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Agenus, Inc. (AGEN)

Business Update Call

CORPORATE PARTICIPANTS

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Member- Scientific Advisory Board, Potenza Therapeutics, Inc.

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OTHER PARTICIPANTS

Mayank Mamtani
Analyst, B. Riley FBR, Inc.

MANAGEMENT DISCUSSION SECTION

Operator: Good afternoon, ladies and gentlemen, and welcome to the Next-Generation Immuno-Oncology Therapeutics Conference Call. At this time, all participants have been placed on a listen-only mode.

It is now my pleasure to turn the floor over to your host, Mayank Mamtani. Sir, the floor is yours.

Mayank Mamtani
Analyst, B. Riley FBR, Inc.

Thank you, John. Hello, good evening, everyone. This is Mayank Mamtani. I'm a senior analyst covering biotechnology companies at B. Riley FBR. I hope everyone's keeping well and thanks for joining.

I'm pleased to welcome you to our expert panel call today to recap an exciting data with ASCO weekend, in particular, focusing on next-generation CTLA-4 agent where we saw Agenus present encouraging early data as monotherapy and in combination with PD-1.

We have with us on the call, Dr. Steven O'Day, who were the leading clinical investigator who presented that data; and also Dr. Charles Drake, and both of these guys are obviously, don't need introduction but they've obviously pioneered the checkpoint inhibitor biology space over the past several years, including in translational research and clinical development.

Before we get started, I need to quickly walk through my disclosures. In the normal course of this business, B. Riley FBR Capital Markets seeks to perform investment banking and other services for companies under coverage, and to receive compensation in connection with such services. As such, investors should assume that B. Riley intends to seek investment banking or other business relationships with any and all of the companies mentioned today.

Agenus currently is, within the past 12 months was, a client of B. Riley FBR. The services provided were investment banking services, and we intend to seek additional compensation over the next three months. B. Riley FBR has managed a public offering of securities for Agenus and acts as a market maker for Agenus' securities.

Dr. Steven O'Day, the Executive Director of the John Wayne Cancer Institute and Cancer Clinic and Director of Providence Los Angeles Regional Research. Dr. O'Day has been at the forefront of new drug development over the last two decades including playing a leadership role in the development of the breakthrough anti-CTLA-4 for ipilimumab, or commonly known as YERVOY, as well as anti-PD-1 antibodies including Merck's pembrolizumab and BMS nivolumab or OPDIVO.

Dr. Charles Drake is a Co-Director of the Cancer Immunotherapy Program and Co-Leader of the Tumor Biology and Microenvironment Program at the Columbia University, Herbert Irving Comprehensive Cancer Center. Prior to joining Columbia, Dr. Drake served as a Co-Director of Cancer Immunology Program at Johns Hopkins Kimmel Cancer Center and has been a lead investigator on several pivotal clinical trials in immune checkpoint inhibitors. We appreciate Dr. O'Day and Dr. Drake spending time with us today.

On the call also facilitating the dialog with me is Jennifer Buell, President and COO of Agenus. We appreciate our panelist spending time with us today. Their opinions are their own and do not necessarily reflect those of B. Riley FBR. We ask them to avoid any disclosure of confidential non-public information. We obviously have a lot to go through in the call. We'll be happy to take questions if you want to email them to me directly at mmamtani@brileyfbr.com.

QUESTION AND ANSWER SECTION

Mayank Mamtani
Analyst, B. Riley FBR, Inc.

Q

So, with that said, Jen, why don't you just get kick us off and just talk about a little bit about what we saw – what we learned from you at Agenus and then obviously we want to hear from the two doctors that we have here.

Jennifer Buell
President & Chief Operating Officer, Agenus, Inc.

A

Wonderful. Thank you very much, Mayank. And Dr. O'Day and Dr. Drake, thank you very much for taking the time to be with us. It's always wonderful to be with you and particularly exciting to do so on the heels of ASCO.

As Mayank mentioned, you're pioneers in the field of immuno-oncology and collectively your work has paved the way to a much deeper understanding of the most validated cancer checkpoint targets, CTLA-4 and PD-1, and also has driven the work that we've been doing here both in how we're dosing the molecules and combining them to optimize their benefit for patients. The durable and curative benefits that we're seeing in some patients are direct result of your contributions. That includes how to administer these agents, and you're also in the forefront of identifying gaps in these first-generation combinations or therapeutics.

Dr. O'Day, you were the first person to dose patients with YERVOY, a first-generation CTLA-4 more than 20 years ago. And you're now the first to dose patients with our next-generation CTLA-4, AGEN1181, which is a multi-functional T-cell engager that also binds to CTLA-4. And we've designed the molecule to approve upon what we believe to be important efficacy and safety parameters and also to expand the patient population of patients who

benefit from a first-generation CTLA-4. And as Mayank mentioned, on Friday at ASCO, you presented exciting data from our Phase 1 trial on this molecule.

So, I'd like to start the conversation by asking you, what have you learned from your experience with CTLA-4 and PD-1 and how has your thinking about this combination evolved? And what do you both believe that we need to expand in order to expand the effective and durable responses for patients with cancer?

Steven J. O'Day
Director & Executive Director-John Wayne Cancer Institute and Cancer Clinic, Providence Los Angeles Regional Research

A

Well, thank you, this is Steve O'Day. I'm delighted to be on the call today. And Jen, thank you for that lead in. It really has been an extraordinary 20 years. I was in the field of melanoma where we had very few therapeutics and about 20 years ago was fortunate enough to work with a small group of investigators that put ipilimumab into human melanoma patients with very advanced disease.

And to make a long story short, we've discovered extraordinary result. About one in four patients who received four doses of a CTLA-4 inhibitor resulted in long-term survival. And these were patients with very advanced melanoma, including brain metastasis. It was the extraordinary finding and it then resulted in almost 10 years of clinical trial research Phase 1/2 and then culminating in a Phase 3 trial that was presented at ASCO. I was able to give the plenary session then in 2010 showing for the first time in a randomized controlled trial that CTLA-4, any drug, in melanoma improved overall survival with remarkable cure and one in four patients.

