Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/role-emerging-therapies-retinal-disease-clinical-practice/15444/

Released: 05/11/2023
Valid until: 05/11/2024
Time needed to complete: 60 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

The Role of Emerging Therapies for Retinal Disease in Clinical Practice

Announcer:
Welcome to CME on ReachMD. This activity, entitled "The Role of Emerging Therapies for Retinal Disease in Clinical Practice," is jointly provided by Clinical and Patient Educators Association and iVista Medical Education Incorporation. This is activity is supported by an independent medical educational grant from Regeneron Pharmaceuticals Incorporation, Apellis Pharmaceuticals, Iveric Bio, and Outlook Therapeutics. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements, as well as the learning objectives.

Dr. Singh:
Hello, and welcome to The Role of Emerging Therapies for Retinal Disease in Clinical Practice, this roundtable discussion. My name is Rishi Singh. I'm your moderator for today's session, in Cleveland Clinic, Florida, and I'm joined by this expert panel of individuals who are going to give us some really great talks on the latest and greatest therapies within retinal disease. First, Dr. Mark Barakat from the Retinal Consultants of Arizona, Dr. Arshad Khanani from Sierra Eye Associates, and Dr. Christina Weng from the Baylor College of Medicine. Thank you all for joining today's program.

So we're going to be covering these learning objectives. You know, anti-VEGF therapy has been around for many years now, and we have had great results with it, but yet see a lot of the drawbacks to its therapy in clinical practice today. And for a talk about some of the limitations regarding this therapy, and what we've seen in our own hands – long-term studies as well as short-term issues with this drug – and we'll talk about the clinical trial data for newer therapies which may extend the durability of this drug over time, as well as help us manage some of these neovascular retinal conditions with alternative therapies. In addition, we're going to be focusing on geographic atria as the new frontier for managing patients with vision loss. We have some emerging therapies, one that's FDA approved and one that's soon to be FDA approved, for this condition, which will help potentially, help patients with this condition, which is certainly one of the leading causes of legal blindness beyond the common ones we take care of in retinal practice. And our activity partnership today is with iVista Medical Education and with Clinical and Patient Educators Association, and this is provided jointly with those programs, and is supported by an educational grant for Regeneron Pharmaceuticals, Apellis, Iveric Biosciences, and Outlook Therapeutics.

So let me turn it over to the first presentation for today, and that's going to be by Christina Weng, who's going to talk about GA therapies, and at the end of today's three talks, we're going to spend a good amount of time discussing these studies and what they mean as far as our clinical practice changes go. So with that, I'll turn it over to Christina. Thank you.

Dr. Weng:
Thanks a lot, Rishi. It's great to be here with you and Arshad and Mark. And it's really a pleasure to present on this topic, which is extremely pertinent right now, given that we finally have our first FDA-approved geographic atrophy therapy, and perhaps a second one by the end of the year. So I'm going to provide a really brief overview. You know, we – there's a lot of discussion and buzz right now, and I'm excited to not only present some of the latest data, but also hear some of your thoughts at the end, when we have our panel discussion.

These are my disclosures, and of note, I am a consultant to Iveric Bio. I will be talking about one of their leading candidates in this presentation. So I was asked to talk mostly about pegcetacoplan, our first and only FDA-approved therapy for GA, and also avacincaptad, and I will be focusing on those two in this next ten minutes. But I thought really that we should start off just by a brief mention of how broad and bustling the investigational landscape for geography – for geographic atrophy is at this time. And by no means is this list comprehensive. You know, GA is a blinding condition. It's thought to affect over 5 million people worldwide – over 1

million Americans – and it's a leading cause of blindness, like you said. Thus far, until recently, we haven't really had any therapies to treat these patients and so it's great that there's so much interest and research going on in these areas. Because dysregulation of the complement pathway is thought to be a significant contributor to the pathogenesis of GA, of course we have several of these that work in that way. So for example, avacincaptad pegol, which we'll talk about a little bit later in this slide deck, inhibits at the level of C5. We're going to talk about that soon. We also have ANX007 in phase 2. This is a C1Q inhibitor, working on the classical complement pathway. And then of course we have others, like GT005, even a gene therapy expressing complement factor I, and also an antisense oligonucleotide looking at complement factor B inhibition that potentially may show some promise. There's also other drugs in the investigational pipeline that work through other approaches. For example, elamipretide unfortunately did not meet the primary endpoint in the phase 2 study. However, it did show some promise in being able to protect photoreceptors, and it's being more closely looked at. It's a mitochondrial modulator. We also have risuteganib, an anti-integrin, small peptide molecule. We've got HtrA1 antibody. Even oral doxycycline is in a phase 3.

And of course, something really exciting is to remember that a lot of these therapies, unfortunately, only slow down the progression of the disease, and so we really are looking to other complementary therapies to help potentially restore vision for our patients and that really lies in the area of cell-based therapies which is also an area of great interest right now.

So again, I am going to focus on pegcetacoplan and avacincaptad in this talk, and we're going to start off with pegcetacoplan. This is the first and only FDA-approved therapy for geographic atrophy. It is a pegylated, cyclic peptide. It binds to C3, blocking cleavage of C3 to C3A and C3B by C3 convertase, and it was FDA-approved on February 17th of just this year. So, really very recent, and it works at C3 which is really a common meeting grounds of all three complement cascades.

