Transcript Details

This is a transcript of a continuing medical education (CME) activity accessible on the ReachMD network. 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/advances-angiostatic-treatment-retinal-disease-demystifying-novel-therapeutic-targets/12490/

Released: 04/30/2021
Valid until: 04/30/2022
Time needed to complete: 30 minutes

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

Advances in Angiostatic Treatment for Retinal Disease: Demystifying Novel Therapeutic Targets

Announcer:
Welcome to CME on ReachMD. This activity entitled *Advances in Angiostatic Treatment for Retinal Disease – Demystifying Novel Therapeutic Targets* is provided by MedEdicus LLC and is supported by an independent education grant from Genentech Incorporated. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements, as well as the learning objectives.

Dr. Eichenbaum:
Welcome to *Advances in Angiostatic Treatment for Retinal Disease – Demystifying Novel Therapeutic Targets*. I'm David Eichenbaum, Collaborative Associate Professor of Ophthalmology at the Morsani College of Medicine at the University of South Florida and I'm Director of Research of Retina Vitreous Associates of Florida and Tampa Bay, Florida. I'm joined by my esteemed colleague and good friend, Charlie Wykoff, Director of Research at Retina Consultants of Texas and Retina Consultants of America and Deputy Chair of Ophthalmology at the Blanton Eye Institute, Houston Methodist Hospital in Houston, Texas.

Learning objectives which you will enjoy include describing the pathophysiologic mechanisms of emerging disease in treatment combinations, reviewing the latest clinical data for improved and emerging combination treatments, and identifying patients who would potentially be good candidates for these pipeline combination treatments for their neovascular macular degeneration and diabetic macular edema.

As an introduction, we're gonna talk about topics near and dear to our clinical hearts. First of all, we know that visual impairment is a growing public health issue in the United States. The projection of visual impairment in the United States is for it to increase over the next thirty years. The good news, of course, is that we have job security, the bad news, of course, is that there are going to be a lot of patients coming to us for help and we are going to see our resources strained with our current armamentarium of therapeutics.

Retinal diseases are the leading drivers of this increasing volume of visual impairment in the United States. On the left side, you see projections for diabetic retinopathy in the United States in millions increasing a- across all various ethnic groups. And on the right side, you see the projections of age-related macular degeneration in the United States in millions increasing in a similar proportion. These both combine to increase the projections for visual impairment in the United States over the next generation.

Current first line therapies for neovascular macular degeneration and diabetic macular edema have demonstrated safety and efficacy in hallmark trials. We have four broadly available agents, including bevacizumab, which is used off-label, ranibizumab, aflibercept, and brolucizumab; brolucizumab is currently only approved on-label for neovascular macular degeneration with ongoing investigations for diabetic eye disease. All of these drugs provide reasonable safety and reasonable efficacy but all of them require a relatively frequent dosing interval to achieve those very good results.

We know that the greatest unmet need in retinal disease as reported by us retina specialists, in the Preferences and Trends Survey recently, as recently as 2018/2019 are that we need a reduced treatment burden for common retinal diseases. We need more efficacious therapies that address non-response or incomplete responders.

On the right side of the slide, we see that there's a direct correlation both in diabetic macular edema and the neovascular macular degeneration between injection frequency and visual acuity across many different studies with a variety of different treatment schema.

The solution is probably targeting novel mediators of retinal disease. Currently, we only target vascular endothelial growth factor, which has been a boon to our patients and a fantastic target as a primary treatment. However, it is not where we stop, it's where we're starting. And that's what we're going to talk about when we discuss novel targets for treatment of retinal disease.

Diseases that threaten vision, including diabetic retinopathy, diabetic macular edema, and neovascular age-related macular degeneration all involve abnormal growth of new blood vessels in the retina that are unstable and prone to leakage and rupture. In neovascular macular degeneration, this leakage is seen on retinal fundus photographs, fluorescein angiography, and OCT images as fluid in the inter-retinal, sub-retinal, and sub-RPE space. In diabetic macular edema, leakage can likewise be seen on OCT. In diabetic retinopathy, neovascularization can be seen on fundus photography, fluorescein angiography, and OCTA and in the worse cases, as vitreous hemorrhage.

Retinal vessel homeostasis of which vascular stability is a key component is a complex process tightly regulated by multiple cell types and molecular mediators. Retinal vascula endothelial cells and parasites take part in regulation of angiogenesis and also in maintenance of the blood-retinal barrier, which is important for the health of other retinal cell types. These cells have a variety of transmembrane receptors that respond to changes in the concentration of different ligands and cytokines in the retinal microenvironment and modulate the process of new blood vessel growth.