So, clearly, this was an important check point that then launched the revolution of immuno-oncology. Very shortly after that, obviously the intensity of our clinical researchers and immunologists and oncologists, Dr. Drake being a primary focus in that whole field discovered that there were other checkpoints and you all know the story, PD-1 then became front and center. I think what I'd like to say just at the outset is that, I really felt that there was a misunderstanding of mechanism very early on. Obviously, CTLA-4 helped a very small subset of patients with melanoma, but it was so dramatic and it produced durable responses suggesting memory after very few exposure doses.

But very soon after that the thought was that the T-cell lifecycle had other checkpoints and that PD-1 obviously seemed to have a lot more activity. And then CTLA-4 sort of got looked at as the poor stepchild, an inferior version of PD-1. I think that was unfortunate because in my mind there're two very separate targets. They do share in common T-cell. But as we know now, T-cell lifecycle is very different in how antigens are processing the periphery of the immune system, the army is built, sent to battle, then they encounter the tumor microenvironment and the battle even begins there, and then they get exhausted. And then they up regulate exhaustion markers like PD-1.

And so PD-1 responses were remarkably more common than CTLA-4 responses. And so, it deserved its front and center, but with time the durability has been less. And we neglected CTLA-4 for a while. What I'd like to reiterate though is, I think that in the last two years, it's extraordinary how CTLA-4 has been brought back, a better understanding of the distinction of the two targets. And now across many solid tumors now six indications, CTLA-4 has been shown in combination at lower doses and even more less frequent doses has been an important background not only in melanoma, but renal cell non-small cell lung cancer hepatocellular colorectal.

So, I think it's here to stay. I think – so, the combination, we obviously need better and then I'll let Chuck and others, we can talk some more about why we need better versions, but the existing CTLA-4 that we have at ipilimumab is a very font and center platform now in combinations.

Having said all that, I think let's go back to what we learned initially as monotherapy with ipilimumab. And remember, well, you may not know, but it really did have a dose-escalation dose response at higher doses in melanoma and the metastatic setting up to 10 milligrams. It was superior in a randomized study than 3 milligrams, but toxicity also increased with dose. And because at the time the toxicity seemed overwhelming, if you really put it in perspective now the gain that we get with the toxicities with CTLA-4 blockade are much more reasonable. It's just that it was a huge toxicity paradigm shift for oncologists back in 2000, 2010. Now we're very fast when managing these toxicities and it's changed things and allowed us to do combinations.

But having said all that, we still want to reduce immune-related toxicity. Not necessarily completely get rid of it, because there is a correlation between mechanism of toxicity and response, but we certainly want to mitigate severe toxicities. And obviously, there is a limiting factor to first-generation CTLA-4 regarding that. What I'm excited about in the next-generation, which we'll talk about is that we need to re-explore the dose, if we have a less toxic drug and that's the hope with AGEN1181 because single agent activity may be still dose-related.

And secondly, we [ph] never reasonably tox (00:10:54) study, very many tumors with CTLA-4. We got a little signal in prostate cancer, so a little signal in renal cell and then it sort of left us as PD-1 was launched. And so, we really don't have a good idea of CTLA-4 across solid tumors, particularly with more potent drugs that I think we have in second generation and less toxicity. So, for those reasons I think both CTLA-4 monotherapy and combination is coming back. And I think it's very clear that this is a critically important target and the most important target at present in combination with the PD-1 background. I've probably spoken more but I want to give that background and we can move into biology.

Jennifer Buell
President & Chief Operating Officer, Agenus, Inc.
A

That was outstanding. And I'll just say that I'm glad that you mentioned the new approvals where IPI and NIVO now have been able to be dosed tolerably and effectively. And now over six different tumors there, they have a label and approval in over six different indications. I'm hoping and looking forward to Agenus' contributions to that and that we have a first generation CTLA-4 as you know as well as the PD-1, advancing in two BLA path trials, monotherapy PD-1 in patients with refractory cervical cancer and the combination, in refractory cervical cancer as well.

And we've presented some data demonstrating that patients with PD-1 monotherapy have response rates of about 14.3% and that's quite comparable to the 14.3% that pembrolizumab was approved on via accelerated approval in this indication. The combination however, is what we're thrilled by. We're seeing 26%, maybe a little over that of response rates. And that's showing near doubling of responses in patients with refractory cervical cancer, which shows a potential best-in-class benefits for these patients. And these responses what we're seeing now are durable. So, we have a number 4 complete responses, 10 partial responses and these responses are very long lasting.

Maybe I'll turn it to you, Dr. Drake, now to speak about some of the learnings about CTLA-4 and PD-1, the mechanism in terms of T-cell modulation, effector, memory cells and some of the underlying immune activity that is helping to drive these variable responses.

Charles G. Drake
Member- Scientific Advisory Board, Potenza Therapeutics, Inc.
A

Sure, I'm happy to. First of all, I would like to just start out by agreeing with Steven actually on the basic points that he made at the very end saying that the immunological pathway is mediated by PD-1 and CTLA-4, very, very different at the molecular and cellular levels.

I actually had a similar experience. I was lucky enough to treat the first kidney cancer patient in the world with anti-PD-1 in 2008. And they had a complete response. And so, we were all excited. This was going to be the next generation that looked like PD-1 was more effective and then maybe less toxic than anti-CTLA-4. But I think that as time has emerged, there are actually – and also the field has accelerated greatly by a series of animal models, which show that if you add PD-1 to something it might always works right.

So, I think the field got a little bit over-exuberant about the idea of using anti-PD-1 in combinations. But really the clinical data hasn't so far borne that out to the degree it has at least with CTLA-4 and that CTLA-4 blockade is approved with PD-1 and six different indications. And it's actually the only immune checkpoint that reliably combines with the anti-PD-1. So, I think that that's kind of what the field has taught us.

