Pyxis Oncology (UPDATE)
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Corporate Speakers

- Pam Connealy; Pyxis Oncology; Chief Financial Officer & Chief Operating Officer
- Lara Sullivan; Pyxis Oncology; President & Chief Executive Officer
- Anthony Tolcher; NEXT Oncology; Founder & Chief Executive Officer
- Glenn Hanna; Director, Center for Cancer Therapeutic Innovation and Medical Oncologist, Center for Head & Neck Oncology; Dana-Faber Cancer Institute
- Jan Pinkas; Pyxis Oncology; Chief Scientific Officer

Participants

- Swayampakula Ramakanth; H.C. Wainwright; Analyst
- Jeffrey La Rosa; Leerink Partners; Analyst
- Leonid Timashev; RBC Capital Markets; Analyst
- Sudan Loganathan; Stephens Inc.; Analyst
- Bradley Canino; Stifel; Analyst
- Tony Butler; Rodman & Renshaw; Analyst
- Sam Slutsky; LifeSci Capital; Analyst

PRESENTATION

Pam Connealy^ Hi. Good afternoon, everyone. I want to welcome all of you both here in-person as well as virtually to our very first Pyxis Oncology Data Disclosure event. This is an exciting day for Pyxis, and as I look around the room, there's so many people that have been with us over the last five years on this incredible journey as we move PYX-201 into the clinic.

On behalf of both myself, our executive management team, our entire Pyxis team, and our board of directors, I want to thank all of you for being here. And most importantly, I want to thank the patients and their families for their engagement in our clinical trial. Again, I think there's so many people that helped us get to this place today, all of our clinical investigators, the vast number of study coordinators that work with us, and the site staff that engage with the patients directly every single day on this trial. So again, we are deeply and completely appreciative of all that.

I'm Pam Connealy. I'm the CFO and COO here at Pyxis Oncology, and it's my honor to introduce both the folks that will be speaking, as well as two really important guests of ours.

So first is Dr. Glenn Hanna. Dr. Hanna completed his fellowship training in hematology and medical oncology at Dana-Farber. Prior to this, he earned his medical degree from Georgetown University School of Medicine in 2010, where he graduated summa cum

laude. He joined the faculty of the Center for Head and Neck Oncology in 2017. We're super honored and thrilled that he's here to talk about our great head and neck data that's coming out today.

Dr. Hanna is the director of the Center for Cancer Therapeutic Innovation, the early drug development program at DSFI, and an associate professor of medicine at Harvard Medical School. His clinical and translational research efforts focus on novel and innovative approaches to treat head and neck cancers. So welcome, Dr. Hanna.

We also have with us Dr. Tony Tolcher. Dr. Tolcher has been with Pyxis since its inception, and it's a deep honor for us to have he and his great staff supporting this clinical trial. Dr. Tolcher has spent nearly 40 years looking after patients, and today, his compassion and drive to care for patients remains as strong as the day he graduated from medical school.

Tony founded NEXT Oncology, with a vision to grow the program's infrastructure worldwide. There's so much exciting activity that's happening within NEXT Oncology that you'll want to check out as he continues to expand globally.

Dr. Tolcher is a graduate of the University of British Columbia in Vancouver, Canada. He performed his residency in Internal Medicine at the University of Toronto, and his fellowship in oncology at the University of British Columbia. He followed this with a research fellowship at the National Cancer Institute in Bethesda. And before founding NEXT Oncology, he served as the director of Clinical Research at START for 10 years. Dr. Tolcher was the director of Clinical Research at the Cancer Therapy and Research Center in San Antonio from 2003 until April of 2007.

And prior to that, he served as the associate director at the CTRC's Institute for Drug Development from 1999 to 2003. Dr. Tolcher is also a fellow at the National Cancer Institute. So please join me in welcoming both Dr. Tolcher and Dr. Hanna.

Joining me today from the management team of Pyxis Oncology is Dr. Lara Sullivan, and she'll be leading us in the discussion around PYX-201 today. Dr. Lara Sullivan is the president and CEO of Pyxis. And prior to joining Pyxis Oncology, Lara was the founding president of SpringWorks Therapeutics, a clinical stage biopharmaceutical company she conceived of, founded, and spun out from Pfizer.

As a biotech entrepreneur and advisor, Lara has leveraged her expertise in asset evaluation, portfolio management, and start-up financing to raise nearly $500 million from seed capital through IPO. While at Pfizer, Lara held a variety of executive roles, including vice president, Pfizer Medical, and vice president, Worldwide Research & Development, where she led strategy, competitive intelligence and portfolio operations for the company's early-stage R&D pipeline. And as many of Lara's excellent negotiation with Pfizer allowed us to bring in PYX-201 with superior economics associated with it.

Early in her career, Lara held a variety of roles in management consulting, private equity and investment banking. Lara holds an M.D. from the University of Pennsylvania School of Medicine, and an M.B.A. from The Wharton School at the University of Pennsylvania, and B.A. in Comparative Literature from Cornell. So I'm excited for Lara to share the data with us.

In addition to myself, Jan Pinkas, our chief scientific officer, is also joining us today. Dr. Pinkas is the chief scientific officer of Pyxis Oncology. Prior to joining Pyxis, Jan was the senior vice president and head of Translational Sciences at Magenta, where he was responsible for all therapeutic programs from development candidate nomination through Phase 2, with particular focus on toxicology, clinical pharmacology, and biomarkers.

Prior to this role, Jan worked at ImmunoGen as vice president, Translational Research & Development, where he led nonclinical and translational R&D related activities in discovery through late-stage clinical development. Dr. Pinkas obtained his PhD in Molecular and Cellular Biology from the University of Massachusetts at Amherst, and his undergrad in Biology from Johns Hopkins University. So we're excited to be here with the presenters and our key opinion leaders and guests.

I do have to just give the whole forward-looking statement. You guys can read this here. I don't think we have any lawyers in the room that are going to yell at me.

I'm going to turn over the presentation to Dr. Lara Sullivan. Thank you.

Lara Sullivan^ Thank you. I'm already losing the audio here. Hang on one second. I'll just put this in here. Can you all hear me? Okay, terrific.

All right. Thanks, Pam. Thank you, everybody, for making time in your busy schedules to come in and hear the outcome of our last five years' journey. It's a very exciting time for us, as Pam mentioned. What we're going to walk you through today is a bit of the journey through the biology that started it all, as well as the clinical data that we've accumulated, and the path forward that we intend to take to optimize the benefit that this asset can bring to patients.

They say it takes a village to raise a child. I swear it takes a city to raise a drug. It takes many, many, many hands. And what you see today will reflect all the efforts, not just of the team, the investigators, as Pam mentioned, but also the scientists who got it all started. These were the folks inside Pfizer, the chemists who spent all the time optimizing the different components of this molecule, which actually confer some very important advantages that translate into clinical benefit.

So we've got a lot to walk through today. I'm going to ask for your attention for roughly the next hour, and I'll try to make it as clear and simple and straightforward as possible.

So we're going to talk about, first, what's novel and exciting about this molecule. One of the key features in the antibody-drug conjugate space is related to the potency and the

stability of this construct. And so we're going to walk you through some of the parameters of the construct and how that influences its behavior in people. Then we're going to talk about how well this agent has been tolerated, and finally, where we've seen the strongest signals in humans.

So I can tell you the headline message here is that this very differentiated molecule, which is taking a unique approach to its target, has a very attractive stability profile. It behaves very well in people. We have a very nice half-life. We have a stable molecule that's going exactly where we want it to go. It's not doing anything it shouldn't do prematurely or after the fact. I'll show you that data in a moment.

The patients who have experienced this asset, this program, 80 of them have been dosed so far. They found it to be a tolerable experience. These are late-stage patients, often those that enroll in Phase 1 clinical trials. This is their last hope. And so, these patients come in. Some of them have been on 8, 9, 10 prior sources of treatment therapy. So when these patients are enrolled in our trial, we take very seriously both their experience on our molecule, but also the potential outcome that might offer them some extension of life and some quality of life.

We've seen a very strong signal for our head and neck patients who've enrolled in this trial, and we've also seen evidence of benefit in five other tumor types as well. So six different cancer populations have benefited in the course of this trial from our PYX-201 program. That includes lung cancer, ovarian cancer, HR-positive breast, triple-negative breast, sarcomas, and head and neck has been a very clear, strong signal. You'll hear from us how we plan to further develop this asset across each of these indications here.

So first, to understand the data, I think it's important that you understand what we're doing. The target that we are addressing is called EDB. That stands for extra cellular domain B. This is a splice variant of fibronectin. Fibronectin is an extracellular component within the tumor that provides structure for the tumor cell.

The antibody-drug conjugates that are approved and on the market today, and the vast majority that are in development, frankly, clinical development, if not all of them, address targets that sit on the cell surface. Our target sits in the extracellular environment. This confers some real benefits to us and to the patients, because that extracellular environment is present in a variety of different tumor types. And so that's one of the reasons that we think we've seen such strong activity across multiple tumor types, and that this agent can be ushering in a new way of thinking about using antibody-drug conjugates compared to how people have been using them thus far in the past.

So we essentially hit this extra-domain B target in the extracellular environment, and we cleave our ADC, which means we discharge the chemotherapy, and then the chemotherapy begins to do its work killing the tumor. So what you see outlined here is a distribution of how the target is expressed in a variety of different tumor types, and these are solid tumors, meaning they're organ system tumors.

We looked at 10 different tumor types, you see them represented here, to see how frequent or common our extracellular-domain B, our EDB target, showed up. And then we looked at normal tissues to see whether the target showed up there as well. And what's very unique about this program is that we see this target very strongly expressed in tumors and negligibly expressed in normal tissue.

So pick one of these tumor types, liver, for example, you see a high bar chart. That means the EDB is strongly expressed in the tumor. And right next to it, a little teeny line that signals essentially zero expression in normal tissue. That's super important when you think about tolerability for patients, because if that target was sitting in normal tissues, when we dose our drug, the drug could go to the normal tissues and cause unintended side effects.

So as we looked at this data preclinically, we anticipated that when we would bring this drug into humans, that we would see a clean safety and tolerability profile. And what I'm going to show you shortly is that our hypothesis has been proven largely correct. And Tony will provide some commentary on that, as he's been one of our investigators in this study.

So what's happening here with this agent is that this extracellular-domain B target attracts the ADC in the tumor. The ADC arrives at the tumor and essentially the payload, which is the cytotoxic chemotherapy component, is discharged in that extracellular environment. We believe that the payload at that point is killing tumor cells through passive diffusion. All the other ADCs that are out there that are approved get internalized, engulfed by the tumor cell.

Ours is going in passively and killing the tumor cell. And then as the tumor cell dies, the payload has a second chance at killing the next tumor cell, and the next tumor cell, and the next tumor cell, and this is called the bystander effect. We believe this is a key component of the mechanism, and also a key component, again, of how this is working across a variety of tumor types. Because once you start this cascade, the presence or the density of the target that you need to start the cascade is less relevant. You've triggered the ADC to do what it's doing, and now it becomes a killing machine.

