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Office of Orphan Products Development

TISSUE AGNOSTIC THERAPIES IN ONCOLOGY: REGULATORY CONSIDERATIONS FOR ORPHAN DRUG DESIGNATION PUBLIC WORKSHOP

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C O N T E N T S

C O N T E N T S - Continued

P R O C E E D I N G S

OPENING REMARKS

DR. LEWIS: Good morning, everybody. We thank you for joining us today at the Great Room at White Oak Campus of FDA. We also have many who are attending on webcast online and we welcome you as well.

I'm Debra Lewis. I'm the Acting Director of Orphan Products Development and I thank you for joining us today at our regulatory considerations for orphan drug designation and tissue agnostic therapies in oncology.

This is our public workshop. We are glad to have you with us and we're very excited on this excellent day that Commissioner Scott Gottlieb will be doing our welcoming remarks. Dr. Gottlieb is just one day shy of one year as our 23rd FDA Commissioner and I think most folks recognize he's taken a huge commitment to the rare disease community in developing rare disease products.

In orphan products, you may have seen we now have a commitment to 90 day response for our orphan drug designations. We're able to sustain this through

our modernization plan. And not only has Dr. Gottlieb supported us in this endeavor, but also was very instrumental in bringing about this meeting today.

So it's with great pleasure that I introduce to you Dr. Scott Gottlieb, Commissioner of the Food and Drug Administration.

(Applause)

WELCOME

DR. GOTTLIEB: Thanks a lot. Thanks for having me here today. I actually didn't realize it's been a year. It feels like it's a little longer than that.

I want to thank you for the opportunity to be here and really commend the group on the remarkable work that's been done over the last year with respect to the orphan drug program. It really owes to the dedication of the professional staff in that office and across the whole Agency. And that dedication to these issues that we've made, I think, some meaningful progress in advancing the policy related to these issues and some of the adjacent issues.

We're seeing right now tremendous promise and

opportunity for the ability to understand target diseases and the underlying molecular basis of disease much differently than we did in the past. It's much less common today when a new medicine's put into development where the biological basis and rationale for how drugs should work isn't clearly understood at the very outset.

In fact, I'd say more and more if you look at what's going on the investment side of healthcare and the life science sector, having a firm understanding of the mechanism of action is increasingly a prerequisite to funding a new drug development program.

And I can tell you that with some firsthand experience having worked on the venture capital side of this industry before coming into FDA, that if you didn't have a really clear understanding of the molecular basis for how a drug might work to target a certain disease, it was very hard to get, to get those endeavors funded.

In fact, it's just, it's a matter of fact, I think, that a new drug is much less likely to be developed in the first place because of that, if the

biological rationale for the molecular entity isn't established early in the beginning of the drug development program.

This wasn't always the case and it wasn't the case just a short time ago. If you look back a few decades ago, drug makers were investing in huge facilities to do high throughput screening as they shifted through random hits to find drugs sort of like a needle in a haystack. Now medicine is designed more intelligently against predetermined targets on molecular scaffolds often one atom at a time if you look at what's happening with respect to structure based drug design and technologies like that.

This opportunity also compels FDA to adapt our policies to accommodate and leverage these same scientific advances. And so we're here today to talk about some of these openings.

Being able to confront disease based on how it develops and not simply how it appears at the time of diagnosis is a key evolution in how we approach scientific research and medicine. And these approaches aren't just theoretical anymore. FDA is opening a door

to these methods and embracing new regulatory constructs like basket trials and master protocols that make these approaches easier and more efficient.

One of the opportunities we're going to discuss today, which I'm especially focused on, is the prospect of granting orphan designation based on molecular subtype. I want to make sure we're taking every possible step to advance these opportunities. We want to be proactive here. We want to lean forward in these kind of chances.

I want to make sure we've properly aligned policy incentives to encourage more intelligent and effective drug development. This challenges us to take up some novel policy questions and that's what we're here today to probe.

We're now able to target very rare subtypes of disease with treatments that are tailored in a way that allows them to intervene at the molecular formation of a condition and deliver potentially superior results. In this way we'll have more opportunity to arrest or even prevent disease altogether and not just treat symptoms or manage the slow progression of a condition

or the rate of decline in function that comes with certain diseases.

This is already happening in multiple clinical settings, but these approaches are most obvious in oncology. Historically FDA has used a histology-based approach to oncology drugs, both in the designation of diseases as orphaned conditions and the approval of indications for treatment of tumor types where it was based on the anatomic site or the histology.

Evolving knowledge, though, of the molecular and genetic basis of cancer has led to refinements of the categorization of malignancies based on molecular subtypes. And so the new guidance that we'll develop on tissue agnostic drug development approaches will speak to these opportunities and how we'll grant orphan designation in these situations.

We've already granted three such orphan designations, two in cancer and one for a rare inherited eye condition called retinal dystrophy. These same approaches in principles may also lead to much more efficient development programs. In cases where we can generalize a response based on a molecular

subtype, successful basket trials based on biomarker type will be more efficient, faster, and cheaper, allowing patients to access scientific advances potentially much sooner.

And so, among the questions we'll be taking up today, the evidence needed to consider a biomarker as defining a tissue agnostic disease for purposes of orphan designation. We'll also ask questions about how FDA should approach requests for a product intended to treat, for the treatment of, a tissue agnostic disease as well as histology-specific disease.

In very short order, it seems clear that our understanding of diseases is changing from a site and tissue orientation to a molecular basis, and this is especially true, as I said, in oncology. With this medical paradigm, our approach to medicine will be transformed through more tailored therapies aimed at molecular targets.

Today we're going to be advancing the discussion on how we can capitalize on these scientific opportunities as a matter of policy and how FDA can adapt its approaches to embrace and foster the

development of these new scientific approaches.

I want to thank you all for joining us. I especially want to thank the professional staff of FDA that have been working very hard on making these kinds of opportunities available for patients. Thanks a lot.

(Applause)

MEETING OVERVIEW AND GOALS

DR. LEWIS: Thank you. Commissioner Gottlieb, we really appreciate our welcome, getting us off onto a good course. I have a few just administrative announcements I want to make sure folks know. Silence your telephones. If you have not signed in at the registration desk outside, please do so. They can talk to you about lunch plans, as well as get you set for that.

For our online attendees, there's an e-mail. If you have issues or problems you can e-mail into the OOPDorphanevents@fda.hhs.gov. And I thank our crew of logistics experts over here for keeping us straight through the day.

I also want to note as Dr. Gottlieb said, that the Office of Orphan Products has been just tremendous

in support of all of our programs in doing this. I have some acknowledgments up on the screen. We had a meeting workgroup which Christine Mueller and Dev Jillapalli, Medical Officers from Orphan Products, have done an outstanding job of trying to corral us and bring us together on these issues.

I also want to thank the rest of the meeting workgroup which is up on the screen, partially from Orphan Products Development, partially from the, our oncology colleagues in CDER. From as well OMPT who's provided us tremendous logistics for today.

The whole group has been great across FDA, including we appreciate even going to have some backup today if we need on testing issues. We have that from CDRH. They'll be joining us as we get into the panel discussions and be available.

I want to talk a little bit about our panelists. They've been coming from many areas. We've asked different groups and we thank them to give us suggestions on how to get good representation for many areas, whether it is from the, the development side, the research side, patient representation, the getting

access to products, how do all these things come together, as well as just the expertise in the scientific area. So, I will show you a list right now of our panelists, but we'll meet them more closely a little bit later in our program.

As you can see from the agenda, we'll start with some presentations. So, I'm not going to go through all of my panelists right now. Instead I'm going to go, to talk a little bit about our agenda.

First today we'll have a little bit of time where we meet the issues. We'll talk about the science, we'll talk about the perspectives from oncology, and we'll have a little bit of a background, kind of a 101 on designation exclusivity so that when we get to the panel discussion we're really prepared to go.

So it's, I want to get started if we can with our first presentation and that will be provided by one of our panelists, Dr. David Hong. Dr. Hong is from University of Texas MD Anderson Cancer Center, the Deputy Chair Department of Investigational Cancer Therapeutics, Division of Cancer Medicine, and he's

going to get us set with some background on the scientific questions and clinical considerations. So thank you very much, Dr. Hong.

PRESENTATION - SCIENTIFIC BACKGROUND OF TISSUE AGNOSTIC DRUG DEVELOPMENT

DR. HONG: Thank you. I want to thank Deb and Dr. Gottlieb and the organizers of this workshop for inviting me here to talk.

So I'll tell you, it is an incredibly exciting time in oncology, and as an oncologist and as a clinical trialist, you know, I never anticipated that we would actually even get to this time of kind of tumor agnostic therapy. And since the recent approval of pembrolizumab, it's really kind of opened up a lot of interesting questions and perspectives. Okay.

DR. LEWIS: I'm back. I would like to -- oh, I'm only going to, in for a moment and mention the importance of this meeting for us. As we talk about, just as Dr. Hong was saying, the, the policy questions that have come up for us in Orphan Products have raised a lot of great, how the science and the policy come together. And it's such an exciting time that we've

had to start grappling with these and I think we are ready for a fantastic look from Dr. Hong about these issues.

DR. HONG: And, great. So, these are my disclosures. So, you know, this has really kind of blown up in the context of both media. It has now been present in a number of actual medical media platforms, but has now gone into actually the lay media. And it's engendered actually a lot of discussion and debates amongst oncologists and also clinical trialists.

And this is one of the hottest tickets at AACR. Dave Hyman, who's a champion of precision oncology and also basket studies versus, besides who's, who's I think very thoughtful about these issues and is a critic of these tissue agnostic indications.

And so the critics would argue, the critics would argue that we are headed towards in some sense the unknown and maybe even disaster. And people have argued that, the critics have argued that we are opening a Pandora's Box where we will explode not only wrong therapies, but even budgets and medical costs.

So, I was asked to kind of try to frame this

issue of tissue agnostic therapy in the context of a scientific frame and also what are the questions, what are the issues in the context of clinical trials.

I don't, I think that you have to also include here this issue of tumor biomarker agnostic biomarker studies because you really cannot talk about a clinical trial or the scientific rationale without that 'cause we are in a way reclassifying a disease not based upon histology, but really based upon a pathway or a marker.

So, Dr. Le is here and I'm not going to be able to give justice to her research, but this is what really set off this and opened this idea of, of tissue agnostic therapy. And so I think this is a perfect example as to how we can frame scientifically what we should think about when we think about tumor agnostic therapy.

And as you can see here, this landmark paper showed significant activity in patients with MSI-high tumors across histologies with anti-PD-L1 therapy, in this case pembrolizumab.

And this, this was a culmination of data that the FDA had accumulated from a number of keynote trials

showing that across histologies you had a number of significant responses, but more importantly, these responses were durable and there was clear clinical benefit.

So, what is the scientific framework? And Dr. Le gave a great lecture at this past ASCO on kind of their hypothesis that brought about this investigator initiated trial that eventually led to this approval. And that really formed three thoughts, the scientific basis of this. One was is that if you looked across all these histologies, you saw these infiltrating PD-L1 positive CDA tumor cells, whether it was colorectal, whether it was endometrial, whether it was gastric.

In addition, these mutation, this aberration of the, of the mutational pathways led to multiple mutations or high TMB or high tumor mutational burden, which led to frameshift alterations leading to what are called new antigens, therefore, leading to targets for these anti-PD-1 therapy.

And so Steve -- sorry. Steve was there at that lecture and gave kind of the, the background and he'll go into more details about this, about what led

the FDA to look at from a scientific viewpoint why this was approved and that these tumors across histology shared same common pathological characteristics, but more importantly, they shared similar molecular and immunological characteristics, mutational load, and new antigen burden, which eventually led, based, the scientific basis for this approval.

But this story does not always carry across all different kind of tumor agnostic ideas. One is the story of BRAF. And many of you know that BRAF inhibitors have already been improved in melanoma, but the thought was that maybe since BRAF occurs in perhaps most different, BRAF mutations occur at least, occurs in most types of tumors, perhaps a tissue agnostic indication is warranted.

However, when they tested this, particularly in colorectal, we found that indeed this pathway was not as similar to that in melanoma. In fact, elegant research done by Prahallad, et al, and others have shown that this pathway is different when you inhibit it with a BRAF inhibitor. Vemurafenib induces an up-regulation of this facile EGFR in colorectal.

And since then there have been other clinical trials showing that perhaps in combination with EGFR inhibitors such as cetuximab, plus other agents such as irinotecan, which I have done with Dr. Kopetz can overcome this lineage. But what BRAF, the story told us was indeed lineage does matter in some instances.

Likewise, recently Dave Hyman reported this in Nature, reported this at the last AACR in 2017 showing that neratinib in blocking HER2 mutations depends exquisitely on histology, does depend on lineage. And if you look at this graph, it's not just one mutation like in BRAF V600, but multiple alterations along that HER2 gene looking at responses in different histologies. You see that in different histologies such as breast, you have exquisite response, but in other tumor types such as bladder or colorectal, there's almost no response to inhibition of this pathway.

So, this story tells us that -- what these examples tell is that definitely when we think about tumor agnostic therapy, we need to have a scientific framework, a hypothesis such as with pembrolizumab and

anti-PD-1, that may cross the threshold of histology and lineage.

One question I think that comes up in all of this is how many tumor types. How many tumor types do we need to have before we consider a truly tumor agnostic therapy? And I think that question is a much more nuanced question that entails not just a scientific question, but also a regulatory question.

This is an example of a trial that one of my colleagues, Dr. Subbiah, recently reported at AACR, and this is a RET inhibitor. And we saw exquisite activity in a number of tumor types, lung, medullary thyroid, papillary thyroid, but what he doesn't show here is, is that they were one-off responses in diseases even like pancreatic and cholangio.

So how many tumor types do we really need from a scientific perspective to say that this, this hypothesis kind of runs across the spectrum of diseases?

So, let's talk a little bit about tumor agnostic biomarkers. I think there are several questions that we need to ask when we talk about tumor

agnostic, because again, reclassifying this disease as, rather than based upon histology, rather by molecular phenotype, and we do that by identifying a biomarker that can identify that molecular immunological phenotype. And the questions are, is this predictive across lineage and histology?

Is this consistent and reliable across these lineage in the cells, the actual test itself, and is there a concordance in kind of in the real-life setting both between labs and different types of tests that may look for that?

And so, ideally we would like to have a biomarker like Danielle Lei who's smart enough to set her, her Girl Scout cookies right outside of a marijuana dispensary in San Francisco, right? And is able to, to capture all these customers. I want to remind us that there are many different types of tumor agnostic biomarkers, risk markers, diagnostic markers, activity markers, and particularly when we talk about tumor agnostic biomarkers in this setting, we're talking about predictive markers.

And ASCO recently in 2006 had a definition of

what that is. It's a marker that identifies groups of patients who receive different degrees of benefit. I don’t necessarily agree that you need to require a randomized trial, but I do agree that association needs to be specific to a given treatment, that it helps maximize that benefit received from a given treatment, and minimizes harm from treating patients, and that it needs a test for interactions to determine whether a treatment effect is different in patients who are both positive or negative.

And obviously we, again, this case with MSI-high, whether it's by PCR or IHC, suggests that this is clearly a predictive marker of benefit from anti-PD-1 therapy. But there are other examples. One is a trial that I've been involved in and NTRK fusion is right now in the crosshairs of whether or not to be approved or not.

And this shows it's a complex assay, whether it's by FISH or NGS, but what we've seen is, is that in every single patient who has an NTRK fusion, whether by NGS or by FISH, we see an exquisite response and an almost 80% response independent of histology,

independent of, of the fusion partner, independent of age.

But, you know, assays and biomarker tests are a complex thing and many of you guys who are involved in that know this, and that even the history of ALK fusion testing has undergone a number of different reiterations over time. And one question is with, for example, with, with pembro and MSI testing, is to what extent are these two tests coherent.

And there's two ways to test for MSI-high status. One is MSI PCR and the MMR IHC. In the community, you know, pathologists will either order the PCR or IHC, or sometimes ideally both, but there are discordances between these tests. And Russell Broaddus presented this at AACR, he's a pathologist at our group at MD Anderson, and he argued really the most accurate test is really to combine both a PCR and the IHC.

And you can see that there are some discordances across different histologies, right? This is a, a, this is a report that was published in 2002

all by, what they found was that, that these, the,

sorry, the MSI testing was much more accurate in colorectal cancer relative to endometrial. So, what is that threshold of accuracy? What is that threshold of concordance that we would come to agree to as a, both as an Agency and as a community?

Likewise, this is, this is test data from an ongoing trial, a trial that a colleague of mine, Dr. Mike Overman, looked at MSI status in colorectal cancers in the nivo trial ongoing. And what they showed was that there was a discrepancy between different labs, and central labs versus local labs showed a discordance of almost 20%. And what is that threshold as both as an Agency and as a, and as a community will we be willing to consider?

I think one interesting question that may come up in the near future is this issue of kind of threshold and tumor mutational burden, which MSI kind of falls underneath, as you know, as I shared that MSI patients have these very high tumor mutational burdens, is likely going to be something that may come up as a possible agnostic application. And that there have been groups that showed that across different

histologies with PD-1 therapy, there can be benefit based upon mutational burden irregardless of histology.

And most recently at AACR there was a data presented on lungs showing that with nivo in ipi, significant, significant benefit could be achieved in patients with certain threshold of high tumor mutational burden.

This is data from Dave Hyman and the MSK group that showed a retrospective analysis of patients who had, they looked at tumor mutational burden and benefit from anti-PD-1 therapy across different histologies. As you can see, there were a number of patients who did, tumor types that did receive benefit. But as you can see on the cutoff, there were different cutoffs as to benefit.

So, what is that -- how do we design clinical trials? How do we make indications where there are different cutoffs in which a biomarker is either positive or negative, since most of the tumor agnostic trials, at least one, has really been a binary plus or minus present biomarker?

My last section is on consideration of

clinical trials and I think there are three questions that emerge from this. One is what is the best endpoint when we design tumor agnostic clinical trials? Second, what is the best trial design, and lastly, are randomized clinical trials really needed in this context?

This is the Phase 1 trial that Eunice Kwak ran on ALK-positive, with crizotinib, ALK-positive non-small cell lung cancer. And this trial obviously showed incredible response in this subset of patients, but led to an eventual randomized Phase 3 trial and led to the approval of crizotinib in second line non-small cell lung cancer. And clearly what it shows is that response, even in an early setting, can be predictive ultimately of approval and benefit.

And we've looked at that in our patient population, which is primarily Phase 1 refractory patient populations. We looked at close to 1,000 patients, did, did response ultimately lead to correlation with survival and we showed that in this, in this analysis that we did in 2015. But most of these trials were specifically precision medicine or

targeted agents or cytotoxic agents.

But there have been others. Ritchie, et al, this was a recent paper that was published in JAMA Oncology, that showed that other therapies, such as immunotherapy, may actually benefit from a different surrogate marker like progression-free survival. This was an analysis, a meta-analysis that was done showing that six-month progression-free survival is actually a better predictor of 12-month overall survival than response rates in 25, comparing Phase 2 to 25 randomized immunotherapy trials.

So, what is the best trial design? To date the trial design that people have most used are what are called basket trails where you have different histologies targeting one certain pathway. And that's contrast from what are called umbrella trials, which you have one type of cancer and different genetic mutations testing multiple different drugs.