It was approved based on two registration studies, called DERBY and OAKS, for pegcetacoplan, and these are interesting. We'll talk a little bit about the details shortly, but these two trials enrolled patients who were 50 years old, and – excuse me, 60 years old and older, who had visual acuity of 20/320 or better. GA lesions were measuring anywhere between 2.5 to 17.5 millimeters squared, and that is important to note that either with or without subphobial involvement was a part of the inclusion criteria here. If the lesions were multifocal, at least one of the lesions had to be 1.25 millimeters squared. And essentially they enrolled almost 1,300 patients, randomized into these groups, so either pegcetacoplan was dosed monthly, every other month, or sham – and sham was broken up into monthly and every other month, just to preserve masking. The primary endpoint of the DERBY and OAKS study was at 12 months they looked at the change in total area of the GA lesions based on fundus autofluorescence. And then, they went through 24 months and looked at a variety of other prespecified secondary endpoints, including BCVA, low luminance BCVA, reading speed, and even NEI-VFQ. And then some of these patients rolled into a 3-year, open-label extensions study called GALE, which we'll learn a lot more about in terms of long-term outcomes.

So here's the efficacy data to start off with, and an interesting thing happened in this set of trials, where OAKS – one of the two pivotal trials – did meet the primary outcome, and the other one – DERBY – just narrowly missed it. And so, what you're seeing here is essentially – let's start with OAKS – you can see, a 21% reduction of GA lesion growth rate over one year in the monthly arm, 16% reduction in the GA lesion growth rate in the every-other-month arm, which is in blue, and both of those are compared to sham, which is in the gray line. And then DERBY, you can see the numbers were a little bit more modest. They did not reach statistical significance again. But one thing that you can see in both of the trials is that you can see that the curves begin to pull apart as you enter the months 12 through 18. And you can see that here and all the way through months 24 as well.

You can see that the curves continue to pull apart after that first year, and that effect is magnified. Interestingly enough, even though this was not the primary endpoint, in DERBY, the percentages in reduction of GA lesion growth rate did reach statistical significance when we are looking at the nominal P-values.

So when we look at secondary outcomes, again no statistically significant difference in terms of BCVA or some of the key secondary endpoints that we mentioned earlier, at the 24-month time point, like maximum reading speed, microperimetry. They even had this index called the Functional Reading Independence Index. However, and I think one of the challenges right now, is really trying to reconcile sort of structure and function in these GA trials. And you know, does it matter? Should we be treating these patients if we see structural improvement or anatomic improvement but not necessarily functional improvement, at least not at the 24-month time period? And that's really a topic of discussion right now, because many of us believe that eventually, yes, along a long enough time horizon that we would appreciate that.

And interestingly, there's a lot of other studies going on right now, including various post-hoc analyses. This one was released recently, which was published in Ophthalmology Retina, where they used an artificial intelligence-driven OCT analysis to look at some of the patients who had been treated with pegcetacoplan in PHILLY which is the phase 2 study, and they looked at the junctional zones of those patients treated with pegcetacoplan and it suggested possible preservation of photoreceptors. There's other studies also, suggesting possible preservation of RPE. There are some data that was just presented at ARVO, for example, and also different functional measures like microperimetry. So we will learn more with time.

Now what about safety? Well, in terms of safety, there was a higher rate of exudative CNV development noted in the pegcetacoplan group versus sham. You can see that circled in pink there. One thing I want to point out is that even in the sham group, you can see that

just as part of the natural history, there are some patients that will convert to exudative lesions. But definitely, there seems to be a trend, and it seems to be dose-dependent, that there is CNV development with pegcetacoplan treatment. It's something that we'll have to address as we begin to treat our patients. There's also some other adverse events that have been monitored closely, including intraocular inflammation and even ischemic optic neuropathy, that are being closely looked at.

And now I just want to spend the last few minutes here talking about what we might hear about next. So, avacincaptad pegol is a pegylated RNA aptamer that inhibits cleavage of C5 into C5A and C5B. So it works a little bit further downstream from C3, which we just talked about. But essentially, it inhibits the priming of inflammasomes and formation of the membrane attack complex. We'll likely hear about this soon, because the PDUFA date is August 19 – so later this summer. Pretty exciting – this would potentially make a second approved agent that we have. And this was approved based on two pivotal studies called GATHER1 and GATHER2. They were similarly designed, but with some slight differences. In GATHER1, it looks at a variety of different dosages for example, in all patients who were treated monthly, whereas in GATHER2, you can see they were treated monthly for the first year, and in some of those patients, in the second year were still treated monthly and some of them were treated every other month. But both of them had primary analysis readouts at month 12, and again looking at the mean change in GA area lesion growth. And one of the key differences, even though everything else was very similar in terms of inclusion of lesion size between 2.5-17.5 millimeters squared, in this study the patients were not center point involving. So that's one key difference between the first set of studies with DERBY and OAKS, versus the GATHER studies. And additionally, the lesion had to at least partly be involved 1,500 microns from the foveal center.