Now, the third component of the mechanism is an immunogenic cell death. So this is recruiting the immune system locally now to join the fight against the cancer cells. And one thing that's really important to understand about this mechanism is the first two components that are mediated by the payload, by the cytotoxic chemotherapy that's optimized for killing is that this third component is where we can call our friends in the immune system and maybe some of our other cancer treatments that are out there, like immuno-oncology agents that are approved to help us.

So we see through this mechanism, a very strong monotherapy killing opportunity to reduce tumors in patients. And at the same time, we see a mechanism that marries very nicely with approved therapies that are already out there, namely immuno-oncology. This type of mechanistic approach, though, is very flexible and adaptable, so we believe that

this could be potentially a more universal combination agent, where it could also partner with other ADCs who have non-overlapping toxicity profiles, who have other types of payloads that can be synergized with ours. So you'll see how the safety profile now becomes very important in understanding the ultimate potential of where this agent can go.

So I'm pleased to announce that we have entered, Pyxis has entered into a new clinical trial agreement with Merck to develop PYX-201 in combination with Keytruda. This is a really exciting collaboration. We've been thrilled to work with our colleagues at Merck over the last several months in thinking about the clinical trial design, the protocol, getting the IND submitted to the FDA, which we just heard yesterday, has been approved.

The supply is on its way to us, as we speak, and we anticipate that we will be dosing our first patients, combining PYX-201 with Keytruda, starting early in the first quarter. So you'll hear more from us about our overall development plan as we continue to walk through the data. But we're deeply appreciative of our colleagues at Merck, and I think they, like us, have seen the potential of this kind of combinatorial regimen based on the biology that I just described to you and the mechanism.

So just a little bit about our ADC construct. As I mentioned, this construct was developed by the scientists at Pfizer. They spent many, many years optimizing and tweaking each component of the ADC. One of the benefits that a pharma brings when they do this kind of work is the resources to do empirical testing and figure out what exactly is the right linker, what exactly is the right payload for that target. Smaller biotechs typically have to make their best educated guess, and then they hope for the best that the pieces they've put together will work.

Here, and I know this firsthand since I was at Pfizer when this science was being developed, Pfizer, at that time, did empirical testing, so different combinations of linkers, payloads against the target. So the molecule we have here represented the best choice of linker, the best choice of conjugation chemistry, and the best choice of payload, all fit for purpose for our target.

So when we had the opportunity to look at this preclinically, we were extremely impressed with the amount of work that went into developing this construct, and we had very high hopes on how it would behave in humans as a result of that kind of preclinical and empirical testing that Pfizer did.

So some of the features that Pfizer optimized for is stability. The stability of an ADC is super important. You don't want that ADC breaking apart before it gets to the target. If it does, then it wreaks havoc in the body. You have unintended side effects in patients. If the ADC holds the payload too tight, then the tumor isn't killed. So this is a really important balance to get right.

And Pfizer did a beautiful job in identifying a site specific conjugation chemistry approach that married with the Value-Cit linker technology, which is more common in existing ADCs, allows us to have just that right balance of holding on to the payload, to getting it where it needs to go, and then letting it go. So that site-specific conjugation chemistry really plays out as a very important feature of this construct.

Some other things that Pfizer did was they took the payload, which is an MMAE-based payload. It's a microtubule inhibiting payload, and they optimized it for potency and permeability. And again, when we think about our mechanism with this component of passive diffusion into the tumor cell to kill, we need that permeability. We need that potency. And as we've seen in the clinical results, I think they selected the right recipe for that.

So the other thing that this whole construct kind of brings is a predictable drug to antibody ratio of 4. Now, what you want is a really homogeneous drug-antibody ratio. You might have an average of 4, but if the variability, as the construct is pulled together, ranges from 0 to 8, you're going to have problems in the body. If you have a tight range around 4, you're going to have more predictable behavior of this ADC. We have a very tight range in this drug-antibody ratio of 4.

So putting that all together, you see hit in the PK profile, an example of the features of how our ADC behaves versus another approved agent. In this case, we chose Padcev at a similar dose level. Padcev has general conjugation chemistry. It is not site-specific.

And you can see ours on the right with the site-specific; Padcev on the left, without. The deviation between the blue line and the pink line is essentially Padcev having less stability, and that payload being dislodged into the bloodstream sooner and earlier. This leads to a lower half-life. It leads to more unintended side effects for the patient. It also essentially creates some limits on the ability to dose up in higher dose levels. Ours has a beautiful superimposed curve here.

Now, when we look at this same behavior of our agent, as we increase dose levels, we escalated from 0.3 mg/kg, all the way up through 8 mg/kg as we've conducted this clinical trial. We see that exact same behavior. And the significance of this bears out in our hypothesis that there is no hidden target of EDB in normal tissues elsewhere in the body, as I showed you in that preclinical graph earlier.

Now, we're seeing in people, when we measure the concentration here of our agent in the bloodstream, in fact, there is no ADC going elsewhere in the body. So this is called an antigen sink. We don't have an antigen sink issue here. Again, that bodes really well for the drug going where we need it to go.

Before I get into the safety data, Tony, you've been doing work in the tumor microenvironment, the extracellular environment for a while now, and I'm just curious if you had any comments or any perspectives you wanted to share about the biology or even what we're seeing in terms of the construct in people.

Anthony Tolcher^ Well, thank you. Yes. So I've been in the ADC field since the early ‘90s, when BR96-doxorubicin was the first of the antibody-drug conjugates, and I've seen about a hundred or so in development. And one of the things that got me excited, and you know why I'm actually participating and have been involved with Pyxis was the idea that you could target not only the tumor cells, but also the tumor microenvironment.

And why is that? Well, because if you think about it, our conventional approach is kill tumor cells. But if you're able to kill tumor cells, but also kill the normal cells that otherwise nourish and support the tumor, then you can have, I call it, a double hit here. And this is really important, and you'll see some data shortly that will indicate that. Because fundamentally, the issue is that what we think of as tumor, yes, it does have tumor cells, but it's actually rich in so many other cells. And hence, this is a quite a unique strategy. Other people have not tried this as a rule, and I think this is what makes us really different.

Then, if you look at what we used to have all the time is that normal tissue sink, and again, this is something that's very much restricted to the tumor cells on the tumor microenvironment. We're not having to deal with this particular target antigen in so many other normal tissues, and that's where so often we end up with normal tissue toxicity, which limits our therapeutic index. So this is bottom line.

Why am I interested in this? It's a completely different way of using ADCs, targeting the tumors, yes, but targeting the tissue micro environment and the stroma. And there's no other one that I'm aware of, at least, doing this approach.

Lara Sullivan^ Excellent. Thanks, Tony.

Lara Sullivan^ So if we flip to the next slide, we're going to walk now through the clinical program and the data that we have accumulated here. So as I mentioned, we've dosed 80 patients in this trial.

You see the 10 different tumor types represented on the slide that were eligible to participate. We enrolled patients in nine of them, and this is often based on what patient populations are at which site, as well as you go through the trial, and then we begin to identify where we're seeing early signs of activity. And so then we try to enhance our recruitment of patients so that we have enough of a sample size of patients to be able to make real, meaningful insights and conclusions.

The patients that enroll in a Phase 1 clinical trial such as this are extremely sick. They've often been on multiple lines of therapy prior. Our median line of therapy for the patients enrolled in this trial was four past lines of therapy. We had some patients with as many as 10 lines of therapy. These patients are often deemed to have to meet a minimum requirement of at least three months of life expectancy. So they're coming in, typically, having been through a number of different treatments and, clinically, having fought their disease for a fair amount of time.

So it's important to keep that in context as you think about the data, because the data I'm going to show you, which is showing benefit in this patient population, is extraordinarily powerful in the context of patients who are so sick, and still their tumors have been able to respond to PYX-201.

So what we've done here through this dose escalation component of our study, first time in people, this first time any drug has targeted EDB, so we have to go very slow as we're working our way through the different dose levels. We identified an effective dose range, and identified dose range of around 3.6 to 5.4 where we saw tumor responsiveness, meaning the tumors were shrinking, or clinical benefit, and where we saw patients really able to well tolerate this therapy.

We did some exploration at some higher dose levels. We dosed it an 8.0 mg/kg level. This probably exceeded what you call the maximum tolerated dose in humans, and that means that was probably a bit too potent. So we no longer are exploring the 8.0 dose.

We do believe there may be a potential additional dose level somewhere between 5.4 and 6.6. We took a look at a 6.6 dose level. We had some very sick patients at the 6.6 dose level. And being the first time in humans, we decided to proactively manage our enrollment around the 5.4 dose level. So the data you'll see today is primarily focused at the 3.6 through 5.4 dose level.

As we continue to develop this agent, we'll probably do a little bit of work to see if there's another dose between 5.4 and 6.6. And in any case, what we're seeing right now already are some pretty compelling, strong signals of efficacy and activity for patients.

So jumping in now, as I mentioned, you can see here the histogram, or the distribution of patients by tumor type, as I mentioned, a very heavily pretreated population for prior lines. And we've summarized here some of the key treatment-related safety events that you monitor during a trial such as this.

A few key themes jump out when we take a look at this data. This data represents 77 of the 80 patients that we've dosed. Three of them were dosed after the data cutoff. And we see one patient out of 77 who discontinued therapy for treatment-related reasons, just one. That's a 1% discontinuation rate over the entire trial, 3% at the 5.4 mg/kg dose. This is an extremely important statistic to pay attention to because it doesn't do anybody any good if you have a powerful cancer-killing drug that patients can't stay on. There's really no point. So you really want to know that your patients are able to stay on the therapy for a significant amount of time.

And to give you some context for this particular statistic, the Pfizer scientists who created our PYX-201 molecule have used that exact same ADC construct, the linker and the payload in another ADC that they had worked on, targeting HER2. So this acid is no longer being developed by Pfizer. They attributed it for commercial reasons.

But in their Phase 1 trial, with the same exact linker payload that we have, they had a 50% discontinuation rate at 5.0 mg/kg. We have 3% at 5.4 mg/kg. So that speaks to the importance and the power of the specificity of the EDB target and the extracellular targeting mechanism, and how much that translates into real clinical benefit to patients who can stay on this therapy.

We've had no Grade 5 treatment-related AEs. We have had a handful of dose reductions and dose delays. So this means, as patients are being treated, sometimes they have a tolerability challenge, either from their disease, from some other medication they're on, or from our drug. And sometimes it's prudent to reduce the dose to allow the patients to tolerate it better. And what we found in 35% of the patients for whom they had a dose reduction or a break from their dosing, their tumors continued to shrink. So in the absence of being dosed with 201, so that gives you a sense of the durability that we are seeing and the effectiveness of our agent here.

So I'm going to hit the highlights on a couple more safety stats, and then I'm going to ask Tony to comment again because, as I said, he's one of our investigators. He's been treating these patients, and I think his perspective will be useful to you.