And this is one of the basket studies that has been highlighted recently, both in the New England Journal and number, and has led to a number of recent Approvals, led by Dave Hyman at MSKCC. As you can see,

this was a trial where they targeted the BRAF V600 gene, allocated a number of different histologies and tumor types, and what they found from the study was, is that indeed there was significant activity in different histologies, right? Non-small cell lung cancer showed significant activity, which eventually led to further studies in the Rohr study showing significant activity.

Also in anaplastic, which recently achieved approval. The most, and also Erdheim-Chester, which is a rare type of lymphoid malignancy which shows incredible activity with this basket trial.

But there are critics who say that these basket trials are underpowered. They have problems with prognostic heterogeneity, etc. And some people argue, Don Berry and Brian Hobbs at our group, our Bayesian statistician, argue that there are ways to improve this. Adaptive enrichment designs have been used in umbrella studies such as I-SPY and BATTLE to really powerful effects. And one can use Bayesian basket trial designs with what are called hierarchical modeling based on exchangeability.

I'm not going to try to explain this in a

nutshell here, but essentially the idea is, is that using Bayesian statistics you can actually group these different arms showing better sensitivity and specificity and true effect across these different histologies.

The last question is do we need a randomized clinical trial? And I would argue to you not necessarily. And in fact, I would say that for rare tumors and orphan diseases, it is almost impossible, if not impractical. And in fact, the FDA history would suggest that the test of time does show that randomized clinical trials are not always necessary.

This was an analysis that we did of all FDA approvals from 1973 in Oncology through 2006, over 68 drugs. Thirty-one of those drugs were conducted without a randomized clinical trial. And if you looked past that, many, many years past that, only one of these drugs after post-market approval were rescinded, gefitinib, and many of these went on to get further additional uses. Nineteen of the thirty-one went on to additional uses. So therefore, and to some extent the test of time showed that randomized clinical trials are

not always necessary.

And these are just some of the most recent approvals that are based upon nonrandomized clinical trials. And as you can see, both progression-free survival shows that maybe there are, there's clinical benefit and we'll see what the test of time is in the context of the kind of post-market. But we'll see. But I suspect that these two will move on and show true benefit.

I want to remind us that as Steve has mentioned in, in his past lectures, that, you know, approval is not necessarily a clinical trial, right? That I think the FDA has had really kind of thoughtfulness and forward-thinking in the context that, you know, you really kind of look at the, the weight of the full evidence.

And this is the case, for example, in not only in pembrolizumab, but also in our NTRK application, larotrectinib application, where we've really, the FDA's really taken into consideration three different trials, both the Phase 1 and the Phase 2 adult, which I helped run, and also the pediatric Phase 1 to kind of

bring back together the, the cumulative data and this rare subset of patients.

So that is the end of my talk. I want to thank all my colleagues who helped me bounce a lot of ideas, and also many of the people here who I stole slides from. And thank you very much.

(Applause)

DR. SUL: Thank you, Dr. Hong. So, with that background information on the scientific rationale for considering tissue agnostic drug development in oncology, our next speaker, Dr. Steven Lemery, will talk a little bit about the regulatory perspectives. Dr. Lemery is an Associate Director in the Division of Oncology Products 2 in the Office of Hematology Oncology Products. He also led the team that reviewed the MSI-high application for pembrolizumab for solid tumors. So, he's, you know, what I consider our office expert in this area. So welcome to Dr. Lemery.

PRESENTATION - OFFICE OF HEMATOLOGY AND ONCOLOGY PRODUCTS (OHOP) PERSPECTIVE

DR. LEMERY: Thanks, Joohee. So, the first part of my talk will, will cover some, much of the same

information that, that David covered. But the second half sort of really switches onto what the purpose of the, of the meeting here is today. So as has basically been mentioned, traditional development paradigm has been based on a single tumor type or a biomarker in that tumor type. For example, previously untreated pancreatic cancer or HER2 positive breast or gastric cancer.

So, I'll briefly touch base about the, the case study of pembrolizumab, which David also talked about. This is very, very, very simplistic. So, for anyone who's a true scientist in this field, you know, this is simplistic, but mixed matched deficiency is caused by, generally caused by, mutation in the one of four DNA repair proteins. It could be the result of Lynch syndrome, which is a cancer predisposition syndrome, or a somatic mutation of one of these four proteins.

It can also be related to inactivation of, of DNA that inactivates one of these four proteins, and especially in colon cancer that's probably the more common cause of mismatch repair deficiency and it's usually diagnosed with immunohistochemistry.

Again, this is simplistic. The microsatellite instability is in essence the phenotype of deficient mismatch repair. Microsatellites are, are pieces of DNA that are short repeats. Their lengths are variable from person to person. And if someone has microsatellite instability, this can be detected through either PCR or next generation sequencing.

So, for the Keytruda, pembrolizumab, approval microsatellite instability or deficient mismatched repair, not the organ, defined the indication. And this'll be important subsequently when I'll talk a little bit about indications versus disease.

Here's a slide that talk, that shows the prevalence of microsatellite instability in different tumor types that was shown in one paper. And of note, the, the second one -- some of these are more common tumors than others. The second bar is COAD, is colon cancer, and I think READ is rectal cancer. So those are more prevalent cancers. And so when you take the prevalence of MSI and colon cancer, it probably would not meet the threshold for orphan status, which is 200,000.

Some of these, though, like for, for example, neuroendocrine tumors, they're, they're very rare tumors and when you take a subset of them that are microsatellite instable, it makes an extremely rare tumor. So, some of these tumor types are extremely rare. And even when you look at colon cancer, this is the, the incidence and, or prevalence in all-comer patients in the metastatic setting, which pembrolizumab was approved for. It's a much more rare -- it's, it's less common.

So why does having deficient mismatch repair MSI matter? So as David mentioned, the, this causes a greatly increased number of mutations in tumors. Some of these mutations may be targeted by the immune system and pembrolizumab can facilitate an immune system response in some of those cancers.

So, this was a cartoon that basically shows the mechanism of action. So again, you have these increased number of mutations. Increases the probability that you'll have a neoantigen, which the T cell can respond to. However, the, you know, cancers have a clever way of, of preventing this immune attack and one of them is through the PD-L1 system. So

pembrolizumab can block PD-L1 and result in an immune attack against the tumor cell.

So as was stated earlier, this is the data supporting the approval. So, a response rate of, of, I think about 39% all-comers. And, you know, there may be differences in some of the tumor types in the qualitative response rates. You know, again, some of these patients have received different, different numbers of, of chemotherapy. Their immune systems may be different. So that may explain some differences in, in response rates across tumors. However, we didn't really observe a, sorry, a qualitative difference, but there may be slight quantitative differences.

What was really impressive is that these responses appeared very durable. This is in contrast to what you, what we've historically seen with cytotoxic chemotherapy where responses last in the order of, you know, a couple months.

Also of note for this -- this is biomarker-directed development. So, in colon cancer in Dr. Le's initial study, none of the patients with microsatellite stable tumors responded. You know, this shows that in,

at least in colon cancer that MSI did appear to be an important biomarker for selection of, of benefit.

There's also limited activity of immunotherapy as single agents in many microsatellite stable, quote, unquote, "cold tumors." So, you know, pancreatic cancer, we haven't seen a lot of activity with different checkpoint inhibitors in, in this tumor.

There are responses in certain other tumors that are microsatellite stable, what we call hot tumors. These are, include lung cancer, melanoma, and these patients often have high mutation burdens. Their tumors have high mutation burdens due to other reasons, smoking in lung cancer, or UV exposure in melanoma.

So as was mentioned, we thought there was a strong scientific biological rationale. We thought there was compelling clinical data. And there's been a favorable risk/benefit profile of pembrolizumab with similar response rates in other indications that were studied. So for example, melanoma has a high response rate, a similar response rate, and had a favorable risk/benefit in randomized trials, you know, and lung cancer as well.

So although, although tissue agnostic approval has been granted, tissue agnostic approvals may not be appropriate for all targets. And David mentioned the, the BRAF example. So it's as single agents or, or as, as double agents of BRAF/MEK inhibitor alone, there, they've shown to be effective in BRAF mutant melanoma, non-small cell lung cancer, anaplastic thyroid cancer, and as a single agent, vemurafenib, has been approved for Erdheim-Chester disease. However, as a signal agent or as a, as two agents together, they're less effective for BRAF mutant colorectal cancer.

It should be noted, though, that knowledge of these effects in melanoma where randomized trials had been conducted, have facilitated approvals based on very small trials and some of these other indications. So we approved anaplastic thyroid cancer. It was based on fewer than 30 patients. Same thing for Erdheim-Chester disease. And, you know, we saw very high response rates in these, these tumor types.

Anaplastic thyroid cancer is, is a devastating cancer. We saw a response rate that was similar to melanoma. The response duration was similar to

melanoma. So we felt it was, it was, you know, these patients have the highest of unmet medical need. It takes, you know, these are really, really rare tumors. It took, I think, over four years to enroll about 23 to 26 patients that have anaplastic thyroid cancer. So, we thought it was appropriate to approve in that setting.

So we, when we granted the approval of pembrolizumab, the, the question can be asked is was the approval for a disease or an indication that included many diseases? So, this is sort of what the, what we're getting here today. So as, in OND we, we approve an indication in essence which could be for either of these two scenarios; however, orphan drugs are approved for diseases.

The only, interestingly, the only place when I did my talk at ASCO last year that I found a definition of the disease was in the food regulations. And this sort of, it didn't really apply to, you know, the setting that we're talking about today. So damage to an organ, part, structure, system of the body such that it does not function properly. Or a state of health leading to such dysfunctioning. And this was to

differentiate supplements versus a drug.

So how should disease be defined? Should we define by indication, quote, unquote, "MSI-positive cancers" which is, you know, lumping, or by splitting? Do we, do we define disease as cholangiocarcinoma, microsatellite unstable cholangiocarcinoma, microsatellite stable cholangiocarcinoma? And you can go really, you know, you can really keep splitting and splitting and splitting.

So, arguments against splitting for the MSI example that we approved. So, many microsatellite unstable cancers share common histological characteristics. So many, you see lymphocytic infiltration. You see medullary type patterns. A misspelling there. And microsatellite tumor share increased mutation burden and a response to checkpoint inhibition.

However, you can make an argument against splitting. I'm sorry, for splitting. So mismatched repair deficiency or microsatellite instability is not the only molecular finding in patients. Other driver aberrations may differ in different cancers. There may

be differences in the natural history of some of these patients with different cancer types. So, for example, FOLFOX is a commonly used regimen for colorectal cancer. Would that be effective to treat patients with glioblastoma? Probably not.

And I'll, I'll briefly mention NTRK in a few slides, not the, simply as a, as a disease entity. So an NTRK fusion-positive child with infantile fibrosarcoma is not going to be the same as a disease of the NTRK fusion-positive non-small cell lung cancer. You know, however, should we split ad infinitum? You know, you can make the case whether we get -- you know, you can make an almost infinite number of orphan drug requests if we keep splitting.

Other splitting considerations. So maybe company, you know, we have, we've approved pembrolizumab for, for tissue agnostic MSI indication. Company B may not, may not pursue a tissue agnostic indication. So an example of this is nivolumab was approved for a microsatellite instability high colorectal cancer based on data on patients with colorectal cancer.

As I stated, this may, MSI colorectal cancer may not be orphan, may not have met the criteria for orphan status, but maybe MSI-positive endometrial cancer or neuroendocrine tumors could have. You can see how this could be a situation where companies could try to, you know, you know, game the system in essence. And so we have to really think these, these scenarios carefully.

You know, there, there's a benefit of orphan development, orphan status where, you know, we're trying to encourage development in rare diseases, but, you know, there's also the, the flip side where you want competition in the market. These are expensive drugs.

You know, and I have the second bullet, is what are the effects of orphan drug designation if Company B or C requests orphan status for MSI cholangiocarcinoma? Maybe this differs if it’s a PD-1 inhibitor, or versus a small molecule that doesn't target that biomarker. You know, when should a tissue agnostic orphan designation be granted?

You know, historically we've done it at any

time, but, you know, should it be early? Should it be late? When we have sort of sufficient information that this is likely to be a tissue agnostic pathway? These are some of the questions we'll discuss today.

So as was mentioned, orphan drug designation has been granted for NTRK fusion-positive cancers. In toto, in toto the FDA felt that this met the, the criteria. You know, and, you know, as a question does it make sense -- would it make sense to have separate designations for an enumerable number of NTRK fusion-positive cancers?

So I think in the, in the New England paper, I think that were 12 cancers listed. Put that with an additional factor of they're different NTRK fusion proteins, and then over 10 different fusion partners. And as you can see, if you mix and match them all together and submit a separate request for each one, you know, you can almost, you know, go infinite number of applications.

How will tissue agnostic approval impact development for biomarker negative populations? This is one that we're going to have to think about policy wise

as an, as an Agency. So, should MSI patients be excluded from clinical trials of single agent PD-1 inhibitors? If not, how to assess whether an effect is driven solely by the biomarker. At a minimum, the biomarker should be identified in these trials.

And as a hypothetical example, you know, if you have a, if you have a drug that has a 40% response rate, how do you consider randomized trials in, in non-biomarker selected patients, you know? It may differ depending on what the response rate is in microsatellite stable patients. Is it 1%? Five percent? Ten percent?

Also, what is the incidence of prevalence in that cancer type, which, you know, if the, if it’s super rare, if the prevalence of a biomarker's super rare in that cancer type, 1%, it may not matter if you're measuring that biomarker in the rest of the patients.

How will tissue agnostic approval impact development for biomarker negative populations? Again, it's taking on the prior slide. What if the investigational drug is a cytotoxic or a multitarget TKI? Presence of MSI may not matter. Again, these are

scientific questions, but what about orphan disease designation which is, which is what we're taking about today?

So in summary, tissue agnostic approvals is a potential pathway for approvals if scientifically justified. Tissue agnostic orphan drug disease designations have been granted, but there are challenges once a, once a designation is granted. You know, what about requests from another company for a non-tissue agnostic indication with the same biomarker? What if it's the same pathway? What if it’s a different pathway?

There's going to be a lot of sort of scenarios I think that we're going to go through today and, and, you know, I think everyone will see it’s going to be a challenge to, to just, to go through.

(Applause)

PRESENTATION – OFFICE OF ORPHAN PRODUCTS DEVELOPMENT (OOPD) PERSPECTIVE

DR. LEWIS: Thank you, Steve. I really appreciate this transition that we're making where we're talking first with Dr. Hong's presentation on the

science, on these issues to ground us there, and then as we move to the questions that are really in our focus today, which is about orphan drug designation in this context and also our exclusivity.

So, we knew it was important to talk a little bit about our orphan drug framework for designation and exclusivity. And so I'm going to do a, as you said, kind of a simplistic look at how these elements work together, but I think it's critical as we talk about this in our discussion a little bit later today.

So, if I can go to the next slide. The goals that we have in this part of our program is to give you this overview. You'll learn a little bit about designation. Many of you know it closely, so please bear with us. And then we'll talk a little bit about our exclusivity framework and how that works. We'll provide that context of these, these issues with the tissue agnostic elements that we've talked about today already.

We'll even talk a little bit about diseases and conditions and indications, and we'll introduce some of these issues that are so relevant as we go

forward.

So, many of you are familiar with the Orphan Drug Act. It facilitates the development of drugs for rare diseases. It provides financial incentives that are going to reduce the costs of development. And the idea is that there are rewards then to these sponsors. Some come right with designation and some come only to the first successful sponsor for a seven-year marketing exclusivity.

This Act, the Orphan Drug Act, first came about in 1983, but it's been amended a number of times and most recently just with the Reauthorization Act in 2017. We've also issued regulations and they help us implement; they help us safeguard and protect those incentives to be sure that we're doing things properly as we designate and as we provide exclusivity. And I've given that citation here for you, 21 CFR 316, that will go through those elements.

So, when we do designate, we're designating for, by our law and our regulations, for a rare disease or condition. And so you saw Steve struggling a bit with, you know, what definition should we be using on

disease as we go forward. But I want to share what's in our, our law right now.

There's two parts to it. There's one part that we're going to focus on and one we won't. The A there, we're going to focus on the part of the definition that it affects diseases that are affecting fewer than 200,000 persons in the United States. And that's really what our topic will be today.

There is another provision. It's not used frequently. In fact, only three times in our history, where a sponsor's able to show that they have a disease that affects over 200,000, but the sponsor would be unable to recoup their costs of development.

So, I'm going to set that aside for a little bit and just go to one other aspect that has to be part of the designation, and that's that the drug must show some promise for the prevention, diagnosis, or treatment of that rare condition or rare disease.

So, you may be wondering, well, wait a minute, I've heard about orphan subsets. What is that? You know, you just told me that we deal with things under 200,000. In our regulation, there is a provision

called the orphan subset and it's defined there and I give that citation to you.

A rare subset of persons within a common disease, what does that mean? And many people misinterpret this and miss, and I don't know it'll be a big element today, but I'm going to include it because a little bit of completeness in case this comes up.

So, if you have a rare subset of persons with a disease that's not rare, but the use of that drug could only be used within that subset, that is where we're going to be talking about right now.

I'm saying that if you take a common disease, we always, always when we do designation we pair together the drug and the condition. And when you look at that, you look at that mechanism and how it works, and you have to be certain that either through some aspect, some property of that drug, would not be appropriate to use outside that subset.

So, could be because of toxicity. That's a thing that happens where you would only be able to use this very toxic drug within the subset. It could be the mechanism of action is such that it would only be

useful in this orphan subset. Or it might even be clinical experience that shows it does not work outside, across the whole disease.

So, these are very unusual circumstances. A lot of people think we have subsets often, but it's not. It is not a common thing and we, this definition will still safeguard the Orphan Drug Act intent. It prevents misuse from people who sometimes think that this is dividing a disease inappropriately.

So, I'm going to move from subsets and really from designation for a moment and talk about exclusivity. And I'm skipping a lot of things. What happens when you get designated? There are certain incentives you get. You get tax credits reduced now to 25%, but you also get a waiver of user fee for the application. But I'm going to skip now to exclusivity because that's our other topic we want to talk about today.

An orphan exclusivity provides seven years of marketing exclusivity to that first sponsor that successfully gets that indication for, and specifically that indication. It will mean FDA cannot approve that

same drug for that same indication for seven years. And I have a few points I would like to make about that.

That is that, the drug is actually, usually approved for an indication that's within the whole orphan drug designation. We will designate a whole disease, and I'll talk in a moment to you that the exclusivity comes to the approved indication alone.

That, it's also important, that that same drug has not been previously approved for that same indication. So, it's not that everybody comes along with a designation will get exclusivity. We'll always look to see if the same drug has been approved for that same indication in the past.

And I'll also talk in a moment about a part of the framework that tries to balance protecting the exclusivity with providing patients with a superior product when that's necessary. So, if a superior, clinically superior product come along, you'll see it won't actually be blocked from market by that exclusivity.

So, right now we, we've focused a little bit.

We're going to be talking a lot about how to designate and we'll designate for the disease. We, we want to focus just for a moment on disease versus indication. In the Orphan Drug Act, FDA grants this designation for rare diseases and conditions. So, we'll be talking about diseases.