And so let's take a quick look at the efficacy and safety in this set of studies. So, both of these studies did meet primary outcome, and you can see that there was anywhere between a 14.3-27.4 reduction in the mean rate of growth of the GA area. And again, just like in DERBY and OAKS, you see this pulling apart of the curves, as you enter past month 12. In GATHER 1, we have the next six months after that, between months 12 and 18 where the curves widened. So again, speaking to a potential magnified effect, the longer a patient is treated. And again, very similarly to the other set of trials, there were no statistically significant differences in the visual acuity or the low luminence BCVA at 12 months. Also, a lot of other post-hoc analyses that are going on right now – in fact, one that was recently read out – showed that there was a 44-59 percent risk reduction in the rate of vision loss of greater or equal to 15 letters in those who were treated with avacincaptad versus sham over 12 months. And so again, suggesting really trying to correlate structure and function, and tie that together so that we can make a meaningful story and a meaningful case for treating our patients.

In terms of safety, it's interesting to see how many findings really parallel that of DERBY and OAKS. Again, a higher rate of exudative CNB development noted in avacincaptad pegol treated arm versus sham. You can see that circled in pink there. Interestingly, there were no ischemic optic neuropathy events or endophthalmitis that I've become aware of yet, with avacincaptad. There was one case of intraocular inflammation in GATHER1.

So I know we're going to talk a little bit later – Rishi, as you said, as a group – but some of the things to just kind of think about, I think a lot of it comes down to patient selection, and the timing of intervention. When is the best time to get involved and start treating patients? How do we find these patients in the community? A lot of them actually don't live within our practices. Are we going to dose the way they were dosed in trials? Are we going to put our own spin on things, as retina specialists, like we often do? How should we be imaging these patients? How are we supposed to manage the associated CNV that we do see with some of these treatments? And then of course, just being, you know, eyes-wide-open for any safety issues down the line that we might see in the real world that weren't necessarily detected in the trials. And so I'll hand it back to you, Rishi. Thanks so much.

Dr. Singh:
Thank you, Christina, for that really comprehensive review of all of those drugs for geographic atrophy. What an exciting place to be, because we finally have therapies that we might be able to address this. But we'll talk about some of the pros and cons of that in our discussion session, so thank you for bringing up those topics and we'll get to them at the end. And now I'm going to turn it over to Dr. Arshad Khanani, who's going to review some of the recent studies with PHOTON and PULSAR.

Dr. Khanani:
Thanks, Rishi. It's a pleasure to be here with you, Christina and Mark. So over the next 10 minutes or so, I'll be reviewing the results of the phase 3 PHOTON and PULSAR studies. Here are my disclosures. So before we get into the trial design and data, let's talk a little bit about aflibercept 8 milligram, which is the drug that's being looked at in these trials. It's a novel, intravitreal formulation, and it is 70 microliters, so a little bit more than what we usually inject. It is aflibercept, but it is higher dose, and the idea is that is four times higher molar dose compared to the currently approved aflibercept 2 milligram, and the idea is that this can provide longer effective vitreal concentration and enable more sustained effect on VEGF signaling. So the idea is, can we maintain disease activity control for a longer period of time, because this agent has a higher molar dosing.

So let's look at PHOTON study first. It's the phase 3 pivotal study. It's a multicenter, randomized, double masked study in patients with diabetic macular edema. Patients could be naïve or previously treated, and patients were randomized into three different groups: aflibercept every 8 weeks – that's the 2 milligram; or aflibercept 8 milligram every 12 weeks or 16 weeks. And patients in the aflibercept 2 milligram group received five monthly injections as a loading dose, versus in the 8 milligram group, they only received three loading doses, so something to keep in mind as you look at the data.

And they randomized 1:2:1, and you can see the number of patients – 167, 328 and 163 – so this is a quite large study, and the primary endpoint was at week 48, and it was mean change in BCVA. So this trial is designed for noninferiority like many of the recent trials, while reducing treatment burden by showing greater durability. And the key secondary endpoints included multiple different ones. The one that's important, obviously, is also the diabetic retinopathy regression – two-step or more – in these patients at week 48. And the study is two years, and there's an optional one-year extension for the study, if patients sign up for it.

Here's the dosing schedule, and dose regimen modifications, so you can see how the dose was adjusted based on disease activity. I think it's important to look at the disease activity criteria, which was greater than 10-letter loss of BCVA, due to persistent or worsening DME, and greater than 15 micron increase in CRT. So in this program, they have used both vision and disease – and OCT criteria to extend or decrease treatment interval, and you can see how these different groups were extended, based on disease activity or not.

So here are the results. These are the one-year results. We are waiting for two-year results later this year. Primary endpoint was met in both 8-milligram groups. Aflibercept 8 milligrams every 12 weeks, and 16 weeks, had noninferior BCVA compared to aflibercept 2 milligrams every 8 weeks, as you can see on those curves. Patients gain anywhere from 7.9 to 9.2 letters. The 8-milligram every 12 weeks met the noninferiority margin of 15% in the proportion of patients with two step or greater, improvement in DRSS at week 48, and the safety of aflibercept 8 milligram was comparable to that of aflibercept 2 milligram, and I'm going to cover that in the next few slides, after I show you the OCT.

Here's the mean change in central thickness. As a reminder, patients in 2-milligram group received five loading doses compared to three loading doses in the 8-milligram group. And then you can see that what we see here is that in both 8-milligram groups, four weeks after the last monthly dose, you can see greater reductions in CRT compared to 2-milligram. So something to keep in mind – we do keep – see some fluctuations in all groups. Remember, these are averages, so I think there are many patients who will be stable, while some will have fluctuations.