I would say a slight exception to one thing that Dr. O'Day said. In prostate cancer, I was actually fortunate to be the one of the international PIs on our potentially pivotal Phase 3 trial. And what he's right about is that we had to use a higher dose, right? So, definitely with CTLA-4, there's dose response relationship, but we almost won. In prostate cancer, we had a hazard ratio of 0.8 and our p value was just on the edge. It was 0.53. And so, we really came pretty close with a high dose of it in prostate cancer. And that's not what you see with PD-1 monotherapy in prostate cancer.

I think the other thing to keep in mind is, from an immunological basis, studies from [indiscernible] (00:15:13) group and then several other groups, really Steve Reiner and actually we've repeated some of these studies in our labs. And now, we really, really believe them. And the idea is that actually PD-1 blockade is important in T-cell biology and that it basically really exploits the effector phase. So, basically, T-cells have two jobs. One is to go ahead and kill. And the other one is to turn into memory cells. And so, PD-1 definitely augments the effector phase and that's why you see a nice response rate. But that does come at the expense of forming memory and that memory phase is actually more strongly supported by CTLA-4 blockade. And I think that's really kind of an easy way to think of why the combinations are usually additive and sometimes even a few are synergistic actually.

So I think that with all those things together, I do suggest that Dr. O'Day and I totally agree that CTLA-4 has been sort of marginalized to some degree for a while. But I think the emerging data really played out why CTLA-4 is an important checkpoint and then why new approaches to versus standard ipilimumab might be advantageous.

Jennifer Buell
President & Chief Operating Officer, Agenus, Inc.
A

Thank you very much. And Dr. O'Day, do you have anything to add to that?

Steven J. O'Day
Director & Executive Director-John Wayne Cancer Institute and Cancer Clinic, Providence Los Angeles Regional Research
A

No. Yes, sorry I may have slighted the prostate group, but I remember that that was very close. And in fact, I was so disappointed because essentially there was a 94% chance that that was a positive study so to speak. So, and relatively cold tumors like prostate cancer with very few infiltrating T-cells normally, it just makes the strong point that CTLA-4 may work better in some diseases than PD-1 and it makes a strong point. And it's based on biology and the two together always seemed to be a little better, but there are diseases where CTLA-4 by itself maybe the best drug of the two.

I don't think that's fully appreciated by the wider community. But I'm just delighted to see it now back front and center and to be involved with the sort of full circle for micros to put the first CTLA at ipilimumab be involved with

that group in around 2000 and then this year or last year, to put really the first AGEN1182 second-generation in a person. So that was exciting.

Jennifer Buell
President & Chief Operating Officer, Agenus, Inc.

A

Well, that's a perfect segue and an opportunity to start talking about some of the next-generation approaches for CTLA-4. And I also want to ensure that we cover in this category, the opportunity to potentially really delve on the learnings that we have to-date and how there may be monotherapy opportunities for anti-CTLA-4, given our enriched understanding of the biology now, as well as other non-PD-1 combinations that we can contemplate as well.

So transitioning to the next-generation CTLA-4, where there has been quite a bit of activity and notably also at ASCO, our AGEN1181 is Fc-engineered and we've designed this to increase the dwell time, the time between the antigen-presenting cell and the T-cell interaction to increase immunogenicity. Of course, to activate T-cells, but also to improve timing. We also with the Fc-engineering, we believe that we can now dose and benefit patients who have poly-morphogen in their CD16 allele. And those patients appear to have had no response or suboptimal responses to first-generation CTLA-4.

The molecule is now in the clinic and perhaps, I can ask you, Dr. O'Day just to highlight a few key features, a number of your patients have been treated with the therapeutic and give your perspective about this molecule. And perhaps, then we can turn it over to Dr. Drake to talk about how this approach may differ from some of the other approaches that are in the clinic?

Steven J. O'Day
Director & Executive Director-John Wayne Cancer Institute and Cancer Clinic, Providence Los Angeles Regional Research

A

Yeah. So I've been fortunate to be involved and sort of to lead the initial Phase 1 trial and what I like about it is sort of an adaptive design. We're doing sort of parallel Phase 1 monotherapy, AGEN1181. And then as we clear doses, we are then starting that lower clear dose into the combo. So I think we've treated a little over 20 patients with these. And what we've seen obviously it's early days for efficacy and all that. What you really want to look at obviously early on is toxicity signals both with the monotherapy and the combination. We've seen what we might expect with the CTLA-4 blocker with skin and some GI toxicity that's been manageable.

What we're particularly interested in based on the FC engineering and the complement aspect of this is the neuro endocrinopathies, particularly hypophysitis, which is one of the more significant endocrine toxicities that you don't typically see with PD-1 inhibitors. You tend to see more thyroid and other but with CTLA-4 and with ipilimumab anywhere from 10% to 15% of patients can knock out their pituitary glands. Where it's not life threatening, it does produce lifelong need for hormonal, adrenalin and thyroid and testosterone in men replacements. So it's not a trivial issue since these tend to be the long term survivors.

So, anyway, we're – based on preclinical models and the FC engineering there was this hope that they really didn't see these neuro endocrinopathies. And so far, again, in 20-plus patients, we have not seen any of these neuro endocrinopathies, so that's encouraging. Otherwise, it's been a fairly reasonable toxicity profile without any new signals.

And then of course we have seen some responses. One in monotherapy at a very low dose and in a disease endometrial that it doesn't have a track record in CTLA-4 and had the haplotype, the low affinity haplotype that you would expect to have a very low response based on melanoma data with ipilimumab or the first generation. So, for all those reasons, low-dose disease that had not previously been a CTLA-4 disease so to speak and a low

affinity haplotype that's really exciting. And it was a complete remission and it happened within 12 weeks of starting. So very dramatic and it's been durable. So, that's again one patient but exciting.

We had another patient at the very lowest dose of the monotherapy that's had ovarian cancer and had now almost a year and a half now of prolonged stable disease. And so that's been – she's tolerated it beautifully. And then we've seen a combination patient, again low dose of CTLA-4 of AGEN1182, 0.3 milligrams with full dose PD-1 and we've seen a very nice response rate, multi-focal ovarian disease that was progressing through chemotherapy after multiple regimens and now having almost an 80% shrinkage with most recent scans, again very dramatic, very early.