But FDA when they do a marketing approval, they approve something for an indication, which is generally, as I said earlier, a little narrower in most cases than the designation was. And I'm going to give a couple of examples because I think it'll be helpful to you.

The first example on, on the left is that we might designate for mantle cell lymphoma and that's, that's a rare condition. Not -- we aren't going for a particular indication there. But once a product gets approved, it might be approved for a much more narrow indication. And the example here is the treatment of adult patients with mantle cell lymphoma who've received at least one prior therapy. So, you'll see in a moment that's the indication we'll give exclusivity for even though the designation is broader.

And there's a second example for you on this slide. It's about designation for sickle cell. We may designate the entire disease for sickle cell, but when it comes to market the approved indication, maybe to reduce acute complications of sickle cell in adults and pediatric patients five years age and older. So we'll have to deal with that indication when we look at the exclusivity determination. That is where we'll be giving exclusivity and it's narrowly protected only for that approved indication.

So, what's the implication that, why am I making such a big point about the disease versus implication? Well, oftentimes we'll read in the literature people who haven't made that distinction and it might misguide them when they talk about this. So we find that the way this works, we're reserving the designation for the rare disease, but the exclusivity is very limited to the approved narrow indication.

So that means the products can come to market which are not within the narrow indication. It's, and a subsequent sponsor can seek that, that drug for also a different indication within the same disease or a

different disease altogether. So, understanding how that works will help when you're reading other material and help in our discussion today.

So, we've got a diagram of this. This is how important this is for us, that we have a scope of exclusivity from mantle cell and you can see that was our designation in the whole blue circle, is to represent the whole disease. And then when we have an approval for the indication of patients with mantle cell that received at least one prior therapy, that red circle there is what is protected under exclusivity. Not the rest of the disease blot.

And then similarly if you have a second indication that comes along for the treatment of patients who receive no prior therapy, that's a different population. They may receive exclusivity just for that narrow group there. And so you can see not everything is protected by the indication. So, it’s worth understanding because of the confusion we sometimes see in the literature.

So, I mentioned that, let's say I wanted to Seek,I’m a sponsor and I want to seek designation or exclusivity for the same drug that was already approved

for that same indication. Can I do that? Well, not normally, no. Once something is approved, you are, we are not going to designate it again, and we're not going to then be giving it the, the various incentives for the development.

But if the sponsor can provide a plausible hypothesis of clinical superiority at the time of designation, we'll evaluate that, and if it is an appropriate plausible hypothesis of clinical superiority, then we will consider it different and we will designate, the idea being balancing that framework of getting superior products to patients with rare conditions.

But what happens then if they continue on to approval? Will they automatically get exclusivity? No. They have to demonstrate that there's a clinical superiority finding in their, in their data. What kind of clinical superiority do we mean? There is a definition and the citation's there for you.

It means that that product is more safe or

more effective, or it's going to provide a major

contribution to patient care. And that's in unusual cases that we go there. Generally we're looking for greater safety and greater effectiveness. I don’t know that this will be a big topic today, but it's worth touching on now.

So, what will be a big topic today? The big topic for us comes as we're moving historically from looking at anatomically based or histology based cancers. As you heard already, that has been the tradition that we expected studies for each individual anatomical or each specific cancer. So Orphan Products will align its incentives to what the expectation is with, within the development paradigm.

So that was, that was working well until we came to a point of now we see the questions that are based on specific molecular markers. We ran into this earlier in our program. As we would see in orphan subsets, we would see, all right, we had non-small cell lung cancer, which is not rare, but then there were particular markers that even when you added those markers together still were under the 200,000. It wouldn't be expected to work outside that group. So

therefore, we began in this process to, to have a subset, an orphan subset for specific molecular markers.

And now we've gone further down this line that for purposes of orphan designation and consider, and that consideration, as well as, as we're moving to exclusivity, we have to recognize that now there are two tissue agnostic diseases or conditions, as we call them. You'll see throughout our talk today we'll probably be, are we talking, are we diseases, are we talking indications. But the two, the two groups that were considered were the MSI-high and the NTRK fusion-positive.

Within MSI-high when you added all the groups together, there were too many. You can't qualify for orphan drug designation on MSI-high because the prevalence over 200,000. But in the NTRK fusion-positive, even when you added all the groups together, it was under our 200,000, and that's why we have two current designations for NTRK. And as you heard earlier from the Commissioner, we also have one in ophthalmology.

So, it's not that we think that this tissue agnostic or agnostic situations are confined to oncology. Oncology's in the frontlines of considering these things, but it's going to be an issue across diseases. Today we're focused on oncology.

So, these sort of principles that have evolved but we want to discuss today, is that we, we considered the prevalence, this cumulative count of all the relevant cancers within a particular marker. And as you saw, if it was over 200,000 we did not think we should subset. Once that decision is made, we did not think we could continue to subset individual cancers.

But then we became aware it's not as simple as, as it first seems. For example, with MSI-high, that was over 200,000 and it couldn’t receive designation for MSI-high gastric cancer. But what about those that are not MSI-high? How do we, how do we deal with those? Those will be questions that we hope our panel can help address.

So is it possible that you may receive designation for that rare gastric cancer, you should if the drug works out the MSI-high target in gastric

cancer?

So, we have questions about overlapping or different diseases. Can a tissue agnostic disease overlap with the histology-specific disease? Should they be considered completely separate? The example that I'm providing here was the one we've seen case studies for, pembrolizumab, which was approved for the MSI-high tumors, but it's also approved for gastric cancer. Where the populations overlap, what are these implications for us?

We've talked within our groups, within our workgroups, and today we'll be talking within our panel and audience about designation, approval and exclusivity, mainly really designation and exclusivity.

So, one of the considerations really important, that people need to keep in mind, is that a lot of what we've been looking at is a retrospective kind of look at what, what we know how about these cases. But for us the timing is really critical because sponsors seek designation very early in development. So, a drug may be designated for a histology-specific cancer, but then after development it may turn out that over time it's

later approved for a tissue agnostic indication.

We have to think about previous approvals and how that might impact our designation and our current approvals. We've tried to develop some predetermined scenarios that we'll be talking about in our panel. They might be tough to, to stay on track, but hopefully we'll be able to discuss some of these scenarios and get some great input.

We know that there are difficult situations that we may not be able to fully cover today. We know that tissue agnostics are going to be involved in combination therapies. We know that the testing is important, that genome profiling for trials may be relevant. We've not seen really a difference in the pediatric aspects of tissue agnostic development, but there may be discussion on that as well.

So in summary, this is just a quick overview, but I, we think it's important because that's really our topic. So understanding the context of designation and how that works, and the exclusivity and how that works, is critical to be able to discuss the topic. We've given a little bit of context for designation and

introduced some of these issues for orphan drug exclusivity and designation.

What I think I'd like to do now is just to remind people that as we're going to be going on break and coming back and our panel's going to go to work. I want to let you know Joohee Sul, Dr. Sul, is going to co-moderate this panel. You saw her a moment ago when she introduced Steve Lemery. We've worked together in a great way where she's done a detail with our group, so has a little bit of experience, and so hopefully between us we can keep track on the discussion.

Keep in mind during the discussion, these questions, we'll be using these to help develop a guidance document on this topic. And so we'll be using the input we receive from the public today and working to incorporate that into a guidance. So that's what we're looking for today. That's our goal of the whole program, a broad input on these topics.

I thank everyone up to this section, I think we're going to go on a break now, and then after our break we'll be set for our panel discussion. We'll introduce our panel. In the meantime, everyone enjoy break and

we'll reconvene at 11. Is that right? Eleven o'clock. Okay. Thank you, everyone.

BREAK

PANEL DISCUSSION WITH AUDIENCE Q&A

DR. SUL: The panel discussion, if everyone can take their seats. Everyone, everyone standing, if you could please take your seats so we can get started.

So, we're going to start our, our panel discussion and this will be essentially to discuss some of the scenarios and the topics and the issues that were brought up by the speakers in their presentations this morning. And really to get a sense of, you know, what the Office of Orphan Products is, is facing when they're looking at both designation and exclusivity issues related to the tissue agnostic drug development that's going on in oncology.

So before we begin, it's always kind of nice to know who's in the audience. So I've, just curious who from the audience is from industry? Could you show, raise your hands? Okay. A lot. Which is, which is I think what we kind of expected. What about from patient advocacy? Great. Academics? Government?

There's probably a lot of us here. Yeah. Anybody I'm missing? Oh, yeah, press. Okay. Great.

And I think what, the way we'll start, the way we'll start the panel is first we'll have our panelists introduce themselves and say a little bit about what their interest is in tissue agnostic drug development because some of our panelists didn't get a chance to, to speak. And then we'll move on to get some clarifying questions, particularly if there are questions related to the orphan drug designation process and exclusivity. And then we'll move on to the questions that are included with the workshop.

So we'll start at one end. Just to let everybody know on the panel that when you go to speak, you should press the button on the mic and wait for the red light. That's how you know that you're going to be heard.

MR. KARST: Great. My name is Kurt Karst. I'm from Hyman, Phelps & McNamara here on behalf of the Association for Accessible Medicines. And I certainly have a significant interest in the Orphan Drug Act. I work with numerous companies whether generics or brands

on designation and exclusivity issues. Probably have worked on 100, 200 designations over the years.

MS. SHER: My name's Rachel Sher. I'm deputy general counsel at the Association for Accessible Medicines. And we represent the manufacturers of generic drugs, small molecule, traditional generic drugs and biosimilars.

And obviously our interest in being here today is to discuss issues around exclusivity and sort of the appropriate scope of exclusivity when we're talking about tissue agnostic therapies that, that strikes the right balance between ensuring that there are appropriate incentives for innovation on the one hand and opportunities for generic and biosimilar competition at the expiry of that exclusivity period. So, thanks for having us.

DR. STEWART: Hi. My name's Mark Stewart. I'm here on behalf of Friends of Cancer Research. Our organization's been closely involved in much of the discussions around drug regulatory policy with the goal of ensuring patients have access to innovative therapies as safely and quickly as possible.

And our interest in this is multifaceted both on the science side in terms of the scientific justification and requirements around receiving a tissue agnostic approval.

And then also both on what makes sense for the patients in ensuring that patients have access to drugs, particularly with these agnostic approvals that often rely on diagnostic testing and making sure that the diagnostic tests are appropriately available and have the appropriate testing and methodology in place to ensure that patients are assigned to the correct drug.

DR. LE: My name's Dung Le. I'm a GI medical oncologist at Hopkins and I run clinical trials. And I helped design and implement the very first trial looking at pembrolizumab in a tissue agnostic manner.

DR. MELLIS: Hello. My name is Scott Mellis. I'm a rheumatologist. I work at Regeneron Pharmaceuticals, a biotechnology company in New York. And we're very interested in science-based drug discovery and development. And with our focus on targeted therapeutics, it becomes clear that tissue agnostic

approaches to drug development are rational, both in the oncology area, as well as the non-oncology areas. So, honored to be able to participate in this discussion. Thank you.

DR. STARTZMAN: Hi. I'm Henry Startzman. I'm, I direct the Orphan Drug Designation Program in the Office of Orphan Products Development.

DR. LEWIS: I'm Debra Lewis, Acting Director for Orphan Products Development. And serving as co-moderator with Joohee.

DR. HONG: I'm Dave Hong. I'm at MD Anderson Cancer Center. I'm an oncologist that does really early drug development there. And I guess my interest is, is that you, not only do I do these clinical trials, but a lot of my patients are now coming in with, you know, tumor markers, molecular tumor markers asking for new drugs that target their specific pathways. And so, and we're seeing actual real, real evidence of benefit in these patients.

DR. LEWIS: I'm getting the word from our tech people. In order for people online to hear, we actually have to be uncomfortably close to these

microphones for, for people on the webcast to understand us, even though we can hear in the room.

DR. KUMMAR: I'm Shivaani Kummar. I'm a medical oncologist and I run the Phase 1 clinical research program and the translational oncology programs at Stanford. My interest is actually designing first in human trial of novel therapeutics, trying to incorporate biomarker and patient selection in to see how we can inform and expedite drug development. And similar to David, I'm also interested because patients, more and more patients are coming to us with molecular profiling and how to assign them to clinical trials.

DR. LEMERY: Steven Lemery. As, as Joohee mentioned earlier, I was involved in the, in the review team for the pembrolizumab application. I'm a medical oncologist, hematologist/oncologist by training and, you know, have an interest in, you know, hopefully helping patients at the end of the day.

DR. MOSCICKI: Hi. I'm Richard Moscicki. I'm the executive vice president for Science and Regulatory and Chief Medical Officer at PhRMA, the trade association for pharmaceutical companies. I have a

very long history in my career of strong interest in supporting the development of drugs for rare diseases, and believe strongly in maintaining incentives for innovation to continue the development for those diseases.

DR. RUBIN: Hello. Eric Rubin. Medical oncologist in clinical development at Merck. And I was fortunate to be involved in the development of pembrolizumab for the tissue agnostic MSI-high indication.

MS. GAVIN: Good morning. I'm Pam Gavin here representing NORD, the National Organization for Rare Disorders. NORD is a nonprofit umbrella organization that established itself 35 years ago actually this past week, and through a grass roots advocacy effort to really establish the incentives that we now discuss and, and will be talking about as the Orphan Drug Act.

So, we are here today to ensure that the rare disease patient voices are part of the discussions and that the incentives that were established and refined over time remain strong for the future.

DR. SUL: Okay. So before I ask Deb to

introduce the first topic, just two reminders. Even though we're here at the, the great room at FDA, this is not an advisory committee discussion. And secondly, you know, I think any time you get into discussions about tissue agnostic drug development, you know, sort of the, the natural inclination is to go towards actual talking about the clinical aspects. But this is really a discussion to focus on the orphan regulation issues that are, that are at hand. So just those two disclaimers before starting.

DR. LEWIS: Could I, could I also introduce Dr. Donna Roscoe. She'll be available for us as any questions come up on testing elements. So, thank you for being with us. I know -- were there any clarifying questions? I know I received one during the break. Did anybody have any others?

There, the question I was asked, are we the same or different than in the European framework where we may have limitations on how many designations you can have and what type of criteria exists for designation, multiple designations? And the answer is that we actually, until approval, we'll continue to

allow designations for the same drug for that disease. So, that is a little different than our European and our Australian colleagues. You want me to go ahead with this first? We're going to take --

DR. SUL: Oh, yeah.

DR. LEWIS: Oh, did you?

DR. SUL: Anybody else with any questions specifically related to orphan drug designation or exclusivity? I think one of the, the questions that did come up earlier during the break was related to drug. There were a couple slides, Debra, that you had where you said, you know, if you have the same drug but a different sponsor, you know, I think most of us are used to thinking about drugs as sort of the name brand drug. And maybe you could clarify a little bit about what's meant by drug in the orphan drug regulations.

DR. LEWIS: Yeah. The regulations do set up things differently for small molecules versus large. And so I think Dr. Startzman can give us a little bit about that.

DR. STARTZMAN: Yes, when we're talking about same drug, in small molecule you're talking about the active moiety

and, you know, salts, esters, etc, do not make them different. We do look at things like, you know, differences in covalent bonds, etc. Large molecules, you're talking about, you know, for proteins, if they're minor changes, amino acid sequence that can make a, that would make two proteins the same. You know, they have to be major changes. And again, in a lot of these things we do talk with the Review Division in terms of what makes something the same or different.

DR. LEWIS: So with that, I think that what we tried to do in our preparations, we had some topics that we knew would be important to answer. We'll, we'll try to rotate between those if other comments come up or questions come up. We welcome that. But I want to go to first, Topic One.

PANEL DISCUSSION WITH AUDIENCE Q&A

TOPIC ONE

And this was a question just about -- this goes kind of to the earlier discussions. What kind of evidence would be necessary for FDA to consider a biomarker as defining a tissue agnostic disease for

purposes of orphan drug designation? And again, the, the real key for us is we have to keep in mind that these sponsors often request drug designation very early in development. But if there's any comments to help us in -- now these, just as you said, this is not an advisory committee, but we do appreciate this feedback and that's the purpose of our meeting, to get broad public input so we can consider this going forward.

DR. KUMMAR: So I think -- I mean I'll get this started. I think if you're doing it early on in development, then there needs to be enough evidence preclinically that first a biomarker exists across certain, different histologies. We can debate the number of histologies that it needs to be shown in, but that the biomarker is present and then the modulation of that biomarker has an effect in preclinical models.

I think that should be at least a minimum to sort of consider whether you're going to do tissue agnostic versus just one histology.

DR. LEWIS: Thanks. Other comments?

DR. MOSCICKI: Well, in considering this, you

know, I'm not sure that this panel will have the final say on --

DR. LEWIS: No.

DR. MOSCICKI: -- what should define this and so we think that continued discussions with stakeholders should be necessary in order to really come to any more definitive approach to, to what should define a tissue agnostic disease with that biomarker.

However, you know, I do think that it's important to maintain an attitude of flexibility as we move forward towards that, in order to not dissuade others from pursuing this approach, which is so promising.

You know, I think at the same time it would be useful in that discussion to come up with some idea for sponsors as to what kind of data would be necessary from biomarker negative populations as well, in order to help them decide whether this is something they want to pursue or not. So more about principles perhaps here than actually scientific designation.

DR. LEMERY: Just to follow on, you might want to comment, comment on this, though, is, is that it

sort of can go both ways, is that when you combine everybody together, that's when you sort of, you know, perhaps could go over 200,000, is sort of the cutoff. So, you know, if we start thinking of early on is, is, you know, are we granting a tissue agnostic indication and it starts having indications above that 200,000, then are you potentially limiting sort of disease specific where, you know, you have to debate whether it's appropriate to give an orphan designation in a, in a biomarker of single disease setting.

So I, it kind of goes both ways, is whether we have to really think about, you know, what is, the flexibility and are you really fostering this or not fostering it, and it may depend on that cutoff for that indication.

DR. MOSCICKI: Well, that's why I think, again, making sure that we have the appropriate stakeholders who are focused on these issues at the table when we try to come to those definitions. But I, I think if we get too rigid in those definitions, we may -- the science is so fluid here that, you know, I think rigidity might restrict our ability to actually

make the decisions. And that's why I think flexibility should continue to be considered as we try to nail this down.

MR. KARST: I think it's worth -- sorry. I think it's worth mentioning, of course, hey, this is an evolutionary process. So, you might start out tissue specific and you can go in for multiple orphan designations. And as time goes on, as it, you gain greater understanding, you can go in for a separate tissue agnostic designation. The main benefit here, designation really is the tax credit.

So, if you're doing -- if you get the designation in a tissue specific disease, you'll do the studies. You'll get the, the tax benefit. And again, as time goes on, it may become apparent that it's a tissue agnostic therapy and you could simply request that designation prior to submitting a marketing application and you'll still get the exclusivity in the end provided you get the approval.

DR. LEWIS: So you've talked about flexibility and being able to start with tissue specific, and then with time as more information comes along there would

be a point where there's some agreement. What we've generally done is align ourselves with the Review Division input on how they're viewing things. But others outside have suggested, no, we should be more aggressive and start combining things based on targets sooner. Do people see merit in doing that or is there an issue?

DR. HONG: If you're, if you're asking should you give designations just based upon like a preclinical package versus actual clinical human data?

