs, but there is a necessity to evaluate these drugs in a timely fashion. There is a large public interest in oncology. If you take a look at any of the newscasts that one looks at throughout the weeks, there is almost always a story about oncology or some type of improvement of cancer treatment, or some

type of cancer-related story. Most important, also there is a different risk tolerance for side effects of oncology drugs. As a discipline, we have accepted severe and life-threatening disease. For an oncology drug, frequently we would even accept some mortality that is associated with a specific therapy. One would not see that in other therapeutic areas, for example, the development of drugs for an antibiotic or an antihistamine or some other discipline that treats benign or non-life-threatening diseases.

We have also a very active advocacy group. We have many diseases in oncology. There are probably over 100-plus indications with advocacy groups ranging from melanoma to myeloma to breast cancer to GI cancers to sarcoma, and they want a voice in the development process of these drugs and also the approval of these drugs. It is also a very active area of biomedical research. As I mentioned before, about 40% of all drugs that are being developed in the United States are in the area of oncology. That is much different from when I began in the field in 1979. When I began in the field in 1979, to give you a scope of the activity of drug development in oncology, there were probably, in 1979, about 35 oncology drugs. This year alone we will approve 15 new molecular entities. Last year, we approved about 15. The year before that, we approved 15. The year before that, we approved 15. The year before that, we approved 14. You can see that the field and the complexity of the field has increased. In addition, it's not just about the number of drugs; it's also about the innovation that has occurred. Of these molecular entities that we are talking about, about 50% of these are breakthrough therapy products, meaning that they are substantial improvements

over available therapies. Hence, they really indicate a major advance in the field of the treatment of selective patient populations that are suffering from serious and life-threatening malignancies. We also have biomarker-defined populations, and all of us recognize, for example, in lung cancer how that field has tremendously changed with the genetic subtyping of malignancies. Again, when I began in the field of medical oncology, we had 2 types of lung cancer, non–small cell lung cancer and small cell lung cancer. Obviously this is not the situation that we see in the present therapeutic environment, and this represents an understanding of the basic concepts, the basic pathogenesis of these malignancies.

I just wanted to talk a few words, kind of an FDA 101, to give you the context of how the society has impacted changes in the approval process. The traditional approval process, what is also called full approval of the drugs, requires substantial evidence of safety and efficacy. It is usually required that two adequate and well-controlled trials be done, and it is usually based, the approval, on the prolongation of life, meaning an improvement in overall survival, a better life usually associated with an improvement in a patient-reported outcome, or an established surrogate for either of these. In AIDS, it would be HIV viral load that is an established surrogate. There is no comparative efficacy for traditional approval. In other words, we approve a drug based on a survival advantage. They don't have to be better than a drug that we approved say a month ago or a year ago, etc. It's the demonstration of safety and efficacy, not being better than another drug.

There is another type of approval pathway that occurs, and this is called accelerated approval. How many of you saw the movie *Dallas Buyers Club*? How did that paint the FDA? Quite negatively. In fact, when I was watching the movie, I remember I was watching it alone, I felt like crawling under the seat. Luckily I didn't have a name badge on or anything like that, but it painted the FDA as a very anti-patient, bureaucratic, inflexible—I don't know what other negative word one can use, but it was quite negative. Because of that, not because of the film, but because of the experience with the HIV epidemic at that time and the need to have a more flexible regulatory environment, Congress established an alternate pathway of approving drugs for life-threatening disease, and this is a pathway that's called Accelerated Approval. Rather than demanding that every trial require a survival advantage, it allowed the FDA to expedite the approval of drugs by looking at surrogate endpoints, such as response rate or time to progression or progression-free survival, that is reasonably likely to predict clinical benefit. In these situations, these newer drugs that come out of this pathway must show a benefit over an existing pathway, and they are subject to additional trials after approval to demonstrate an improvement on an established clinical benefit endpoint.