So, we are – what is nice to see and again all of these early studies are let's get to an optimal dose with monotherapy and let's get to an optimal dose of combination, and then obviously expand these cohorts, which we plan to really focus and use our energy knowing the field where would be the biggest impact to get both a monotherapy on the market or a combination in diseases that traditionally might not be colder tumors so to speak. So, we have a very well developed advisory board that is well versed in IO that is really doing its job to think of where we're going to put these optimal combination doses and schedule and monotherapy in the coming months. We're also looking at both a three-week and a six-week monotherapy regimen. So we're looking at a couple different dosing regimens.

Jennifer Buell
President & Chief Operating Officer, Agenus, Inc.
A

Thank you very much. And Dr. Drake, you've been an expert in the area of tumor microenvironment conditioning agent, Treg depletion as a mechanism of tumor progression, tumor escape mechanisms, as well as T effector activity. One of the features of AGEN1181, based on its design is we're anticipating Treg depletion. And perhaps we could ask you to speak a bit about what you believe these next generations CTLA-4s may be able to do? And also what your thoughts are on where to bring these forward both as monotherapy as well as in combination with PD-1?

Charles G. Drake
Member- Scientific Advisory Board, Potenza Therapeutics, Inc.
A

Yeah. So it's a great point actually. So in the lab, we've been fortunate to have an analog of a CTLA-4 depleting antibody, it's a mouse IgG2a and it depletes brilliantly and with that drug we can see activity in tumor types in mice where anti-PD-1 has no activity. And so I'm really very enthusiastic about the ability to optimally engage Fc receptors and potentially deplete Tregs.

And so the mutation that's in AGEN1181, the DLE mutation is unique. It's actually not in any other antibody that's in the clinic now. And if anybody wants to delve into the deep science, we should point them towards the beautiful cancer cell paper actually that shows this molecule compared to native type CTLA-4s and actually several other mutations. So that's why I'm excited about the mechanism.

But the other reason I'm excited I got to tell you is that when you push a tumor, what you get is an expansion of both number and function of regulatory T cells. And by that, I mean if you radiate a tumor, you think that you're increasing the TME inflammatory status and you do, but that's very well balanced by an increase in the number and function of Tregs. And those Tregs express CTLA-4, like highly actually. We published this in Clinical Cancer Research. We recently published the same thing in prostate cancer, hormonal therapy is immunotherapy you get CD8 T cells come in, you're very proud of yourself. And then shortly after, you see a nearly perfect adaptive increase in Tregs. We call this adaptive Treg resistance.

And I have to tell you, it probably happens to everything, it probably happens to PD-1, it probably happens to chemo. And so, I have to say that I think that there is a very, very broad spectrum of tumors and combination modalities that an optimized CTLA-4 has a place in. I think what Steven said is, which I agree with is, one place to start is just reexamine the tumors in which we either didn't carefully explore or which we saw a whiff of CTLA-4 activity, prostate is a very good example.

But then I think going forward like frankly, I mean there's multiple, multiple applications I think that a kidney cancer, there's certainly a good chance that a drug like this is more active in traditional CTLA-4 drugs. I do agree with Steven. I think the place to start though would be to look and optimize an antibody in tumors that we think have a chance of being immunologically sensitive. But then I think going forward, I think that the – frankly, the combination approaches with really most things that are pro-inflammatory in our hands actually benefit from CTLA-4, not blockade by using a CTLA-4 optimized [indiscernible] (00:26:51) antibody.

We have another paper that we haven't published and in progress where we combined it with a cancer vaccine which I've lost sort of interest but I could tell you that it's the same thing. You push the tumor microenvironment with the vaccine, you get more Tregs. If you get rid of the Tregs, then the vaccine works beautifully actually. So, I think that there are really many, many applications for an agent like this, frankly.

Jennifer Buell
President & Chief Operating Officer, Agenus, Inc.
A

Very helpful. Now, maybe I'll just ask for a perspective from your experience. Both of you were at the front edge of using CTLA-4 in tumors and you've seen the benefit, as well as some of the challenges. To see responses viscerally and at the low doses that Dr. O'Day just highlighted, in your opinion how common or unusual is it at this stage to see the kinds of activity that we're seeing?

Steven J. O'Day
Director & Executive Director-John Wayne Cancer Institute and Cancer Clinic, Providence Los Angeles Regional Research
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I think...

Charles G. Drake
Member- Scientific Advisory Board, Potenza Therapeutics, Inc.
A

So...

Steven J. O'Day
Director & Executive Director-John Wayne Cancer Institute and Cancer Clinic, Providence Los Angeles Regional Research
A

Go ahead, why don't you start with it Chuck?

Charles G. Drake
Member- Scientific Advisory Board, Potenza Therapeutics, Inc.
A

Yeah. You've seen more because you do more melanomas.

Steven J. O'Day
Director & Executive Director-John Wayne Cancer Institute and Cancer Clinic, Providence Los Angeles Regional Research
A

Yeah.

Charles G. Drake
Member- Scientific Advisory Board, Potenza Therapeutics, Inc.

A

What I'll say actually is the fact that you're seeing responses at low dose are very clear evidence that biologically this is a different molecule than ipilimumab. I think that nobody could argue that, right? I mean I think that the fact that you see responses at 0.3 and that maybe even spacing it out to every six weeks is possible. I think that this is biologically a different molecule than ipilimumab. So I think that's very important.

I think that what – in terms of the true measure of the clinical activity, I once again will agree with my friend Dr. O'Day in that, I think that the key to really understanding that – certainly seeing responses early is encouraging, right? But I think that the fact that we're getting close to what looks like a recommended Phase 2 dose both as monotherapy and combination really means that within a relatively short time we'll be able to get a better read out for exactly what the activity is. So, I think again the low dose shows very clearly this is biologically different. I think that seeing responses early is encouraging and we really very much look forward to like what happens in the expansion cohorts.