As retinal physicians, we're most familiar with the ligand vascular endothelial growth factor A, VEGFA, thanks to the ground-breaking work of Ferrara started more than two decades ago. This work paved the way for the investigation, approval, and usage of anti-VEGF therapies for macular degeneration, diabetic macular edema, and most recently, diabetic retinopathy. In response to hypoxia, the expression of VEGFA increases and it binds to the transmembrane receptor VEGF receptor 2, which is primarilyy expressed on endothelial cells. This binding triggers intra-cellular signaling cascade, resulting in increased endothelial cell proliferation and migration, new vessel growth, and increased vessel permeability.

Traditional anti-VEGF therapies halt new vessel growth, even in the contents of hypoxia and elevated levels of VEGFA by disrupting the binding of VEGFA to its receptor. Bevacizumab, ranibizumab, aflibercept, and brolucizumab are antibodies, fusion proteins, or antibody fragments that bind to VEGF-A and neutralize its effects. VEGFA is not the only mediator of retinal vessel stability. In the last several years, the interplay among VEGF family members and receptors, as well as additional mediators of endothelial cell junction integrity and inflammation, has been increasingly appreciated and has become specific targets of investigational therapies. Many of these therapies target two or more mediators of angiogenesis and vascular leakage.

Local ocular corticosteroids have been used for decades to suppress multiple pathologic cytokines, but their targeting is non-specific and there is significant adverse events associated with corticosteroid use. Aflibercept is a decoy receptor composed of domains from both VEGF receptor 1 and VEGF receptor 2, which binds VEGFA, as well as VEGFB in placenta growth factor, sequestering these molecules away from VEGF receptor 1 and VEGF receptor 2. In this way, aflibercept represents the first successful application of dual targeting in one molecule. It has been theorized that these additional activities might confer further therapeutic benefit versus ranibizumab and bevacizumab.

More recently, other VEGFs have been recognized for their contribution to the process of angiogenesis. Interestingly, there is an increase in aqueous VEGFC concentration as the direct result of VEGFA inhibition using bevacizumab. The investigational molecule OPT-302 acts in a similar way to aflibercept, except that it is composed of VEGF receptor 3 binding domains and binds and sequesters VEGFC and VEGFD away from endogenous receptors. When used in conjunction with ranibizumab or aflibercept, it is thought that synergistic suppression of neovascular growth and leakage will occur improving outcomes for neovascular macular degeneration and diabetic macular edema over VEGFA suppression, alone.

Inhibition of angiogenesis can be achieved, not only by preventing the interaction between VEGF family members and their receptors, but also by inhibiting the downstream consequences of that interaction. Although the VEGF binding domain of the transmembrane po-protein VEGF receptor 2 is located extracellularly, the activity of multiple vasogenic cytokines is located on intracellular domains. This diffuse pathologic activity can be inhibited by several investigation tyrosine kinase inhibitors, including GB-102 a depot formulation of sunitinib, which inhibits angiogenesis by binding VEGF receptors and other related receptor types, CLS-AX a super-choroidally injected formulation of axitinib, which inhibits angiogenesis by blocking VEGF and platelet-derived growth factor receptors. OTX-TKI an intravitreal hydrogel based axitinib implant and PAN-90806, a topical tyrosine kinase inhibitor formulation that inhibits downstream effects of VEGF receptor 2.

Finally, there are other distinct pathways that have important roles in the regulation of angiogenesis. In the study I mentioned previously

demonstrating that VEGFA inhibition with bevacizumab led to an increase in VEGFC, several other molecules were up regulated, including angiopoietin 2, also known as Ang2. Angiopoietins 1 and 2 interact with the Tie2 receptor to regulate vessel stability as shown on the right-hand side of the slide.

Tie2 is a tyrosine kinase with immunoglobulin and epidermal growth factor homology domains. Under normal conditions, the Tie2 pathway is kept active by the binding of Ang1 and maintains vascular stability through the stabilization of intercellular junctions between endothelial cells, modulated by VE-cadherin and through down-regulation of the VEGF2 expression.