This brings us to the question of what is clinical benefit and what is benefit to patients? The FDA has, in guidance, etc., stipulated that benefit for patients is generally, as I stated before, an improvement in survival, in the quality of life, or an established surrogate, or how a patient feels or functions or survives. This spans across all therapeutic areas, but in an area of very rapid drug development

that we are at now in the present kind of therapeutic milieu that we face, are these the only endpoints that we should be looking at or should we be looking at additional endpoints and calling them clinical benefit? And these other endpoints that I am talking about are response rates, progression-free survival, etc. For example, I think people would be hard-pressed not to agree with me that if a person has a large tumor, say an 8 x 7 cm mass in their chest, and it goes down by 50% to 3 x 3 cm or less, that would not be benefit to the patient given an adequate safety profile. Likewise, if you have a rapidly progressive disease, and you slow the progression of that disease, most reasonable people would say that's a benefit to that individual patient. We in the agency have begun thinking of alternative ways of looking at what constitutes real benefit to patients that we are treating. We take a look at efficacy endpoints, and this is what I'm talking about, it's the endpoint of a clinical trial. When we are selecting a primary endpoint for a randomized trial, or even a single-arm study, a nonrandomized study, we take a look at what endpoint we are looking at—and I will go over some of these endpoints with you,—how accurately it is being measured and what is the magnitude of benefit of a particular endpoint. Obviously, there is a difference between a response rate, that somebody might have, that would be 15%, versus a response rate that would be 80% in evaluating a drug. Likewise, the measurement characteristics, if one had difficulty in measuring an x-ray where the disease was very ill-defined, for example, in peritoneal carcinomatosis, which may not have the same confidence in assessing a response rate as in a patient that had a very well-demarcated tumor that was clearly circumscribed on a

clinical x-ray. In addition, when we are talking about endpoints, we have to take a look at how much interpretation is required and how accurately the timing of the event is required, and this is particularly true for radiographic endpoints, such as time to progression or progression-free survival. As I stated before, the primary endpoint that many of our trials are based on, and that is kind of the gold standard, is overall survival, and that has many benefits to it. It is a direct measurement, as I stated before, of clinical benefit. It's not prone to any bias. Obviously, the patient is alive or dead; there is no interpretation of that event. There is exact timing of the event, and it includes also important safety information. Many people forget that the evaluation of overall survival is not only an efficacy endpoint, but it is also an important safety endpoint. Even when we approve drugs on other endpoints, we always look at the overall survival of patients to make sure, particularly, that there is no detriment in the overall survival of patients.

Why can't we just require all trials to demonstrate overall survival? Wouldn't that make everybody's life really easy? There are certain limitations and situations where it may not be practical to look at overall survival. Usually these trials are longer. They are larger trials. They require a randomized control trial, so one has to do a randomized trial. This endpoint cannot be accurately evaluated in a single-arm trial, and it also could be confounded by crossover. Also, in determining the value of an effect on overall survival, one also has to take a look at the magnitude of an overall survival claim. Obviously there would be a difference in a drug that had a 2-month improvement in median overall survival

compared to a drug that had a 2-year improvement in overall survival. So why can't we use overall survival? I have mentioned some of these issues, but let me just give you some practical considerations. As I stated before, you need a randomized trial, and in some situations that may not be practical. For example, as we deal with relatively rare diseases and smaller populations where you may have 100 patients nationally or a couple hundred patients nationally having the disease, the numbers simply might not be there. In some situations you might have diseases, now that we have had many drugs approved, where the natural histories of diseases, such as in multiple myeloma and CLL and indolent lymphomas, are very, very long, spanning years and years and years, to demand an improvement in overall survival, may simply just be impractical. Thirdly, and most importantly, is a concept, which I will come to later, and that is the lack of equipoise. When one does a randomized study, one has to feel that both of the therapies that you are randomizing patients to are equal. Many times we have antecedent information that comes to us that does not allow us to be in a state of equipoise. Let me give you an example of that. For example, if we have a new drug that has a response rate in a phase 2 study of 80% and the control arm, or the standard therapy, has a response rate of say 10%, who would go on a randomized trial facing a life-threatening disease and go and take a drug that only has a 10% or a 12% response rate. Sometimes we have information that is available to us that allows us not to do these randomized studies. This is becoming particularly true as we look at molecularly defined subgroups of patients or particularly now with some of the more targeted agents or biological

therapies where we have information available to us that really prevents us from doing a randomized trial because equipoise has been lost.

I have listed here some of the other endpoints that we use in evaluating drugs. Many of you are familiar with them; I am sure you all read the oncology literature. Response rates, time to progression, progression-free survival, and their definitions are listed on this slide. These are radiographic endpoints. They usually occur earlier than overall survival and so they are more practical to use in situations where the survival of patients may be very prolonged. The radiographs can be stored. They can be measured by expert panels. They are not confounded by the crossover of drugs, for example. At the time of progression, patients may switch to an alternate therapy and that may confound the interpretation of overall survival. Nevertheless, they do have limitations associated with them. By their very nature they are radiographic endpoints, and we are all familiar with the sometimes subtleties in reading radiographs and that can lead to some potential, even bias, that can be introduced in these radiographic endpoints. Nevertheless, when we take a look at large affects on these endpoints, we believe that frequently these can be interpreted as benefit to the patients as I mentioned previously.