Steven J. O'Day
Director & Executive Director-John Wayne Cancer Institute and Cancer Clinic, Providence Los Angeles Regional Research

A

Yeah, I would agree and I think the fact that we – again it's still some confidence intervals around this statement but I mean certainly not seen any neuroendocrinopathy so far in a drug ipilimumab that we saw a fair amount, 10% to 15%, certainly gives me hope that this might be different from a toxicity point of view. But obviously that's going to be really critical too.

Jennifer Buell
President & Chief Operating Officer, Agenus, Inc.

A

Thank you. And perhaps, Dr. Drake given your experience with some of the other next generation approaches, how do you see the profile, the observations of safety, the absence of the neuroendocrinopathies in your opinion?

Charles G. Drake
Member- Scientific Advisory Board, Potenza Therapeutics, Inc.

A

I think it's very exciting. I mean, so I mean in terms of full disclosure I'm actually the local PI on a competing molecule frankly. It's the BMS version of [ph] IPI, it's a (00:29:50) nonfucosylated antibody. And the idea there is similar, there have been no data presented publicly. We treated the first patient at Columbia actually in 2017. So someday those data will be released. So we can't comment publicly but I think that defucosylation and the DLE mutation are again biologically different actually. And this is shown in the white paper which I encourage people to take a look at.

The other approaches out there include a molecule called the probody, this is a very clever joke, right? So you have anti-body, than a probody, right? So the probody has the antigen binding region masked by cleavable peptide. And the idea of this drug is that the anti-CTLA-4 activity only becomes effective within the tumor microenvironment or that peptide is cleaved by the appropriate protease, hopefully it's there. That's been going along, that probody has been going along. They increased the dose to fairly high level and then saw some toxicity, some CTLA-4 like toxicity. I think that's a very interesting molecule. I think the challenge is that there will always be some tick over for a molecule like that. And so whether that molecule can achieve its promise that is either decrease toxicity with the same activity or the same toxicity with more activity is still remains to be determined. Actually I think it's an interesting molecule. But so far still on development.

There's also a couple of other ideas. There's some bispecifics. I think Xencor has – is in the lead with this. They have an antibody that binds both PD-1 and CTLA-4 and there are several other companies that have a similar construct. The idea there is that you really only work on cells that have both PD-1 and CTLA-4. Yeah, that's a blessing and a curse. That might increase specificity and decrease toxicity and the tumor microenvironment, the Tregs do have a little bit of PD-1 and so this might help increase specificity and some of the CD8s also have a little CTLA-4. And so I think it's a reasonable concept that's still early on for that molecule.

There's a couple of other ones too but I think that again I just keep saying this over and over but I think really my take home point is that DLE mutation that alters the Fc gamma RIII binding is different than any other molecules and I think that this is the lead compound that has that and I think that's why this one is particularly exciting. I have to say I'm a little bit jealous for Dr. O'Day being able to present the data a little bit at this point.

Jennifer Buell
President & Chief Operating Officer, Agenus, Inc.
A

We'll make sure that we share in some of the novel innovations that we have in our hands as well.

Steven J. O'Day
Director & Executive Director-John Wayne Cancer Institute and Cancer Clinic, Providence Los Angeles Regional Research
A

We're in the same sandbox.

Jennifer Buell
President & Chief Operating Officer, Agenus, Inc.
A

Well, maybe this is a nice transition then as we – you've referenced the cancer cell patient and – the cancer cell paper where we actually highlighted the Fc engineering that we modeled in for our AGEN1181 molecule for CTLA-4. In that same publication we also had shared some data on our next generation or our TIGIT molecule. We have a family of TIGITs monospecific approach, that's Fc-engineered as well as the bispecific approach that we're really – both of which we're really quite excited about and they're moving into the clinic end of this year, beginning of next year. Do you think that this Fc engineering, based on your opinion, with the TIGIT molecule may have a similarly beneficial impact on this type of target?

Maybe we'll start with you, Dr. Drake.

Steven J. O'Day
Director & Executive Director-John Wayne Cancer Institute and Cancer Clinic, Providence Los Angeles Regional Research
A

Yeah. I think that's best for Chuck to address.

Charles G. Drake
Member- Scientific Advisory Board, Potenza Therapeutics, Inc.
A

So, definitely. I think that – in terms of me addressing by in terms of that being differential, actually. So I think that basically it was just – the presence of Fc receptors in the tumor microenvironment, to be fair, has not been very well studied. And it probably actually is a dynamic parameter that changes as the tumor evolves or undergoes treatment. But the fact that this DLE mutation allows stronger binding to – through the Fc receptor. It also equalizes binding between the low and the high affinity variant, which are both present in fairly reasonable proportions in the population really means that molecules that incorporate this could be different actually.

And so, I have to say that TIGIT is a very reasonable target going forward. We published a paper in the Journal of Clinical Investigation where we looked at sorted regulatory T-cells from multiple tumor types and did very careful

analysis of RNA sequencing. And TIGIT is certainly one of those molecules actually. And one approach is to try to use a blocking antibody that may be reprograms those TIGIT-expressing cells. But another approach actually is to consider that there might be mostly regulatory T-cells and once again attempt to try to get rid of them with depletion.

So I think that just like – just this is the case where the DLE version of IPI is different than IPI CTLA-4. I think that the Fc-modified TIGIT is certainly going to be different than the other TIGITs that are out there actually. And some of them are particularly engineered to not have any Fc receptor binding. So those are primarily designed to be blockers, right? And so, I think that you'll see what will happen is much like the CTLA-4 antibodies you'll see a very start differences in both activity and toxicity. And I would be – honestly, this is obviously speculative but I would be really surprised if the Fc modified TIGIT doesn't look different than the other TIGITs.