In terms of durability, here are the results. So the large majority of 8-milligram patients maintained the randomized intervals. And you can see, 93% of 8-milligram patients maintained dosing intervals of 12 weeks or greater, really highlighting the durability seen in this trial.

In terms of mean number of injections through week 48, again these patients received different loading doses, and here you can see around eight in the 2-milligram group, and around six in the every-12-month group, and five in the every-16-week groups. Here is the safety. I think things I'm looking for is IOP increases, or inflammation because of volume is higher, we are putting more protein here, so when you look at that in terms of intraocular inflammation, it was 0.6% in the 2-milligram group, and 1.2% in the 12-week group of 8 milligram, and then 0.0% in 16. So all 8-milligram group inflammation rate was low – 8.8%. There were no cases of endophthalmitis or occlusive retinal vasculitis. IOP, again to looking at that, you can see 1.2% of patients in the 2-milligram group and 0.3% in the 12-milligram group, and all 8-milligram patients, 0.2% – so really no meaningful increase in IOP in these patients receiving 70 microliters compared to 50 microliters.

So now let's look at the PULSAR study. So this is a study looking at patients with neovascular AMD. These are naïve patients. Again, just like PHOTON, it's a large, global, randomized study, and here patients received 2-milligram aflibercept or label after the loading doses, so three loading doses and every eight weeks, compared to every 12 weeks or 16 weeks with the 8-milligram. And then they also used the disease activity criteria here. You can see, these were randomized 1:1:1. The primary endpoint, again, was mean change in BCVA. This is a noninferiority study again, and then the secondary endpoints, looking at fluid dynamics in these patients, treated with higher doses of aflibercept. And again, two-year study and then the extension is optional, if patients sign up for it.

This is the dosing schedule and regimen modification. At year one, you can see the opportunities to extend or decrease interval. I think one thing to highlight here again, is the disease activity criteria. This is different than what was used in PHOTON, because these are neovascular AMD patients, and to accumulate fluid is more of an urgency to treat it. So here are the criteria was used with greater than 5-letter loss in BCVA due to neovascular AMD, and looking at CRT, it was greater than 25 micron increase in CRT or seeing new hemorrhage or new onset of foveal neovascularization. So, again, these are end criteria being used, but these are much tighter than what was used for PHOTON, rightfully so, to avoid any vision loss in these patients.

Here is the summary. Primary endpoint and key secondary endpoints were met. Aflibercept 8 milligram every 12 weeks and 16 weeks had noninferior BCVA compared to every 8 week 2-milligram aflibercept, at week 48. And when you look at aflibercept 12 and 16-week groups, with 8-milligram, combined, had superior drying effect compared to aflibercept 2-milligram every 8 week, at week 16.

And here you can see the BCVA. Again, comparable visual acuity gains in all three groups. CRT – again, we see a robust decrease in CRT, after the initial monthly loading doses in all three groups, and you can see it's equivalent in all three groups at the end of first year. You can see some fluctuations here also.

In terms of proportion of patients maintaining Q12 and Q16 intervals through week 48, 83% of 8-milligram patients maintained dosing intervals, 12 weeks or greater, again highlighting the durability of 8 milligram of aflibercept seen in this trial. Mean number of injections at one year – 2-milligram patients had 6.9, compared to 6.1 in the 8-milligram group that was every 12 weeks, and 5.2 in the 8-milligram

group that was 16 weeks.

Safety is again important, for a new drug. Even though we have used aflibercept for a long time, it's larger, more redosing, more volume, again things I'm looking for is intraocular pressure, inflammation and any other signals. We have not seen any cases of ischemic optic neuropathy in either PHOTON or PULSAR. And when you look at IOP increases, again just like PHOTON, we have not seen meaningful increases in IOP in the 8-milligram group, and when you look at intraocular inflammation, again all 8-milligram patients combined, it was 0.7% compared to 0.6% in the aflibercept 2-milligram every 8 week group. So again, no safety signals that are new that were identified in this trial. So bottom line is, we are hoping to have this agent approved later this year, and I think the treatment burden for our patients with neovascular AMD as well as DME is high, and the hope is that with higher, more redosing of aflibercept, we may be able to decrease the treatment burden for some of our patients. So, thank you for your attention. Rishi, back to you.

Dr. Singh:
Great. Thank you very much, Arshad. So great, again, advancements in treatment of retinal vascular disease you saw through some of that data, and we'll talk about that in light of current approved therapies and maybe some other things in pipeline that will hopefully move the needle. Let's turn it over to the next presentation, which will be by Dr. Mark Barakat, who's going to discuss the need for on-label Avastin therapy. Mark?

Dr. Barakat:
Thank you, Rishi. It's a pleasure joining you, Christina and Arshad. As we talk a little bit about on-label bevacizumab. And here are my disclosures. And when we talk about bevacizumab, the first question that at least comes to mind is why do we care? And the fact of the matter is, as a community we love bevacizumab – of course, off-label. So, if you look here we have the new patients starts. If you look at a survey of respondents, two-thirds of us start people on bevacizumab off-label.