As I mentioned before, our thinking at the FDA has evolved over the years on what endpoints to use for the approval of oncology drugs, and this is not only a reflection of a greater emphasis on the patients being involved in the regulatory process, but also on scientific advances that have occurred over the years. I point out to you that it would be kind of static or inflexible to say that we would

use the exact same criteria that we would be using in the 1960s and using those exact same criteria for approval that we would be using in the year 2018 given the amount of scientific information we have now on how drugs may work. In the 1970s, when oncology was in its infancy, and there was a limited set of available therapies; tumor shrinkage or response rate was considered clinical benefit, and used for regular approval. All of the common drugs that are the “old folks drugs” as we would call them, or the antiquated drugs in oncology that we still use and are truly effective, such as vincristine, cyclophosphamide, doxorubicin, bleomycin, you name them, they were all approved on the basis of response rates. Then in the 1980s what happened is we had a development of a lot of toxic marginal drugs and the advisory committee said, “Well, better hold off on these response rates because of the toxicity of these drugs.” You have to balance that toxicity against efficacy. You need randomized trials that show a direct clinical benefit, namely an effect on overall survival. For the most part, that was our belief through most of the 1980s, 1990s, and the early part of this millennium. Then this happened. What is this? It is an understanding of the molecular basis of disease, and this started to change our approach to the evaluation of oncology drugs. This was the approval and the publication of imatinib in CML. What we had here was truly the first targeted therapy with complete hematological responses in 53 out of the 54 patients that were treated. Before this, remember, the therapy for this disease was quite marginal, busulfan and hydroxyurea and interferon. But what we had here was truly a breakthrough therapy, which required a retooling and a rethinking of how drugs should be evaluated. We have

seen unprecedented response rates coming out since the advent of imatinib. We have had enriched populations where we take a look at populations that are defined by biomarkers, by companion diagnostics. We have an environment where we have a very strong understanding of how these drugs work on the disease.

You have listed here some of these early breakthrough therapies with response rates that were unheard of. For example, for ALK-positive lung cancer with crizotinib response rates of 60%, in EGFR-mutant non–small cell lung cancer of 61%, in Hodgkin's disease that went refractory to other therapies, an overall response rate of 75%—truly response rates that we had not seen before. The response rates that we had generally seen for cytotoxic chemotherapies were 15%, 18%, 20%—nothing in the range that we were seeing here with these targeted populations. So here again, being a public agency, one that is tasked with the approval of safe and effective drugs, we needed to rethink how we were looking at these drugs and how we should evaluate them, and just to say we are going to demand an overall survival for all of these drugs would be putting the patients second and putting the clinical trials first. If you could remember one thing from this talk, it is something that I heard from a patient advocate, and it is clinical trials are here to serve the patients. The patients are not here to serve the clinical trials. Hence, we have to rethink with each application we get, based on the information that we have at a specific time, what makes sense for the approval of the drug. It is not simply a cookie-cutter approach of two randomized trials that demonstrate a survival advantage, because here again, with these

response rates that we are seeing with these drugs, how many patients would actually go on a randomized trial in these disease settings to prove a survival advantage?

Nevertheless, looking at response rates does require us to have a degree of scrutiny of these response rates. We generally stated a drug has a response rate of x%, 20%, 30%, 50%, you name it. But there is much more that goes into the evaluation of that number. First of all, the location of the tumor, for example: a tumor in the CNS may have much greater importance to us than a small tumor in the lung, the number of complete responses. If one therapy has a complete response rate of 30% of 40% and another therapy has a complete response rate of 2%, those drugs are markedly different. What was the initial tumor burden that one observes? If one sees a mass in a liver that is 50% or 60% of the liver and it shrinks down by 80%, that's much different than a 1 x 1 cm nodule disappearing from the tumor. How many patients' tumors are reduced, but are not captured in the current RECIST criteria? We also take a look at that, with waterfall plots. Most importantly is the duration of responses. Much different situation if a response lasts 2 years compared to a response that lasts 2 months. We take a look at all of these factors in evaluating these. There are some situations that response rates are obvious clinical benefit, and I have shown two of these here. They are cutaneous malignancies where it is obvious from the photos that the patient has a benefit to these therapies. One is a C-peptide response and the other is in the left-hand corner, a response to basal cell carcinoma with

vismodegib. These are direct evidence of clinical benefit. These do not need a randomized study to demonstrate clinical benefit.