DR. LEWIS: I think where I'm focusing, we, we have specifics on what we would request, but when would we consider grouping? And I think Steve talked a little bit about this. When do you group and when do you split? We are hearing suggestions starting with splitting and then at some point we'll become flexible and we would group.

But is that something that, that should be aligned with the, across our Agency with the Review Division, or is this something that you envision designation happening before an approval, before there's been a tissue agnostic approval? Should we

start grouping?

DR. MOSCICKI: Once again, I think it's really important that sponsors receive the appropriate incentives and orphan drug designation provides such an important incentive. I would hate to see -- I think the sponsors should have the ability to choose the direction that they want to go. And they may choose to start with a tissue agnostic if that is the best way to get a drug to patients, to the broadest group of patients, rather than necessarily splitting it at the beginning. So, I really think choice should be important in, in how this is approached.

DR. HONG: I'm, I'm in favor of flexibility, but I do think that we, as Shivaani already listed, I think you have to have some basis for scientific, you know, rationale. I mean like I think the pembrolizumab is, is a good model. I mean there was clear hypothesis that Dr. Le and Dr. Luis Diaz had shown in their trials.

And, and more importantly beyond just the preclinical, you know, just kind of understanding of this, they actually started putting patients on in

their IIT studies who were not just colorectal and they saw responses across histologies. So I think, in my opinion I think you, you have to have, yes, that preclinical package that, that hypothesis that makes sense across histologies, but I think that in early studies you have to show evidence that hypothesis may actually play out.

And I don't, you know, I don't think it's -- at this point given the fact that oftentimes preclinical data doesn't pan out in, in early studies in humans, that you can just say, okay, here's my preclinical package. I think this is across histologies. I would like a designation. I think you have to have some human evidence that hypothesis is going to pan out.

DR. MELLIS: Yes. If, if I may interject at this point --

DR. LEWIS: And if I can ask to pull --

DR. MELLIS: You're going to do that?

DR. LEWIS: Yeah. Pull that microphone close. I'm, I'm getting word that if, if we turn up our mics, the people online create, it gets feedback for them.

So that's perfect. Thank you.

DR. MELLIS: Okay. So my thoughts on this. I agree with the comments about the importance of flexibility and getting important medicines to as many patients rapidly as possible. With respect to the evidence necessary for designation, my, my feeling about this was that clearly the evidence of rarity is important and that a concept of plausibility and a measure of evidence and a measure of consistency in that evidence for designation is useful.

And currently the criteria for orphan designation evidence indicates, if I understand correctly, that it could be either clinical or in vivo, or in vitro evidence. If it's strong enough that could support designation. Naturally approval is going to be dependent on the quality clinical evidence.

So I think if there's a hypothesis with strong face validity and a measure of, say, possibly even preclinical scientific information, that might be sufficient for designation. I think one of the interesting questions nested in here is with respect to tissue agnostic indication. How many different tissue

types would need to be sampled or examined when you're making a designation decision?

And the, the concept that Dr. Hong proposed earlier about lineage, might you want to have evidence from a number of tumors of different embryonic lineage? That might be helpful. But I think that ultimately at the end of the day, flexibility and the, the plausibility and the potential to, to help patients should be the overarching principles.

DR. HONG: I guess I'm all about helping patients because I see them every day. But, I can't tell you how many times I've seen preclinical factors, they tell us this is going to be the most incredible drug on the planet, and then we get into clinic and it doesn't work.

And so I think that we have to be mindful of that, that right now our in vivo and preclinical models oftentimes do not translate into human beings.

DR. MELLIS: Yeah. That's definitely true, but if we're talking about orphan drug designation, we're not talking about an approval. There's, there's a significant potential gap between getting designated

for, as an orphan drug, and the, and accumulating the adequate evidence to actually achieve an approval. And, and if you don’t get there with human data, you don’t get there. You don’t get approval and you don’t get exclusivity.

So, I'm, I'm not comfortable, I don't know many other situations and maybe our, those of our FDA colleagues here who are in the Orphan Drug office can tell us whether you hold other orphan drug designations to the necessity of having human data before you, before you would grant the designation.

DR. STARTZMAN: Yes, for orphan drug designation, I mean the, we, we love human data, but usually we don’t have it and we will accept animal data, using the product in an animal, an appropriate animal model for the disease. And only if animal data or if an animal, if an animal model does not exist, then we will look to in vitro data.

And we have had people come in requesting designation for what looks like a tissue agnostic disease or condition, and usually we go, if it's not like MSI-high or, or NTRK, we go to the review division

and we say is there information available that this marker could work across different histologies at the present time.

And if they say at the present time we don't have that data, then we have gone back and said, you know, that we would not consider them for, for orphan drug designation at this time. They can still get, the disease then still becomes the, the histology or tumor based, I mean organ based.

DR. MOSCICKI: But you're specifically referring to tissue agnostic?

DR. STARTZMAN: Yes.

DR. MOSCICKI: Okay. Yeah.

DR. HONG: My last comment is I'm not asking for randomized clinical trial data. I'm just asking for a couple of patients across histologies showing that, you know what, that may actually work across histologies.

DR. LEWIS: More?

DR. MOSCICKI: I, I hear you, but I just don't know that we should be asking for, you know, something that we don't ask other situations for. And, you know

while we're very focused on oncology today, and appropriately so, it's inevitable that what's decided here will have precedent in other disease areas. I mean as we learn more about autoimmune disorders and some of the molecular basis that might trigger certain autoimmune disorders, we may find that there are also tissue agnostic opportunities that are molecularly targeted in things like autoimmune disease where these principles established here might very well spill into there.

DR. KUMMAR: Yeah. I think I'm going to hear what David's saying because I'm also a clinician, but I think not to dissuade sponsors from going down this route of a tissue agnostic, I think requiring some preclinical evidence. But I mean if there is clinical, that's great. I mean obviously you were made more confident, but then sort of, because the sponsor's also making a commitment, right?

Going tissue agnostic is not that easy, trying to accrue across histologies and stuff. So, I think having that flexibility and then requiring just preclinical with any additional data that they may have

generated, or just the field has, as a scientific rationale for the biomarker should probably be the basis.

DR. SUL: I think the other issue to consider is timing, you know, because a lot of these designation requests come in early. And again, it's, you know, if you go back to what the Orphan Drug Act was intended to do, is to help with the development. So, I think that's one of the reasons why people come in early.

I'm sort of, you know, playing devil's advocate here because I think I also agree that clinical data would be most helpful in making these determinations. But, you know, again you have to sort of think of what the, what the Act was intended to do, is to encourage the development. And you may not actually be there yet.

PANEL DISCUSSION WITH AUDIENCE Q&A

TOPIC TWO

DR. LEWIS: Thank you. Everyone on our first topic. I think it'll kind of continue in a little bit as we look at perhaps a scenario. Let me see if I can go. Maybe I can't. I see. All right.

Our second topic, we, we tried to actually go into scenarios. And so for the next topic we're going to call 2, we're discussing the different orphan drug designation scenarios. Once the, once Drug A, we're going to call it Drug A, is considered as defining a tissue agnostic disease. So, we've talked about what criteria we might want. I'm asking you now to assume we have considered it to be tissue agnostic for Drug A. And this large blue box here is to indicate that disease, that biomarker-positive solid tumors, that we're now accepting as tissue agnostic.

So, I'll give a couple different scenarios. One, the first one, is when the same drug, this is Drug A, used for, could it receive orphan drug designation just for histology specific disease? And they're not coming in acknowledging that biomarker. They're not saying I want to develop this as a tissue agnostic. They're saying I want to develop it for, for example, pancreatic cancer. Pancreatic cancer under 200,0000.

Now this big blue box here, we're going to say is over 200,000. Can you come in and take these bites of individual diseases that overlap into the tissue

agnostic? Or is that a problem? Does that make sense to folks? Drug A approved for biomarker X. It's, it's not -- I mean it's been designated. I'm sorry. It's been designated or considered to be tissue agnostic. Let me know now what your thoughts are.

Can a sponsor come in, and for the same marker, just be going for the individual disease?

DR. MOSCICKI: Yeah. I think the, when I looked at this coming into here, I thought you were talking about this is histology-specific pancreatic carcinoma irrespective of, not defined by the marker, right? So that's the scenario.

DR. LEWIS: Mm-hm, has overlap. That's sort of we're trying to draw -- there are members of that, of that pancreatic cancer that share that marker.

DR. MOSCICKI: Yeah, so as, as we've thought about these things, we would establish first several principles to think about each of these moving forward. And, and, you know, I think we represent one viewpoint. I recognize there might be others, but, but we believe that the Orphan Drug Act has been enormously successful

and continues to be an important pathway to provide the right incentives for innovation and rare diseases.

And so we should continue to try to keep and encourage policies that maintain these robust incentives for sponsors to do the investments necessary to study drugs to move forward in, in rare diseases, and to do it as robustly as possible once again.

So, and then as we thought about the various convoluted scenarios that can occur when you start overlapping and splitting and so on, we think that a policy that would be simple and most straightforward to, to address most of these is to really consider biomarker-targeted tissue agnostic indications as different from histologically defined disease.

DR. LEWIS: Complete, completely different.

DR. MOSCICKI: Yes, that they are different. They are differently defined. They're not -- and here I know we get into this what is a disease, and what is a condition, and what is an indication?

But we, we feel that if we by policy, whether in practice it’s true or not, but by policy if we would propose that these are, in fact, different and should

be treated as different, we will avoid a lot of the convolution discussions that various different scenarios will inevitably present themselves with.

So, I didn't intend to go first here, but with those principles, you know, we would say, yes, on the scenario based on that.

DR. STEWART: Sure. I have a few thoughts maybe from a different direction. It brings up a point that was raised earlier in terms of like the kind of structure, the clinical trial that led to Drug A getting the approval in the first place for a biomarker-positive tissue agnostic disease and whether pancreatic cancer was originally a part of that and how much information we might want to know on the biomarker negative disease, and whether that information could have been teased out in the original trial that led to Drug A getting the subsequent approval for a histology specific disease that's independent of that biomarker.

You know, and I recognize, and I think everyone in the room recognizes the importance, and the fact that information evolves over time, and I look at that red circle and I think of a patient. So anything

that's outside of that blue line with this new approval is more patients having access to a drug that they may not have had access to before.

So, you know, I look at it as if this information weren't on the label, how does that affect patients and their access to this therapy, and does it benefit patients having this additional information on the label. I mean it ties back to some of our work in terms of ensuring that FDA labels are up to date and have accurate information.

And if, you know, that information isn't critical to ensuring patients have access to therapies, and, you know, it think it's important. But clearly it just depends because you don’t know the time from the Drug A's original approval from the second, and whether it required maybe a new clinical trial, and whether it still meets the spirit of the orphan drug designation. In my opinion, in terms of ensuring patients with rare diseases have access to therapies that they wouldn't otherwise have access to.

MR. KARST: So Dr. Lewis, I think it comes back to how one your, your slides in your presentation.

You designate drugs, biologics for diseases or conditions and they're approved for indications. So it really comes down to what you identify, how you identify the disease or condition. And, and it, so the slide almost answers the question, right? Where we have a biomarker positive tissue agnostic disease that is the disease or condition, can it then, Drug A receive designation for a histology-specific disease, which is a different disease?

So insofar as we're talking about different diseases or conditions, I would certainly think that, that a paradigm here where you could get designation for the histology-specific disease makes sense because you're defining the disease or condition as histology specific.

DR. MOSCICKI: Plus it certainly doesn't rule out the possibility that the pancreatic cancer indication or disease specification is different because it could be that despite the agent being effective in biomarker X positive solid tumors, pancreatic carcinoma might be a unique circumstance where it works even in those that are negative for

biomarker X.

And so, you know, I think to preclude giving an orphan drug designation to pancreatic carcinoma here would not be appropriate. And might cause, again, a dissuasion, if you will, of a sponsor to, to continue to pursue the specific studies that might have led them to think that pancreatic carcinoma was an area that they should pursue.

DR. LEWIS: Oh.

DR. MOSCICKI: Nor should I think we -- nor do I think we should add burden to the sponsor by requiring them now if they believe that pancreatic carcinoma, and they have evidence that pancreatic carcinoma might respond, to try and separate and subdivide pancreatic carcinoma based on the biomarker itself if that's not what they choose to do.

DR. HONG: I would argue it, it depends. And if you were to change that out for colorectal cancer, right, and MSS-high, let's say it was less than 200,000, which is not true, but let's say it is.

DR. LEWIS: All right.

DR. HONG: And you have this data from

biomarker positive studies on the keynote studies that show that zero patients responded to, who were MSS stable, and then a drug company came and said we want to do, try to get, an orphan drug designation in colorectal cancer irrespective of MSI-high status. I would say, if I was an FDA officer, I would say no. Look, look at the biomarker study. Zero out of whatever X patients showed no response in the biomarker positive, you know, pivotal studies. Please do not submit an application. Remember I, I'm all about -- trust me, I'm all about getting drugs to patients. I, I see them every day and I see many of them dying.

But I'm also about do no harm. These drugs do not, are not benign drugs. They cause, can cause severe side effects. So, I think it all depends. It depends on what that biomarker data shows. It depends on -- obviously this is designation. This is not approval. I understand that. But it all depends.

DR. MOSCICKI: That's an important point.

DR. SUL: Are you, are you talking about -- so then are you talking about whether or not for, for an actual traditionally defined disease, whether or not

any responses or activity that you're seeing is actually being driven by the biomarker population and sort of teasing that out, being able to, to identify that --

DR. HONG: Yeah, if that's available.

DR. SUL: If, if the data is available.

DR. HONG: Yeah.

DR. KUMMAR: In reality the sponsor wouldn't go for a biomarker negative unless they have some rationale to say that the agent would have activity in that population. And I think we need to do everything to encourage sponsors to look at biomarker negative also because, you know, we don’t know depending on the biomarker that we're dealing with that maybe its activity is driven by an off target or a second target effect off a small molecule that's being testing.

But in this particular scenario, the difficulty I was having when I was reviewing this is that if, it's still Drug A and if I'm Sponsor A, and it's my drug and I already have a designation for your biomarker positive cohort, that already includes pancreas that is biomarker positive.

So then why wouldn't I just apply to get orphan drug designation for biomarker negative pancreatic cancer and just get the orphan drug for that? Then I'll have for both, right? Or did I just miss this?

DR. LEWIS: No. I think, I think your point is good and it might be a good time then to look at our next scenario. I think we've heard a little bit from each side and why it's helpful for us to hear these discussions is because people have suggested, oh, maybe you should not be designating all of these. Maybe that's a misuse, and as soon as a target is shared you should start to designate as soon as there's a shared target.

And that suggestion has come to the Agency and people have disagreed. We will see as we go along, will we just be staying in the same place where now we continue to designate all histology specific if we look at them as totally different diseases.

But let me just move to run next – yeah, I can, I have to get to right here. You just mentioned target negative. And so another way of, of approaching

some of these questions as we're still talking about the same situation where Drug A was recognized as a tissue agnostic situation for this big blue disease here. And now we have someone requesting specifically marker negative pancreatic cancer. And this might be an easier topic to, to reach agreement on.

DR. MELLIS: Yeah. From, from my perspective, why not? I mean if, if one develops the evidence that in this rare subset of a rare cancer that the drug is likely to be efficacious, then it, the incentives provided by the Orphan Drug Act are important to enable the sponsor to invest, to test that medicine, and see whether it can be brought to more patients living with rare disease.

DR. KUMMAR: Yeah, I think this is exactly what I would think would really help because we do want to encourage, not sort of close it off saying it's just going to be active in a biomarker positive population. So this would encourage people to look at specific subsets. And if it made some of the common diseases rare if you start doing this kind of division of a biomarker negative, so, which would be a good thing

because we want to evaluate across histologies and do this kind of categories.

DR. RUBIN: I would agree and I guess that, you know, one question that was back to what, what level of evidence would you need for the potential for activity in the, the negative population.

DR. LEWIS: Well, one of the things that was said earlier by Dr. Startzman when he talked about the actual evidence we, we prefer human data, we oftentimes need to look to appropriate animal models in general in designation. But it's really the same, the same situation. Someone said, well, we shouldn't, we shouldn't hold tissue agnostic to a different place.

If we have a question about whether, whether we have a proper designation situation, we have a great consult process that we can work across our Agency to be able to do that. So we have some of the tools available to us to help answer these questions.

And so I know we're not, are not seeking agreement, but we really do want to hear people's different opinions. But that is one thing I can say, is that we're fortunate to have terrific colleagues

across the Agency to help answer any questions we have about whether it's disease or otherwise.

And I know we -- do people think we do have adequate tools and, to be able to address the, these questions that we're asking?

DR. HONG: I do -- I think yes and no. I mean one, one question is, I had in the context of biomarkers is, you know, we have this cutoff of 200,000 patients. And I, and I'm just thinking about my own experience with NTRK. Like we don’t really know what the prevalence is in the, in metastatic cancer. I mean we, we assume it's less than 200,000 just because, you know, we've, we've screened patients and we've, you know, there have been larger datasets like from Charis and so forth that have looked at it.

But, but the reality of it is that we don’t really know because, you know, TCGA and even CABIO, they don’t really, they don’t really test the, the population that is really, these indications are for, right? So, so that's one question that, you know, is, is up in the air because I, you know, people always ask me, well, how many NTRK fusion patients are out there?

I said I, to be very frank with you, I don't really know yet. There could be a lot.

DR. LEWIS: And, and one, one of the fine points that we didn't talk about earlier is we have to make our determination for designation based on the science that is present at the time of the application. And so once in a while we're in a situation where something could be designated and then later on, as you talk about, there might be additional testing information that would change that number.

We would not remove the designation because at the time of designation request we will honor that prevalence that's anticipated. But it's at that time. But as new information comes along, we will use that information at that time. Is there anything, other regulatory-wise? I know people might have thoughts about just --

DR. MOSCICKI: Well, this seemed the most clear-cut of all the scenarios.

DR. LEWIS: Yes, I thought it was a good one too.

DR. MOSCICKI: Since there's no, no overlap

theoretically or otherwise in, in the disease or indication. I guess I would ask a question, though. You know, when Drug A -- I, I know you can't give a designation for the same drug for the same indication. Clearly not the situation here. But when you have even in, say, this sort of overlapping situation, just because you have an orphan drug designation doesn't mean you actually will turn out to be successful.

And so, again, I think it's important not to de-incentivize the willingness to pursue another area where it might turn out to be actually effective when the tissue agnostic doesn't end up bearing out. You know, so that's a difference between having already an established market approval versus just having a designation. And something that we should keep in mind as we think about it.

One of the issues that we thought about when we sort of said, you know, the simplest way here to cut this Gordian knot is to just say --

DR. LEWIS: Move up.

DR. MOSCICKI: Okay. I usually don’t have trouble being heard.

DR. LEWIS: You're, I, what, what, my understanding is we're, we're heard in the room, but the electronics are, are not as good as hearing is for the webcast people. Mm-hm.

DR. GAVIN: Debra, to answer your question, we would say that you do have the appropriate paradigm in place to, or the tools in place to address this if you look at these sub, sub-orphan, the sub-common disease paradigm, you could use here quite effectively the draft guidance as an example to reference.

DR. LEWIS: Thank you.