In terms of maintenance, a good plurality – possibly half of patients – stay on bevacizumab long term for maintenance, and it's really become ingrained as part of the meshwork of what we do in retina. So that's great, but what about off-label bevacizumab? Well, compounding carries risk, and we all know this but we tend to overlook it. There have been these clusters of infections. There's these questions of levels. And you wonder, what are we introducing into the eye? But additionally, not only does it carry risk, but it also carries some uncertainty, and by that I mean if you look at what you get in your hand, it's not really the bevacizumab necessarily that you would get in the large quantity. So if you look at this quite interesting paper, on the right-hand side, you see the control group, in terms of the bevacizumab as it's available, and then you look at a compounded bevacizumab on the left-hand side. And if you look and see the concentration of protein, it may not come as a shock to us that a lot of these, if not all of them, are well below the level of concentration that you would expect if you were to get it straight out of the vial. But not only that, if you also look at the clustering – the particle size – on the bottom, you'll see the particle size of bevacizumab as it is straight from the manufacturer. It's a tight spectrum. But if you look above it, you'll see a wide distribution, because you get all these aggregates formed as well. So, what you're getting in your syringe, in the prepackaged, compounded syringe may not be the bevacizumab that you hoped you'd get.

Well, here we have ONS-5010, and this is the investigational ophthalmic formulation of bevacizumab we've all come to know and love, which is an anti-VEGF. I won't bore you with those details; I think we're all comfortable with that. And is the phase 3 pivotal study design that looked at this drug. And here you have a superiority trial, where in the treatment arm, you get monthly ophthalmic bevacizumab, and in the control arm, you get three monthly loading doses of ranibizumab, followed by every-third-month, Q3 month, dosing of ranibizumab. The primary endpoint was BCVA gains of three lines or greater. Also other key secondary endpoints are listed here, at month 11. Of course this was for patients with wet AMD, that were treatment naïve, and the BCVA range is seen here, was between 20/50 and 20/320.

So, there are about 228 subjects that were involved. As you see, close to 90% completed this study, with 103 in the active arm and 95 in the control group. And well-balanced, as you might expect. These tend to be predominantly females that were Caucasian, and 79-80 years old. BCVA, as we can see here, was about 51, 52 letters, so not the greatest vision in the world, and baseline CFEs were roughly – between 420 and 430. And so the primary endpoint was met. The proportion of 3-line gainers, as we can see, whether it's intent-to-treat or per protocol was between 41 and approximately 42% of patients in the bevacizumab arm, which was statistically significant.

And here you see this just laid out over time as well. You see the bevacizumab arm in the light blue, gaining a robust visual gain with treatment and maintaining that gain with monthly treatment throughout the trial.

Key secondary endpoints also shown here, in terms of what the actual BCVA score was, and you have an 11-letter gain in the bevacizumab group, both intent-to-treat and per protocol, which is also statistically significant compared to the control group.

And here you see this over time as well. Again, whether you're looking at the proportion of three-line gainers or whether you're looking at the change in letter score, you see a robust response in the first three months, which is maintained over time and statistically significant in the bevacizumab group.

Secondary endpoints, also categorical. 5-letter gain, 10-letter gain – you see almost 70% of patients in the bevacizumab group gained 5 letters. 56 or percent of patients gained 10 letters or more, and of course we already know that close to 42% of the patients gained 15

letters or more, and these are also statistically significant.

Of course, safety is paramount. It's important whenever we have a new drug coming out. And it's nice to know that the safety signal was well-balanced. There's only one case of intraocular inflammation in this trial, and it was iritis. And frankly, there's just a low incidence of oculative needs throughout all of the three trials with ONS-5010.

So where do we stand now on on-label bevacizumab? So, we know there's a high demand for off-label compounded bevacizumab, and this on-label, ophthalmic formulation addresses those compounding concerns. Their USFDA dealing was accepted. There's a target PDUPA date in August of this year. Conversations with the European medical agencies have gone well as well. As you can see, NORSE1, NORSE2, NORSE3 were the trials. We focused mainly on NORSE2, as it was the pivotal trial, but those have been completed. And with that, we anticipate having an ophthalmic formulation of bevacizumab as part of our arsenal in the near future. With that, I thank you.

Dr. Singh:
Great. So, really nice presentation, Mark. Thank you for giving that. And so we're going to turn over to our panel discussion now, and why don't we start off with Christina.

You know, you presented this data on geographic atrophy, and arguably some of the most controversial, I think, data out there to date. We see that there is a modest improvement in GA growth. Some may call it modest; I'm going to put that in quotes, because I want to hear from you whether you think that's modest. We have an improvement in some patients going on to develop three lines of vision loss, and then you have the side effect profile. So, walk me through how you're going to talk to your patients about this, and what you would kind of rationalize with some of the statements I just made.

Dr. Weng:
Yeah, thanks, Rishi, and enjoyed the presentations from the group. You know, I think it – one of the really interesting things is that when this drug was approved, it was such a historic moment for the community, because we have tried and tried, and had a lot of failed trials with research in the past many decades. And finally, we had something that we could offer our patients, even if the effect was what some people deem "modest." And I was actually quite surprised that it wasn't universally welcomed at first, until I really started thinking about it a little bit more, and I can understand both sides of the conversation, because there are some risks associated with these types of treatments, and also it's – there's still a lot that we don't know about the disease and about the treatment effects. So, to answer your question Rishi, you know, however you regard the percentages that I shared with you earlier, I think what's very important to know is that this is a disease that, in general for the average patient, is going to lead to decline. It only goes one way, right? And I think one of the hard parts to convey to patients, but it's very important in those discussions, is to let them know this is not a cure. This is, unfortunately, not like the anti-VEGF of wet AMD at this point, although I hope we'll get there. This is slowing down a negative slope, right? To put it into math terms. And so, it's sometimes discouraging for people to hear that, but if you think about it, everything that we do in medicine is really trying to buy quality of life for time. Right? For time – you're buying time. And so, even if you can slow down the curve, in my opinion, even if it's "modest," I still think it's something worth considering, and I'm very happy that we do have something to at least offer our patients.