When we look at the distribution of Grade 1/Grade 2 treatment-related AEs, you expect to see a fair amount of these across any agent that's in Phase 1. These are things that typically don't cause patients to leave trials. They may be nuisance effects, perhaps a rash, for example, that is annoying, but is not complicating your therapy. The way we think about this is we want to understand which of these effects are driven by the payload, by the chemotherapy that's inside the ADC, and which ones maybe are caused by, frankly, any other factor. And understanding that helps us better understand where the dosing sweet spot is for patients.

And so when you think about payload-related toxicities, things like neuropathy and ocular tox, can often be challenging enough for patients that it causes them to stop therapy. We've had very little in the way of neuropathy and ocular tox. Some of the neuropathy that we have here at the Grade 1/2 level reflects the fact that we allowed patients who already had Grade 1 neuropathy in their history to enroll in this study. Going forward, we'll be excluding those patients, and as a result, we think that any of our neuropathy data that will be accumulated will be more actually reflective of our own agent.

Neutropenia and cutaneous side effects are often very easily manageable, particularly at the Grade 1/Grade 2 level. In the case of the cutaneous here, we actually see that that can often be like a waste basket of a data label. So you often can get a red rash that itches, and it might show up two or three times, and it's really just one rash that itches.

So as we looked into the data here, we actually saw that the vast majority of the cutaneous side effects at Grade 1/Grade 2 were very easily treatable, very easily resolvable, didn't cause patients any significant problems.

When we look at this same lens through Grade 3/Grade 4, these are the things that can cause patients to potentially stop therapy, or to have serious consequences as they're continuing therapy. You see here in the case of neuropathy and ocular tox, zero, in the case of our PYX-201 agent. Many of the approved ADCs that are out there and other ADCs that are in development have particular challenges in those two areas. We see a couple of our cutaneous and our neutropenia side effects here. Again, they've been treatable and manageable.

And in terms of the non-payload-related toxicity, pneumonitis is something that you always watch out for. We had one patient with a Grade 3 pneumonitis. That was the one patient who discontinued therapy. And typically that can occur in the setting of lung patients, so it's an area, again, we like to keep a watch out for.

When we look at this in the context of the approved ADCs that are out there, what we see here is our tolerability profile is either better than or as good as the approved agents. And this is looking very specifically at the 5.4 mg/kg dose. This is the highest clear dose level when we compared that to the labeled dose for the other agents.

So Tony, I know you've been treating patients, and your colleagues have been treating patients in this study. So just welcome any perspectives you have or comments on the patient experience.

Anthony Tolcher^ So principally, what we do is Phase 1, which are safety studies. And so you have to always put this in context to what you've seen with other agents, but also looking at how do we look at drugs? And so if there's a lot of Grade 1 and 2, these are actually mild to moderate toxicities. They're usually not a major problem. And so when you have a very low number of Grade 3 and Grade 4 toxicities, we generally think this is a safe drug, perform well, especially within dose range that you're looking at.

Now, a couple of things to kind of focus on. Earlier on, they had mentioned some of the skin toxicities, but that is truly a grab bag because some of those patients have alopecia. Alopecia is something that we, as chemotherapists, deal with all the time. So they're not major issues. From time to time, you will see some rashes, but none of them were significant. And rashes, by the way, when they're Grade 3, is actually based on geography, whether it's over 30% of the body surface area. So again, it doesn't mean it is significant in terms of a problem for the patient.

Now, if you look at some of the things that we're seeing here, a low level of Grade 3 and 4 neutropenia, so that means that you can deliver the drug reliably, without the need for growth factors.

The other issue is the low level of significant neuropathy. Neuropathy with any of the auristatin has been a real problem. It may be a problem in those circumstances, again, because of the normal tissue sink, where you end up with this going to it, but essentially not any Grade 3 and Grade 4. And one of the real reasons you actually discontinue Padcev is because of the neuropathy.

Now that may speak also to the fact that this is a very stable ADC. Remember, we were showing that there's very little separation. You can see those lines, they don't separate. So there's very little of the MMAE that's actually ending up that can potentially cause the neuropathy. And so this is actually a relatively clean table, all the way up to the highest dose level and dose range that's been explored. Most of what you're seeing there is well within the margin that we would think is a very safe drug.

Lara Sullivan^ Excellent. Thank you. All right. Now, we're going to take a look at the efficacy, so the power of the agent against regressing tumors.

So what we've laid out here on this slide is the waterfall plot for the 65 patients out of the 80 who've received scans. Not all 80 patients make it to a scan. Sometimes a patient gets sick shortly after enrolling and will discontinue therapy. Sometimes they'll delay therapy. Some patients again enrolled after the data cutoff.

So what you see here is a cross-section, the 65 patients for whom we have scans. This represents all nine tumor types that have been dosed, and all dose levels from 0.3 to 8.0. And what we see is exactly what we had hoped to see, which is clear evidence of activity against tumor. So clear evidence of tumor regression.

I'll call your attention to the bar on the far right. This is a confirmed complete response in a head and neck patient. We've also seen two confirmed partial responses in head and neck patients, and we've seen a number of confirmed and partial responses across lung, ovarian, HR-positive, sarcomas, and tumor regression in the setting of triple-negative breast. So significant evidence of tumor activity.

The clear signal in head and neck is what we're going to spend most of our time talking about in a moment. And before I jump into that detail, I want to share with you the swimmers plot, which shows how long our patients have stayed on therapy. We have a dozen or so that are still ongoing right now. But what's really interesting about this chart is the median time on therapy has been 12 weeks. I understand in the real world of clinical trials that Phase 1, you often see patients that are on, much a fraction of that.

Anthony Tolcher^ So the median time for any Phase 1, and this is documented over 20 or 30 years of clinical trials. So in a Phase 1 study of broad spectrum of different malignancies, the median time is actually 42 days, so six weeks, essentially. And so there's something that's fundamentally different whenever we see an extension of that in a Phase 1 study. The reason that the people come off on six weeks is because that's when their first scan is. So most patients have progressed.

So when you start to see this shift to the right, with a longer one, there usually is a thought there's something interesting going on in this, and especially given the mechanism of action. And when you're out there close to 90 days, 12 weeks, you know that's something to at least pay close attention to because this is very interesting indeed.

Lara Sullivan^ So we're going to jump into head and neck specifically, because I think that's a great -- first of all, it's a very clear, strong signal that we've seen. But I think it's also a great example of the power of this agent that we will begin to see replicated in some of the other tumor types as we build more data sets in those tumor types.

We've been very fortunate in being able to recruit these head and neck patients in relatively earlier in our study here, as we cleared the 5.4 doses. We had six patients at this 3.6 through 5.4 mg/kg dose. We've seen a complete response and two partial responses. As I mentioned, these are confirmed by RECIST 1.1 for a 50% objective response rate. So an incredibly powerful monotherapy response in these very sick head and neck patients.

I think, again, this is where I would just remind you the context of who these patients are. These are patients with a three-month life expectancy, patients who have been on an average of four prior lines of therapy. Some have been on as many as 9 or 10. So these patients are very friable and their tumors have been recalcitrant. And we've seen in our treatment here, a real profound effect on tumor regression.

We were fortunate, in addition to these six patients that have been treated at 3.6, 5.4, we actually treated an additional three patients, two at the 6.6 dose level that we have not cleared. As I mentioned earlier, these patients were very sick. And there was one additional patient at 5.4 whose scan came at Day 97, which was well outside the allowable time per protocol. This patient was dosed, had a side effect unrelated to the therapy, related to his underlying disease, couldn't get scanned. We saw disease regression in that patient too.

So what I'm showing you here is a dense chart. I'm going to take a few minutes to walk you through. What you see on the on the far left are the waterfalls, the data for the six patients that are evaluable. These are six patients who are in the 3.6 to 5.4 dose range, three responders by RECIST, an additional patient that showed tumor regression and reduction, noted as a stable disease, and two additional stable disease patients. So we had a 100% disease control rate in this population.

We saw responses in patients who are HPV positive, and we saw responses in patients who are HPV negative. That's really important because I think as many of you know, and as Dr. Hanna will comment on shortly, HPV status is becoming an important determination of head and neck patient population subgroups. Here, we're seeing that we actually have the ability to treat both of those populations.

The patient in the middle at 5.4 by itself, this is the patient I just mentioned. This patient's scan came well outside the allowable protocol time frame. Very sick patient, this patient had to be hospitalized for something not related to our drug, and the scan was delayed three months. Three months after the time of dosing, this patient had still had a 15% tumor reduction.

The two patients on the right at 6.6 who are not allowed for statistical reasons to be counted, but I'm showing you the data here, were both very sick. One passed away at Week 5 after starting the trial, had an unscheduled scan just prior to that which showed tumor reduction of 8%. This patient had been on several lines of therapy before, and I just can't help but imagine, what if we had gotten to that patient a year or two earlier, earlier in their lines of therapy, when we see this kind of response.

The second 6.6 patient had a tumor regression of 25%. This patient went to hospice at Week 10. Again, these patients, their tumors are shrinking, but they're at the end stages of their disease. So the key for us is to get this therapy into patients earlier in their treatment algorithms, earlier in their lines of therapy, so that as the tumor regresses, we can alter the trajectory of their disease.

Now, on the right, we have spotlighted the swimmers plot that shows the duration for these six patients that are statistically evaluable. And of these six patients, four of them are still ongoing on therapy. So the median time that these patients, the head and neck patients, specifically, have stayed on therapy is 16 weeks. And again, Dr. Tolcher just told us the average is 6.

So of the two patients who discontinued therapy, one is the second from the bottom, in this light greenish color, who was a very sick patient, had a stable disease response, and that's the patient at the very far left. And this patient passed away shortly after stopping treatment. So the treatment stopped because the disease was continuing to progress. The tumor was getting some disease control, but the overall clinical picture was continuing to progress.

The second patient who's no longer on therapy is our complete response patient. The reason for this has to do with some complicated social history for this patient. This patient is in the process of relocating from the U.S. to Europe. We've been working really hard with the patient and with the site investigator to help find a solution that this patient can continue therapy. Right now, a solution hasn't been able to be defined for this patient. But this patient did come back to the site investigator after stopping therapy. About six to nine weeks later, you see the far yellow triangle there, and still the tumor was regressed 100% complete response. So this speaks to the power of the effect of what we're seeing with PYX-201.

I want to emphasize for you, without going into too much detail, these are the vignettes for the three patients who've responded. And for those who know the head and neck market well, you can see the lines of therapy here that these patients have not responded to in the past. These are pretty standard treatment regimens.

In the case of the patient in the middle, this patient didn't demonstrate any tumor regression in the past. And yet, on our therapy, this patient's tumor reduced 50%. In the patient on the right, the best outcome this patient had previously was stable disease, and now this patient has regressed 46% on our therapy. So real signs here of a powerful agent.

And before I jump into how we're thinking of developing this in head and neck, maybe. Dr. Hanna, you can comment from your head and neck expertise, your thoughts on what we're seeing in this patient population.

