



COVID-19 Q&A
Lung Cancer and Clinical Trials
April 17, 2020

LUNGEvity hosted a listening session with Dr. Richard Pazdur, Director of the Oncology Center of Excellence at the US Food and Drug Administration (FDA), Dr. Harpreet Singh, Director, Division of Oncology 2, and members of the FDA Thoracic Oncology Team, and four lung cancer survivors on April 17. Following opening remarks by Dr. Pazdur, the lung cancer survivors asked questions about lung cancer clinical trials in the time of COVID-19. These have all been edited for clarity.

FDA Participants:

Dr. Richard Pazdur, Director of the Oncology Center of Excellence
Dr. Harpreet Singh, Director, Division of Oncology 2
Dr. Erin Larkins, Dr. Adnan Jaigirdar, Dr. Luckson Mathieu, and Dr. Paz Vellanki

Lung Cancer Survivors (patient panelists):

Melissa Crouse, FL
Janet Freeman-Daily, WA
Dann Wonser, OR
Greg Jones, GA

LUNGEvity Foundation:

Andrea Ferris, President and CEO
Upal Basu Roy, Vice President of Research

Below are the opening remarks by Dr. Richard Pazdur, followed by the Q&A.

Opening Remarks by Dr. Richard Pazdur

We are all aware of the problems that we face as a community. These problems need to be faced collectively by all of us, and we are only as strong, basically, as our weakest link. We really want to come together and reinforce that we at the FDA are here for all patients. The Oncology Center of Excellence was designed to collaborate with the external community, and we feel that this is a critical time for hearing from that community.

Obviously, there are many concerns, both economic and health. For people facing cancer, I have a feeling that many times there may be a concern that their voice may not be heard or that they are being lost in the bigger picture of fighting COVID-19. We want to reiterate to the oncology community that we have been doing our regular work in addition to the added work caused by COVID-19. We really have made a concerted effort to continue our review work.

We do not anticipate missing any deadlines. In fact, we have been approving some drugs even before their due dates, which required added work by the staff, to which they are committed. Here again, I think the important point that we want to emphasize is that oncology patients, and particularly lung cancer patients, have incredibly unique needs and that these needs are not lost. We are here for you. We do not anticipate that this current crisis will have a detrimental effect on our core mission at the



Oncology Center of Excellence. That mission is to provide safe and effective innovative therapies for patients who are facing malignant disease. You are front and center in our minds.

We will be having a series of outreach teleconferences, not only with the lung cancer community but with the various constituencies that face the problem of having a malignant disease that could potentially interrupt their therapy and what this may mean to them. We understand your particular needs, and we are continuing our work. You will be seeing in the next couple of months some very interesting therapies that have been approved, not only for lung cancer, but other therapies that will be coming out and hopefully revolutionizing some of these diseases.

At this point in Dr. Pazdur's remarks, Andrea Ferris noted that the FDA in the days prior to this conversation issued a guidance (a document that describes the FDA's interpretation of a policy or regulatory issue) about a number of innovative ways that clinical trials can be flexible in order to be able to continue during the time of COVID-19.

FORMAL QUESTION AND ANSWER SESSION

What is the new FDA guidance? What is the FDA hoping to accomplish with it? What does it mean for patients?

Usually we write guidance just for regulated industry, but this guidance has far-reaching implications, not only for regulated industry—pharmaceutical companies—but also for university investigators, community investigators, and, importantly, patients who are on the trial.

We are totally realistic that the healthcare system faces unprecedented demands on it. It is a very critical time, and we are evaluating where resources are going. We also understand that because of the very nature of this infectious problem, there may be delays in therapies, discontinuity of clinical trials, stopping of clinical trials, missing data, and alternative ways of giving therapies that have to be addressed because it isn't business as usual. We have to be realistic about this as we go forward. We wanted to give guidance on how we may address these problems.