I mentioned before, and I'm going to skip over this, because I have already introduced this concept of equipoise and that is the need for physicians, patients, and all of the stakeholders that participate in clinical trials, to have clinical equipoise when we are conducting a randomized trial. There has to be a belief that these treatments are equal before we randomize patients. If we have preceding information that one drug is better and we are convinced of that, we no longer have equipoise, and therefore we have to question whether a randomized study can be done. Some of the barriers to randomized clinical trials are listed here, and I mentioned these before, visibility and low frequency populations, and this is becoming more of a problem, especially when we are molecularly defining populations of patients where there may be just a couple hundred patients in the United States or even worldwide that may have the disease. By crossover, I mean at the time of progression, where people or patients are treated with the other drug in the other arm. Obviously at the end of the day, the patients will have equal treatments. They will just be administered in a different time sequence. As I mentioned before, there can be ethical issues when intervention is highly active and the comparator has minimal efficacy and is also much more toxic. Aware of these situations, the FDA has had, through the help of Congress, multiple expedited review programs, to enable us to act on safe and effective drugs, and listed here are the expedited review programs. There is plenty of information in the literature if you are interested in explaining each of these

individual programs. I already mentioned accelerated approval, allowing us to approve a drug on a surrogate endpoint reasonably likely to predict clinical benefit. Priority review allows us to approve a drug and cut down our review time of the application. Our most recent expedited review program was breakthrough therapies, and it was instituted in law in 2012. Again, it's for serious and life-threatening diseases. What it really enables us to do is marshal all of the forces of the FDA into a cohesive package to try to expedite the development of the drug and the approval of the drug. Many of us in this audience deal with the clinical development of the drug, but we have to also be aware that a part of the development of the drug is also the manufacturing of the drug and the preclinical development of the drug. Although we can many times expedite the development of the drug in its clinical aspects, we also have to pay attention to the manufacturing aspects of the drug, and this breakthrough therapy designation allows the FDA to work with sponsors and encourages the FDA to work with sponsors throughout the entire development of the drug, basically from the earliest information that we receive promising efficacy of the drug compared to available therapy, and allows us to work on all of the components of the application that will come to us.

Here again I mentioned that in oncology we have about—and I'm combining hematology and oncology—about 40% to 50% of the breakthrough therapies and the other areas are listed here. Here again, this points to the predominance and the interest that the pharmaceutical industry has in development of oncology drugs. This is based primarily on the evolving science

that has really prompted these breakthrough therapy applications and understanding how the drug interacts with the disease. I saw many times the drug companies are evolving from a drug company to a disease management company; because one has to have an understanding of the disease in order really to match the drug with the disease, the appropriate population of patients. That is primarily what precision medicine is all about. This is an interesting graph because it does show you how active the area of medical oncology is. I think we all will have job security for the next decade.

For all of you who are interested, the Moonshot initiatives, which we participated in with the last administration, are listed here, and these are the FDA initiatives. They include seamless design of, and use of expansion cohort studies, to expedite drug approval, large simple trials, reevaluating eligibility requirements, incorporating patient-reported adverse events, into labeling potentially the use of real-world data, and most recently we had our first site-agnostic indication. I just like to mention that was a major area for the FDA to venture into. No longer did we approve a drug on breast cancer, colon cancer, etc.; we approved a drug to treat a specific genetic marker, primarily MSI-high patients with a specific drug. It is getting away from specific sites of disease to approval based on our understanding of how the drug works.

I am going to mention a few words about these initiatives to close my talk. Seamless transition: the whole concept of this seamless transition, or these trials that are listed here, is to deviate from the traditional development of oncology drugs. I think we are all familiar with our routine use of phase 1 studies, phase 2

trials, phase 3 trials, to evaluate a drug, and what this seamless approach does is it starts patients on a phase 1 study then seamlessly they go to a phase 2 trial and specific malignancy, they may go to another trial, but there are not these discrete breaks into phase 1, phase 2, and phase 3 drug development. It's important that this really expedites the development of drugs, because no longer are you breaking them into these concrete phases, but you allow the drugs to be developed in a much more natural manner, a much more expeditious manner, that will still allow patients' safety to be evaluated, but will really escalate the resources, as well as reduce the time for the development of these trials.