Glenn Hanna^ Yes, of course. Can you go back to the --

Lara Sullivan^ Yes.

47:09 Glenn Hanna^ -- prior slide? So a couple of things, head and neck cancer patients are obviously a little bit more complicated. They tend to be sicker than, for example, breast cancer patients, comparatively in this scenario. So a couple of things stand out.

And again, I run the entire early drug development program at Dana-Farber. We have about 70 molecules in our early drug portfolio, eight of which or 30% at any given time, are ADC. So I'm coming at you with a lens of not only being someone who's treated head and neck cancer for 10 years exclusively, but also runs one of the larger head and neck oncology or, excuse me, early drug programs in academia in the U.S.

So I think this is pretty compelling. While the denominator is small, a couple things stand out that were highlighted. One is you're actually getting tumor regression here in a fairly large number of patients that have had a lot of prior therapy and have exhausted pretty much everything we can offer them in the head and neck space.

I think the other thing that stands out here is you're getting some durability. As you see in the swimmer plot on the right, it's not that patients necessarily get dose, get a response, come off, as we heard about from Lara, in terms of toxicity. They're actually maintaining the ability to stay on drug for a period of time. And that's even more compelling in a delicate head and neck cancer population.

The next thing you start to ask yourself on the next slide is, what is the composition of these folks? Because as Lara mentioned, HPV positive disease is biologically completely distinct, and we don't think of that as the same tumor type in head and neck cancer. The drivers of a carcinogen-related HPV negative cancer are not the same. But you're already seeing signal here across the clinical vignettes of patients with both phenotypes, right?

So regardless of PD-L1 status, which is important in the first line setting for advanced disease, regardless of viral association or carcinogen relationship, and then across a wide range of therapies where they previously had not responded, you're seeing regression of tumor in upwards of 35%, 50% and even a potential durable responder who was able to holiday drug and maintain that.

This is impressive. We don't often see this in many of the ADCs that we're exploring now, and I would argue that this definitely warrants additional attention, and is something I would be pretty excited about. If you want sort of stark comparison, there are three

examples of reported data for head and neck cancer with ADC-specific cohorts that I'll reference for you.

The first one came from sacituzumab govitecan. You can forget it because it was underwhelming, presented at ESMO a number of years ago. Now, we've moved on from that. It doesn't look like that's moving forward, especially not with the train that's coming, which is sacituzumab TMT from Merck.

The next drug that was presented data, we got a little bit excited about, was in enfortumab vedotin. This is the EV-202 trial, which is not yet done. This was cohort 9. Cohort 9 was head and neck monotherapy in a similar advanced population, regardless of HPV causality. And that response rate actually, even in about 20 to 30 patients, as presented by Paul Swiecicki at Michigan, a colleague, didn't really break 20%, 30%.

In addition, we had the same issues with that drug, Padcev, in terms of neuropathy, and everybody in head and neck gets taxanes and platinum radiosensitizers. So grandma can't even button her shirt already, and then you're giving a drug that's already going to cause her to need a walker, have physical therapy, et cetera.

And then the third one, which we were excited about, Lova Sun from Penn presented it at ASCO this year, which was tisotumab vedotin. And unfortunately, that's not moving forward for reasons that go beyond my pay grade. But nonetheless, that did look compelling, had the same on-profile, on-target concerns, but did have a response rate, but none of them were in this range.

Now, granted, the sample size is what it is, but I'm convinced, based on what we're seeing and the distinction of mechanism, the safety signal that's been outlined, and how sick these people are, and as Lara is sort of emphasizing, the farther we get along, the more you see that something is active. There's this sort of general equipoise, where the oncologist puts patients on sooner. This doesn't happen in our world, but it starts happening when the Phase 2 doctor gets involved and says, gosh, that drug had some activity, so I'm going to refer that patient sooner. That is a phenomenon that's well described. So these patients are actually going to get a better shot and get on earlier. So all of that context runs through my head, you have something here.

Lara Sullivan^ Thank you. So now the question is, what are we going to do about it, right? We've seen a very strong, compelling signal. I think that the head and neck population has been relatively underserved compared to some of the other tumor types, particularly over the last decade. There hadn't been as much innovation happening there, as say, we've been seeing in the breast cancer space, for example. The current standard of care is still primarily around PD-1s and chemo, and EGFRs and chemo.

We have now recently seen innovation in the space. It's been really thrilling to see that Merus and Bicara have come in with some new innovations around the EGFR target. So there's some real opportunities for patients to have improved treatment. And even in the backdrop of the Merus and Bicara activity in this space, we believe there's a clear and

compelling mandate for the PYX-201 therapy, and a clear and compelling place that we'll be able to find to help patients.

So I just want to walk you through some comparisons to the data of these two new entrants relative to ours. What we looked at here is a comparison of Merus and Bicara's Phase 1 data to our data.

As has been discussed, we are treating, in this study, a very heavily pretreated population, with four prior lines of therapy. We had a 50% response rate out of our six patients. When we look at Bicara, they, too, looked at six patients in a Phase 1 study and had a zero percent objective response rate. They've gone on to show a very nice objective response rate in combination with pembro. But as a monotherapy, it's been zero.

In the case of Merus, they had 43 patients in their Phase 1. But their study, those patients had only two prior lines of therapy. We have had four. They had a 37% response rate in two prior lines of therapy. Ours is 50% in four prior lines of therapy. They had one CR out of 43 patients. We've had one CR out of six. So this gives you a real picture that we're coming into this head and neck marketplace with a very strong position of monotherapy activity.

To emphasize that even more, when you actually look at what Bicara and Merus are doing in combo with pembro, these are the enhanced objective response rates that I mentioned. They're getting to a 54% to 67% objective response rate. That says frontline therapy, first line. We are at 50% fifth line. So as I mentioned in the beginning of the talk today, we are thrilled about our new clinical trial collaboration with Merck, because we're going to be testing Keytruda plus PYX-201 in this population. And we're seeing here in this data, how powerful those pembro combinations are with agents who are coming in at a lower level of monotherapy efficacy than what we are.

So we see a three-prong development strategy here. First, on the far right, this is the combination study with Merck that I mentioned. As I said, we've got the FDA approval clearance yesterday of the IND. The supply is in route, and we'll be starting to dose these patients in the first quarter, with data expected by the second half of this year. So this is the PYX-201 plus Keytruda combo.

Because of our strong monotherapy activity, we're going to be looking at two monotherapy opportunities in head and neck. One is in second/third line for the PD-1 and platinum experienced patients. So these are the patients that are progressing through today's current standard of care.

We're going to be looking at a third study here, this second one in monotherapy, which is the PD-1 and the EGFR experienced patients. Again, these are today's patients who are on Erbitux, who are progressing through, and tomorrow's patients who may not respond to Merus and Bicara. So that population is going to be growing as the innovation continues in this space. So three shots on goal, all three of these studies starting in the

first quarter. Data catalysts coming through the second half of next year into the first half of ’26.

And Dr. Hanna, I know you see a lot of the new entrants in the space. Maybe you can just offer us some perspectives on the development path that we're taking here, and any of the reasons to believe that this could work in those populations that have been identified.

Glenn Hanna^ Yes. I think the first one on the top right is the combination therapy. I mean, as many of you know, who follow head and neck KEYNOTE-048 defined as of now, in 2019, the standard of care, which for PD-L1 expressing patients is monotherapy with pembro, or your choice of chemoimmunotherapy, which is platinum and 5-FU or platinum-taxane. And then regardless of PD-L1 status, you have the chemo-IO option.

So one issue around that is many of us in the field who develop head and neck cancer drugs have been inching in and sort of itching, excuse me, for this idea of an ADC-IO combo to be a modern, contemporary version of chemotherapy, mitigate the need for a platinum-doublet. Between you and I, 5-FU doesn't really add much, other than having to put in a port and mucositis, and having to come back for growth factor and a disconnect.

So, yes, you can give a taxane, but it would be very nice to have a contemporary active monotherapy ADC like PYX-201 to combine with Keytruda. Plus, if we're seeing response rates like this, one shy point for many companies has been, well, chemotherapy actually gives you about a 35% response rate in that setting, the historical chemos. You're already seeing upwards of 30%, 50% activity in monotherapy.

So with checkpoint inhibition and combination addressing the IO component, you could see response rates in the 60%, 70%, prove that you're just as good, if not better, and/or show the FDA that or the agency that your tolerability is better, and they eat that up, right? Patients want to be on therapies that are either comparable or better, but have good tolerability.

And actually, one thing Lara didn't mention is the schedule of the drug. The schedule is every three weeks. Bicara’s molecule is weekly, or at best, every two weeks. And Merus’ is every two. That actually matters quite a bit in the world we live in. People often have an issue getting in to get drugs, even when they're efficacious, because of logistical and social reasons.

But going to the second and the third pieces of that puzzle are probably the most important. You have monotherapy data, but you have to sit here, as we have, and think about what's going to happen when and if Merus’ drug, petosemtamab and ficerafusp alfa do or don't get approved. So let's go there for a second.

Let's go to three first. For a patient who's had a first line chemo-IO option or IO, they're going to have the ability -- let's say Merus crosses the finish line in both their first line or second line. They might get peto in the first line combo, or as a second line single agent. Fine. But they're going to be EGFR experienced. They're going to be PD-1 experienced,

and they're not going to want a traditional chemo. That is a smart market to think about right now.

Those are the patients that I'm dealing with in clinic, in the contemporary academic setting. They've already gotten their IO in the community. They come to me. They've done the Bicara trial. They're doing the peto second line trial. And now, they need something right now. And you're stuck with crappy old things like methotrexate, which doesn't work and is basically water; capecitabine or 5-FU. You're reaching for weekly carbo and 5-FU or a study like this.

So that is a very smart space to be thinking about, this so-called post-PD-1, post novel EGFR. And you know what? If both of them fail, hopefully they don't, for patients, you still have cetuximab, and it still works, and it works better after PD-1. But it doesn't matter. You're developing in the post-PD-1, post-EGFR experienced setting. It's a very, very smart space and a very low bar, sadly, for patients to be in and be thinking about already.

And then, of course, in the second line, in the top left, there'll still be the traditional patient who gets chemo-IO. Whether or not these two head-to-head novel EGFR modulators make it through the finish line, it doesn't matter. You still have activity as a novel payload directed therapeutic after chemo-IO. So this is actually quite thoughtful, sharp and contemporary in anticipating what could happen over the next two to three years, while you're getting data in all of these spaces. So I think that's a smart bet.

Lara Sullivan^ Thank you for those perspectives. So I think we're going to just move from head and neck. Now, I want to touch on the signals we've seen in the other five tumor types, and then we'll summarize our development path forward, and we'll make time for questions. I'm sure you have questions for us and for our guests.

So as I mentioned at the beginning, when we looked at the entire data set, we saw signals in sarcoma, non-small cell lung, ovarian, HR-positive breast, and triple-negative breast. And so here is a spotlight of the responses for those five tumor types in the 3.6 mg/kg through 5.4 mg/kg dosing range. And you see the mixture of the confirmed responses and the unconfirmed responses.