The guidance is relatively general. The major focus of the guidance is patient protection. That comes first. We want to make sure that we are not endangering people's lives by their mere participation in a clinical trial, especially those patients who are having ongoing therapy. However, we also want to ensure that patients get the best medicine, and many times this can be accomplished by participation in clinical trials. We anticipate disruption, and we wanted to have a prospective discussion about it. It is always easier for us as regulators to address a problem prospectively before something happens and design how we are going to address problems rather than seeing how we can remedy a problem after it happens. This guidance was an attempt to prospectively address some of these problems.

Why did we issue the guidance? Because we realize that there may be problems, so let us address them prospectively.

What are we hoping to accomplish with this guidance? To offer prospective information for the stakeholders (regulated industry—pharmaceutical companies—but also for university investigators, and community investigators).

What does this mean for patients? We are here for you. We want you to continue your therapies, but we have to be cognizant that the healthcare system is facing unprecedented demand. And also we have to be interested in your ultimate safety because we are not only facing the issue of cancer, but also a

possibility of concomitant exposure to the virus. These are the main issues that surrounded the development of this guidance.

What would you say is the most important thing for lung cancer patients to know during this time from your perspective?

We want to emphasize that we are laying out what we foresee some of the problems are likely to be and how we are going to address them, but I think that the number-one take-home message, again, is that we are here for the patients. We have not abandoned the patients. The COVID-19 issue is a societal problem that is right in front of us, but we also have to be cognizant of the fact that we have a disease such as lung cancer for which we are anticipating 150,000 American deaths this year. We have to keep the message going that this is an important disease for which we need to have ongoing progress while we are fighting the COVID-19 pandemic.

I do not anticipate any regulatory issues as far as slowing down work here at the FDA. As I stated, not only are we meeting our review deadlines, but we are also exceeding them and approving drugs in a shorter period of time. Obviously, we have to be cognizant that there is a potential disruption in patients entering clinical trials. Several pharmaceutical companies have altered some of their trials due to safety issues, but I would expect that once things have somewhat stabilized in the medical community, there will be an acceleration of eligible patients going on them. There might be a momentary decrease followed by an escalation in the numbers of patients who go on clinical trials.

Q and A with patient panelists

Q1. What if patients miss visits to the doctor during their clinical trial due to COVID-19?

We understand the disruptions due to the COVID-19 virus are likely to result in missed visits and delays in treatment, and some patients will even probably be lost to follow-up.

The guidance is very flexible on this. Our plan is to work with the pharmaceutical companies to address the issue of missing information and protocol deviations in a way that will still allow us to evaluate the results of the clinical trials for new lung cancer treatments, so the results of a trial will hopefully still be valid.

We plan to take a flexible approach while ensuring that the results can still be relied upon. The companies, per the guidance, are only asked to document these deviations. They'll need to include a separate section now in their clinical study report in which they summarize any sorts of protocol deviations, such as missing visits due to COVID-19, how they have impacted the results, or why they should not have impacted the results.

In addition, we are going to be asking them to propose plans for how those sorts of things will be handled when they are analyzing the data. They can submit those plans to us and our clinical team, and our statistical teams will be looking at those plans with them and working with them to make sure that we can still use the data from the study.

Q2. There are some areas of New York that are not doing some of the procedures that are required as part of a clinical trial. For example, bronchoscopies. How can patients be accommodated with these kinds of variations?

The way most trials are written, even if it is a protocol required procedure, a participant is not necessarily going to be kicked off the study if they can't get the procedure done. For the patients, I think that's the most important part.

A lot of time those procedures, something like bronchoscopy or tissue collection, are really more to answer scientific questions. They won't necessarily impact the major outcomes of the study that we are interested in, as far as approval, so they shouldn't have a big impact on interpreting the data.

Because we are usually dealing with randomized trials, missing data, if it is because of missed visits, should be randomly allocated to both arms. That is the most important thing when we take a look at a trial—to assure ourselves that there is no bias that has been introduced into an arm of the trial. If it is just because of an external medical problem that's occurred because of COVID-19, the missing data will be in both arms of the trial rather than a bias being introduced.

I want to add, regarding protocol deviations or violations, that we expect them with every trial. Usually they are quite minor. We look at them, but often they do not really affect trial integrity.