When it comes to actually making those decisions, Rishi, I think it gets a little tricky, and I think more so for this disease than perhaps a lot of the other ones that we treat on a daily basis. This is really going to involve shared decision making with the patient, because like I said, there are a lot of unknowns such as who is the ideal patient that we should be treating. We don't really know that quite yet. And additionally, it's a lot of treatments, right? It's every month, or every other month, at least if you're looking at what the trials did, and there are some adverse events that have been observed, although fortunately with CNV, which is really one of the most prominent ones, those have responded really well, at least from what we have observed in the trials so far, they've responded well. They often don't need indefinite treatment of anti-VEGF.

We have to think about things like ION, and we're looking closely at IOI, and all of that, so there's a lot of unknowns still, but for some patients having that additional however-many-months of visual acuity is very well worth it, and I do think that having those discussions with each individual person is important. But I'd be curious to hear what the rest of the panel thinks about that.

Dr. Singh:
Yeah, Arshad, you're very close to a lot of this data. You were a participant in some of these trials, too. Tell us about your take on this.

Dr. Khanani:
I think, Rishi, I agree with Christina. I think it's an important advancement for our field to have one treatment, and possibly another one in the future. I think – personally, I think patients and retina specialists are spoiled because of excellent anti-VEGF treatment. I think we need to think of this disease that will progress in 100% of patients, 100% of the time, and I think we have to think about it differently, like we used to think about neovascular AMD in the PDT era. So here, recently at ARVO, we saw the visual function data that Christina mentioned also in her presentation, from both programs, looking at functional benefits. And of course, each program looked at it in a different way. But I think conversation needs to go in that direction. If I show patient an OCT image and FAF, and we show the lesions are growing, that's helpful but if I tell a patient that if you get treatment, this is your risk factor of maintaining, or this is your percent

benefit, then I think it's meaningful. For example, the data for avacincaptad that Christina shared. You know, if I tell a patient that there's a 56% reduction in losing three lines of vision at one year, it's meaningful, or if you looked at the pegcetacoplan data, that in the right patient, if it's – you are saving a line of vision with treatment, that's meaningful. So I think the conversations need to go in that direction.

And the other thing is, I think Christina mentioned it well, that it's a shared decision making. I think we have to look at this disease and give the risk and benefits of treatment up front. And I think the patient population that doesn't get talked about in these trials is our patients with neovascular AMD, that are getting treatments and that's well-controlled disease, but they all lose vision because of progressive geographic atrophy. I think those patients are more open to get injections, because they are used to it and they get them anyways. So I think, as a field overall, we are going to learn about it. Personally, I offer this to every patient, and then make a decision based on where their lesion is, what their activity is, where their vision is, and how compliant they are going to be, because essentially we are looking at lifetime of treatment without having a real biomarker of treatment success. So, I think great advancement, but we can do better and will continue to look at new programs, as Christina mentioned, and hopefully we have better treatments in the future.

Dr. Singh:
Mark, I'll let you comment quickly before we move on to discussing high-dose aflibercept. Any additional thoughts to offer about this sort of thing?

Dr. Barakat:
The only additional thought, because all points are well taken, well said, is it is very rare that a new agent and possibly second, come out that just change the standard of care, and I think the standard of care bare minimum is to have inhibition.

Dr. Singh:
Mm-hmm. Great. Great comment. Okay. Let's switch gears and talk to Arshad about, you know, high-dose aflibercept. You know, Arshad, this study, while meaningful, I think has some opportunities to show us a little bit more data. We haven't seen year two data yet. Give me a prediction, as far as what you think is going to happen in year two, based upon some of the year one findings.

Dr. Khanani:
I think, Rishi – great question, because I think we have seen that the drug is safe, and it's working well, and we have seen durability. As you and I know, that in other trials, we have seen vision going down slightly in second year, and part of it is whether it's disease progression or undertreatment of patients who needed treatment. So I think I'm very interested in seeing not only just the durability in second year, but also visual acuity and maintenance of anatomy. I think we also need to see more data on the drying effect, and seeing how we can use 8-milligram aflibercept in our practice, as Christina said, is going to come out. You know, you're going to have a this summer, and then aflibercept high-dose will come out at the same time essentially, so we'll have multiple new agents. I think it's always good to have options, and we'll see how this agent performs. I think the patient I'm looking at will be the high-need patients, and if I can see improvement in anatomy with 8 milligram, then I will be convinced that this is a stronger agent. So yeah, more to come but looking at BCVA, durability and also safety in the second year are some things I'm looking for.