MR. KARST: I'm curious how the scenario, curious how the scenario really differs from the first one. I mean maybe Dr. Startzman or Dr. Lewis can answer. And if somebody went in here for designation, would they not receive designation for pancreatic cancer, right? Just as in the first example. And then they'd simply get that designation and ultimately get approval for the, you know, biomarker X negative pancreatic cancer patient.

So it's kind of that, getting that piece of the pie approved. Is it, is it really any different

than the first scenario where you're getting designation for a specific disease or condition here, whether it's pancreatic cancer or the tissue agnostic biomarker?

DR. SUL: So actually I'm, I'm really glad you asked that question because it seems like, you know, the consensus up here is that, that there really is no problem with identifying this biomarker X negative histological disease as a separate entity. And, and I -- and maybe I'm just not getting it, but in my mind, you know, there's a huge difference in defining something by the absence of a biomarker versus the presence of one.

I mean if you think about something like non-small cell lung cancer where you can slice that pie into, you know, multiple different biomarker positive populations, does that mean that everyone who's ALK negative is the same cancer? I mean I, I guess I'm still behind then in not quite seeing this as, as definitively as a separate disease.

And part of it is, I think, also that, you know, it, it really goes back to that crucial question,

the slide that, that Dr. Lemery put up, is, you know, what is the disease versus an indication? And I think, you know, part of the issue is that that Orphan Drug Act was really, you know, conceived at a time before the science came out. It just may not be -- some of the way that it's written may not be a great fit for how we're thinking about things now.

You know, in my mind a disease is something that, that effects a body or a person. You're not going to go see a doctor for, you know, a specialist in NTRK-positive tumors. You go see a breast cancer doctor or a colon cancer doctor. You don’t go to see an ALK-positive oncologist. So, in my mind the disease is still, you know, what affects the, the person.

DR. LEWIS: Perhaps, perhaps if this is something that's really getting people hung up on about the disease, you may want to think about is it proper to incentivize and provide -- is that the good use of the Orphan Drug Act to, when we recognize that we could be able to generalize across? Now this is not this scenario, but just in general to address this question. If we can generalize across the disease, is it

reasonable that we divide it into all of its member pieces? Or should we be incentivizing it as a group once we know?

DR. MOSCICKI: The more incentives the better.

MR. KARST: One thing I'll comment, comment on is that I think you've shown it here as the, the red circles overlapping with the square --

UNIDENTIFIED MALE SPEAKER: Sorry to interrupt. Could everyone bring the microphone a little closer, especially when you're speaking side to side?

MR. KARST: But it could be different if, obviously you could have different circles if that red circle was outside the square or inside the square. Not to have more complexity, but that, that is, could be part of it.

DR. LEWIS: Yes, yes.

DR. MOSCICKI: And, and recognizing that maybe the science is only at a certain point in how you define biomarker negative or positive. But you already established that you have to work with what you know at the time that you know it. And, you know, so I, I

think that you still have to assume that you can differentiate these. Otherwise, why consider the biomarker positive population, I would even argue.

So I think the other part here still comes back to this idea that, yes, it's positive that, possible that for biomarker positive solid tumors in this scenario you might have an 80% response rate. But let's say in biomarker negative pancreatic, there's something about pancreatic. Maybe it's how it expresses the biomarker on its surface, but still has a similar basis for a mechanism of action of the drug that you now get a 40% response. Maybe it's not the same, but it's still certainly worthwhile and certainly an orphan drug designation, right?

DR. STARTZMAN: And just, you know, from my perspective if I would see this scenario, I would be having a tendency to say, you know, my, my question would be why aren't we expanding it to pancreatic cancer instead of designating it just for biomarker X negative? I mean that's really the question.

MR. KARST: I guess the only reason you would is if pancreatic cancer were, let's say, over 200,000,

and you had specific data showing that, you know, biomarker X negative and your product worked only in that population, then it would be designatable as an orphan. I mean, but I agree with you. I mean broadest designation policy, possible, it's been your policy for decades.

DR. STARTZMAN: Because that's why we picked pancreatic cancer.

UNIDENTIFIED FEMALE SPEAKER: I want to go back to the, the point someone made about whether the red circle is outside or inside the square. And that's a very relevant point because we're talking about very early development. These biomarkers still haven't been clinically validated and they haven't shown clinical utility in some cases.

And it does have a huge, huge impact on how you accrue patients, because we're talking about very early studies where sometimes you have preclinical proof of biomarker efficacy, but you don’t have an assay that's been developed and you're sometimes accruing patients based on histology, not necessarily on the biomarker profile which may come later on.

And I would really love to hear CDRH's

thoughts on this. But it does have an impact because we're still talking about designation, not approval. And as you're, you're accruing patients for the studies, this does have an impact. So that was a point I wanted to make.

DR. LEWIS: Sure.

DR. ROSCOE: Is this on? I think she kept seeing me raise my hand because I was desperate to say something. Because in this model you really do need to understand and have a really good working definition of the biomarker because what is negative is going to be defined by however you're measuring that biomarker. If you're looking at wild type, wild type is only defined by the mutants that you're actually looking for.

Dr. Hong mentioned there's a threshold. You could easily have a test that has a high threshold to define biomarker positive, but the inverse of that is not going to necessarily be biomarker negative. And now you've designed a trial that efficacy may be coming from the residual biomarker positives that you're actually calling biomarker negatives.

So, this is significant, and what we saw with

MSI-high was what went forward was that a biomarker was defined based on the standard of care testing and a lot of knowledge was understood about that in terms of the concordance between the IHC and the classic PCR for the five loci, but what's come out of it now is a lot of NGS testing with, you know, numerous denominators on the panel and different thresholds.

And what you can see when you look at abstracts of literature, very interesting information going forward from like meetings like AACR and ASCO, is that the prevalence with these NGS tests is different. It varies from like 3 to 15%. So that's not in the best interest of the patient. I've been at meetings where I'm listening to people talk about false negatives with IHC because their NGS test is detecting it, but what is the evidence for that?

We don’t have any response, which goes again back to what Dr. Hong was saying, is give me a little bit of something so I can work in the best interest of the patients. Patients have to be really educated now and ask what test am I actually getting tested with because if they're really interested in being motivated

to get that therapeutic, they want a test that's going to have a high prevalence on that biomarker.

UNIDENTIFIED FEMALE SPEAKER: And I'm going to add one more point to that, which is we've been talking about rare diseases, and one thing we also have to think about if we're taking about the biomarker interfaced with the histology and the disease is what is a rare biomarker? We have data on prevalence of disease. We don’t often have data on prevalence of biomarkers in that context of histology.

DR. SUL: So yeah. I think those are -- they're, they're definitively good points and, and certainly, you know I think we, we consider these, especially during the development process, and when we're looking at these trials and how these trials are designed.

But, you know, I think when the, the Office of Orphan Products are, are getting these applications for designation, these are often coming in way before, you know, any tests are being developed and the clinical trials are being designed.

And I think this is, again, you know, we're

sort of running into overlapping discussions where there's the drug development side of things and the clinical trial design side of things versus the designation, which is really, again, I think, you know, what Deb said earlier, sort of recognizing an entity for potential incentives and, you know, what are the, the thresholds for that.

DR. KUMMAR: But I think one thing -- I mean I don't think any one of us is thinking that the biomarker negative cohort is a homogeneous cohort of pancreatic cancer, right? I mean all it is, based on what Eric was referring to, is that you have a preclinical package or some rationale to say that maybe this drug will have activity in a biomarker negative pancreatic cancer.

It may turn out to be because it's biomarker Y. It may turn out to be that the biology of X is different in this particular population. And so you'll see a different response rate in this.

And so I think it's just incentivizing sponsors to investigate this population and then if the response is, people will go figure out why it's

working. But I think having some sort of designation that kind of encourages people and not just go for the low hanging fruit of just biomarker positive.

UNIDENTIFIED FEMALE SPEAKER: Can I ask a question?

DR. LEWIS: Yes. We're, we're broadening our format.

Dr. SUL: Can you please state where you're from, your name and where you're from?

MS. SEARS: Yeah. My name is Abitati (phonetic) Sears (ph). I work in the (inaudible). So one of the criteria to get orphan designation in a subset is that your, your drug is not appropriate outside of the subset, right? So in this case, or in the other case, if you get your orphan indication of the blue square and then you come and you show that your activity works in the biomarker negative, pancreatic, would you lose orphan for the blue? Because now you're showing that you actually work outside a subset?

DR. LEWIS: Thanks for your question. I, I think it is worth clarifying this. If you do -- in this case we just said that we've considered this

target to be, to be a tissue agnostic target. But let's assume that you're saying, yes, it has a designation. The only thing that we're adding to that is somebody else coming along, say, for this other specific designation. You will not, it will not affect the blue square's designation. It will stay in place.

The only time we generally have the authority to remove a designation is if at the time of the request the, there was evidence that it didn't, it wasn't eligible at that time. There could have been an omission of information that should have been there. It could have been an error. But if at the time they weren't eligible from omission or -- what else do we have there?

Just generally have, it would be that you weren't eligible at that time. Maybe the prevalence was shown to be over that, but it was not identified. That's very uncommon that we remove a designation. And this would not be a scenario where a designation would be at risk because at the time of the first one, the information qualified for designation.

DR. STARTZMAN: Yes, and I think in this

we're not really talking about subsets. I mean we're talking biomarker X solid tumors is a disease. It got designated if, if that's the case. In this it doesn't really necessarily, but let's say it was. Let's say it was under 200,000 and it got designated for biomarker X positive solid tumors. And then later they're coming in and talking about pancreatic cancer more in the histology defined disease. So we would say that's a disease. So we're not talking about orphan subsets.

DR. LEWIS: So if they're both rare, both the blue box and the, and the pancreatic were rare, that's one set of circumstances. But I think sometimes when people think about this question, they think if the blue box represented a common condition, a grouping that we believed was over the 200,000, then, one of our panelists has said more incentives the better and that, that is, that is a philosophy.

But some people will say, no, you need to really ensure you're incentivizing in a way that doesn't allow -- some people have said gaming of, of the Orphan Drug Act. Or other such things. But we look at it as we have protections, just as Pam Gavin

was saying. We have protections that allow us to protect the Orphan Drug Act and we want to do that responsibly.

And that's -- whether it is we should allow the, this to be looked at as two different diseases is a very important aspect, or whether we should really consider the overlapping and, and subtract out that overlapping aspect.

Those are, those are questions that are important to us. Does that answer your question? Okay.

DR. MOSCICKI: Yeah. The, the consideration by some of, regarding that this is some kind of gaming, again, I think is often misinformed. And I think it's important to make sure that we clarify the fact that, let's say this product gets approved for biomarker X positive solid tumors and then three or four years later comes along with the idea, you know, there's evidence that this stuff really might work in, in biomarker negative pancreatic carcinoma.

So it's important to recognize that when the seven years is up for biomarker X positive solid

tumors, it's up for that. It, it doesn't extend that exclusivity. It's only, related to the unique indication that came along later because of additional scientific work that was done by either, by someone to, to recognize that that, in fact, was a, a good place to use this drug.

DR. LEMERY: I guess I'll give you a scenario that I'll become the CEO of the 28th different PD-1 inhibitor and I'm going to decide to investigate in --

DR. MOSCICKI: Get out of the business.

DR. LEMERY: -- tissue agnostic MSI setting and yet I'm going to, I'm going to do my strategy where I'm going to request an application first in MSI positive, pick a tumor type that'll sort of, you know, that, that cut will be under 200,000, but yet the whole broader population will be above, you know, knowing full well I could submit the application three days later with a tissue agnostic, you know.

You know, those sort of scenarios could happen where -- so I'm hoping to get the incentives, you know, being the 28th one I'll have, you know, exclusivity to prevent biosimilars in the market.

I think that, so there are potential, you know, ways where companies could sort of creatively think about opportunities to use the system that maybe really aren't the intent of the, you know, really fostering innovation.

You know, I suppose that's possible, but again, I think the original intent is to incentivize sponsors to conduct these studies. You know, if you, if you said you were just carving out biomarker positive solid tumors, you are carving out pancreatic within that subset, then that would make sense, right?

But, but if you're actually getting new information on biomarker negative pancreatic carcinoma, you know, that to me is important. That's what we want companies and sponsors to do. We want to get more data to understand how to better treat our patients. So that's why the Orphan Drug Act is there.

MR. KARST: From a generic drug perspective, I definitely agree. I mean it's important to have very black and white lines. Sorry, very black and white lines on the indications and the scopes of the various exclusivities for generic drug manufacturers because as

you have staged approval, staged periods of orphan exclusivity, generics have to be able to carve out those orphan protected indications.

So, if you have a bleed over on a graph like this, it makes it very complicated to create a label for generic drug manufacturers that omits that protected population. So, I definitely agree with Mr. Moscicki that it's good to have very defined periods to certainly foster generic competition.

DR. LEWIS: Perhaps we can look at something a little different. It looks very similar, but what it's, we're again starting with the same blue box, but, but what happens in this scenario is should FDA consider orphan drug designation limited to histology specific disease, but it's this, this drug has a different active moiety.

So now it's a different drug, but it does have the same or similar mechanism of action. In other words, we expect it to be a histology -- I'm sorry, a tissue agnostic type of drug. The sponsor only comes in, though, with their histology-specific tumor information. Again, we're using pancreatic cancer as

rare, but they're only submitting for the pancreatic cancer, and yet we would expect this different drug to be very similar in action.

DR. LEMERY: And that was sort of the example I just gave about a PD-1 inhibitor for looking only at endometrial cancer, neuroendocrine tumors, something like that.

DR. HONG: I think it depends, again, and I'm a big believer that, you know, we, I agree that the orphan drug designation needs to be flexible and needs to give incentives. At the same time we shouldn’t be harming our patients. And even those patients who are eventually going to go on a clinical trial because of this designation. And if we have data to say that this drug has no clinical, you know, necessarily any more benefit than an existing drug out there, I'm not entirely sure, you know, you could give it a designation, let alone --

DR. LEMERY: Let me --

DR. LEWIS: Yes.

DR. LEMERY: I think a, I think a better example is not necessarily, people are thinking of PD-1

and that it doesn't work in pancreatic cancer. It may be, I don’t know the incidence, but like take, you know, PD-1 positive gastric cancer, which has an indication in pembrolizumab or, you know, something with the response rate may not be 0%, but it may be, you know, your indication in the biomarker positive is a 40-60% response rate. But you might have an unselected 5 or 10% or, you know, maybe even high -- you have a different response rate and there may be a population in there where the drug works at, and so there are, you know, clearly for melanoma and lung cancer and some other indications, you know, these drugs are working through an independent pathway besides MSI. So whether it's PD-1, whether it's, you know, TMB, all kinds of other biomarkers are being studied, but, you know, perhaps you can get a single disease where the company studies in and, you know, proves that they do a randomized study, for example, in, and gives predominance of evidence that the mechanism of action is not driven solely by MSI, that may be the situation here.

So pancreatic cancer is probably not the best example if everyone has PD-1 inhibitors in their head.

But, you know, perhaps another, you know, cancer we're not thinking about that really hasn't been studied very extensively might be a better example.

DR. MOSCICKI: Yeah. Plus I'm a little confused why there's even a question given that there's a different active moiety. I think we've been very clear about this in the past, right, that a different active moiety is a different drug and has the same ability to -- it's not the same drug. It is a different drug even if it has a similar mechanism of action.

And we know that there are plenty of examples of similar mechanisms of action, but differences in adverse events, differences in toleration, difference in, you know, even effectiveness, or duration of action based on the difference of the moiety despite the mechanism of action. So, you know, I, this also seemed pretty clear cut.

DR. LEWIS: There's -- do you want to explain that subtlety of the, of the data?

DR. STARTZMAN: To me it was just, again, it's

whether you designate for -- early in discussions about all of this we talked about -- when we were talking about tissue agnostics, there was, there was talk that if you target a specific, we'll just say, you know, biomarker that is eligible for tissue agnostic, that becomes the disease. And then all the sudden these other smaller, you know, you know, like pancreatic cancer, etc., would not be eligible.

I do think that like for instance you can say that outside that biomarker driven tissue agnostic disease you could see a benefit in, in, say, in pancreatic cancer, etc. But that was what we were really trying to, to determine in these. If it targets a biomarker that's eligible for tissue agnostic can they still get designation for a histology-specific disease?

And in this case we were saying, well, say the drug's different, but it still works through that biomarker, can you get designated for the pancreatic cancer?

DR. MOSCICKI: Yeah, but it's different.

DR. STARTZMAN: Well, but I mean let's -- in

the, in the same one, I think you had said you could get designated for the pancreatic cancer. So yeah, so it's different, I think.

DR. MOSCICKI: I mean I start there, but I would still go back to the same principle that these are different diseases. They're defined differently. And so, so the answer would be yes there and yes there.

DR. LEWIS: I think the, the, as you were just saying, Chip, there was, if, if you follow your approach that everything's different, yes. It's always going to be yes and yes. If you look at it from the perspective it depends for those situations where you have the same mechanism, but we don’t have any data to, to talk about the tissue agnostic mechanism. It's all about the individual cancer.

Would we expect to have tissue agnostic information? Would we require that because we have already recognized that this mechanism has a tissue agnostic attribute to it? So --

DR. MOSCICKI: Yeah, but the moiety is different. I mean we have different ACE inhibitors --

DR. LEWIS: Yes, the --

DR. MOSCICKI: -- we have different -- you know, they act -- the mechanism of action could be the same, but we know they have different profiles. We know responses differ and we should not, you know, deny an incentive to a company that wants to bring an alternative to the patients because it has a different moiety despite a similar mechanism of action.

I thought the more interesting question here might be, you know, could a different moiety then get the same biomarker X positive solid tumors, right?

DR. LEWIS: Yes.

DR. MOSCICKI: And, and once you say that, then why would you say no to even moving outside the blue box? You know, so that's why I, you know, again, this one didn't seem to be that complicated.

DR. LEWIS: So to interpret your, what you just said, would the designation in your mind be either of those? It would be either the tissue agnostic or the histology specific?

DR. MOSCICKI: It could be as long it was truly a different active moiety. The lawyers can tell me different, but.

DR. MELLIS: Yes. Yeah, I would like to agree that each drug that is different drug should be evaluated on its own merits. And it does seem like our state of knowledge is in rapid evolution and our state of practice is in rapid evolution. But if indeed there's, there's a literature out there that says that biomarker positivity may have something to do with efficacy in, in one or another cancers, particularly this one, then, you know, maybe, maybe it ultimately does behoove the sponsor to, to test in the positive and the negative subsets prior to approval.

But fundamentally, I think each drug should be evaluated on its own merits.

DR. KUMMAR: Just to extend that question. So when the sponsor comes to you for the pancreatic cancer designation, and you already know that this biomarker may have X, may have something to do with it, would you ask for data preclinically that would be in biomarker X positive and negative before you give this designation for pancreas overall?

DR. LEWIS: I think that, that was an element of the question. Should, should we be asking -- when

we are familiar with this mechanism of action, should we be asking those questions or do we confine ourselves to the pancreatic cancer?

DR. KUMMAR: So my two cents would be, yes, I think you should ask because if there is no evidence of biomarker negative that they have generated, their, all their activities actually in biomarker positive pancreas, then I think either they need to go back and generate for negative or just develop it for the positive. It shouldn't go to patients without some evidence to say that it has activity in biomarker negative. So I think asking that question's valid at that point.