I have listed here on this slide some of the interests we have had in these seamless designs, and this has been adapted and eagerly employed by the pharmaceutical industry to develop breakthrough therapy. One of the other areas that we were interested in working with pharmaceutical industry on is the development of large simple trials where we evaluate drugs, focused on electronic health records, and the real-world experience of how these drugs may be used. These trials attempt to reduce the amount of data that is collected, concentrate on hard, easily measured endpoints, and really try to reflect how the drugs will be used in the real-world. Most recently in *JCO,* there was a series of articles looking at modernizing and reevaluating eligibility criteria. I think anyone that has been involved in clinical research knows some of the problems associated with putting on clinical trials. You have a patient, you are evaluating them, and then for some reason they are not eligible for the clinical trial. Listed here are some of the areas that we were concerned about, CNS involvement,

performance status, organ dysfunction, HIV positivity, younger patients, prior malignancies. We at the FDA want clinical trials that represent patients that eventually will use the drug, so having very restrictive eligibility criteria does not allow us the chance to really evaluate patients that are, at the time of approval and post-approval, going to be using these therapies, and they also, therefore, lead to slower accrual of the drugs. We have been working with the pharmaceutical industry, with ASCO, with other professional groups, to really broaden the eligibility criteria, to ask the pharmaceutical industry rather than just pasting and cutting eligibility criteria from one protocol to another. To say do these eligibility criteria make sense? Should they be reevaluated for the specific drug, for the specific population that is under review?

One of the other areas that came up in the Moonshot is really the greater use of patient-reported outcomes in our clinical trials. And we have a whole group of people in our Oncology Center of Excellence looking at how to incorporate the patient voice and the patient experience. Some of the problems that we have had historically looking at patient-reported outcomes in oncology is that frequently our trials are not blinded. That may allow the creep of bias in the evaluation of these endpoints, as well as missing data and the fact that most of these are single-arm trials where you don't have a comparison to look at patient-reported end outcomes. Nevertheless, we do have a renewed interest in looking at this and how to incorporate patient-reported outcomes into clinical practice.

In the end, the FDA is in an impossible situation, and I have been in that impossible situation. You are either approving drugs too fast, you are approving

drugs too slow, you are approving the wrong drug, you are being overly regulatory, you are being overly conservative, you are being overly liberal. It all points to one individual's point of view and how different people take a look at a different body of evidence. But what we try to do is establish a balance of safety and efficacy. In oncology, we are facing a different population than other therapeutic areas. We have heard from patients—and I pointed to the movie, the *Dallas Buyers Club*, which was the early scream for a voice of the patients in this process—that patients want to have drugs earlier. They are willing to take some risk. Drug development is a risky business. It is a risky business economically for the pharmaceutical companies, because only a minority of drugs will make it to market. It is a risky business for patients, because many times they do not know, if they are taking a drug, what side effects that individual patient will experience. Risk has to be shared by the community. Risk has to be shared with the FDA when we make a regulatory decision. If every decision that we made was the correct decision and we never took a drug off the market, my answer would be or my statement would be, we are way too over-conservative. You cannot have perfection being the enemy of the good, and therefore, this is an inherently risky business that we have to be in. And we try to establish a balance between the risk and the benefits of a specific drug and all of the regulatory decisions that we make.

My last question is one that I started out with. How will the dynamics affect the advanced practitioners, you that are sitting in the audience? As I stated before at the beginning of my talk, what we are facing is a changing environment,

a changing environment that is for the good. It is good for the patients. We are seeing changes in how drugs are evaluated. We are seeing changes in the clinical trial processes. We are seeing better drugs that are coming out, but we have to be open to that change. My statement to you is, don't be part of the change; be the change itself. And I thank you for your attention.