Some of these patients recruited into the trial a bit later in the calendar year, so we're still waiting on some data. For some patients in breast, for example, we have some triple-negative breast, some HR-positive breast data that's still outstanding. So these signals are early.

My key message here is they're very promising. And when we look at what's going on in our head and neck patient population, we believe that there can be some additional stories that look like that out of this data. But this data is a little bit earlier. We want to do a little more exploration to characterize it. We want to better understand the competitive landscape here, and better understand potential patient subpopulations before we commit to a full scale development plan in any of these five particular tumor types.

What we do see here in these tumor types, just like we saw in head and neck in the overall data set, is the same theme around durability. Here, it's 85 days, 12 weeks, I think is what that translates to. I can't read without my glasses.

So we have a few patient vignettes here in these other tumor types that just give you a sense of the quality of the signal. You'll see this with the materials that come out. But just to hit a few high points, in the case of the ovarian patient, with the confirmed response, that response came deeply and quickly. This patient showed minus 72% tumor regression.

The lung patient in the middle is a patient that was on seven prior lines of therapy and has driver mutations. This patient had a minus 29% tumor reduction in their first scan, and then minus 42, so technically not a confirmed response. But for all practical purposes in the real world, this patient had essentially what clinically would appear to be a confirmed response.

And then this triple-negative breast patient on the right, we don't have a scan for yet, because this patient is recently enrolled. At Week 4, so scans come at Week 6, at Week 4, this patient went in for a clinical visit, and you can see they had some cutaneous lesions on the left photo. And in the right, those lesions had completely gone. This is a patient who progressed through Trodelvy and IO. And so we're very eager to see how this patient scan shapes up in terms of the tumor regression for the primary lesion.

So overall, in terms of the development path we're taking forward, we see a clear focus on head and neck, with the three programs that we discussed earlier, all launching in the first quarter, all with data expected second half of next year into first half of ’26.

With the collaboration, the clinical trial collaboration we have with Merck to test Keytruda in combination, we actually have the ability to test other tumor types besides just head and neck in combination with Keytruda. And based on biology, the clinical treatment practices, we're taking a look at HR positive, TNBC and sarcoma in combination with Keytruda, and we have room to do other tumor types there as appropriate. So that Keytruda combination study will be kicking off also in the first quarter.

As I mentioned, the signals in these other five tumor types, the two breast, the ovarian, the lung and the sarcoma is a bit earlier than the head and neck signal. So we're going to be doing some more exploratory work, both looking preclinically at what other combination agents could make sense, particularly in ovarian and lung, but also testing a few additional patients in monotherapy, so that we can make better informed decisions about a development plan in those five tumor types.

So in summary, I think what you see here with PYX-201 is a very well-behaved ADC, with a clear safety profile that's beneficial to patients, allowing them to stay on therapy for a significant amount of time, longer than what you typically see in other Phase 1

trials. Clear efficacy benefit in head and neck, to the point that we feel going into that marketplace, we're coming in with a clear monotherapy advantage from the way we've seen the patients respond. And then exciting early signals in these other five tumor types that we're going to be doing some work over the next couple months to better define where these can sit in the treatment landscape.

And so, with that, I think we'll actually open it up to a little more commentary here from Dr. Tolcher and Dr. Hanna, and then we'll open it up to questions from the audience. So I appreciate you're hanging with us through a lot of information.

And maybe we can just spend a few minutes before we open it up to the general questions, on any additional perspectives, maybe, Dr. Tolcher, I'll start with you, that you have when you think about the clinical benefit accruing to patients. And I have a couple of your slides here, if you wanted me to put those up. Yes.

Anthony Tolcher^ So a couple of things, when it comes to ADCs, this is an unscreened population. We haven't selected for those that are high expressors. So if you go back and look at that original slide that was shown, you see the columns of different malignancies and the expression range that occurs for EDB. Well, think about it, maybe responses only happen and people have a fair amount of that.

So when you see a broad spectrum of responses in a Phase 1 study in an unselected population, that's very interesting because it might mean that by selecting patients, those who are high expressors or medium expressors, you might actually be able to push many of these other indications into a responsive population.

There's one thing also that fits what we are thinking of as the mechanism of action, and I'll get the next slide on, if we can. This was a patient of ours who had ovarian cancer. So I'm going to bring your attention to the quite obvious, right middle lobe tumor there, the metastases.

Lara Sullivan^ Sorry.

Anthony Tolcher^ So why is that important? So if you look at -- and this was actually unscheduled. They only had one dose. You have substantial tumor necrosis and actually cavitation. What does cavitation mean? Well, cavitation is important because sometimes that tells us that we're actually having an effect on the tumor microenvironment.

One picture that's not probably in there or maybe --

Lara Sullivan^ We have it.

Anthony Tolcher^ Yes. Good. Oh, you did. Yes.

Lara Sullivan^ Yes.

Anthony Tolcher^ So what you can see, it's actually that little pink circle to the right, if it was moved over because it actually bisects, unfortunately. You've got an empty hole area within the lung. Why is that important? Well, it again tells you that you've not only killed the tumor, but you've actually killed the tissue that was surrounding it. Some of it's going to be normal. So there's actually a relatively small hole.

Again, these are rather substantial metastases, both of which that disappeared, and you can see the speed with which this happens. So again, mechanism of action, targeting the tumor, targeting the tumor microenvironment. What do you expect when you're targeting tumor microenvironment? You expect to see cavitation and necrosis. You tend to see normal tissues where a hollow out that you actually see here. So again, this was a very interesting case of patient that responded very quickly, and it really speaks to the proof of concept, you might say, as to the mechanism of action.

Lara Sullivan^ Excellent.

Glenn Hanna^ I think I would just add, if you look at the tumor types that actually were included in the original trial, many of them are plagued by having fibrotic microenvironment. So PDAC is one of the classic examples. You can have a great drug, but if it can't penetrate the fibrous wall of the tumor, it's useless.

So one of the enormous sort of potentials of this agent, which seems to be demonstrated right, is look at the tumor types, you're talking about fibrotic, serous tumors; soft tissue sarcomas, which are inherently made of soft tissue and connective tissue; head and neck tumors, I guarantee all of those patients are irradiated. These are fibrous scarring, anoxic tumor environments that don't often respond well to traditional agents.

So the mechanism that's proposed actually lends to this idea of, can you somehow break down or target, or adhere to that fibronectin skeleton and then get a drug in? That also has a lot of potential for combinatorial strategy, right? We've already seen the DAD study from our institution that combined ADCs. Think about combining something like this with one of the more traditional ADC approaches, as Lara mentioned, or even an EGFR modulator.

One of the things that someone may bring up is like what about, biologically, what's the rationale for sequencing this after something like immunotherapy, or chemo, or EGFR? There's actually a really strong rationale. You've already sort of primed the immune system as best you can with T cell biology. You've already cytotoxically blown up as much as you can with chemo agents that damage DNA, and then you're signaling down regulating EGFR. But what happens is actually the tumor ends up changing its phenotype, this idea of a mesenchymal or epithelial mesenchymal transition, where the cells become more sort of a stromal effect, the neighboring cells start to become fibrotic.

Wouldn't it make a lot of sense to then treat a patient as exemplified by that third cohort where you've given PD-1, you've targeted EGFR, and now, you have a novel EDB-

binding fibronectin-adhering, stromal targeting ADC. That's actually quite elegant if you want to speak from a biology standpoint.

In addition, it's distinct mechanism. So, I think all of those things and then these clinical vignettes sort of give you equipoise and sort of give you a sense of what's distinguishing this molecule from the space.

Lara Sullivan^ So, I think that's a really very helpful biological context. And I guess one of the questions we get a lot that I'd be curious maybe for both of your perspectives is, and it builds, I think, on what you were just saying, Dr. Hanna, why do we think this signal is coming through so much stronger in head and neck right now, and what could we expect then from any of these other tumor types as we think about the development path forward?

Glenn Hanna^ Yes, I mean I think the things that I was sort of preempting, one is I'm thinking about when hearing about the mechanism, I'm reminding myself of sort of what tumors may lend to this sort of destruction or adherence to this fibrous milieu that they live in? As we heard, these are not just tumor cells. It's a vast network of cells that make up a cancer or a tumor.

And so, I think something like very anoxic or oxygen-depleted, radiated, scarred type tumors may lend to these kinds of therapies. And perhaps that's why head and neck tumors respond well would be one hypothesis.

I think the other is potentially, the patients that were treated in that early group of six to nine in the head and neck cohort, with the monotherapy, they were experienced to some of these other agents in the platinum setting, the immunotherapy prime, many several of them had had EGFR at some point, keeping in mind they had four median lines of therapy, which is already quite a bit. We don't even always get that many shots on goal in head and neck before patients expire.

And so, I wonder if you're sort of setting yourself up for an enrichment to do well with that group because you've already sort of upregulated a mechanism that addresses this fibrous environment.

Again, that's all sort of something I'd want to explore with paired biopsies and sort of in a -- in a future study. But you're certainly getting that signal now even with a small denominator. And the story is sort of fitting together.

It's really nice as a drug developer when you can sort of understand a hypothesis for a drug, see safety, understand the mechanism radiographically, clinically, and then sort of start to think of where you can place something.

I think you all realized a lot of placement in oncology that happens in large pharma is just because they have two assets and they want to put them together. But it'd be nice on our end if something actually has biological rationale, which is why we're sitting up here.

Lara Sullivan^ Yes. Did -- Dr. Tolcher, anything to add to that or …

Anthony Tolcher^ No, I just -- I'll use the same phrase, shots on goal, because even though I'm not a head and neck doctor, you will see a broad spectrum of different malignancies. And again, since they're not yet selected and we've not really drilled down on it, there may be other indications where one can get a single agent benefit or alternatively in combination with many of the therapies, whether it'd be chemotherapy, whether it'd be immune therapy, and so on and so forth.

And so, this is something that I don't usually jump on a plane and travel from San Antonio all the way up to New York City often, but it's, I think, I believe strongly that we're seeing something, it's something important here. And so many drugs, so many ADCs fail. They fail because they just don't have a lot of responsiveness.

I wrote in a review a few years back that we had to raise our bar higher, and the bar had to be seeing complete responses. If we're not seeing complete responses then I think we've not really got a powerful agent and a powerful ADC. And I think these images here we're showing you are pretty compelling, pretty compelling.

Glenn Hanna^ The other thing is monotherapy, right? So, more and more, I'm seeing trials come across my desk that are -- I make the joke that by dose cohort 3, they're already adding a second agent and the elephant in the room is, do you really believe your drug is going to do anything if in cohort dose 3, you're adding something that's already on market?

This is demonstrated single agent activity across a large number of patients and a stepwise approach into adding in a second agent. So that speaks to the enthusiasm one would have to -- and you just have to look at the program of trials that we're enrolling right now that are already sort of lending to that.