DR. MOSCICKI: Well, yes, but I don’t know that we should force sponsors who have reason to believe that pancreatic cancer in a clinical trial will respond to suddenly now redefine their approach that, and you know, for, who knows? Maybe the biomarker X is a propriety test and are we suddenly going to say now you've got to go do a proprietary test even though you've shown us that, in fact, it works in pancreatic carcinoma?

So, you know, I would be careful about saying that you should mandate testing in that scenario.

DR. SUL: I mean I think though at the same time it could be a little artificial to, to ignore the, the data that's out there about the mechanism of action and, and, you know, the effectiveness of the product. So, at the same time I think it would be okay to consider, you know, asking the sponsor for a rationale for why they feel that it wouldn't necessarily apply in the biomarker positive all-comers population.

You can ask, you know. They don’t -- you can ask just because I think it's, it's also, you know, it's also a way for you to indicate for the, for the office to indicate that you're aware of, you know, what these implications are and how these products are, are working.

DR. LEWIS: Question?

MS. HOLLOWAY: I have a question. I'm Jamie Holloway. I'm a patient advocate. And so I think that the, I think I would agree completely with Dr. Sul that you can't ignore the science that's already there because perhaps in pancreatic cancer or whatever your

rare disease is, you just have a higher prevalence of this biomarker.

And so you're maybe seeing overall a good result, but really it's just a really good result in the positive people and not a good result in the negative people. But by putting them in this group, now you're treating the negative people who should be treated otherwise.

And so you're, I think you need to at least look at the biomarker if you know that that's going to be important in the mechanism of action. And if, and if you look at it and you can say, okay, it's not, then that's fabulous.

But if it's, if it's clear delineation, I think that's something really important for the patient population when they're making treatment decisions.

DR. LEWIS: Thanks.

DR. MOSCICKI: So in that case you would make -- let, let's say that the clinical trial was conducted without access to the biomarker assay, so there's no data on the biomarker in those pancreatic cancer patients. Yet you know that the product works in the

clinical trial, now are you going to make the sponsor go back and do another clinical trial in which, and, and make, you know, patients wait with pancreatic carcinoma another year or two for that other clinical trial to be done with the biomarker?

DR. SUL: Hopefully the review division will have given the advice prior to the, to the trial being underway.

DR. MOSCICKI: I know, but we're in this hypothetical situation.

DR. HONG: And that hypothetical situation, if you're seeing activity in, in patients, irregardless of the biomarker, then you have a strong, you know --

DR. RUBIN: Yeah, and it just goes back again to where if the circle's separate from the square or not, right? I mean if the circle's separate from the square and you've got activity, it's pretty simple, right? You know.

DR. STARTZMAN: But understand that the orphan drug designation does not determine who you're studying

this in. You don’t, if you get orphan drug

designation for pancreatic cancer, you can then determine whether or not they're positive for the biomarker and, and enroll patients positive. Or you can, you know, it's, it's up to you how you're going to develop it.

DR. MOSCICKI: Yeah, if you have that ahead of time, but, you know, that was not the scenario presented here, right? So, I'm just saying that we should be careful about demanding information that doesn't exist if it doesn't exist.

MR. KARST: I think it's worth pointing out. I mean all the scenarios here we've, we've looked at the red circle and the blue box. But there are potential issues lurking if you get rid, rid of the red circle. So, do different biomarkers, groupings of biomarkers, constitute different diseases or conditions, right?

So, two, versus three, versus, you know, four, you may add on over time. Assuming they are different diseases because they're, they're different biomarker groupings, presumably you'd have to seek separate orphan drug designations for each, you know, added

biomarker. And then if you get these staged approvals over time, there is at least, I think from the generic perspective, there is a possibility of multiple seriatim periods of orphan drug exclusivity.

And it does occur in the oncology space right now where you're approved first for third line, then get second line, then you get first line. And each time you get a period of orphan exclusivity and there are, of course, labeling issues for, for generics in terms of the labeling of the brand changes. And then how does the generic get approved?

I know FDA's dealt with that recently in the context of bortezomib, but it seems like it's also potential here just within the, the blue square there where there could be staged approvals over time, multiple seriatim periods of exclusivity, and suddenly, you know, generic drug manufacturers faced with the, the issue of how do you adequately label the product given that the brand now has new labeling.

DR. LEWIS: It does bring us to the question -- we've talked about designation so far and how we should designate. We can take a few questions, but

then I think we'll save the exclusivity part 'til our after lunch. It might be a bit much to try to move into that scenario now.

But I do agree the exclusivity issues are some of our most tricky to think about. And areas, depending on your philosophical look at the designation, that may influence your exclusivity perspective as well. But perhaps we can take a question or two from the audience before we break for lunch in about five minutes.

ANGELA: I'm Angela, Angela. No financial disclosures. My question would be, what is it about the current Orphan Drug Act that has prohibited us from getting to this point anyway? Without any new change or programs or legislation, what was it that prevented the current Act from moving forward to get new drugs adopted in the small markets?

I mean that's what it was intended for anyway. And there seem to be a lot of financial incentive that if you open up new markets, you get paid more money. Your research is rewarded in a number of different ways. So what was it about that incentive or the program that failed?

DR. LEMERY: I don't think we're saying that there's a failure here. We approved, you know, BRAF mutation positive anaplastic thyroid cancer based on fewer than 30 patients. So I don't think it's a failure of the Act. That's not why we're here. We're here to discuss how to apply the act given the, given these new approval considerations. You know, we approved the pembrolizumab.

Approval for tissue agnostic, you know, there are, there are patients in there that have, you know, very few tumor types studied, so this brought the drug to the market for patients much faster than would have done, I mean exponentially faster, than would have been done under a traditional paradigm where you have to study each disease separately.

So I think there's not a failure here. We've, we've clearly moved faster on some of these than, you know, than anyone would have ever expected. This is just a new way to apply the law, which is not necessarily written for sort of modern day science.

DR. LEWIS: And I think that that is right. We've been really excited to be a part of this time

when there is so much advance going on and we've been able to take advantage of that in so many ways. And that's why we've had so many records in approvals and just very exciting lifesaving therapies coming forward.

What we're trying to do now is we have moved forward just as, as you were saying. We have designated. We have approved. We have provided exclusivity, but it's not ever a bad idea to self-examine, to take a look and see what is it that we could do better.

But as we've heard, people think we have these Tools, and we're now excited to hear from you about different ideas about how to do this better, both in the designation phase and exclusivity phase. And you may actually, we might end up right where we were in these two or three that we've done.

But I do agree it's, it's really, actually an exciting time to be implementing the Orphan Drug Act and the tools that it's given us and to developers have been terrific, so.

DR. HONG: I, I agree with Steve and Deb here. I don’t think it's the limitation of the law up to this

point. To a large extent it was kind of the structure of, of oncology in a way and, and the science. I mean, you know, if you think about, you know, kind of biomarker driven science, it's not like we've been doing this since 1943. This is really since the early 2000s that has, and it's really exploded in the last several years.

And I, Joohee said that she can't imagine, you know, doctors not treating like breast or pancreatic. But, you know, to be honest with you, I, I run a clinic where people send me patients not because I'm a GI expert, which I have an interest in, but really because I run a trial that, that is NTRK and I have, and I have the most experience in our, in our group on these NTRK fusion patients across histologies.

Likewise, there are other folks in my group who are immunotherapy experts and they get, see all different types of patients because they, they know how these drugs work and they know how they work in these patients who have metastatic refractory disease.

So there is -- I think there is a feasibility in the future that we will be treating patients as, I'll

be an NTRK fusion doctor or whatever, you know. But less so of that -- probably in the metastatic scene, less so in the earlier settings, but --

DR. LEWIS: And we want to keep, we want to keep aligned with that. That's probably what we're hearing most about here, is as the Orphan Drug Act moves forward, as orphan products move forward, we want to maximize the use of these tools. And so that's why we much appreciate people coming with their different perspectives on helping to do that. And we have another question from the audience.

MS. HOLLOWAY: Okay. So I, I'm curious. I think obviously it seems like we're going to be moving towards having a lot more of these orphan designations and sort of by definition you're getting smaller populations. So, I'm curious if anybody has any thoughts about considerations or experiences with how to do a clinical trial when you're already starting with such a small population to begin with?

And you mentioned, you know, an approval based on a small number, but I'm wondering if there are considerations for remote possibilities so that

geography isn't going to be a barrier to accumulating enough patients to perform a trial?

DR. LEMERY: Eric, have you, have you done just, you know, just-in-time enrollments? I know some in industry have done different ways to sort of foster, you know, quick, quick opening? I can also say that we've worked in a few cases with companies where, you know, with compassionate use, often it's the, the, the investigator who requests it and you don’t get much information.

But like for drugs that have really been seen as, they're really active, really are in development, we've worked with companies that say, you know, maybe you should submit those to your own IND and collect, you know, basic information regarding that patient. And those have fostered, you know, help foster applications in some cases.

So I think, you know, we do recognize that, you know, a patient in New York is going to have, or Houston, a much easier access to a trial than, you know, you know, a small town in Iowa or Montana. So, but there are different mechanisms. And I know

industry has worked in different ways to, to do this as well.

DR. RUBIN: Yeah. And I think there are also an increasing number of databases where, you know, many people at the time of diagnosis they're, they get a test, an NGS test or something that really gives a pretty board profile of, of their disease. And that's kept, that's accessible later on. So that if, you know, down the road a new drug comes along and it happens to match with a particular mutation they have, you can find that patient. And consent's allowed so that they can be contacted and they can be put onto the trial.

MS. GAVIN: We're also working with patients, patient organizations and disease states early on to help them establish natural history studies so that they're coalescing communities together. And we're also excited to be working with some companies who are looking at subsets, creating a subset study within a study whereby, where we're basically joining that natural history study with some of their pre, pre-early clinical designs.

So we think that will also help because we, we in the natural history studies, we, we go to patients where they are, where they live.

DR. MELLIS: Yes, the natural history studies are so pivotal, but they can also be integrated with biomarker assessment and biomarker collection and really having patients ready to go when a protocol and/or therapeutic might be available or a candidate therapeutic might be available for testing.

It also brings up the topic of master protocols that Dr. Gottlieb mentioned earlier in the day. Those, those are going to be so instrumental in helping enable remote enrollment and, and the evaluation of multiple therapeutics.

DR. LEMERY: And in some cases like NCI, I think NCI-Match has actually had a lot of sites that aren't necessarily at your MD Andersons and, and Sloan Kettering, they are at, you know, smaller sites. And hopefully that helps, but, you know, clearly there's, there is a need especially with, you know, you take, you know, NTRK, for example, which, you know, it's, these, at least they're --

We don’t know the exact prevalence, but it's not easy to find a patient with an NTRK fusion in a lot of cases because patients aren't just being tested. So I don’t know if you have experience with patients traveling and how that's been facilitated to --

DR HONG: So, so the trial has, the company at least have been working with, Loxo, has been very accommodative in trying, in getting patients. They recognize these patients are rare. So they've been accommodating in that, getting patients if they're identified in the community, whether they're from, you know, California, whatever to, to our center or sites that are running these trials.

So, but I, I do agree that we can definitely improve whether through master, master trials or some other ways to try to get these drugs out in the community. And one, and one question I have, which I know this is probably a whole new topic, is this right, right to use issue that's going to come up, I'm sure, at some point and how this affects the orphan drug, or orphan drugs and, you know, I'm sure that's a whole --

DR. LEWIS: Yeah. It is actually a different

topic, but, but what I, what I would suggest is that there is a lunch hour right now. So we can, we can take a break from our conversation. If we can reconvene then at 1:30. We have about 45 minutes more. We'll talk about exclusivity and we'll also focus a lot if folks have additional input and questions from the audience, we'll try to work a little bit on that.

I really appreciate everyone's attention and patience with everything this morning. If you have any suggestions, please do come up and let us know. Otherwise, we'll reconvene at 1, 1:30. Thanks very much.

LUNCH

DR. SUL: Okay. So I think we have almost everyone back here up here on the panel. So I think we'll go ahead and get started with the, the second panel discussion with involvement from the audience as well. We welcome the audience to participate. When you come up to the mic, please, as we've heard all morning, please speak closely to the mic and please state your name and, and where you're from.

And so this afternoon I think we're going to

move on a little bit away from the, a little bit away from the designation, still related, but talking a little bit about exclusivity. And we've heard all morning about how we should have as many incentives as possible and that incentives are good. But I think sort of the, the corollary to that is that, you know, what are the implications of these incentives. So what comes with these incentives and, you know, part of that is exclusivity and how that might impact drug development.

So we're going to move on to the exclusivity questions and I'll turn it over to Debra.

PANEL DISCUSSION WITH AUDIENCE Q&A

TOPIC THREE

DR. LEWIS: Thanks everyone for coming back on time and we're able to, to move along. As Joohee said, we're going to move to exclusivity. I think that folks can feel welcome as questions do arise to come to the microphone and, and raise a question. But we also did have some prepared scenarios.

Again, it brings us back to some of the specifics. We know that we're not going to know every

scenario, but what we learn from this is your input on some of these principles. It helps us. We can see right away about how people address these questions in ways that will help us.

We also do have some questions that we'll try to intersperse from our folks who are webcasting with us today. But I could start I think with our Topic 3 on exclusivity.

And this question is up on the screen now and it's about discussing how FDA should determine the scope of orphan exclusivity when a drug receives marketing approval for a non-orphan tissue agnostic indication. For example, a prevalence that's over 200,000.

So it might help you to think about this perhaps as like the MSI-high. That's a situation wherein the blue box, it receives approval, but then the same drug subsequently receives marketing approval for histology specific indication. And then that indication had received orphan drug designation. And again, we're sticking with our example of pancreatic cancer. Its indication, its disease in designation was

under 200,000. The indication, we're just using pancreatic cancer in general.

How should we provide marketing exclusivity for that pancreatic cancer approval if it's got a great overlap with the, with the already approved tissue agnostic that was not rare, that's over 200,000? So in this case you've had a non-rare and now coming into it an approval. Should that exclusivity overlap? Is it a different disease as was suggested by some?

And so this question is one that helps us understand a principle and we just appreciate your thoughts on how we approach that.

DR. HONG: Can I ask a couple questions about the scenario?

DR. LEWIS: Please do.

DR. HONG: So, so we're assuming that, one, that the pancreatic cancer indication, you know, one, went through this FDA office, had good clinical trials that suggested efficacy, etc., enough that you guys felt that this would indicate a true orphan indication, and, and assuming this was irregardless of the biomarker. The biomarkers were not necessarily a part

of that trial or, or the development in a sense.

DR. LEWIS: So at the designation stage, which may have been very early, may have even been before the tissue agnostic characteristics were recognized. I'm going to assume that just for a moment, just it could be different, different aspects to it. But we don't require a whole clinical trial. As we talked about before that, that level of evidence.

We, we love to have clinical experience, but, yes, you can assume that the evidence was sufficient for designation of that pancreatic cancer indication.

DR. LEMERY: A better way to simplify things, and please correct me if I'm wrong, just to say like this example is you have, you know, Drug X is approved for the tissue agnostic and then you have the second approval. So, I'm a generic company and I want to come in and I want to get approved for biomarker positive cancer.

So would, and your question I think in the scenario is would the generic be approved for biomarker positive cancer or biomarker positive cancer except biomarker positive pancreatic cancer? Is that sort of

what you're getting at? So that's what I just wanted to clarify for the audience.

MR. KARST: So it seems, I mean if, if they're different diseases, right, the biomarker X versus pancreatic cancer, the exclusivity runs to the indication for the drug, pancreatic cancer.

Seems to me it's a very easy carve out if you're going to, if you're viewing this through the paradigm of the indication and the disease or condition here that's been designated, that it's an easy carve out and generic can get approved for the biomarker X population.

DR. LEWIS: So by carve out you mean that you're looking at those as an overlap of the approvals?

MR. KARST: Correct. So let's say biomarker X is approved today and pancreatic cancer's approved three years from now, right? So generic comes in and you've got the orphan exclusivity on the pancreatic cancer indication extending out. They'll just omit that distinct indication from their labeling, again, under the rubric that biomarker X is a distinct disease or condition that's indicated in the labeling and

pancreatic cancer is a distinct disease or condition in labeling.

DR. MOSCICKI: And that position would be consistent with the principle that we outlined at the beginning where you would give exclusivity just for the pancreatic cancer indication. And otherwise it gets really convoluted when you start looking at overlapping, testing, the issues that came up over whether, where does the test positive/negative, now/versus later, all that gets in the way of trying to make a crisp decision. And in the end we end up with data that we've been looking for in pancreatic carcinoma related to this.

DR. STARTZMAN: Yes. The alternative would be to, to give exclusivity just for pancreatic cancer that's biomarker negative --

DR. MOSCICKI: Right.

DR. STARTZMAN: -- because it's already approved for, for biomarker positive tissue agnostic, which would include pancreatic cancer that's biomarker positive.

DR. MOSCICKI: Yeah, but I'm not sure what the

legal argument for that really is because if the clinical trials didn't particularly differentiate on that basis, then I'm not sure how you would try to do that. So I, I just say it's always just cleaner to say that that's what, if that's what the clinical trial studied, if that's how the patients were identified, then that's how you should act.

DR. KUMMAR: Well, the problem with the whole scenario, it goes back to the fact that if the trial was done without the biomarker being incorporated in it, you don't know that the activity that's being shown is all driven by the biomarker positive population. And so, I mean on the surface it's, I think it's in theory to just say, okay, the exclusivity is for pancreatic cancer only. And it starts from when you approve a pancreatic cancer, but I don't know how you approve it without knowing the biomarker when you know, when you put it in context of what the existing knowledge exists, right?

DR. LEWIS: Mm-hm.

DR. KUMMAR: So, and again, to the point that was brought up earlier, is that I don't know if

necessarily in that situation it's fair to the patients that are biomarker negative to be treated with a drug that hasn't -- to be -- or a drug on the market that hasn't shown activity in that population. What if all of it is driven by the biomarker positive and we are actually claiming to the patients that you have an X percent response rate from this drug in this disease which we don't know, right?

So I don't know how, and if you know that there is biomarker activity, how do you actually approve without knowing the biomarker in the clinical trial?

DR. LEMERY: I, I guess the only thing I would mention there is, is that that's more of a scientific discussion that would be had with review teams and the companies about the basis for approval and whether that biomarker has to be assessed within the clinical trial, you know. And we, we would have to assess whether the, the effect is completely driven by patients with a biomarker. It's probably less of an exclusivity issue.

DR. SUL: Yeah. I, I would agree with that and I think that's why it makes it, you know, really

difficult to have these carve outs within a disease. And also, if you think about it, you know, if, if the sponsor -- let's say in this scenario that the sponsor's developing the drug for pancreatic cancer after they've already gotten the, the original indication, approval for the original indication, and they're developing it knowing full well the biomarker positivity and potentially, you know, capturing that data in the study and seeing, well, look, they, there are responses across the board for whatever reason, you know, whether you're biomarker positive or negative, there's responses across the board because there's something about pancreatic cancer where this drug is, is, has activity, you know.

And, and I think in that case the, the drug development really was in that disease and therefore that's really where the exclusivity lies. And it would be almost artificial to carve it out just for the biomarker negative population.