INTRODUCER I wish I could speak as extemporaneously as Rick does, but unfortunately, I need CliffsNotes. Thank you, Rick, for the wonderful discussion. If I may I would like to keep you on the stage for a couple more minutes. As I mentioned at the top of the presentation, I have known Rick and Mary for many years. What I didn't mention is the impact Mary had on the development of JADPRO. Please join us to take a look at this short film:

I first met Mary and Rick in 1993 at MD Anderson in Texas. Right at the first moment that I met them, I just felt as if I had known them all my life. During and after the two and a half years that I spent being treated for malignant melanoma, I had the good fortune of having Mary and Rick as very solid friends who helped me to understand what I was going through and how I was going to win this battle. And after the battle was completed I had the opportunity to talk to Mary about something that became near and dear to me, and that was to give my thanks to the advanced practitioners who were instrumental in all two and a half years of my treatment, which is the reason why I had the opportunity to create the *Journal of the Advanced Practitioner in Oncology.* I am very grateful that I have had the years of friendship with Mary and the continued years with Rick. Mary was kind compassionate, sensitive, soft spoken, and just an all

around wonderful person. In all the years of her experience as an advanced practitioner, I think Mary's favorite was dealing with the patients themselves, and I always admired how much she cared. I knew that if we could create a publication that spoke to Mary's needs as an advanced practitioner, we'd know that we had done a good job, and with Mary in mind, that's what we try to do.

Rick and I have asked many of Mary's relatives to come up to participate in this announcement. Today, for the first time ever, along with my two Harborside Partners, Anthony Cutrone and Conor Lynch, and the entire APSHO Board of Directors, it is a great pleasure to announce the inaugural Mary Pazdur Award for Excellence in Advanced Practice in Oncology. This award will recognize and honor an APSHO member who consistently demonstrates exemplary leadership and outstanding contributions in clinical practice, research, education, collaboration, and/or mentorship. We will begin accepting nominations in December of this year for the 2018 award. This prize includes a small grant, a trip to next year's conference, and recognition in the pages of *JADPRO* and at next year's *JADPRO* Live conference. It also includes this beautiful crystal award in Mary's honor. We are all delighted to present the prototype of this award to you, Rick.

RICHARD PAZDUR What can I say, Jack? There are so many ironies in my wife's illness. My wife, for many of you that do not know, died of ovarian cancer after a multiyear battle. It is such an irony to have the disease that you treated and were involved with, and it provides so many opportunities of how to approach that disease, but nevertheless it is a bittersweet experience. She

approached the disease with a great deal of strength. From the very beginning, she knew exactly what she was facing after her laparotomy. It's so ironic, because on Thanksgiving Day, that will be the two years anniversary of her death, and to have a death and a commemoration of a death on a Thanksgiving is particularly painful, but nevertheless that is what God gives us so to speak. The thing that is most appropriate with my wife is her love of nursing. I first met her in 1979 on my first day of fellowship at West Presbyterian St. Luke's, so there is another irony there, and we worked together as a team throughout this. Any success that I had in my career, I owed it to my wife. She had a love of nursing that stemmed from her family. Her mother was a nurse, in fact I was mentioning to Jack a very interesting story: my mother-in-law Shirley Bagby started nursing school in the late 1940s/early 1950s—this was at Presbyterian Nursing School—and at that time, when you got married, you had to quit nursing school believe it or not. Boy, have we come a long way, haven't we? So she left nursing and then reentered nursing after her family was raised and became a school nurse. A testament to her interest in nursing had a profound impact on Mary, and then Mary, as the oldest daughter of eight children—and that's why there are so many people up there—had an impact on their careers, and almost all of them are nurses, doctors, or other healthcare professionals, and her sisters, one of them is a school nurse taking after her mother at The University of Chicago, another is a psychiatric nurse, another one is a neonatal nurse, and Michael is her oldest brother and is a dentist. All of them had an impact on the healthcare profession, as well as the next generations. Her nieces and nephews and they are all nurses,

including a nurse anesthetist, a nurse practitioner, and an ICU nurse, and our good friend Carol who stood up at our wedding and has been a friend of Mary's and another really profound advocate for the field of nursing. On behalf of our family, I thank Jack and *JADPRO* and the organization for this beautiful gift. It is something that in this day we will truly remember for the rest of our lives. Thank you.

INTRODUCER I do want to tell you that Dr. Pazdur and I would like to invite you to meet with us immediately after this presentation in the APSHO booth in the Exhibition Hall. If you are interested in hearing more about the award and hopefully there will be an awful lot of you that would like to submit some nominations for the award. We would be more than happy to talk to you about it. You will also be able to find more information on our website as well.

FEMALE SPEAKER Thank you, Dr. Pazdur, and thank you, Jack. This award is a wonderful idea and a special tribute to a member of our profession. Like Jack, I hope many of you apply.

[END]