In disease states, such as diabetes, neovascular macular degeneration diabetic retinopathy, and proliferative diabetic retinopathy, the concentration of Ang2 is elevated in the vitreous whereas the concentration of Ang1 is constant in these states. As a consequence, Ang2 competitively displaces Ang1 at the Tie2 receptor, deactivating the Tie2 receptor and inhibiting its vessel-stabilizing activity. Ang2 also potentiates the vascular destabilizing effects of VEGF and can also destabilize intracellular junctions directly by promoting internalization of VE-cadherin, a molecule that is an important component of cell-to-cell junctions. Ang2 is also upregulated by inflammation and perpetuates a hyper-inflammatory state by recruiting inflammatory cells into inflamed tissue. This could be particularly relevant in DME in which inflammation may play a role in disease progression and resistance to anti-VEGF monotherapy. Together, these attributes of Ang2 highlight its importance as a therapeutic target and retinal disease.

Therapies that target Ang2 have the potential to restore vascular stability by restoring the function of the Tie2 pathway. Faricimab is a bi-specific antibody that targets both Ang2 and VEGFA, and it has been shown to restore the activity of the Tie2 pathway, inhibition of the VEGF receptor pathway, and restoration of VE-Cadherin modulated cell-to-cell junctions, and thus abrogating vascular permeability, choroidal neovascularization lesion leakage, and inflammation in vitro and in vivo.

AXT107 is a type 4 collagen-derived peptide that suppresses angiogenesis through interaction with integrins, which associate with and regulate the localization and activity of transmembrane receptors, such as VEGF receptor 2 and Tie2. When AXT107 binds integrins, the association with VEGF receptor 2 is disrupted, leading to inhibition of VEGF receptor 2 signaling and increased internalization and degradation of VEGF receptor 2. AXT107 also binds integrins associated with Tie2 receptors and when this association is disrupted, Tie2 receptors cluster. And as a result of this clustering, Ang2 begins to act as a Tie2 agonist, similar to how Ang1 acts, inhibiting angiogenesis, vessel instability, and inflammation and instead, supporting vascular health and stability and inhibiting the VEGF receptor 2 pathway.

Several other immunomodulatory pathways are targets of early phase investigational therapy. The kallikrein-kinin system is a potential target of therapies to reduce inflammation and vascular permeability associated with retinal disease. Interestingly, in vivo studies demonstrate that this mechanism functions independently of the VEGF pathway to induce retinal edema. Inhibition of this pathway has had mixed success with several clinical trials ending in failure. THR-149 is a plasma kallikrein peptide inhibitor that reduces vascular leakage and is still in development for DME.

AKST-4290 targets eotaxin, a chemokine that is elevated in vascular macular degeneration and might benefit patients whose disease is refractory to anti-VEGF treatment or as an adjunct to anti-VEGF therapy.

ICON-1 is a recombinant modified factor 8 peptide found to the FC portion of human immunoglobulin G1. It binds tissue factor, which is highly expressed in the neovascular tissue in age-related macular degeneration. Activation of tissue factor in neovascular macular degeneration leads to increased inflammation and increased VEGF expression and a positive feedback loop.

Together, these pathways represent the targets of the next generation of therapies for neovascular retinal diseases. In the next section, we will discuss recent clinical trial results for some of these therapies with my good friend Charlie Wykoff.

Dr. Wykoff:
David, that was a fantastic summary of some incredible biology and a lot of really exciting work going on in clinical trials. Over the next ten minutes, I'm gonna talk about recent clinical trial data for novel therapies focusing on later phase data. In particular, as David mentioned, there's a lot of programs looking at novel therapeutics in this space. But today, because of time, we're gonna focus on trials that have data from phase 3 or are actively enrolling in phase 3. And in particular, we're gonna talk about two molecules, faricimab and OPT-302.

So first, let's unpack faricimab, and there's a lot to go through, here, so this will be most of our time. Faricimab now has data from phase 2 programs in both DME and neovascular AMD. This slide summarizes the phase 2 DME program with faricimab called BOULEVARD. Remember, this was a monthly faricimab trial with two doses of faricimab compared to 0.3 mg ranibizumab in which we saw robust and atomic outcomes with faricimab and visual acuity outcomes, no matter how you looked at this data, faricimab appeared to be a stronger agent than ranibizumab.