DR. KUMMAR: No. I think the scenario you present where they're looking at both populations and showing activity and you're convinced with the data, I

think it's straight forward that you should probably give it to pancreas and then the exclusivity. It's when the biomarker's not being assessed, that's when the problem is.

DR. SUL: Yeah. And, and I think again that's more of a review issue within, you know, the review division rather than something that the, that the Office of Orphan Products would determine.

I mean certainly if they had a question about is it possible that the, the response or the activity is driven by a specific population, they would bring that to us and hopefully we would have, you know, have that same question.

DR. STARTZMAN: And, and I think one thing that needs to be understood is when we designate, you know, we designate something, the exclusivity goes to the first sponsor to get approval. And that's why in this case the, the sponsor got approval previously for this tissue agnostic, which includes a portion of pancreatic cancer patients.

And that's why when pancreatic cancer subsequently gets approved, there is, there are those

who would think you should carve out the part of the pancreatic cancer that already has an approval from that drug unless they can demonstrate superiority, in which case they could get exclusivity of the whole thing. If you consider them separate diseases, then there's no problem. You just give exclusivity for pancreatic cancer.

DR. MOSCICKI: So you'd have to demonstrate clinical superiority for the same drug, against the same drug.

DR. STARTZMAN: In order to get exclusivity.

DR. MOSCICKI: Right. Great incentive.

DR. LEMERY: And, I mean on the flipside, it's, I mean ultimately I don't know how much it, it, it matters because the generic company will still be able to market for the biomarker. So, it, it doesn't really matter at the end of the day for this example.

DR. LEWIS: So no additional discussion on it, and if, if I'm hearing, is there, I, it's very clear your suggestion is that, the fact that they, that there

is a previous approval for that same drug for those

same patients, we should consider it as just a different disease. Anybody have any, any other aspects on that?

DR. HONG: It sounds like a lot of our debate is going back to what Steve was mentioning, what is disease, and in the context of biomarker what is disease?

DR. LEWIS: Mm-hm.

DR. HONG: And I think in, in this, in this context with regulation and how we sparse out things like orphan designation, exclusivity, then we really need to have a, you know, since this, since this notion of biomarker disease is really truly a new entity, we really have to have, I would argue a high bar about what that is.

And that entails a lot of what, you know, and you guys have a perfect model of this, I think, with the, with MSI-high disease, that there seems to be uniformity, not necessarily across every single tumor type known in existence, but at least a uniformity in quote, "many," and you can define many as however you want, across many different histologies. And that

there is a truly predicted biomarker and then you define that as, as kind of a separate disease.

But I think that bar has to -- however you guys want to define it, has to be a little bit higher than just saying, oh, you know, they, there's some similar characteristics across these different tumor types.

DR. LEMERY: I think that would be more a review issue bar and maybe orphan designation considerations of with -- I know we've some discussions, but I think it's --

DR. LEWIS: Oh, move into the mic.

DR. LEMERY: I think exclusivity, I think exclusivity it may not be, you know, 'cause here you're, you've already given orphan designation and you're, you know, deciding what, you know, what indication you give exclusivity for.

DR. MELLIS: Another point is it, it's possible that the tissue agnostic indication that came before might not have included examination of pancreatic cancer specifically. And in this, in the second instance, this development program for the

orphan indication of pancreatic cancer is a lot of work and it's providing a lot of useful information to the field. And it's going to be of benefit to patients and it's essentially an innovative endeavor. So I, I would hope that incentives would be maintained to encourage that.

DR. LEWIS: Okay. With that I'm going to, I'm going to go to our Topic 4, which is, oh, Topic 3B. We have another piece to this. I'm sorry. So we're still in the same scenario. We have Drug A receiving market exclusivity. Oh, this is a little different. Drug A is receiving market approval for pancreatic cancer. It's a histology specific, but Drug A has orphan designation for all cancers that are tissue agnostic.

So, I think what we have some idea where this discussion may go, but for us it was still -- we still receive so much input that we consider grouping and now it sounds like we're very much into splitting. But it would be helpful to us if you could discuss whether Drug A should receive exclusivity only for the, the biomarker positive pancreatic cancer or, or should get broader.

DR. MOSCICKI: So I think we need a, a little clarity on this example, though. And for pancreatic cancer indication it says it received marketing approval, but it didn't say that it, that, that was, that it had orphan drug designation prior to that market approval or not. So did it or didn't it? In other words, does it now have, did it have orphan drug designation? Is, is it a -- does it have exclusivity for the first approval?

DR. LEWIS: Does the pancreatic cancer indication have --

DR. MOSCICKI: Yeah. So, I, I read this, that you have marketing approval that was established for the drug in pancreatic --

AARON FRIEDMAN: It has designation for the biomarker, the blue box.

DR. MOSCICKI: Yes. But, not --

AARON FRIEDMAN: But it's approved --

Dr. MOSCICKI: -- for pancreatic cancer.

AARON FRIEDMAN: -- for the red circle.

DR. MOSCICKI: The red circle has no orphan drug exclusivity --

DR. LEWIS: That's right.

DR. MOSCICKI: -- assigned to it.

DR. LEWIS: That's right.

DR. MOSCICKI: Okay.

DR. LEWIS: It's only, it's --

DR. MOSCICKI: That, that's an important piece of clarity.

DR. LEWIS: It is. It is. Mm-hm.

DR. MOSCICKI: Yeah.

MR. KARST: But in that case, I mean it seems --

DR. LEWIS: So we're really looking at what's the scope then of the exclusivity. Since it has the designation for the tissue agnostic, it has approval, it has approval for the pancreatic, but not necessarily any designation or, or therefore any exclusivity.

DR. MOSCICKI: Yeah. So I, I know this is going to sound odd coming from me, but, but again, I, I, I still think incentives are important to maintain and given that the new indication for biomarker

positive solid tumors has the orphan drug designation and that does include pancreatic carcinoma, you know, in, in that there was no other competing issue with that, then it seems like you would include that population in the new orphan drug designation.

DR. LEWIS: That, that is interesting given that we were looking at them as very different.

DR. MOSCICKI: I know. I know. I know.

DR. LEWIS: Mm-hm.

DR. MOSCICKI: Yeah, so that's kind of --

MR. KARST: It, it seems if we're following the, the paradigm of what is the disease or condition here that, and if you have designation for the biomarker that is the disease or condition and you obtained approval for a different disease or condition, which is pancreatic cancer, so the, it would, consistently with what we've been discussing there, there simply shouldn't be any exclusivity in this scenario because it's a different indication than that for which you have orphan designation, at least in this case.

DR. SUL: So --

DR. MOSCICKI: That would be true to my previous principle.

MR. KARST: Yeah. That's true.

DR. LEWIS: But, not, but, yes, so that -- just so we're clear on that, you're, you're staying consistent with that --

MR. KARST: Correct.

DR. LEWIS: And you're talking about the, the incentive perhaps --

DR. MOSCICKI: Yeah. I think the order in which this occurs is what I, I'm sort of thinking here.

DR. LEWIS: Right.

DR. MOSCICKI: And why I departed a little from that principle and --

MR. KARST: It, it might be in the way the question is worded. Where it says Drug A has orphan drug designation for all cancers that are biomarker X positive. But the designation really wouldn't be for the cancers, right? It's for just the biomarker positive tissue agnostic disease?

DR. MOSCICKI: Oh, oh, I see. Yeah.

MR. KARST: Right? So they don't actually

have the designation for the cancers. It's for the biomarker.

DR. MOSCICKI: Yeah. And it says it's for only biomarker X positive pancreatic carcinoma. Is that true? You're not --

DR. LEWIS: So --

DR. MOSCICKI: -- going to include the other solid tumors in the --

DR. SUL: I, I think the other clarifying point about this, this question also is, or, or this scenario also, is that, that the approval is only for the pancreatic cancer.

MR. KARST: Right.

DR. SUL: You know? So --

MR. KARST: They never approved it --

DR. SUL: Yeah. They never approved it for the biomarker --

DR. MOSCICKI: Right, right.

DR. SUL: -- positive --

DR. MOSCICKI: Right.

DR. SUL: -- tissue agnostic.

DR. MOSCICKI: No, no. I understand that.

DR. SUL: Yeah. But the, the designation is there. So, I think that's where the, the question is.

DR. MOSCICKI: But, but the second part says whether Drug A should receive orphan drug exclusivity for only biomarker positive pancreatic cancer and not other solid tumors?

DR. SUL: Because it's only approved for --

DR. LEMERY: It wouldn't get exclusivity if it's not approved for the --

DR. SUL: Yeah.

DR. LEMERY: -- for the use, right?

DR. MOSCICKI: Right. But it, it doesn't sort of say --

DR. SUL: I think, I think the question is should it get --

DR. MOSCICKI: I'm really struggling with what --

DR. SUL: -- exclusivity for --

DR. MOSCICKI: What did it get approved for?

DR. STARTZMAN: Take the --

DR. SUL: Pancreatic, all, all-comers.

DR. MOSCICKI: And it never got approved for

the other solid tumors.

DR. SUL: Exactly.

DR. MOSCICKI: Oh. Yeah. Well. Okay. The answer is it should only be for the biomarker X --

DR. MELLIS: Question. If, if a drug has been approved already and is on the market for a rare cancer indication like pancreatic cancer, could it subsequently receive orphan designation and exclusivity after the approval has been completed?

DR. LEWIS: If, if I understand the question, once something is approved, the same drug for the same indication, we will not designate that after that unless there's a, a plausible hypothesis for superiority. And --

DR. STARTZMAN: Yeah. Unless, unless the sponsor submitted the request for orphan drug designation prior to the submission of the market application.

DR. LEWIS: Yes.

DR. STARTZMAN: They could submit prior, but

not get designated until after the approval.

DR. MELLIS: Oh. I see.

DR. STARTZMAN: In some unusual --

DR. LEWIS: Mm-hm. Yes. We've had that --

DR. STARTZMAN: -- situations.

DR. LEWIS: -- that situation where it takes a while. They submit the, the, their designation and then they get approved and the designation actually occurs later. But those are, that's an unusual situation.

DR. MELLIS: So. Okay. Thank you.

DR. MOSCICKI: So the other thing, piece of information then was that the data failed to show that it fulfilled the needs of a, a tissue, tissue agnostic indication.

DR. LEWIS: Not necessarily.

DR. HONG: And this -- well, I, I think I understand the question.

DR. MOSCICKI: But isn't that key to whether you get market exclusivity --

DR. SUL: So, so I think this is sort of an indication of how --

DR. MOSCICKI: -- whether it --

DR. SUL: -- complicated the issues are.

DR. MOSCICKI: -- failed or didn't fail.

DR. HONG: So what you're saying is, is the pancreatic indication was approved --

DR. MOSCICKI: Yeah.

DR. HONG: -- and then you have a designation for kind of tissue agnostic biomarker. So, the question is then even though -- so now that you have a pancreatic indication that's approved, should then the biomarker X pancreatic tumors also get a drug exclusivity? I, in my opinion, no. I think you have to wait until the biomarker X positive solid tumor -- because, you, you don't know entirely whether or not, you know, what is truly driving the, the, you know, the approval in the pancreatic, right, if you haven't gotten the biomarkers in pancreatic.

DR. MOSCICKI: Yeah. I think it's all data based here. It's -- this is, this is where you do have to have data.

DR. SUL: Yeah, and I --

DR. MOSCICKI: Principles aside, I would say

then the principles stand that the answer is no unless you have data.

DR. HONG: You agree with me.

DR. MOSCICKI: Huh?

DR. HONG: You agree with me.

DR. MOSCICKI: I do.

DR. HONG: Oh, my God.

DR. MOSCICKI: And, yeah, that, that, by those principles this would be no. But it -- unless the data was very clear --

DR. HONG: Yeah. I agree.

DR. MOSCICKI: -- that it was -- showed biomarker X positive pancreatic carcinoma efficacy.

DR. SUL: Right. And so then in this scenario then there would be no exclusivity because the sponsor had not prior to the marketing application received orphan designation for pancreatic cancer.

DR. MOSCICKI: I can buy that.

DR. SUL: So, yeah. Okay. So I think that's, that's the clarification, you know, we wanted to make.

JAMIE HOLLOWAY: So thank you for clearing that up 'cause that was my confusion. So I think the

distinction between disease and indication is important. But it's also important to remember that in the overlap of the red and blue in there is like people, right? And so the thing that could be difficult is if you have a pancreatic cancer patient in the red bubble who is on the drug and depending on the timing of this they get moved to the bottom half of the bubble and now they're in the orphan drug designation.

So, it could very potentially be that a drug that they had access to at a more reasonable rate is going to be more expensive because they're not going to have the generic option because now they're excluded, or they're part of the exclusivity bubble. And so, I mean it's a very, it's a very fine line and I'm glad that there's a multi-stakeholder discussion because I want drug development for rare cancers, but I also want patients to get the drugs in the end.

But I think just considering that the overlap, there's people in all of those overlaps, and that, you know, it's going to, it's going to affect their access to the drug. And it seems, it seems cruel to say we've done some new research so now you, you don't get

generic even though your, your buddy over there in the other half of the bubble gets the generic drug. So, that's just something that I would hope that we could at least consider as the discussion goes forward.

DR. LEWIS: It, it's at forefront of all of our, of our thoughts about the people who are being affected by this. So, I appreciate you bringing up as we're looking at diagrams that they're representing the people who have these conditions and it's well, well taken. Thank you.

MS. GAVIN: So we don't support extending exclusivity just for the sake of it. There has to be benefit to the patients. I'd also make a comment on generics. There's a big difference between generics in the common diseases in, versus the rare diseases. At least that's what the empirical data has shown to date.

Unfortunately, you need multiple generics on the market for any measurable reduction in costs, which doesn't help the rare disease community very much, unfortunately, unless we can do something about it in some other way, shape, or form.

DR. LEWIS: Thank you. I think we've covered

this particular scenario. I've got yet a, another part of C, 3C. I think we, we still are having Drug A receiving marketing approval for all cancers that are tissue agnostic and the prevalence is over 200,000, which means that it did not receive any designation for the tissue agnostic approval.

But Drug A has an orphan drug designation for this pancreatic cancer that's histology specific and should Drug A receive marketing exclusivity for the biomarker positive pancreatic cancer, that overlap part? So any clarifying needed or are, are we good?

DR. MOSCICKI: Yeah. I need clarification here too 'cause to me I, I, I'm, I need to know are we defining the indication by the presence of the biomarker or are we defining it by the histology of the pancreatic cancer? You know, to me that, that's sort of a critical question of the indication that's given. And what do we really intend by that related to whether or not you get exclusivity?

DR. LEWIS: So if your question is, are we considering the -- in this particular case, the designation piece is for the disease pancreatic cancer.

But we, we have an approval for an indication for the tissue agnostic. And so our question then is does it, does it cross over -- like we've talked previously that the histology specific and the tissue agnostic just should be considered separate and different.

And so that might guide you when you look at this situation where the indication that was approved is an indication of tissue agnostic and now we have a designation for a disease, pancreatic cancer, that does include the same people, the same people with pancreatic positive. Should there be any exclusivity given or should there not?

DR. MOSCICKI: Yes, but if -- I, I would say if, if you came out so that the indication was defined as biomarker X positive pancreatic cancer, then the answer would be no. But if it, if the indication is for pancreatic cancer, then the answer is yes, you know, because --

DR. LEWIS: Don't you need clarification?

DR. MOSCICKI: -- then you, you know, if it's really defined by the presence of the biomarker, that, that's a problem, right? If that's, if you're not

approving it for all patients with pancreatic carcinoma, but only for those that are biomarker X positive, then I think you, it is the same disease, right, rather than a different disease? But if it's pancreatic carcinoma without, you know, necessarily the biomarker, then those are different diseases and you should get exclusivity.

DR. LEMERY: I guess there's some overlap, but there, but there's, there's overlap and, you know, it may depend on, on the prevalence of the biomarker and the effect on, on negative. However, I think the, the corollary, the important corollary is that a generic could potentially get marketed for biomarker positive, X positive disease, right?

So you still could market it for, theoretically for a biomarker positive pancreatic, patient with pancreatic cancer. You just can't put pancreatic cancer in your, in your labeling; is that correct or am I incorrect?

MR. KARST: I mean this scenario is just a, a flip of 3, 3B. I mean it, so the answer is going to be essentially the same as 3B, which is there wouldn't be

exclusivity because that for which designation was granted. Again, assuming we're talking about the disease or condition if it's the biomarker versus the actual histological site.

You know, if there are distinct items here, then they don't line up and therefore you can't get the exclusivity because you didn't get approval for the drug for the designated indication, or for the designated disease or condition.

DR. SUL: And so, I mean, again I think this is, this is sort of one of those situations where, you know, there's the letter of the law and then there's sort of the spirit of the law. So if, if the whole purpose of the Orphan Drug Act is to, to incentivize the development, so presumably the sponsor came in for a designation for pancreatic cancer. I'm going to presume before the biomarker X field had developed.

So they had intended to develop the drug for pancreatic cancer, but then they went on to develop it for biomarker X positive solid tumors, but there -- it's just by default because they had come in earlier with the designation for pancreatic cancer that they

would be even in contention for exclusivity now.

It seems a little bit, again, it sort of seems like a, a forced situation there. You know what I mean? I mean it's, it's not like, it's not like they went into this deciding that they wanted to develop the drug for biomarker positive pancreatic cancer.

MR. KARST: And, and if things do change during the development process, you know, they, they go from, so cancer specific to, you know, agnostic, they can simply go in with a new --

DR. SUL: Exactly.

MR. KARST: -- designation request right --

DR. SUL: Right. They would, they would have come in with a different designation.

MR. KARST: Right. Yeah.

DR. SUL: And I think it would be, the onus would be on the developer or on the sponsor to do that, to recognize, okay, well, you know, we want to come in with orphan designation at that point --

MR. KARST: But you could because --

DR. SUL: -- rather than trying to carve out based on some prior designation.

MR. KARST: Yeah. And they'll, they'll be aware of this beforehand 'cause Orphan Drugs will have issued its guidance by then saying what their policies are. So they'll, they'll be aware.

DR. STARTZMAN: Well, another issue with this would be if we did grant exclusivity, would be a sponsor could come in knowing that biomarker X positive solid tumors is over 200,000. They could come in for designation for pancreatic cancer, gastric cancer, esophageal cancer, etc., you know, all these separate designations.

And then when they get the tissue agnostic approval, they would get exclusivity for the biomarker X positive, all these different. So they could kind of --

DR. SUL: Double check.

DR. STARTZMAN: -- get designation, you know, essentially get exclusivity when, for a --

DR. HONG: Hopefully they won't play that game, right?

DR. STARTZMAN: Huh?

DR. HONG: Hopefully they won't play that kind

of --

DR. HONG: Or is that -- so is that allowed? That would be allowed under this, right?

DR. STARTZMAN: If, if we --

DR. HONG: That, is that what you're trying --

DR. STARTZMAN: If, if we granted the exclusivity.

DR. HONG: It is.

DR. STARTZMAN: That's why keeping them separate --

DR. SUL: I think that's the letter of the law again. First it's the spirit of --

DR. HONG: It's the letter of the spirit of the law.

DR. SUL: Right.

MR. KARST: If the law allows it, it'll happen, so.