In the wake of COVID-19, we are expecting a significantly higher number of protocol deviations and violations. We expect to see them, and we will work through them with each sponsor. They may choose to give them to us in groups, like all of the missed bronchoscopies, for example. We will look at them on a case-by-case basis. We are expecting to see these, and we are starting to prospectively discuss with a lot of companies how we are going to handle missing data as well.

There are always problems and always missing things in clinical trials, so we expect that. Again, we are more interested in whether there has been an introduction of bias, and that's how we'll be looking at missing data.

Q3. If we can't get to see our doctor in person for the trial, can we have a telehealth appointment instead?

This is a challenging time. There are a lot of restrictions that have come about with regard to travel and to having access to healthcare facilities. We recognize that patients will not be able to go to the trial sites for their protocol-specified visits, but absolutely there are alternatives. The answer lies in modern technology and the availability of and access to that. These techniques, telehealth and virtual visits with videoconferencing, should be implemented and done in a controlled fashion, where there is a strategy in place. The healthcare coordinators and the trial coordinators can implement them.

In a situation where patients are hundreds of miles away, an option is to see whether there are local areas where the pre-specified follow-ups, or even the safety follow-ups, can be done.

Q4. If I live far from the clinical trial site, can scans and blood draws be done locally rather than at my clinical trial site?

This should be feasible. It is a matter of the trial coordinators and investigators synchronizing with the local laboratories and CT scan facilities so that the trial-specific procedures are used. In essence, this will provide flexibility without violating or creating any discrepancy in the data or any disparity in the data validity and the integrity of the trial.

This could be done preemptively in a systematic way. If we recognize that there is a need for this, it could be put into the protocol as an amendment. As long as the data are well captured in a randomized setting, or even documented, we at the FDA should be able to assess that accordingly.

The FDA has put out this guidance, but also each individual company, in conjunction with the investigators or cooperative groups, is making decisions collectively based on their assessment of patient safety resources and access to the drug.

We are allowing these things. We also can't enforce or force investigators to become more flexible, but we really hope that they are being more flexible; it's in everybody's best interest. A lot of our guidances can be difficult to read, but we think this one is succinct and helpful.

Q5: Can investigational drugs be shipped to the patient? If yes, how big a supply? And for how long can that go on?

Your question basically fits the purpose of the guidance because the guidance is, again, to ensure patient safety while balancing flexibility and maintaining trial integrity. Clinical trials should be able to get their oral medications shipped. If it is not feasible for you to go into the clinic, or if it's not safe for you to go into an alternative site, secure methods of receiving that oral medication should be used. That is what the guidance is trying to communicate.

As to how long it can go on, I do not think anyone here really knows how long we are going to be in this new situation we are in. Ideally, preferably, we would want it to be a priority that patients are safe. So, hopefully, however long it is necessary, you can continue to receive your oral medication.

Q6. If I need to have my liver function tests evaluated every six weeks or even every month in order to continue receiving my oral medication, could I have the tests done locally?

Likewise, at some point, in order to ensure your safety, you may need to go into a local lab or local imaging center to make sure that your safety is being maintained. This is certainly true for investigational drugs for which we need to check your labs every so often. I think that the guidance provides for that.

Q7. My investigative drug is infusion-based, and I am wondering whether those of us who are getting weekly hospital-based infusions might have an opportunity to get those infusions delivered at home instead.

The simple answer is that it depends. There are a lot of different infusions, a lot of different hospital-based infusions, and each case will have to be evaluated on an individual basis. For example, at one end of the spectrum are conventional drugs such as gemcitabine, for which we know the safety profile, and

at the other end are CAR-T cells, for which there could be a serious infusion reaction. It would not be entertained that CAR-T cells would be given at home because a patient would have to have the necessary support system available to handle an acute infusion reaction.

In the guidance, what we are saying is that we are encouraging companies and investigators to get in touch, to have a conversation, to get into discussion with the appropriate FDA review division, and in consultation with us to design an alternative method or option for hospital-based infusions.