Based on that phase 2 data that was quite strong, faricimab was then studied in the paired phase 3 trials YOSEMITE and RHINE. These were randomized, double-masked, multi-center global studies comparing faricimab to aflibercept. The key inclusion criteria are listed here. Essentially, patients had to have central-involved DME with visual loss with visual acuity between 20/40 to 23/20. This is the design of the phase 3 program. These were identical trials, YOSEMITE and RHINE, again these were global programs. Each of these trials had three arms. The comparator here, the gold standard was aflibercept given five monthly doses followed by every eight-week dosing, through the primary endpoint that we'll define in a moment. Then there were two arms of faricimab, patients were randomized equally to one of these three arms. There was fixed dosing faricimab shown at the top, 6 mg faricimab given for six monthly doses followed by every eight-week dosing through one year. And then there was faricimab given according to what we called a PTI or personalized treatment interval. Essentially, this was four monthly loading doses and then essentially the application of a treat-and-extend protocol within the confines of a double-masked trial through the one-year primary endpoint. The one-year primary endpoint is shaded here in yellow, which was changed from visual acuity at year one, defined as the average from weeks 48, 52, and 56. And ultimately, all of these arms will continue the same dosing through 100 weeks. The primary endpoint was met in the DME program and essentially showing equivalent visual acuity outcomes between aflibercept and faricimab. Faricimab given either every eight weeks after loading doses or according to a personalized treatment interval.

The anatomic data here, however, s- told a slightly different story. Here on the top of the slide, you see the visual acuity outcomes, again, very similar comparable anatomic excuse me, visual outcomes between each of the three arms in both of these trials. And then at the bottom, you see central subfield thickness, or CST changes over time and what you're seeing is very strong and appearing to be better drying with faricimab either given fixed q 8 or according to PTI compared to the aflibercept arms.

These anatomic benefits appeared to extend to specific fluid cad- cavities, specifically if we look at intraretinal fluid in the top graph, here. We see superior inter-retinal fluid resolution with faricimab across both YOSEMITE and RHINE at the weeks 48, 52, and 56 endpoints. Whereas in the bottom graphs, here, you see comparable efficacy of aflibercept to faricimab with resolution of subretinal fluid.

From a safety perspective, these are the common adverse events through the one-year endpoint. We saw no difference in the outcomes of these safety events between faricimab and aflibercept. This slide we put in specifically to talk about inflammation. Inflammation has become quite an important topic in the development of drugs across the vitreal space. And here, we're just being very descriptive. I do not believe there are any, meaningful difference here between the drugs. But the percentages are important to quote specifically, and they are 0.32 to 0.96% of any IOI with aflibercept compared to 0.63 to 2.24% with any IOI with faricimab. There were no cases of retinal vasculitis in any of these DME patients.

Pivoting now to talk about faricimab in neovascular AMD, these were the two phase 2 trials that led the groundwork for the phase 3 program in neovascular AMD AVENUE and STAIRWAY. The key finding in these phase 2 studies was actually the signal for durability. Remember, STAIRWAY looked at intervals of dosing out to every twelve or even every sixteen weeks and saw comparable visual acuity outcomes compared to monthly ranibizumab. Based on these phase 2 trials, the phase 3 program, the TENAYA and LUCERNE trials were designed. These again were randomized, double-masked, global studies designed to compare aflibercept here to faricimab. Key inclusion criteria were visual acuity of approximately 20/32 or 23/20, with treatment naïve AMD due to neovascular AMD with a center involving lesion. Here's the trial design, again these were identical trials across TENAYA and LUCERNE. The comparator arm here again, aflibercept, remember in DME they were five month loading doses consistent with the global label, here there are three monthly loading doses with aflibercept, again consistent with the global label and then every eight-week dosing. In comparison, patients randomized faricimab received four monthly loading doses and w- and were subsequently treated either every eight weeks, every twelve weeks, or every sixteen weeks, according to a key time point of disease activity assessment at weeks 20 and 24. Specifically, if there was an indication of increased fluid status or an indication of decreased vision or new hemorrhage, then patients were continued at a specific interval with the longest potential interval being every sixteen weeks.

Again, here as very much seen in the DME program, the primary endpoint of visual acuity was met with non-inferiority between faricimab and aflibercept in both of these programs. The longitudinal visual acuity trajectories are shown at the top very similar central identical acuity outcomes between the drugs and at the bottom, again you see very comparable anatomic outcomes, here in the neovascular AMD population.

For safety perspective, the common adverse events are shown here, again with no meaningful differences between the different medications. And then s- pointing out specifically IOI here because of the importance across our field in the percentages of any IOI event in the aflibercept arms were between 0.6 and 1.8% and in faricimab ranged from 1.5 to 2.4%.