Dr. Singh:
Great. Mark, you know, you look at this in the armamentarium of what we have. We have off-label Avastin. We currently don't have the on-label Avastin, as you mentioned, yet, but we will have it in the near future. Where does this high-dose aflibercept fit into your treatment paradigm for patients, would you say?

Dr. Barakat:
I mean, this is a million dollar question, right? So, as Arshad mentioned, typically whenever a new agent comes out, it's the high-need patient, or frankly it's the patient that might be well-controlled at Q4, Q6 week dosing, tried multiple agents already, and I want to see if I can extend that patient.

I always – I would love to see a little bit better drying effect, because I believe anatomy. I have a hard time believing that the vision that I get in my clinic, and if I see a nice improvement in anatomy or a little longer durability, that I think to me, would be a good sign that that would be an agent that I can go with. Ultimately, I'm not expecting better vision because that's unrealistic.

Dr. Singh:
Christina, I know your background, obviously, is with your MV, but you also have a business degree, I remember right. And you've done some work in this area about economics of these things, and everything else. What are your thoughts on high-dose therapies versus traditional therapies from an economic standpoint? Do you have any comments about what that means for practices and payers?

Dr. Weng:
I think a lot of it, Rishi, is going to be coming down to pricing, right? And so, we are very fortunate to have a lot of effective agents, but it's really hard to go up against off-label bevacizumab, and Mark talked about this earlier, that we are as a community in general – you know, we turn to that drug a lot. So it's hard to say, but I guess if you're thinking broadly and thinking that the pricing may be in parallel with some of the other agents that we have, any time that you can reduce an injection for a patient, that's potentially cost savings for the entire system. But more importantly, I think that sometimes we think that, you know, a reduction – maybe one or two or three injections –

like you see in PULSAR and PHOTON may be very modest. And perhaps it is, and of course we always wish we could do better, but you've done a lot of work in this area, Rishi, with like the social impact of these injections for patients, and I'll tell you, I just thinking to my own patient population, reducing, you know, by two or three injections over the course of the year is incredibly meaningful to a lot of patients – not just from their, you know, not wanting to get needle in their eye, but also the risks that are associated, even though they're low with intravitreal injections. And all of the social burden that is carried with that – for example, someone having to come to the appointment with them, et cetera. So I think these long-range durability agents, to answer the question, have many different benefits that potentially can be offered, including economic but also to the entire societal system.

Dr. Singh:
Yeah, I think you're absolutely correct. That's a great point about those racial and socioeconomic disparities that exist in the population, and where an injection or two saved a year, can make a big difference, albeit that the cost might be slightly differential. That's going to be huge for them, so that's a really great point. So that's a great entrée to Mark's presentation. So Mark, you know, you heard about the studies that were done for these drug trials, for – obviously for on-label bevacizumab, and I think one of the big misnomers that people remember in the community or think about in the community, is that, is this now just on a biosimilar mark.

So what can you tell us about what differences are between on-label bevacizumab as part of these program trials in NORSE-1, 2 and 3, and biosimilar for example?

Dr. Barakat:
Oh, sure. Great question. So, by definition a biosimilar is an agent that is modeled after an approved reference agent. And the fact of the matter is, even though we use off-label bevacizumab all the time, there is no approved ophthalmic formulation of bevacizumab. So by definition, there – this is not a biosimilar. This is the first-time agent, bevacizumab ophthalmic formulation. Number two – as I mentioned before in our talk, we sort of take it for granted, you know, the purity that comes with our ophthalmic formulation, the manufacturing – all those things, that complete package – when we use, you know, on-label medication such as ranibizumab or aflibercept or you name it. It really isn't there with compounded bevacizumab. So there is a certain risk that you take, so it's most certainly not a biosimilar. Not that there's anything wrong with being a biosimilar, but there's definitely differences.

Dr. Singh:
Great. Yep. Arshad, you know, when you have on-label bevacizumab, and you've had off-label for years, how does this fit into your armamentarium for taking care of patients?

Dr. Khanani:
I think, Rishi, the main thing is safety and efficacy, right? So if you have an on-label agent, then you prefer that, compared to an off-label or component agent. The only issue becomes is the price, and I think Christina and you touched on it. I think if the pricing is very close to, let's say, an agent like, you know aflibercept 8 milligram, or faricimab, a dual inhibition – then I think it becomes challenging to get approval from insurances, in terms of, you know, having this compared to second generation anti-VEGF, as we like to call it. But if the pricing is closer, or much less than, you know, second generation, then I think it's a meaningful advancement for the field where we can switch patients, or start patients that we're going to be starting on compounding – compounded bevacizumab to this. So I think it's all going to depend on economics of the practice, and insurance companies are going to be paying close attention to that, based on the price. Do we have to step through a compounded bevacizumab to get to a branded bevacizumab, whether compounding will be available or not? Because now we have an approved agent, so there's a lot of different questions so I think it will all depend on the insurances, the payers and the pricing, in my opinion.

Dr. Singh:
Yeah, I agree with you. Christina, tell me about the need for on-label bevacizumab. You know, you – we've used it for awhile now, off-label. Is there truly a clinical need, or do you feel like we're totally fine with what we have right now with an off-label agent?