I think the other thing I just wanted to point out was the biomarker question. Many people on my side get sort of pushy about this idea of, "Well, do you have biomarker selection?" That's so, so important.

And I would argue, the point that was made that it's nice to see something that's acting across a wide range of malignancies perhaps because of its distinct mechanism, but think of the opportunity there.

If later on we're able to actually identify high expressing patients with an H-score or some sort of cutoff, these response rates could achieve sort of 70%, 80% in selected populations. So that's even more enticing and something that sort of warrants further exploration on the tissue that the patients in the early trial will provide.

Lara Sullivan^ Excellent. Thank you for those very insightful comments. We're clearly enthusiastic about the potential here and a lot of great things to be done clinically with

patients in the development path forward but also to the points that were made around the biology and the scholarship around patient selection opportunities.

Jan's team's been hard at work collecting -- the clinical team's been collecting the biopsies and Jan's team's been assessing them. And we're looking forward to -- as we continue to increase the number of patients that were treated and we have a greater dataset to draw upon, to being able to inform some of these hypotheses.

So, maybe now would be a great time to open up for questions from folks either in the room, on the video, or if you're sending something through chat, if you're shy. Maybe we -- RK, maybe we'll start with you and maybe we'll sort of work our way through the room.

QUESTIONS AND ANSWERS

Swayampakula Ramakanth^ Good evening. This is RK from H.C. Wainwright.

Lara Sullivan^ And feel free to ask questions for any of us, CSO and CFO as well.

Swayampakula Ramakanth^ Sure, sure, Lara. Certainly, very interesting data in head and neck and obviously, promising considering the late-stage patient status here.

A couple questions. One, the non-responders, what was the treatment status of -- or treatment experience status of these patients prior to coming into this -- into this trial? And also, are there additional patients within that dose range yet to be evaluated, especially among the head and neck cancer patients?

Lara Sullivan^ Yes. So the head and neck cancer patients have all been fully evaluated. We still have several ongoing so we're continuing to monitor those.

In terms of the patients who did not achieve a partial response or a complete response in head and neck who have a stable disease picture, I'm just looking at their prior treatments on my notes here. And you see a similar pattern in terms of three, four, five prior lines of therapy.

One of these patients was progressive disease and three out of the five prior lines of therapy in stable disease. So, some of these, quote "non-responders," they're actually stable disease in our -- in our -- in our study, don't even have a history of ever responding.

So, I think that's -- when we see that, I think that for us, that's very suggestive of the points that were made that as we can move maybe earlier in lines of therapy, given the power of the responses we have seen for some of those patients, some of these patients who haven't responded to anything may finally have a shot here in the monotherapy setting and, of course, with the power of Merck's Keytruda in that study as well.

And so, I don't have the data right in front of me for every single patient right now, but thematically I can tell you that's a pretty consistent finding. In other words, the patients who stayed at stable disease or had progressive disease, we haven't been able to discern anything distinctly different about them yet relative to those who have had a partial response, confirmed or unconfirmed, and I think that -- some of that ties into the biology and the patient selection work that was referenced earlier and that Jan's team is going to be tackling.

Glenn Hanna^ So, I just wanted to comment that I think some of the things that will emerge, you saw the early HPV signal in both -- in both cases, which is nice to see. PD-L1 status may or may not end up being relevant, at least not in the monotherapy question, but we've learned that local regional versus distant disease, very different biology. And actually, the data from Bicara is quite striking for the local regional population. Again, very fibrotic, dense, persistent tumors versus low volume, distinct, clonal, distant mets.

So, one thing that I will sort of encourage Lara and the team to do when they get a larger amalgam of head and neck data is to understand if there is a local regional versus and/or distant signal. It's too early right now based on what I have seen.

Swayampakula Ramakanth^ Interesting. A couple more questions. One, on the next set of trials that you are planning to do, you had one trial set up for first line/second line. How easy is it to get patients into such early lines of therapy, especially when there are drugs out there?

Lara Sullivan^ I think -- I think there's a few answers to this question. One is the data, right, speaking for itself, that attracts the investigators and the trust of the patients to participate in it. One thing that I think is important for everyone to be aware for this trial, it's been underway about 18, 20 months, we've had waiting lists nearly throughout the entirety of this trial.

So, in the early days, I would say those waiting lists were driven by curiosity around the biology and the mechanism. Over the summer, when we dosed 30 patients between Memorial Day and Labor Day, and there were patients who weren't able to be served because the slots were getting taken, that was driven by the investigators' direct experience with this agent.

So, while we know there's a lot of oncology trials out there and a lot of options, and Dr. Hanna and Dr. Tolcher are probably dealing with anywhere from 70 to 100 trials every year at their centers, this data is speaking to the investigator community, number one.

Then number two, the other factor that is also extremely important in being able to get trials underway is the execution prowess of the team. We have a very experienced Head of Clinical Operations. She's set up a really very productive and powerful clinical trial site infrastructure prior to this study, 18 sites global trial. That's more sites than you typically see in a Phase 1.

Why did we do that? We did that because we were presuming success, so we could then get these sets of trials launched quickly. So, the expertise of the team is an equal determinant ultimately into your ability to execute this kind of clinical trial plan.

Swayampakula Ramakanth^ Last question, Dr. Tolcher was almost answering my question when he started talking about there are potentially other tumors that he would like to look at. So, can you tell us a little bit more on that thought, especially with the data that you have right now?

Anthony Tolcher^ Yes, without going back, but look at the tumors where you see an expression that's been previously documented. And just because you see some of the tumors there, there are probably other tumors where it's not been documented because nobody's bothered to look. So, I would start there, and that's five large indications quite frankly.

Now, you're not going to go into some tumors where MMAE is not going to work like colorectal and things like that, but many of the ones that you saw in the triple-negative breast cancer and non-small cell lung cancer, for example, ovarian cancer, these are tumors where the payload is going to have some anti-tumor effect based on at least past experience.

My feeling though is, at this point, it's still early. One would like to see that also get enough patients with each of those malignancies, but also understand are the ones that are responding somehow high expressors of the target. That's a logical next step at least in my mind to see where this is going to go. But, again everything revolves around money, so there's only so much that one can do with the resources that you have.

Pam Connealy^ That's right.

Anthony Tolcher^ That's the truth though, yes?

Pam Connealy^ Yes.

Anthony Tolcher^ But I think there's a clear signal in head and neck, so that makes sense. I -- I'm not in charge of spending the money, but I think there's many other indications here that I would be very interested in pursuing.

Lara Sullivan^ Great.

Pam Connealy^Great.

Lara Sullivan^ Jeff.

Pam Connealy^ I think there was some more. Yes.

Lara Sullivan^ Yes, Jeff is next.

Jeffrey La Rosa^ Hi, Jeff La Rosa, Leerink. Can you reflect broadly on the tumor types that you did or didn't show activity in the outside of head and neck, allude to antigen expression as well. I know we don't talk about that data, but HR-positive breast was one that you showed that didn't have much fibronectin but showing pretty strong activity.

And then PDAC where there's a lot of stromal maybe didn't show as robust activity. So, just if you could just speak to your reflections on holistically with the tumor types and the antigen expression and the activity you saw.

Lara Sullivan^ Sure. I'll comment and then maybe Jan can comment as well. So, going into this trial based on our understanding, the biology and to your point that pancreatic is a highly stromal tumor type.

Given this mechanism, we had high hopes that this might be a place that we could really make some breakthroughs in pancreatic. And I think as everybody in this room knows, pancreatic has proven to be very, very difficult to crack.

We saw -- we dosed, I think it was 17 patients maybe across all the dose levels if I remember correctly. We saw a real fair amount of stable disease. We actually had one unconfirmed P.R. in pancreatic as well and a fair amount of stable disease and, of course, some tumor progression.

Interestingly, I think the stable disease and the durability that these patients with stable disease in pancreatic have been able to maintain on therapy has been quite interesting to the investigator community.

How to sort of put that in context of our development plan going forward is a little more challenging for us as drug developers when we don't have that clear RECIST response rate shining through.

That being said, I would throw kind of the thinking around understanding that in the context of some of the further work that we need to -- we need to do to better understand the biology overall.

Maybe, Jan, you can comment a bit about the EDB expression profile, the various tumor types and maybe what we're seeing play out and some of the next steps you have in identifying where to go from here.

Jan Pinkas^ Surem, yes. Thanks, Lara. So, Jeff, I would argue that when you look at target expression, head and neck is probably one of the highest indications from a target expression perspective. Thyroid as well but we didn't enroll very many thyroid patients.

But from some of the top tumor types that that we have where we've seen activity, they really fit into that higher end of that bucket. We just had some data released at the Connective Tissue Oncology Society meeting last week that -- and a couple of the

sarcoma subtypes have very high, like chordoma, have very high EDB expression as well. So, I think to-date, that data, I think, is starting to line up at least at a high-level view.

I think the other part, of course, from what we've seen so far, I think the numbers are still small to really make and see any simple direct one-to-one correlation between high, the highest target expression and response.

And as Lara alluded earlier, we're implementing some digital pathology-guided staining and scoring. And this gets to some of the comments that Glenn was making, that it's not just a certain target expression level, right?

We're in that for many of these indications, a median H-score of about 150. There are dozens of mathematical ways to get to a similar H-score number. And this likely is going to have a big role on what and where and what's the pattern of EDB, where it's expressed within the tumor, how much, and other interdependencies that we're really just starting to explore now once we're getting into more homogeneous patient cohorts. Lara?

Lara Sullivan^ This is just one of the appendix slides you'll see when the materials come out, but we've cut it by tumor type, so you can look at it at your leisure. But you can see the pancreatic dynamic that we mentioned here.

The H.R.-positive is early, so we're pleased with the tumor regression we're seeing. And again, we have a few more patients that are -- were dosed in this trial that we're awaiting data for. And when we see data like that, taking a look at another 10 patients, maybe from a monotherapy perspective, could be really informative around whether the signal holds or not. So …

Glenn Hanna^ I just want to add, Lara.

Lara Sullivan^ Yes, please.

Glenn Hanna^ Keep in mind too, when we do these assay screens, a lot of these are commercial platforms. You don't know which patients had primary tumors tested versus metastases, and we all think cancer's so simple, right?

Obviously, it's extremely heterogeneous, and we're doing our best to target. But across different tumors, there's a lot of heterogeneity. How many of these patients were radiated at the sites that were tested would be something I would ask. So all of that's something the team will think about.

But I think that actually flips the narrative back to this idea that you're actually seeing a little bit of activity across a large number of tumors. That's more encouraging, because then you can start to treat a large number and understand, do the biomarker selection later. It's actually harder to do it the other way, right, is to have a really slam-dunk biomarker and find those sort of special patients is very challenging in the -- in the

modern now non-genomic era. So, I think that's actually -- I think that's a strength of the data that was just shown.

Lara Sullivan^ Yes.

Anthony Tolcher^ One other point I'll just comment. Everybody has gone -- I wrote an article about the fact -- the tyranny of the antimicrotubule when we were left with maytansine and MMAE and hematological malignancies. And now, we've got the tyranny of the TOPO1 payload.