Jennifer Buell
President & Chief Operating Officer, Agenus, Inc.
A

Got it. That's very helpful. We've actually been able to share publicly some data, pre-clinically both with our TIGIT monospecific as well as the combination, demonstrating superior tumor control and pre-clinical models compared to competitive molecules in our hands. So, from our perspective it certainly does play a differentiating role with this particular target. I was curious to hear your take on that. Thank you.

Steven J. O'Day
Director & Executive Director-John Wayne Cancer Institute and Cancer Clinic, Providence Los Angeles Regional Research
A

Sure.

Jennifer Buell
President & Chief Operating Officer, Agenus, Inc.
A

Mayank, let me go ahead and open it up, there were a few questions I think that you had specifically on the ASCO landscape related to TIGIT target.

Mayank Mamtani
Analyst, B. Riley FBR, Inc.
Q

Yeah and maybe since we have both Dr. O'Day and Dr. Drake, maybe if you could comment on the Roche's firstline lung cancer study data that we saw from the CITYSCAPE study and just your general comments on the path forward. And then obviously I know we are still very early with the monospecific, and the bispecific approach for our Agenus, just kind of high level thinking on where this could go. And then we also obviously know there's the Arcus molecule and there's also a couple of other molecules in the TIGIT landscape. Maybe Dr. Drake if you want to take that?

Steven J. O'Day
Director & Executive Director-John Wayne Cancer Institute and Cancer Clinic, Providence Los Angeles Regional Research
A

Yeah. So – well, obviously this is not an area that I have been that involved with, but I – so I don't want to – I've seen the lung cancer data and I'm aware of the target. But I think it's reasonably encouraging data with response rates that were approximately doubled. I think response rate in – when we've done PD-1 plus, we've been through a lot already, not to get back to CTLA-4 but obviously it is the one player that has held its own. And not based on the response but obviously but obviously durability and long-term survival.

But, so I'm – we went through the IDO experience with insight. And anyway, this is encouraging. It's a randomized Phase 2 trial, reasonably good 70, 80 patients per arm. Their response rates were better. I am much more

interested in plateau of PFS curves at 12 to 18 months, to really see if the next immunologic manipulation will both recruit either change ratios like what Chuck said in the tumor microenvironment of pro anti-tumor effects as well as suppressive effects. So – or bring in additional molecules that can affect outcome. So obviously, macrophages and repolarizing them and myeloid derived stem cells that are all immunosuppressive.

So I think the phenotype of the microenvironment is critical to making a big change and we will see. But it's certainly an early signal that that looks promising. I know they're launching a large Phase 3 trial and whether it's premature or not, in my mind, it may be based on waiting for a more durable data but such as it is. Chuck, do you have some thoughts?

Charles G. Drake
Member- Scientific Advisory Board, Potenza Therapeutics, Inc.
A

Yeah. I mean, so I think that the story is not too dissimilar from I think what we're learning from CTLA-4, that is, careful studies that TME show that CTLA-4 is mostly expressed on a regulatory T cells, although there's a fair amount on CD8 to be fair. TIGIT is similar, there's more on the regulatory T cells than CD8 and Ana Anderson and Vijay Kuchroo have a very beautiful paper in the Journal of Clinical Investigation, kind of really in animal models at least suggesting, it's almost only on the Treg that matters. And so, that gives you sort of a immunological rationale for this combination, a rationale that's not dissimilar from the PD-1s and CTLA-4 rationale actually. And so, the response rate differences is encouraging.

I guess the thing that bothers me a tiny bit is that there were several other anti-TIGIT molecules in the clinic, BMS had one and I think, three or four other ones, Arcus. So like – they just missed this? I mean...

Mayank Mamtani
Analyst, B. Riley FBR, Inc.
Q

I think Merck had one of these too, right?

Charles G. Drake
Member- Scientific Advisory Board, Potenza Therapeutics, Inc.
A

Yeah. Merck had one. So I mean to be fair, – I mean to be fair, Roche did a fair number of patients. This was about 60 or 70 patients if I recall correctly in each arm and it looked like it was placebo-controlled. So, maybe this is a little bit more compelling than some of the IDO data. But I think what Steven says is true. Obviously, we would prefer to see – an initial response can sometimes be a little misleading in these studies. So seeing a longer PFS are potentially no less a signal, I think what we've need to see.

But to be honest, we go back to the thing that you guys just said in the beginning, right? So if a TIGIT works, right, that's great. Would an Fc-optimized TIGIT work better? And the answer is probably, right? So, I mean, this is not a bad thing. I mean if this was correct and this is TIGIT activity, I think that exploring the pathway with next-generation molecules more quickly than we did with CTLA-4 might be a good move forward.

Mayank Mamtani
Analyst, B. Riley FBR, Inc.
Q

Right. Okay. And another question I got in terms of just thinking about the path forward and specific tumor types that – and then keeping in mind the CD16 allele high activity there. I'm just curious if any one of you can take this question on where this can kind of go forward, what could be your path? And I know the advisory board, all that what we still have to see. And will – maybe, also would be helpful if you could comment, like can CTLA-4 in some tumor types can actually start becoming a backbone and we can start thinking about it as PD-1 and maybe there

are other agents that would need to combine and I'm obviously thinking – I think there's some data with Treg, for example, other alternative approaches where CTLA-4 actually works really well in that combination.

Steven J. O'Day
Director & Executive Director-John Wayne Cancer Institute and Cancer Clinic, Providence Los Angeles Regional Research
A

Yeah. Well, let me take a crack. I mean, I think everyone has historically wanted to combine something with PD-1 that isn't CTLA-4 because they're worried about its toxicity profile. And this notion that it doesn't really have much tumor coverage, so to speak. It was sort of a melanoma drug that didn't work elsewhere.

So we – I think like coming back to the beginning, I think of them as very different drugs and mechanisms and they only share a T cell, but a different life cycle. So, as we understand the biology better of how CTLA-4 works, there may be drugs combining with CTLA-4 that are optimal to PD-1. I mean, TVEC, and drugs like that, that have activity as a priming agent.