This slide is important to digest. This includes all four of these faricimab phase 3 trials: the DME program on the left, and the, and the AMD program on the right. And what you see is the indication of durability. So, the gray portions of these pie charts represent the

proportions of patients at every sixteen-week dosing in the PTI arm in YOSEMITE and RHINE and in the fixed q sixteen-week dosing arm based on disease activity assessments in TENAYA and LUCERNE. And you see remarkably similar percentages. When you add that to the part of the pie charts in blue, you see that across the DME and the neovascular AMD programs between 70 and 80% of patients are achieving every three-to-four-month dosing by the end of one year. Quite a meaningful signal for durability, again within the confines of this phase 3 programs.

Pivoting now and now discussing OPT-302, this is another medication with quite promising data. We do not have phase 3 data for this, for this molecule, yet, but we do have very robust phase 2b data that we'll, that we'll digest. As David went through, this is a molecule that we hope is additive to VEGFA inhibition by blocking additional family members within the VEGF group. The primary outcome of this phase 2 trial was mean change in visual acuity at week 24. The design of this trail was 366 patients, so quite large, double-masked, randomized, phase 2b trial. Patients with visual acuity of approximately 20/60 or worse were randomized equally to either monthly ranibizumab 0.5 mg or OPT-302 plus ranibizumab, either given in the high-dose 2 mg or the lower dose 0.5 mg to 0.- of O- O- OPT-302. In the primary endpoint was at week 24. And here was the primary outcome data, quite promising to the field. On the left here, we saw visual acuity benefits with the high-dose OPT-302 plus ranibizumab gaining over 14 letters of visual acuity, compared to 10.8 letters with ranibizumab monotherapy. And on the right, again, you see improved anatomic outcomes with the addition of OPT-302 to ranibizumab, suggesting there may be an additive benefit of VEGFC and B blockade with OPT-302 in addition to anti-VEGFA and monotherapy.

From a safety perspective, there were no signals of safety concern with the addition of OPT-302 in addition to ranibizumab. And this is particularly relevant to this study because this involved two separate injections where patients received ranibizumab, waited and then received a second injection, either sham in the ranibizumab arm, or OPT-302 in the two additive treatment arms. Based on this positive phase 2b data, OPT-302 has moved forward into two global phase 3 programs called ShORe and COAST in which OPT-302 is being combined in ShORe with ranibizumab dosing and being combined with aflibercept in COAST. These are both going to be two-year programs with the primary efficacy endpoint being at the end of one year.

With that, I would love to engage my colleague and dear friend David Eichenbaum for some questions.

Dr. Eichenbaum:
Well, that was a fantastic presentation. That, kind of, took the basic science we talked about in the first half of the presentation and brought it to where we're actually applying it in later phase clinical trials. And I'm very excited about both the late phase faricimab and the late phase program with OPT-302. Both have very encouraging results and let's start with faricimab. I frankly think that given the durability results faricimab pending its real-world experience, at least our early real-world experience, has the potential to be a first line drug in common retinal disease. It did show about half the patients up to sixteen weeks in all disease states across four studies and it showed 70% of patients at twelve weeks or more across four studies for neovascular macular degeneration and diabetic macular edema, those are pretty impressive numbers. What do you think? If faricimab performed like it looks like it could in the real-world, would that be a first line agent for you?

Dr. Wykoff:
I think you summarized that beautifully, David, and, you know, two thoughts, really, I mean, first of all, what a tremendous amount of energy, effort, and resources went into these programs. I mean, to have two global phase 3 programs read out simultaneously is, is, is such a, a rare event, I mean we've never had anything like it in retina for sure and it, it really is exciting to be able to see the data from two programs, right? 'Cause if you saw the durability in one program, you might think, 'Well, it might be an outlier, but who knows?', but to see this durably across two programs, that does feel a little bit different than what I see daily in my clinical practice with, with patients with-

Dr. Eichenbaum:
Mmmhmm.

Dr. Wykoff:
-our current standard of therapy is quite promising. I think it's exciting. You know, our field has, has really needed a more durable safe agent for a long time and we were all excited about brolucizumab and abicipar and, you know, hopefully those agents may still come to be widely used if we can figure out some of the safety issues. But right now, they are unfortunately, sort of, minimally used because of those safety concerns. This could fill that void. So, I have a lot of patients that look forward to trying to get dryer, trying to get longer intervals. This is hopefully going to be meaningful for the field.

Dr. Eichenbaum:
And that's the aspirational spirit. That's exactly what we were hoping when brolucizumab came out, I was very brolucizumab-avid as a HAWK-

Dr. Wykoff:
Yeah.