So, everyone coming up with ADCs with the same payload, the lessons of chemotherapy resistance are that you're -- it's not going to work as well, that's why we don't give the same drug over and over again.

This is unique because in many of the indications that we're looking at, we're not dealing with a competitor, a side-by-side competitor ADC that's got MMAE. In fact, actually, you're looking at a competitor that might be a TOPO1, so they're not mutually exclusive, so you could actually come in and it would not be cross-resistant.

And that's very appealing if you think about it, trying to say, "How can we find our way to having an indication that's going to lead to approval?" I actually feel more sorry for many of the targets that are being selected now and going into the study where it's antibody A plus a TOPO1 inhibitor because if the ones that are farther along lead to resistance, coming in with another similar payload doesn't make any sense quite honestly.

Glenn Hanna^ The other thing I would say from a thinking ahead clinically in terms of development and sort of where to place your bet, this is also a prime molecule where you would consider a potential for radiosensitization because if it can produce a destruction of fibrotic environments and cause hypoxia and cavitary lesions, what could small-dose radiation, pulse hypofractionated radiation do?

Well, we saw a very promising drug, xevinapant sadly basically collapsed within a 24-hour period based on the Phase 3 readout of the TrilynX study. We're in desperate need of contemporary modern radiosensitizers. So, again, that's not the discussion for today, but the potential of this molecule to be explored in that setting is pretty significant, particularly in head and neck and other tumors.

Lara Sullivan^ Leo, did you have a question?

Leonid Timashev^ Yes, thanks, Lara. I just wanted -- I know we're focusing on the efficacy side. I wanted to maybe ask a few questions. Thanks. A few questions on the safety side. So, there was one Grade 5 event in the trial. So, I guess I want to know what your level of confidence is that that wasn't treatment-related and then maybe any kind of color you can provide around what happened to that patient, whether that was the same as the head and neck patient that died, and then maybe one follow-up as well.

Lara Sullivan^ Yes, it was not the same patient as the head and neck patient that died. I believe that was a Grade 5 not-related sepsis, if I remember correctly. So, we -- just to give you a bit of visibility into how these things are typically handled in a study like this, there's a safety committee that meets every two weeks.

Our team, in addition to the discussions that we have with the investigators as the data rolls in, they are combing that data, combing those situations very intensely to understand what the etiology of that particular event is.

On our end, as we have those dialogues with investigators, we then have a data Q.C. period leading up to data being presented like it is today. And these kinds of events, particularly when you get to those high-level grades, merit a lot of additional scrutiny from us as well as from the investigators.

So, typically, there's a dialogue back and forth. We see the records that have been posted into the database. Oftentimes, we also request additional supporting materials so we can better understand the context behind that particular event.

And if there's situations where interpretation, because medicine's an art at the end of the day, we know that, so it's judgment, right? This is a judgment-based field. Until you get to the statistical significance of Phase 3, there's a lot of judgments going on.

And typically, it's a dialogue. At the end of the day, the investigator has the final say on the attribution of these events because those investigators are the ones who know their patients the best.

So, we have a high confidence in our processes and procedures around these types of events. And in that one in particular, given the etiology of sepsis and some of the clinical picture that that patient was experiencing, we're confident in the way that was documented.

Glenn Hanna^ I mean, I would just say, you have 80 patients across many dose ranges, very sick, early drug trial, multi-site. You're not getting anything, you're not pulling a cover over an investigator who's experienced. That's a pretty safe denominator and feeling good about safety. And I was not involved in this first part. That's important to say.

Lara Sullivan^ Yes.

Glenn Hanna^ I didn't contribute to the data for the early part.

Leonid Timashev^ Got it, okay. And then maybe just as a follow-up, I guess there were -- there was at least one case of pneumonitis as well. I mean, you, guys, talked about how prior lung cancer may be a factor for this.

I guess how -- I guess maybe can you elaborate more on that as to whether the drug was exacerbating something, whether it's really the prior therapies and this patient just exacerbated on their own? I guess …

Lara Sullivan^ Yes.

Leonid Timashev^ … whether you think as you progress maybe into lung cancer that pneumonitis might be something that you need to watch for?

Lara Sullivan^ Yes, I think -- I think every drug developer taking a look in lung cancer has a high bar up. And certainly, every drug developer has a high bar up for pneumonitis in any -- in any patient.

In that case, that patient actually, that pneumonitis actually happened to be the one that we profiled here, which is this lung cancer patient I mentioned in the middle. So, this patient had seven prior lines of therapy and the driver mutation, a very strong response. Grade 3 pneumonitis, which actually resolved pretty quickly is my recollection, and the patient discontinued therapy, as we mentioned earlier.

I mean, maybe Dr. Hanna and Dr. Tolcher can comment on how you, guys, think about pneumonitis, the management of it, and sort of any of the concerns from a particular tumor type population to Leo's question.

Anthony Tolcher^ So, a couple things just about pneumonitis. So, right now, there's powerful signals in certain ones, usually with exatecan as the payload. And that's well-documented within HER2 and the like.

Lung cancer's unique because many of those patients have had prior radiotherapy and a number of other drugs. Plus, you're also dealing with what we oftentimes see, which is radiographic pneumonitis with some symptoms.

But you can't always say, is it related to the investigational drug or is it related to something else, including sometimes simple things such as prior immunotherapy that was administered immediately beforehand, prior radiotherapy, and are we seeing COVID, because we still see COVID actually and it's one of the things when you see pneumonitis or a ground-glass, you actually have to test for it.

So, oftentimes, you're looking to see, is there -- is this signal coming up time and time again? That's how it was sorted out within HER2 was the fact that it would happen over and over and over again in the original Phase 1 studies and the Phase 2 studies. So, there was an obvious signal because it was repetitive.

In this case, one case, you really can't draw any conclusions one way or other. So, I would say it's performing well, there's -- it doesn't seem to be an obvious signal in the patients who've been treated so far. And then one will find out with a larger denominator.

Glenn Hanna^ I mean, I would just sort of add to say that there are plenty of drugs that are on market that cause pneumonitis. There are -- this is a well-documented entity. Patients often can be -- are scanned and there are, as we heard, many other reasons to have ground-glass opacification in the peripheral lobes.

Every single one of my patients aspirate as a head and neck oncologist. They all have biapical scarring from radiation to the neck. So, one thing that I think you were alluding to, at least I think about, is when this drug is combined with PD-1 inhibition, there will be rather unique and stringent criteria around what is accepted for that potential risk in exploration of pneumonitis.

But that's been well-documented and sort of worked out in a lot of the combinatorial trials with PD-1 inhibitors.

So, I think -- and it's generally manageable. To the point made, sometimes it's not even clinically detectable, it's just found on scans and you're basically just saying, "Well, I'll give you a Medrol pack or I'll give you a little Z-Pak, or maybe you wouldn't do anything, you'll just monitor oxygenation and pulse ox."

But the reality is, I don't want to downplay that pneumonitis isn't serious, but what we're more concerned about, I think, is, does the pneumonitis lead to some sort of significant event like hospitalization, protracted steroids, and dare I say, sort of end of life issues? Certainly, we're not seeing that.

And that's why many of the drugs on the market that cause pneumonitis are on the market still, because even though we see it, it doesn't necessarily translate to those serious, scary events. And so …

Lara Sullivan^ Excellent.

Glenn Hanna^ … I'm not that concerned.

Lara Sullivan^ Okay.

Pam Connealy^ I think there's actually a question from Sam Slutsky from LifeSci, who's actually in London today. Can we? How are we? Are we -- are we able to get it? (OFF-MIC) Okay. Why don't we -- okay, you want to go next? Yes. And then Brad and then Tony, and then we can go back to Sam.

Sudan Loganathan^ This is Sudan from Stephens.

Lara Sullivan^ We'll stay here all night if you, guys, want us to.

Pam Connealy^ I know, right? I'm fine with it.

Lara Sullivan^ This is obviously five years of work, so we're happy to …

Pam Connealy^ That's right. Brad said he was here all night with us, so we're …

Lara Sullivan^ The Red Bull's outside.

Sudan Loganathan^ Thanks. This is Sudan from Stephens. Again, thanks for all the details today and the presentation. Firstly, I just wanted to kind of reference, with the ADCs, obviously, and HER2 kind of brought about the thought that high, low, and medium expression of certain targets are -- it could be targeted by ADCs.

So -- but even as you look at the Keytruda combination, does that -- does the expression of EDB still play a strong factor or is the combination going to help kind of -- still get into more cancer types with high or low expression of that?

Lara Sullivan^ Yes, I think -- I mean, I think that's a really interesting question as we think about two different target expression patterns. I don't know, Jan, maybe you want to comment, and then our clinicians if they had any perspectives to share on that?

Jan Pinkas^ Yes, I think it's an incredibly important thing for us to follow. I mean, obviously, we want to understand what that relationship is between target expression and response. I think probably one of the best examples out there now is Elahere in ovarian cancer is looking at going to lower folate receptor expression levels in the platinum-sensitive setting.

So -- and HER2 is by far the best example where they've redefined what does it mean to be HER2-positive from the early days of Herceptin. Now, they've defined a new ultra-low population that I'm sure makes people pull their hair out trying to even measure. So, I think the only way for us to understand that is in studies as we go forward that we actually generate high-quality data that can inform us on those relationships.

Pam Connealy^ Thank you. Brad? Oh, sorry.

Sudan Loganathan^ One quick second one. Yes.

Pam Connealy^ Okay, go ahead.

Sudan Loganathan^ All right. And for the -- for -- as you kind of develop and then the other cancer types as well, if an ADC, an internalizing ADC, is used as a prior therapy, is -- does 201 still have the opportunity to kind of maybe as a second or third line come in and still have that effect because of the different characteristics that have this mechanism in action or is there -- is that been elucidated yet between using it internalizing versus not internalizing?

Lara Sullivan^ Yes, I appreciate that question, it's a great question. And we actually had a handful of patients who had been on prior ADCs and had progressed through them. Not enough yet in our dataset to be able to really see the pattern, but I think, to your point

around mechanistic complementarity, we absolutely think there's a place, whether it's sequential or even in combination, that if you have the non-overlapping safety effects or side effects as well as differentiated payloads, there's no reason to think that a patient who progressed through a prior ADC wouldn't respond here.

And I wish I had the couple of cases at my fingertips on that. We can -- we can talk more offline. But we did have a handful of patients, and I think one who did respond that had been on a prior -- a prior ADC, actually, I think we have it right here …

Pam Connealy^ Right here, yes.

Lara Sullivan^ … for this -- this patient we haven't seen the scan yet, but we've seen the cutaneous lesions resolve, so that bodes well. And there might have been, I think, another one.

Pam Connealy^ This is about 14% of our …

Lara Sullivan^ Yes, so we had a couple more.