And the obvious with those data with CTLA-4, with ipilimumab that certainly looked in my mind better than their combination with PD-1 and yet they went to a large Phase 3 with PD-1. So we need to be smarter I guess in terms of the combination. The other thing I would just add is, I think one of the most exciting areas I think is in the microenvironment is with TKIs and VEGF-based therapies. And as people know, lenvatinib is getting more and more interest across solid tumors as a combination with PD-1. And Chuck can comment, the renal cell data looks tremendous and melanoma data is probably forthcoming. But with the bar that the resistant PD-1 patients overcoming that secondary resistance, which is a high bar but my sense is if a new drug can do that then its benefit in naive, IO-naive patients is highly likely to be equally, if not better.

So some of these drugs, I think the obvious place to look for benefit is if they can reverse a resistant phenotype after PD-1 exposure. And anyway, so these are areas that we're looking at. Obviously in melanoma with AGEN1181 obviously CTLA-4 can be used in sequence after PD-1 or even in resistant patients. And that would be a great area to look at as a single arm to see if you could overcome resistance.

Charles G. Drake
Member- Scientific Advisory Board, Potenza Therapeutics, Inc.
A

Yeah. I agree, I would say that in addition to the phenomenon of adaptive Treg resistance, which again occurs probably to many if not most on prior therapies, rationalizing CTLA-4, there is another phenomenon, I think, Steve, you kind of hit on it. It's adaptive myeloid resistance. So basically the same thing happens with radiation, you see initially a beautiful influx of activated CD8, T cells [indiscernible] (00:44:52) again proud of yourself but then it's balanced by both Tregs and then later on by myeloid cells, right?

And these myeloid cells fall into several categories, M2 macrophages granulocytic MDSCs, monocytic MDSCs. The reason I think lenvatinib is a nice part because lenvatinib blocks multiple TK, multiple tyrosine kinases and some of those are critical for the function of these myeloid components. So, I think in terms of combinations, another way to think about going forward is to consider that other suppressive component of the TME. In addition to the evil Tregs for which AGEN1181 should be a very good drug to consider some of the myeloid targets that might be involved in mediating that resistance.

And certainly, as you mentioned, I mean certainly the TKIs not only lenvatinib, cabozantinib probably does similar things as well. We have a paper in review where we looked at the immunological effects of cabo and find reasonably similar effects on the myeloid compartments and there's other drugs that fall into that too. But I think that thinking about a little different, right, thinking about pushing the tumor and then worrying about the Tregs,

AGEN1181 good idea, then thinking about what are you going to do about the myeloid component is another way to think about combination [ph] perhaps (00:46:04).

Steven J. O'Day A
Director & Executive Director-John Wayne Cancer Institute and Cancer Clinic, Providence Los Angeles Regional Research

Yeah. I can't wait to get CTLA-4 PD-1 and TKIs in combination because I do think it's just very delicate ratios of effectors and suppressors that can just turn it into full – particularly if they can keep the regs away and keep the myeloids away and then drive the CD8s. I think the dynamics of that's going to be really exciting. But CTLA-4 both drives fresh T cells, right? The primed expanded T cells as well as the PD-1s really focusing more inhibition on these exhausted cells that have gotten out there but are losing the battle. So, there's tremendous mechanistic opportunities to hit this at multiple sites and I just hope I'm here in the coming years to really witness this because I think there's going to be some dramatic forward. I mean it's going to be exciting this next 10 years.

Mayank Mamtani Q
Analyst, B. Riley FBR, Inc.

We absolutely need you. We absolutely need you to...

Steven J. O'Day A
Director & Executive Director-John Wayne Cancer Institute and Cancer Clinic, Providence Los Angeles Regional Research

I'll try to stay healthy, or Chuck will take over for me.

Charles G. Drake A
Member- Scientific Advisory Board, Potenza Therapeutics, Inc.

It won't be that long, man, it's going to be fast.

Mayank Mamtani Q
Analyst, B. Riley FBR, Inc.

[indiscernible] (00:47:19) in the next six months, we'll not even remember what this timeframe looked like...

[indiscernible] (00:47:22)

Mayank Mamtani Q
Analyst, B. Riley FBR, Inc.

But quickly, maybe, Dr. O'Day, if you think about this next level of innovation and I'm thinking more [indiscernible] (00:47:34) let's start with melanoma, I mean that's kind of the typical line of thinking which is obviously [indiscernible] (00:47:44) for the mechanistic reasons that we just discussed.

Like is it a new paradigm that it was maybe [indiscernible] (00:47:50) seems like a high risk approach but like how do you think about the agents that are obviously coming along in large volumes? And how do you develop them differently going forward than what was the understanding maybe 10 years ago? Could you just comment on that?

Steven J. O'Day A
Director & Executive Director-John Wayne Cancer Institute and Cancer Clinic, Providence Los Angeles Regional Research

So, I guess, I had a little trouble my phone was – had trouble – can you repeat the question?

Mayank Mamtani
Analyst, B. Riley FBR, Inc.

Q

Yes, so a little [indiscernible] (00:48:12) question, which is basically asking you as we talked about clinical development like 10 years ago we obviously start out with melanoma and then we think about other tumor type...

Steven J. O'Day
Director & Executive Director-John Wayne Cancer Institute and Cancer Clinic, Providence Los Angeles Regional Research

A

Yeah.

Mayank Mamtani
Analyst, B. Riley FBR, Inc.

Q

...depending on the immunogenicity. But what we know about all these TME suppressors, it's always tumor-specific and the targets obviously are guiding us to different ways. So, how do you think about drug development maybe in 2020 as you think about a newer target coming along?

Steven J. O'Day
Director & Executive Director-John Wayne Cancer Institute and Cancer Clinic, Providence Los Angeles Regional Research

A

Yeah. I mean, I think obviously melanoma has been a prototype, its UV signature, its mutational burden, and kidney cancer also to a certain extent. But melanoma has just been such a prototype of a tumor that's visible to the immune system. And we now know that that it does recognize it is foreign and it also battles and then. But so each tumor types are really depending on its source and its mutational and neoantigen signature.