It may be, as you are suggesting, that home nursing is an option; another option might be an alternative site where a trained professional who is not in the study can supervise the administration of the infusion. The main thing is let us have a discussion. Let us have a conversation and figure this out because in this case, not one answer will fit for everyone. I think that in communication with the FDA, we could optimize your safety and the safety of other patients while still providing these necessary medications.

Q8. Is the FDA allowing new trials to start and open trials to continue?

The short answer is yes, the FDA is allowing new clinical trials to start. However, there are a few situations in which drug companies are deciding not to open up new trials, particularly in areas that are heavily impacted by COVID-19. There are a number of considerations that they are probably taking into consideration when deciding whether or not to open up the new trial. Is it safe? Is it feasible for these trials to be conducted? Is there access to the investigational product? Are there any issues with the manufacturing or the availability of the drug? If they do collect data on trial, can the data be interpreted down the line so that we can actually get meaningful results from the trial?

There are provisions and guidance in the FDA guidance to help provide feedback to companies regarding opening up new clinical trials. Again, we are talking about flexibility for sponsors in terms of allowing telehealth and telemedicine visits, allowing local labs to be utilized and imaging at local centers to be utilized. There are also some recommendations in the guidance as well regarding informed consent. Usually it is obtained in person. However, we can also use an electronic informed consent, and there also can be phone conversations to obtain informed consent as long as the signed document is being sent back through fax or a secure email. We are providing some guidance there to try to make this possible.

Q9. If the trial is suspended due to the virus, will it be possible to resume that trial at a later date and pick up where it was left off?

It will depend on the trial itself, and that is going to require some discussions between the drug companies and the FDA. For example, how far along is the trial? How well can we interpret the data that we already have? Maybe if the trial is not very far along, resuming the trial once it's safe and reasonable might make better sense.

Q10. If the patients are showing some benefit, will it be possible, even if the trial is suspended, to continue using the investigational treatment?

There are a number of ways that patients would have access to the investigational products. For example, there are expanded access protocols and also single-patient INDs [investigational new drugs]

that allow patients to receive an investigational product even if it hasn't been approved for that particular indication.

At least with the larger companies, thankfully what we have been seeing is that for the trials that are ongoing, they are not necessarily halting the trial itself. They are usually suspending new enrollment and not opening new sites, but in general they are trying to keep the patients who are currently on study continuing on study. So, it is not necessarily that they are closing down the whole trial and kicking everybody off. That may be the case for some smaller investigational studies at academic centers where they are not able to do the support.

Q11. What if someone who is on a trial contracts COVID-19 and then needs to be treated for that? I know that it depends on the experimental treatment as to whether that continues during the treatment of the COVID-19, but what happens afterward? Can they go back on the trial?

It probably depends on how long they missed the actual drug. Many protocols have, for example, a 56-day window in which you can miss administration of the drug. I think certainly it is something we expect to be able to discuss. We have not broached that yet, but I am certain that it is happening and so I think it is another one of those "it depends." And you know, I think if everything is documented carefully, certainly there is a great amount of flexibility provided that the trial integrity is maintained, and patient safety is maintained.

But know that this is not unique to COVID-19. There are many times when a cancer patient has an infection due to bacteria, due to another virus, the flu, etc., and therapy must be interrupted. And usually there are provisions in the protocol that prospectively state that after a certain period of time, a patient would either continue or would then have to come off the study. So, this is not a unique situation that we are approaching now. This has been seen in almost every clinical trial with provisions written in the protocol about concomitant infections or other emerging medical situations that may either allow the patient to continue depending on the severity and the disruption of therapy, or allow the patient to come off therapy. Generally, if the patient is responding to the therapy, even if they have to come off the trial, most pharmaceutical companies will allow the patient to receive the medication. Usually, that is through a single-patient access to that medication. Here again, I think that everybody is interested in a drug that is providing benefit; the sponsor, the FDA, and obviously the patient want that therapy to continue for patients who are benefiting.

Q12. A lot of the changes that were implemented for the COVID-19 pandemic have made clinical trial enrollment much easier for patients. Will these waivers for the health and increased spacing between clinic visits and scans remain in place after the pandemic is over?