Glenn Hanna^ And there's already data for taking a specific target, so not even mechanistically distinct, just a specific target, switching the payload in a follow-up trial and seeing activity. I was being very careful not to reference some of the trial data that I'm involved in, but there is definitely data emerging across several trials where mechanism aside, it's just -- it's a payload switch, it's you're maintaining the target expression, which probably wouldn't be the case across all drug development but things that are more canonical like HER2, perhaps TROP2, etc., or earlier on may be maintained. And that's something that's just now emerging, but it has been shown in a handful of ADC studies.

Lara Sullivan^ All right.

Pam Connealy^ All right. Brad, yes.

Bradley Canino^ Brad from Stifel. Thanks so much for the presentation. Great to see all the details on the slides as well. Can you just talk to the baseline tumor burden location in the head and neck patient that had the complete response?

And then as a follow-up, Dr. Hanna, if you can speak to whether that's a useful characteristic or aspect to think about to judge the quality of a drug in an early trial?

Glenn Hanna^ Yes. Lara, maybe you can comment.

Lara Sullivan^ Yes, so, in terms of that particular patient, we had the PET scans here previously. They're not -- they're not displayed now. It was like, I think, 25.9 by 23.8. Maybe it's written there.

Pam Connealy^ Yes.

Jan Pinkas^ It's there.

Pam Connealy^ She can't see that.

Lara Sullivan^ I can't see it without glasses. 16.3 millimeter tumor completely resolved. David, do you remember the specific anatomical location for that complete response patient?

Unidentified Speaker^ Yes, so that was a patient who had …

Lara Sullivan^ David's one of our clinical development leaders.

Unidentified Speaker^ That was a patient who had a distant metastasis in soft tissue of the -- of the pelvis and had both a complete radiographic response and more importantly, a complete response on FDG PET. So, a complete metabolic response as well.

Glenn Hanna^ But to your point, you're getting at what I was alluding, one of the things we're thinking about as some of these candidate drugs that look good, for example, the Bicara and the Maris drug coming in, is what's the differentiation between someone with an HPV-positive distant met responding at a preserved site externally or the very difficult persistent oropharynx cancer HPV-negative that we've radiated and given chemo to and now, it's this fibrotic granulating scar and now, you have to go on additional treatments, how do they respond?

So, this idea of local, regional and/or distant response is something that's going to be very much paid attention to across these studies. We do think as oncologists, head and neck oncologists, those are very biologically distinct, even within HPV positivity.

If you're -- so, I would think of them as sort of dually important. HPV is one consideration biologically, but then where the tumor is, and that's just a sort of a reality regarding what the treatment has -- what treatment has been -- the cancer has been exposed to, but then also the anatomical location.

So, for example, if you still have tumor left after chemoradiation in the throat, you're sitting next to the carotid sheath, you've got vascular concerns, you've got bleeding risks, you've got swallowing concerns or performance status, diet's affected, all of these little subtleties.

And so, it will be important to understand and there's no reason -- actually, there's a compelling reason to think that this would actually be quite helpful in that scenario because again, it's not modulating the neutrophil count, it's not creating a bleeding risk or vascular concern and it's dealing with a fibrotic anoxic environment.

So, I'm actually quite excited to see what this drug can do in the local regional setting. So, I think -- but it's a very important point. Those are the details that Maris and Bicara are fumbling with a little to understand what -- where their drug is sort of landing.

And one of the key stratifiers in the -- what's called now the [FORTIFY] study, which is ficerafusp alfa-pembro versus pembro, the Phase 3 that's launched, one of the key stratifiers is local regional versus distant disease for that reason.

Anthony Tolcher^ But it's more than just small disease disappearing because I think that ovarian cancer patient, I think no one in the audience would say that was minimal disease. That was pretty substantial disease that disappeared.

And so, I mean, the drug works, I think it's punching above its weight and I think at least my own personal opinion, it's due to both anti-tumor effect as well as targeting the tumor microenvironment.

Glenn Hanna^ And keep in mind, a cavitary lesion can be punched out and completely dissolved volumetrically, but the RECIST measurements are the same and that's the bane of our existence. But it's the reality of how the agency works.

So, people have come up with scores like these modified scores to understand Choi criteria, for example, how things volumetrically shift or density, and so, that may be something to look at. I didn't see those clinical images, but something I would say to Lara and the team is start looking at some secondary ways to assess response like we did with iRECIST initially in I.O.

That response rate could be much higher if we're looking at volumetric regression because to us, that's meaningful. When it's your grandma getting that drug, that's a real response. But to the FDA, you have to sort of hit that threshold of right large diameter 30% regression.

Pam Connealy^ I think Tony's next.

Lara Sullivan^ Tony, yes.

Tony Butler^ Tony Butler, Rodman & Renshaw. Thanks very much for being here. Dr. Hanna, you emphasized in one of the three 201 trials, patients who may come in second and third line who've seen EGFR and/or PD-1 inhibitors in the past.

The question I want to ask is, before Bicara and Maris readout, you're going to have data, full datasets around KEYNOTE-689. And so, I'm curious, does that actually shift the thought process about how to treat first-line patients who come in that is on neoadjuvant? And then how do you actually sequence a drug in second or third line after that? That's question one.

Glenn Hanna^ Got it.

Tony Butler^ Question two is, in all of the three studies for 201, is the goal to have HPV independence and otherwise, in other words, it doesn't matter if they're positive or negative, and they're -- it doesn't matter whether they're PD-L1-positive or negative. Just what is the overall goal there, or is it just simply PD-L1-positive in HPV-positive or negative? Thank you.

Glenn Hanna^ So maybe I'll answer the second one first because it's easier. My recommendation to the team would be to maintain -- be agnostic based on what we're seeing with some activity in PD-L1 positive and negative patients because again, mechanistically, we know PD-L1 is not stagnant. You biopsy someone and then a week later, you choose a different site, get a different score.

So, the reality is we're not even sure that this drug necessarily relies on that prior biomarker. So, I would say, definitely encourage Lara and the team to go -- understand the PD-L1 expression in prior lines and the benefit, particularly in the combo trial with pembro, but I wouldn't -- I wouldn’t develop it out the gate as a PD-L1 selective agent.

Secondly, HPV agnostic right now, for sure, we don't know, those still can be hypoxic and fibrotic tumors, and you're already seeing activity. Your C.R. was in an HPV-positive patient. So keep the net wide, I would say, agnostic until you know otherwise.

Whereas with cetuximab and EGFR-based drugs, there's a clear biology, years of mechanistic understanding as to why you would restrict to HPV-positive -- or excuse me, HPV-negative. That being said, KEYNOTE-689, very important press release, 689 was neoadjuvant pembrolizumab two doses for high-risk, resectable head and neck cancer. It's expected to change practice, right, because it met EFS, event-free survival, and major pathologic response endpoint.

And so, if a patient -- the good news I can answer because we already have patients who are on the precursor study, sadly, who failed. So, what most of the trials are doing now is, if someone had neoadjuvant immunotherapy, had surgery, chemoradiation for head and neck cancer, and unfortunately, they recur, we've generally said, wait at least 6 to 12 months of washout from the prior PD-L1 exposure to then allow someone to be seeing a new -- a PD-L1 again in the advanced disease setting.

And that could change, right, because maintenance pembro is included in the 689 trial with chemoradiation. But my guess would be similar to platinum exposure. You'd want to wait, and there'd be a resetting.

The immune system is not stagnant, as you all know. You get a cold and we see changes in our lymphocyte counts, etc. It's the same idea. When you introduce new therapies or time and evolution has gone by, there'll be a chance to reintroduce the checkpoint inhibitor. And we've even seen patients re-respond after being off for long, long periods of time with intervening therapies. So, I think that's how the field's handling it now.

So, I don't think, which is important from an investor standpoint, that 689 is going to do anything to this in the negative fashion. It's just going to be that those entry criteria for the combo study are going to say something like, if the patient had prior PD-1 exposure in the definitive setting or adjuvant setting in the last six to 12 months, they would be ineligible. And I think that would be a small number of patients because it takes surgeons a long time to get comfortable with the data. It did in cutaneous, so give that a few years.

Pam Connealy^ Great. I think we have one on the phone, yes.

Operator^ Thank you. (Operator Instructions). We ask that you limit yourself to one question. Please stand by while we compile the Q&A roster. Our first question comes from the line of Sam Slutsky with LifeSci Capital. Your line is open.

Sam Slutsky^ Hey, thanks for taking the question to everyone. May have missed this, but just for the HNSCC cohorts you're taking forward, are you testing three different doses in that? And then how many patients are you looking to enroll across the combo study and then the two monotherapy arms?

Lara Sullivan^ Yes. No, thanks, Sam, I appreciate you're asking that, you didn't -- you didn’t miss it. I really -- we actually hadn't touched on it. So, as I mentioned, we've gotten the doses through 5.4 cleared.

In the -- in study number one, the first second line combo therapy with Keytruda, we're going to start the dosing at 3.6. We're able to escalate up, right, as the patients -- as we see how the patients do in that combo dose. The pembro dose will be fixed.

Pam Connealy^ Right.

Lara Sullivan^ But we will titrate up for the PYX-201 dose. In the other two studies, the second and third line monotherapy studies, both of those are going to be starting at the 5.4. So, as I mentioned, we see an opportunity to continue to do a little bit of testing between the 5.4 and 6.6 level that we had mentioned at the beginning. We can do that in the context of an amendment to this existing dose escalation study and test a handful more of patients.

If another dose level clears, that will be available to both the monotherapy study and the combo study. We're very happy with the 3.6 through 5.4 data that we've got now. So, if there's another dosing option, great. If not, we're full steam ahead as planned here.

Pam Connealy^ The number of patients.

Lara Sullivan^ Oh, number of patients. I think in the -- in study number one for the combo therapy, it's like 40, I think, to start with, right? And then in the two monotherapy arms, I think we're looking at, what, similar, 40 …

Pam Connealy^ Yes.

Lara Sullivan^ … each? And depending on, of course, how quickly, these are open-label for us, right, how quickly we see data, we can always accelerate our data readout if we start to see signals that come onboard earlier.

Right now, we're assuming for those catalyst timeframes later this year, early next, that could include potentially an interim readout, or if the recruitment goes quickly, speed to a full dataset would be great.

Sam Slutsky^ Got it, thanks.

Operator^ Thank you. (Operator Instructions).

Lara Sullivan^ Any other questions in the room? Okay, I know we've thrown a lot of information at all of you today. We really appreciate your time and attention. We're super excited about taking this program forward and the potential benefit for patients that we'll be able to accrue.

And the team is available if you have further questions tonight or if you wish to reach out to us, schedule some time, we're happy to follow up. And thank you again for your time and support.

Pam Connealy^ Any of the research analysts that would like to meet with a small group of the management team, we're available after this meeting.

Lara Sullivan^ Okay, yes, management's available for any of the analysts that wish a deeper conversation. Right now, we'll stick around. And otherwise, thank you.

Pam Connealy^ Yes.

Operator^ Ladies and gentlemen, this concludes today's conference call. Thank you for your participation. You may now disconnect.