And is really going to be different but there are common methods like Chuck was talking about. I mean, I think we're understanding the players, the orchestra that the tumor is involved with and that milieu is really, really interesting and it has both common elements to and then very unique elements.

So I still think disease-specific biology and clinical experts are going to be critical to figuring the targets out because there will be differences. But I'm also encouraged by when we find targets that are effective like PD-1 and CTLA-4, how broadly they can be applied. I think the bigger issue will be once the immunologic sort of understanding of the tumor and its microenvironment are understood, we may need direct cytotoxics, whether it's radiation, chemotherapy, targeted drugs for brief bursts to disrupt and allow that platform to take over. And colder tumors may be more work than warm tumors but warm and hot tumors still kill people because of these ratios.

And we're just getting a lot more sophisticated, it's going to be a really exciting time to – I think we need our disease specialists but our immunologist and biologist, too.

Jennifer Buell
President & Chief Operating Officer, Agenus, Inc.

A

Dr. Drake...

Mayank Mamtani
Analyst, B. Riley FBR, Inc.

Q

Great. And maybe – sorry, Jen. Go ahead.

Jennifer Buell
President & Chief Operating Officer, Agenus, Inc.

A

Let me just – no problem. I'll just say one comment and thank you, and thank you very much for your vision and your leadership in this space, both of you. I'll make a point that optimizing combinations is so critical in the underpinnings as to how we've designed our portfolio. And we will have some very exciting data that we'll be reporting out on in just a couple of weeks at AACR that may help us to elucidate the best ways of approaching some of these combinations and we're looking forward to doing them together with you.

Mayank, please go ahead.

Mayank Mamtani
Analyst, B. Riley FBR, Inc.

Q

Yeah. I guess my final question, actually, you set that up nicely, Jen. Maybe if, Jen, you want to start the first end of this question and I want to ask Dr. Drake also. Essentially, for the upcoming – for the remainder of 2020, what are some datasets that we should be looking out for specifically in the checkpoint inhibitor space? And obviously, mostly in our combinations because a lot of monotherapy activity is kind of – at least with PD-1 is out of out of the way, but obviously CTLA-4 monotherapy, I think we'll learn more.

So, maybe, Jen, can you just set the stage for AGEN1181? What sort of we should expect through the remainder of 2020? And then maybe, Dr. Drake, broadly, for the space, it would be helpful what should investors focus on.

Jennifer Buell
President & Chief Operating Officer, Agenus, Inc.

A

I'll just take a moment. I want to make sure we turn it over to Dr. Drake. We have, for AGEN1131, we have some interesting data, as I just mentioned, coming up at AACR looking at best ways to optimize combinations for patients with cancer looking for those long, durable, curative responses and broadening the patient population to do so. We'll have some data at AACR. We're also going to have some additional clinical data as the trial matures. And as you know, we've been very aggressive at getting this data out. So you could look for data at upcoming major medical conferences.

And beyond that, our BLA filings are actively underway and we're planning on filing those this year. So we're ideally – once we've secured the filing we'd be looking to release an update on the data to date. So, I'll turn it over to you now, Dr. Drake, to address the remainder of the question.

Charles G. Drake
Member- Scientific Advisory Board, Potenza Therapeutics, Inc.

A

Sure. I mean I think that some of the other combinations are going to have some more mature data towards the end of the year. LAG-3, which I have a vested interest in, went in to the clinical long time ago. So hopefully we'll see some data from DMS, from lenvatinib. And there's a couple of other anti-LAG-3s in the clinic. There'll be some TIM-3 data as well.

In terms of the TIGIT pathway, I think many people forget that TIGIT pathway is a parallel pathway. So as TIGIT binds to PVR but there's another pathway PVRIG binds the molecule called PVRL2. And there is an antibody against PVRIG in the clinic from a small company called Compugen that gave a little bit of data I think at ASCO and they'll be – they're going forward at the triple combination.

But the other thing I think that investors – if I was an investor, the other think to keep an eye out for on to combine. And I think Steven said this very well actually. So the idea is you probably need something to treat the tumor and radiation chemotherapy. Those are good things. I think that in addition to – and so for somebody to

combine with IO, the drugs that are really seeming to – really be rising quickly in interest is the antibody are conjugates.

So we saw data from anti-B7H3 from ADC from Macrogenics, and prostate cancer were some nice responses there, there's a similar drug from the Daiichi Sankyo on the clinic. And in bladder cancer, this is going to be the lead actually. So we're going to have enfortumab as the backbone in first line and then we're going to add checkpoints to that actually. And I think that, unfortunately, not CTLA-4 which is, we should be adding at this point. But still, I think that what, Steven, said is the basis for many combinations, we'll include something to get rid of the tumor probably in many cases, PD-1 blockade still, but CTLA-4 blockade as well. So, I think that's what we'll see over the next couple of months, I hope.

Mayank Mamtani

Analyst, B. Riley FBR, Inc.

Q

Great. Lots to come. It looks like we are just starting out 2020, and from Dr. O'Day's vision, we are like just scratching the surface here on the immuno-oncology innovation that's ahead of us. I think we are – with that, we're out of time, Jen. Are there any questions out your end or any closing remarks? Otherwise, we can close the call.

Jennifer Buell

President & Chief Operating Officer, Agenus, Inc.

Thank you very much. No closing touch for me, just great appreciation for your time and participation in the call. Thank you.

Mayank Mamtani

Analyst, B. Riley FBR, Inc.

Thanks. Thank you, Dr. O'Day. Thank you, Dr. Drake.

Steven J. O'Day

Director & Executive Director-John Wayne Cancer Institute and Cancer Clinic, Providence Los Angeles Regional Research

Thank you.

Mayank Mamtani

Analyst, B. Riley FBR, Inc.

We really appreciate it. And thanks to everyone for joining us and please, everyone stay well and healthy. And back to you, John. Thank you.

Operator: Thank you. Thank you, ladies and gentlemen this does conclude today's conference call. You may disconnect your phone lines at this time and have a wonderful day. Thank you for your participation.