DR. SUL: Yeah.

DR. LEWIS: Did you -- were you leaning forward there? Could you say that again?

MR. KARST: Oh. Sorry. I said if the law allows it, it will happen, so.

DR. SUL: Exactly.

DR. KUMMAR: So I guess the question I had is that if they're doing a biomarker X tissue agnostic trial and then they come in -- I mean it's fine that, I know, I don't feel strongly about penalizing them just because they came earlier with pancreatic cancer and changed their plan. But then we have to make sure that the biomarker X clinical trial had enough number of pancreatic cancer patients with biomarker X positive to say that stand alone it wouldn't need approval for pancreatic cancer, right?

Because I mean not all -- once you have these multi-histology, it could be ten histologies, but you come with the eleventh, presuming that it's also biomarker X positive. So then how many, how do you independently power to say now you want to get a pancreatic cancer approval? So should it have X number and show positivity to do that? Because I don't think you can just extrapolate.

DR. LEMERY: I, I think we're talking about potential situations where a drug has multiple pathways of, of action. You know, it, it's not just through MSI. It's the mutation burdens through, you know, we

don't really know the -- I mean if you have a clean, if you have a clean TKI that's, you know, it may be less of an issue, but if you have a, maybe if you have a dirty TKI that affects multiple pathways you can see a scenario -- I mean it's not likely, but it's possible if you have --

DR. KUMMAR: I don't know, but I'm saying if we, if the approval is for pancreatic cancer, is there enough evidence to support pancreatic cancer stand-alone approval? Or have enough patients with pancreatic cancer that are biomarker X positive being treated and shown to derive benefit?

DR. LEMERY: Well, I think for -- to get an approval on pancreatic cancer you'd have to show that the drug is safe and effective in patients with pancreatic cancer.

DR. KUMMAR: Yeah. That's what I mean. I mean you can't take the biomarker X --

DR. LEMERY: Right.

DR. KUMMAR: -- tissue agnostic where you have your three, four patients of each histology, small study, to kind of do it, right?

DR. LEMERY: Well, right, but I think we're talking about -- the, the pancreatic cancer circle here is talking about both patients who are biomarker positive and negative. So you would have --

DR. MOSCICKI: Yeah, but your -- it's very confusing 'cause you're talking about exclusivity for the biomarker X positive.

DR. KUMMAR: Biomarker X positive.

DR. MOSCICKI: And, and, you know, so now you've sort of redefined it. It's no longer just histologically based pancreatic carcinoma. Now you've redefined it by the biomarker presence, which now makes it belong to the blue subset. That's why we're here.

DR. SUL: So I, I don't know that's it's really redefining as much as it is we're going to pluck these patients out of the -- the original approval is for a tissue agnostic indication, biomarker positive. However, because you already previously had designation for pancreatic cancer, you could have had it for gastric or whatever, whatever other smaller subsets.

We're just going to pluck out that -- we're carving out that group to provide you with exclusivity.

It's not saying anything about, you know, the, the approval and activity in that.

DR. LEMERY: Yeah, but -- so I mean just take the -- I, I mean you could -- here you could think of PD-1. So MSI, all indications above 200,000, and then, you know, whatever Merck, BMS, any of the companies come in with, you know, an, an indication solely in neuroendocrine tumors or bladder cancer, you know. How do we deal with that here? Should -- do you, how do you assess the MSI population who has both neuroendocrine or bladder cancer in, in those scenarios and I think that's their question.

DR. LEWIS: Okay.

DR. MOSCICKI: Yeah, but that's part of the convolutions here, is sort of putting in after the fact, you know, the plucking out as opposed to the fact that they early on had an orphan drug designation for all pancreatic cancer, assuming the clinical trials showed an, a, an efficacious benefit in undefined pancreatic carcinoma based solely on the histology.

Then to retrospectively pluck out the biomarker X doesn't seem right according to the

original principle that I was trying to say. Then, then in fact, that is a different disease and still deserves.

Now if instead, you know, the sponsor sought to get biomarker X positive pancreatic carcinoma, conducted the, based on this and didn't have evidence that biomarker negativity contributed to the benefit, you know, that's a very different scenario. So like I've often heard in these buildings, it depends.

DR. LEWIS: Thank you. Due to time I'm going to be sure that we -- oh, I, I think we had -- maybe this one just was -- so I think that may wrap up our, our, our topic questions.

There are some that came from outside in the webcast. Are there also anybody who has a, a question from in the room? Do you want to, do you want to start at the bottom one?

Okay. Let's start at the top.

Oh, okay. I'm going to go. We have from our second discussion a situation where Company A seeks an

indication for a specific tumor type and it's, they're saying ALK in non-small cell lung cancer and they gained exclusivity for this orphan population, all right?

So, Company A indication for a specific tumor type and gains exclusivity for this. How would FDA handle the approval of the same drug for a tissue agnostic indication in the future? Would the exclusivity for ALK non-small cell lung cancer preclude Company B from gaining a tissue agnostic indication for all cancers expressing ALK positive until Company A's exclusivity expired?

And with this situation, what would be the situation where Company B would get a carve out in their label excluding the protected subset?

DR. STARTZMAN: From the discussion that we've heard today, it sounds like we would consider tissue agnostic to be a different, you know, disease or condition or indication from the more tumor specific. It would be just the ALK positive non-small cell lung cancer, and therefore the exclusivity would not carve out that from the, from the tissue agnostic approval.

DR. LEMERY: So I guess, so in this scenario you would have, just to simplify, you have ALK positive lung cancer gets approved, it has a certain exclusivity. It may have orphan designation, the tissue agnostic has orphan designation. It gets approved three years later. Once the exclusivity runs out for lung then a, a generic company could market their product for ALK positive lung cancer, but they couldn't include the ALK positive tissue agnostic in their label until the exclusivity runs out for the tissue agnostic.

DR. HONG: But I, you know, there's, there's a similar -- I mean entrectinib, for example, targets both ALK and NTRK, right? So, I could see a situation where they've applied for or let, let, let's say they get exclusivity for ALK positive cancer, but then they apply for a designation or they get exclusivity for tumor agnostic in NTRK in the future or something like that. I could, I could totally see that being a conceivable, reasonable pathway.

DR. LEWIS: Mm-hm.

MR. KARST: Yeah. It, it, it, if you, if you

view it in the light of, if you almost rename them. Say, you know, indication X is multiple myeloma and indication Y is leprosy. Okay, two very different indications and, and if we view these as that way it actually becomes very easy. Carve out one or they both get their own periods of exclusivity if they're both designatable, and once one period ends it, it's no longer protected, then generic can come in and get approval for leprosy while the multiple myeloma indication is protected, for example.

DR. SUL: So it sounds like what you and I think many others on the panel have proposed is really to think of them as almost completely unrelated diseases, which I think is very difficult given what we know about the, the science and why we're having this discussion.

MR. KARST: Right.

DR. SUL: Yeah.

MR. KARST: I think, and not being a physician, but, but, yeah, mentally I think it is difficult to separate them because they are so close to one another, but if, if the paradigm here, again, is

that they are different diseases, then they are, in fact, different diseases as different from, you know, multiple myeloma and, and leprosy, right?

Now what it's going to come down to, though, of course, is how the labeling is going to be written for these products and how you describe a tissue agnostic product, you know, the biomarker versus one that's organ specific, right? So the, the devil will always be in the details particularly when it comes to labeling carve outs and generic approvals, but --

DR. MOSCICKI: I, but I would agree that data will always matter.

MR. KARST: Yeah.

DR. MOSCICKI: Right? In the end it will matter, but, you know, I, I, I think to some degree it, it doesn't help to confuse in a way the science with the policy because, you know, we, you have, you're having this discussion partly because the scenarios seem awfully convoluted in so many ways, right? And so many different ways to think about them.

So I think the principle that we were advancing is to simplify this by making a policy, not

changing science, not trying to, but, but treating this in a policy manner by saying, by establishing this policy you get clarity. And, and it's much easier to work and make those decisions that you need to make.

DR. SUL: I think -- and that's, that's definitely true when you, when you sort of start out with a, with a standing principle that then you kind of refer back to when you're making decisions. But I think part of the concern that the, the Office of Orphan Products has had is what are the, ultimately the implications later on down the line.

Because, you know, we're not just talking about designation for designation's sake. We're talking about the incentives and the exclusivity that comes with it and the potential to block, you know, access to, to other drugs.

DR. LEWIS: I think, I think it's true that, that certainly a policy that simplifies things is appealing and it's something that has been discussed as a way to help us through some of these scenarios. But I do think the consideration of the implications is something that we'll be thinking about as we take in

all of this great input we've received today. And as we're going forward on a guidance document, looking at what are those implications.

Certainly, I do appreciate simplicity. That's a great, that's a great opportunity, but we want to ensure that we get this balance right between giving the incentives and protecting the intent of the Orphan Drug Act, ensuring that we are doing the right thing for these people who are actually having these conditions.

And so a lot of complexity. Some of the questions we've received, people trying to understand a little bit about the testing aspects and are we going to be looking at responses and changing our decisions based on responses. Are we going to -- somebody even was looking back for clarity on questions about will we designate multiple products for the same, multiple same drugs for the same condition up until that approval. And, yes, we will.

So people are, are going to be struggling with some of the inputs and the implications of what's been said, but I do think we're coming close to the end of

our time and I just want to give an opportunity for our panelists to, to say if you have a particular final thought as we just come across.

I'm going to start down on the other end. We started with introductions down with Kurt. Pam, do you have anything as we come across down here that we want to just say as closing thoughts?

CLOSING REMARKS

MS. GAVIN: Thank you. Just to -- a couple of really quick thoughts and maybe reinforcing some of them that were made earlier. I think providing as much data to OOPD as possible to help understand the context and as best you can because you can't predict the future is important.

And I think also to remember that these are patients that we're dealing with here and it's hard just following the conversation. And when we talk about the science to recognize that what does that mean for patients. As a patient can I be in both the red, the red circle and the blue box? It doesn't seem logical.

So we've got to think through these processes,

as well as what does the implementation look like from a sociopsychological and socioeconomic perspective because it, it runs all the way through to the end to access.

DR. LEWIS: Thank you.

DR. RUBIN: So I guess I'll sort of echo that. I think both the tissue agnostic approval and pathway and, and orphan drug designation, they're both good for patients. And I think although there are complexities that come into play with having both around, they're not opposing, and I think that it was a good discussion today. And I think, I think it can be worked through in individual situations to, to preserve the intent of both.

DR. MOSCICKI: Yeah, I would echo that and I, I, I believe that the Agency deserves good recognition for bringing this topic and discussion forward. I think for its forward-thinking on tissue agnostic indications and it's willingness to take on the complexities that that innovation has engendered.

And, you know, I think that I've already had my say about simplicity and the virtues of that. And

I, I, I also want to come back to while affordability is important, there's no question about it for patients, we still have 7,000 rare diseases and only 500 approvals. Although that's great that we have 500, but largely thanks to the Orphan Drug Act.

So those incentives remain important and I'll leave it with that.

DR. LEMERY: Nothing, nothing else to add. Just, you know, thank everyone for coming and giving their, their input.

DR. KUMMAR: Yeah. Thank you for having me on the panel. It's been a very interesting discussion. My only two cents, simplicity and then sort of encouraging is all great, but here we're not talking about two diseases. It's, part of the biomarker disease is actually part of a bigger whole.

So, I think it's not as simple as pluck it out or let's treat them as leprosy versus myeloma. This is a subset of a bigger whole. And so I think each has to be reviewed very carefully in the context of the larger knowledge base and what the exclusivity, as well as the approval would have an impact on which patient gets

treated which way.

So, I think it has to be thought through each case individually.

DR. HONG: Yeah. I, I, I echo the same thoughts as Shivaani. I think this is a complex issue, but I, I, I applaud the FDA for, for doing this because I know, you know, for many of my patients it's, it's, it's, it's really, I think, big hope. And I, and, and I think going back to my, my last comment, I think oncologists are behind you guys. We're still trying to catch up in some sense to the science and to the regulation.

DR. SUL: I just want to thank everybody and, and for their input and for, for participating and spending the day talking about this complicated topic. And I did spend some time in the Office of Orphan Products and my head would spin sometimes trying to wrap myself around some of these issues.

And it's a very different way of thinking from being on the Review Division. And so, you know, I really appreciate, you know, what the Office is up against, especially with this new science.

And one thing I will say is that, you know,

whenever I was struggling with something I would always try and come back to what the original intent of the Orphan Drug Act is and, and, you know, actually printed it out and, and pasted it on my desktop just to remind me, okay, this is really what we need to focus on. And so it, really whatever we can do to, to keep the incentives there for developing these products is important.

DR. LEWIS: Thank you.

DR. STARTZMAN: I just want to thank everybody. I think the discussion has been, has developed good guidance for how we can deal with this evolving science. And thank you.

DR. MELLIS: I'd like to echo the, the comments of my previous, previous panelists who spoke and thank everyone and thank the Agency in particular for this truly visionary science-based initiative. And, and I'm confident that the complexities can be worked through and that we can really work together to bring forward new medicines for patients in need.

DR. LE: Yeah. I just wanted to say that encouraging a tissue agnostic approach actually is a

way to provide access to patients with orphan diseases 'cause they aren't really included in a lot of the other studies.

DR. STEWART: I think I mostly will echo what other people have said, but first thanks to the FDA for providing a platform to discuss this important issue that truly does give access to patients to innovative therapies. And recognizing that, that tissue agnostic drug approvals and drug development is really changing the landscape. And recognizing that policy needs to be able to capture that.

So I think moving forward it's, it will be critical to really think about how we are going to define diseases and whether every biomarker that may exist across tumor types truly rises maybe to the level of being defined as, as a disease or simply just a biomarker that, that exists.

And in addition I was, I'm glad CDRH was here and I hope there's additional opportunity to discuss the important role that the diagnostic plays in this conversation. And particularly when it comes to making sure patients do or don't receive a drug that's

been approved based off of a, a, of a biomarker.

MS. SHER: Again, just echoing our thanks to FDA for holding this meeting. I think it's a reflection of FDA's long tradition of ensuring that we're really looking closely at the need for innovation on the one hand and competition at the end of the appropriate exclusivity periods. We share that commitment and really appreciate this Commissioner's and this FDA's focus on the importance of access to generics and biosimilars. So, we really appreciate being able to be a part of this today. Thank you.

MR. KARST: And I echo those comments as well and I think, you know, throughout the history of the Orphan Drug Act we've -- Orphan Drugs has constantly been faced with the new technology and science and it creates new issues. But at the end of the day, you know, whether we're talking about fusion proteins or gene therapy, sameness issues, there's always that elegant simple issue or resolution and there's a very complex one.

And I think we have that here as well and, and, and, and I would hope that the Office ends up

writing guidance and following, following that pattern of adopting the very clear-cut, black and white, easiest way to implement the act.

DR. LEWIS: So thank you, all our panelists. I don't know, Donna, if you want to make any final comments from a testing aspect?

DR. ROSCOE: Yeah, actually I would just like to say one thing and that's that as you're developing policy, it's very important to have the definitions in place and the -- because the definitions really enable you to move that policy forward. And I think perhaps in this setting part of that of establishing definitions is appreciating the uncertainty around those definitions and identifying.

Because when you talk about a biomarker, a disease defined by a biomarker, you need to understand is the biomarker driving the disease or is it just an outcome of the disease, because now you really aren't defining disease if it's the latter.

So, understanding the uncertainty around those definitions and then perhaps provocatively thinking about ways to incorporate that uncertainty into the

clinical trial designs so that you can move forward the orphan product while maintaining an understanding of the science that's coming out of it.

DR. LEWIS: Thank you. I want to thank all of our panel today. You've come from many different perspectives and given us a lot to think about, whether it's approaching simplicity, whether it's thinking in more specific definitions, lots of input that we appreciate.

It is an exciting time. We're not just at 500. We're almost at 700 approvals now. And the people who carry this out in the Office of Orphan Products Development, I just treasure you. You're, you're fantastic. So, thank you so much for all the preparation.

Our, our logistics folks, I can't say enough about Joohee. I, I just lost sleep wondering, you know, I hope you're okay. Get here safely today. So I think that all of you who've provided your comments today we, we appreciate it.

There is still an opportunity to provide comments. We have a docket that's open until early

June. So please do submit your, your thoughts, your input.

I want to also thank Nina Hunter who's been terrific support from us from OMPT. Oh, there's our panelists who've just shown up again. But these are tough questions. We do, you're right, focus a lot about these scenarios and making sure we do this right, and your input is just so critical to us.

Everyone made a great sacrifice to be with us today. Nicole Wolanski, thank you for your fabulous support as well. That whole group. Christine, thank you. Dev, thank you. Chip, thank you for being up here.

And if there's any other final comments, raise your hand right now. Otherwise -- oh, there is one. I see one in the back. Here you go.

[Uros Djekic (Shire)]: It's, it's -- and I'm sorry for --

DR. LEWIS: No. That's good. That's good.

[Uros Djekic (Shire)]: -- for, I guess, asking the question late, but I guess given obviously the title and the focus on oncology products --

DR. LEWIS: Mm-hm.

[Uros Djekic (Shire)]: -- and the implications for the guidance document that is going to be applicable, I guess could you comment to the extent possible how this discussion and information and topics would apply to non-oncology designations? And will there be maybe two separate guidance documents or to, to the extent possible?

DR. LEWIS: All right. Thank you for the question. Yes. We have focused today on oncology and acknowledging full well that this is not a, a set aside by itself, that, that the many important advances outside of oncology are critical to rare disease issues in general.

So will there be two guidances? Right now we'll focus originally on this oncology. Where we see principles that are generalized, we will, we will certainly try to include that. We'll try to think about what we've heard today. And in the future we, of course, want to, to be able to make use of that guidance, whether -- I can't really speak about how soon.

One of the things that is, that we started here is because we had some experience and it helps the Agency to get a little bit of experience with something. And as we get a little more experience outside oncology, that's where those principles might show themselves to be simple and able to be applied simply, or they may even turn out to be a little bit different.

For example, it's not always tissue agnostic, but agnostic in a sort of an analogous way. If you look at our ophthalmology, it's right there in the retina, but it's still grouping different conditions into one setting. So, we've been saying tissue agnostic, but in our minds we're thinking like you are, how does this apply to other agnostic situations that we'll be encountering.

I know there's more work coming up in the near future looking at these types of issues. So, I thank you for your question. It just drives us more and I know Christine's always asking me on this question. So we, we hear you and respect that need for the future.

So with that, nothing else? All of you, thank

you so much for joining us and for those who made this possible, my appreciation. Everyone take care and I hope you have safe trip back. Thanks so much.

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I, KeVon Congo, the officer before whom the foregoing proceeding was taken, do hereby certify that the proceedings were recorded by me and thereafter reduced to typewriting under my direction; that said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

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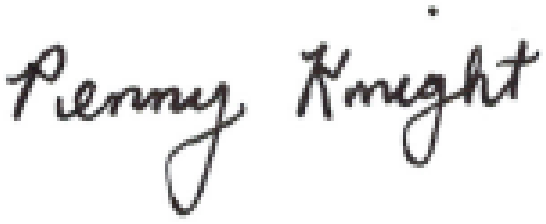

May 17, 2018

Date Penny Knight

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