I can tell you that this has been a really great lesson in decentralized trials, and it is an ongoing lesson. We, the oncology group, have been talking about decentralizing trials, bringing more access to more patients, particularly our oncology patients who tend to be more vulnerable, perhaps because of geography, ethnicity, or age. All of these are barriers that prevent our U.S. populations and patients around the world from enrolling in trials. My personal answer is that I hope so. I think that the FDA as a whole will need to reconvene and review the lessons that we have learned from this, how it has helped patients and how we can proceed in a manner that really helps address some of these barriers that have been pervasive that I think this flexibility is helping to address. So, again, my answer is that I hope so. The official answer is that we will have to all reconvene as an agency after the pandemic is over.

Q13. What general discussions have been going on at the FDA about clinical trial design?

This is a time when we can see how we can be more flexible in our approaches. Clinical trials are here to serve the patients. The patients are not here to serve the clinical trials. And I think that many times in the course of doing business, we all forget that. We are so concerned about the integrity of the trial, the pristine nature of the trial, that we forget it. It is all about the patient. That goes with any discussion, whether we are talking about endpoints, whether we are talking about frequency of visits, or the way the trial is conducted; we really have to take a step back and look at this.

This is something we have always been doing in the Oncology Center of Excellence, trying to see what the optimal clinical trial design is. Does it make sense even to do a randomized study? That is particularly important in some of these lung cancer subsetted populations in which you have tiny populations and cannot even do a randomized study. That requires us to bring along other regulators and other parts of our agency, as well as international regulators. We have a strong commitment to that. We are also having discussions with our international regulatory community. We have a vast outreach in the Oncology Center of Excellence to discuss these issues. We have a monthly meeting with Australia, Canada, the EMA (the European Regulatory Agency), Switzerland, and Japan during which these issues are discussed; COVID-19 is also discussed. We had one last week with the Chinese regulatory authorities that oversee oncology drugs. They were very interested in how we are handling clinical trial issues here. We have Project Orbis in which we do joint reviews. In fact, we are expanding that to even more countries to have a multiple operative regulatory environment. COVID-10 is a pandemic, and it affects all nations. Interestingly enough, oncology trials are international trials, so this is not just about the United States. It is about a worldwide problem that the international pharmaceutical companies have had to address.

Q14. If the FDA is making these adjustments due to COVID-19, is it possible that that will make it difficult for us to get drug approvals in other countries later?

I do not think so. Here again, no regulatory agency is immune from the voice of the patient. All government agencies derive our power from the patient through their representatives. We are not an entity independent of the people whom we serve.

Q15. A lot of patients are having problems around interoperability of EHRs [electronic health records], where they're being treated in one institution and need to transfer their records to a different one, and it's not happening. Are there any sort of initiatives going on among the various agencies to try to address this?

Yes, and here again I think this crisis, this pandemic, has demonstrated a need for that. I have always been greatly surprised that this has not taken front and center stage. Compare medical health records and the problems that we have with interoperability of the various systems and compare that to the banking system, which operates fairly flawlessly with confidentiality. When you do ACH transactions from one account in New Jersey to California, it occurs like magic; the money is there, and there is no problem, and confidentiality is obviously maintained. If it occurs in one industry, the technology is there. It is just getting the groups together. Out of the problems that we are facing can come solutions.

Q16. Could you comment on your ideas about financial support for participation in a clinical trial?

I did my clinical training at the NCI, and we were spoiled there because patients got flown in. They stay at hotels. With patients outside the NCI, you do run into issues where you cannot get a clinical trial covered sometimes. Now, usually if it is a further-along study you can, but there are some insurance companies that will not cover phase 1 clinical trials because the drug is not proven. So, there are a lot of issues out there, and I do not know how without a broader approach you can cover that.

Closing message from the FDA

You can expect to see some really exciting approvals in the next few months that we are expediting. We would like to emphasize again that we are working really hard around the clock are dedicated to you, our lung cancer patients. We hope that this message is received. We have not forgotten you. If anything, we are keeping you at top of mind and remembering that the faster we can get these life-saving therapies out to you, particularly these oral molecularly targeted drugs, the sooner you may have new options for you in the setting of this pandemic.