Dr. Weng:
It's always hard to answer questions like that, Rishi, because like Mark covered so nicely, I do think there are some pertinent benefits that are very important. For example, you have one patient that ends up getting endophthalmitis, or a group of patients, like we've seen outbreaks over the years, and absolutely is it worthwhile to try to avoid that? Sure, it is. But if you're coming down to numbers, those types of events generally are pretty rare. So, you know, I think it's always nice to have an on-label product, right? And you avoid some of the risks associated with compounding. You avoid some of the medical/legal issues that we always worry about, even though so many of us use off-label, off-label bevacizumab. However, one of the things I do worry a little bit about, and Arshad alluded to it, is will the accessibility of off-label bevacizumab change once we have an on-label product? And I don't know what the answer to that is. It worries me a little bit because there's definitely pockets of our nation and world, of course, that depend heavily on off-label bevacizumab, and regardless of what the pricing may be – surely it's not going to be $50 or $75 a pop. I can pretty much predict that. And so, that is a social concern that I do think about a lot. A lot of the questions, and sort of the order that we approach these different agents, as more comes into our toolbox, I think are honestly going to be dictated, at least in some part, by payers and some of the algorithms that are set. But I do – I am curious to see how this will play into, sort of, the other options that we're going to have – biosimilars, other agents that are coming down the line, other on-label agents that are coming down the line, and of course the off-label version of bevacizumab. I'm just curious if anyone has thoughts about that.

Dr. Khanani:
I think Christina brings up a really good point that I failed to mention, is this will be for neovascular AMD. We don't have trials for DME or RVO, so if you have compounded bevacizumab completely off the market because of this, what do we do with our patients with RV and DMV? That's just something to keep in mind.

Dr. Weng:
And to that point, Arshad, you know, there is NORSE 4 and NORSE 5 and NORSE 6, which are looking at RVO and DME, so even though we don't have them in the imminent future, you know, they might also be coming down the line. So – but you're right, we'll have to see.

Dr. Singh:
Yeah. Let's switch gears a little bit, and talk a little bit about other therapies. You know, you all are very aware of therapies that are in the market or coming to market, in pipeline. Tell me one drug that may excite you. Let's start with Arshad – one drug that excites you in the pipeline that you're interested in seeing in practice because it may improve your outcomes or durability.

Dr. Khanani:
It's a very tough question, involving many of them, but I would put as a field, gene therapy. I would not put one drug. I think if we can have gene therapy, whether it's intravitreal, supercolloidal, subretinal, for neovascular AMD, or DR, or geographic atrophy – anything like that, where you are one and done in a subset of patients and then others you decrease treatment burden – I think that would be a meaningful advance, in my opinion.

Dr. Singh:
Great comment. How about you, Mark? What would you say is the one area or class – let's put class of drug, where you think you'd be most interested in seeing it come to market, because you think the preclinical data, the clinical data looks very, very good right now?

Dr. Barakat:
Well, class-wise, I'd be interested to see a tyrosine kinase inhibitors, only because that's durability and that's me having to inject the patients less frequently, and there's many shots on goal in this. There's multiple companies looking at this, and different approaches, different deliveries. But, aside from class, I think we're entering the era of bispecific compounds. And, bispecific compounds are just fascinating to me because now, you get to have more than one toy – and faricimab opened that door – but faricimab will only be the first.

Dr. Singh:
Mm-hmm. Mm-hmm. Okay. How about you, Christina?

Dr. Weng:
This is what's sad about going third, is those are the two responses I had.

Dr. Singh:
You can repeat the others. Don't worry, no pressure here.

Dr. Weng:
Gene therapy, I think, is phenomenal because it really gives us the most significant leap potentially, in terms of reducing treatment burden, which a lot of these trials are really after at this point. I was going to also say TKIs. I really like looking at different mechanisms of action. I like the broadness of that. So I'm going to go with OPT 302, which targets VEGF-C and D, only because, you know, it works, sort of, in conjunction with our anti-VEGF-A agents and I like that it's a different mechanism of action and potentially might allow us to raise the bar when it comes to efficacy, rather than just looking at durability, which it might also offer. I like that potential, but of course, we have to see what the trials show.

Dr. Singh:
That's wonderful. That's great. Good. Well, I – you know, this has been a fantastic roundtable. You all have presented some of the most cutting-edge therapies we have to date, for these conditions, and you know, as somebody said tonight, we are very blessed in our field to have agents that have such great track records. You know, I – my job now is quite broad, and sometimes I talk to people in other specialties like rheumatology and oncology. And they get excited when they have somebody who has, you know, a 10% better response, or maybe lives three or four months longer. And I look at this, and I think we are doing phenomenal work here, and again, part and parcel to all of you on this roundtable, who do all of this amazing research, each and every day, that puts this field forward. So thank you for what you're doing, and thank you for watching this program. I hope you found this educational. For those watching, we've covered a lot of topics today. Obviously, these are therapies that are either in pipeline or soon to be out in your practice, and I'm sure we're going to be coming back at some point, and talking about – a year later – what these therapies have done to us. So, I appreciate the discussion, and please stay tuned for additional questions to complete your CME credits, and thank you for watching. Good night.

Announcer:
You have been listening to CME on ReachMD. This activity was jointly provided by Clinical Patient Educators Association and iVista

Medical Education Incorporation. This is activity was supported by an independent medical educational grant from Regeneron Pharmaceuticals Incorporation, Apellis Pharmaceuticals, Iveric Bio, and Outlook Therapeutics. To receive your free CME credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.