Dr. Eichenbaum:
-investigator.

Dr. Wykoff:
Yeah.

Dr. Eichenbaum:
And I, and I, w- I do utilize it but I utilize it minimally and less than 5% of my patients all told-

Dr. Wykoff:
Yeah.

Dr. Eichenbaum:
-and, you know, at this point in 2021.

Now you struck on a really compelling point. Treatment naïve is one thing, and those patients come to us every day, but the vast majority of all of our clinics are the treatment experienced patients and those are the ones that we usually turn loose on new agents, especially the tougher cases, and-

Dr. Wykoff:
Right.

Dr. Eichenbaum:
-I have the same patients. I, I'm gonna look at virtually all of my patients who I can't extend past six or eight weeks and talk to them about the option of trying faricimab and going longer in neovascular macular degeneration or diabetic macular edema. Similar to what I did with brolucizumab until Macular Society 2020 when the IOI data really began to come out, but I-

Dr. Wykoff:
Right.

Dr. Eichenbaum:
-really think that there's a large proportion of established patients who are looking for this.

Dr. Wykoff:
I completely agree. And, you know, it doesn't have to be a homerun, it-

Dr. Eichenbaum:
Mmmhmm.

Dr. Wykoff:
-doesn't have to be a cure. You know, we talk about gene therapy and that's very exciting and, and these other things that are, that are really, sort of, amazingly game-changing agents. This doesn't have to be a cure, if it can just bump those every six weeks out to eight or ten weeks, that's a huge value add for that patient and their family.

Dr. Eichenbaum:
Yes.

Dr. Wykoff:
And so, I, I really, even incremental benefit-

Dr. Eichenbaum:
Mmmhmm.

Dr. Wykoff:
-can have a big translation of value for our patients.

Dr. Eichenbaum:
OPT-302, that's an interesting one because the data is earlier, right? We're-

Dr. Wykoff:

Right.

Dr. Eichenbaum:
-looking at now, phase 2 data.

Dr. Wykoff:
Yep.

Dr. Eichenbaum:
-and there's been promise for combination for a long time with only this-

Dr. Wykoff:
Right.

Dr. Eichenbaum:
-this Ang2 bispecific benefit coming all the way through phase 3. You know, we did see some proof of concept with the Regeneron's phase 2 anti-Ang2 co-formulation nesvacumab-

Dr. Wykoff:
Yeah.

Dr. Eichenbaum:
-so th- that leaves some consistency. OPT-302 has really compelling because it is something else standing out on its own, but we saw that similar compelling phase 2 data with anti-PGF, so-

Dr. Wykoff:
Yeah.

Dr. Eichenbaum:
-I'm not sold on OPT-302 yet, but I'm encouraged by looking-

Dr. Wykoff:
Yeah.

Dr. Eichenbaum:
-forward to enrolling that phase 3 trial for-

Dr. Wykoff:
Yeah.

Dr. Eichenbaum:
-something else, other than the Ang2 Tie pathway that I could leverage perhaps and get even more options for patients.

Dr. Wykoff:
Yeah. It's fascinating. You know, I think we certainly there's durability plays, there's efficacy plays, and there's definitely an overlap there, right? We all realize that if you undertreat patients and they don't do well, that's not an efficacy problem, that's a durability problem. So, there's definitely an overlap, but the basic scientist in me and you, David, is enthralled by this concept of, yeah, these additional growth factors-

Dr. Eichenbaum:
Mmmhmm.

Dr. Wykoff:
-cytokines like you mentioned kallikrein, all these other biologies, these have gotta be relevant. This disease process-

Dr. Eichenbaum:
Mmmhmm.

Dr. Wykoff:
-and, you know, maybe w- one molecule like faricimab will be the treatment we need and, and we can stop it invading, but I don't think so. I, I really see a future that's not easy to create this future, but a future where many of these cytokines are targeted, maybe with multiple agents in a very targeted way, based on aqueous tumor profiling on individual basis-

Dr. Eichenbaum:
Mmmhmm.

Dr. Wykoff:
-who knows where this field will take us, but I really look forward to being able to purse out these individual pathways that are meaningful, maybe in certain subpopulations. There are so many new approaches to this space, but I think it's exciting. We need it, you know, the anti-VEGF therapies have created incredibly high a bar, but there's no question in my mind that we can do better than that. And I-

Dr. Eichenbaum:
Mmmhmm.

Dr. Wykoff:
-and I look forward to that future for our patients and to continue to build it with you, David, and the rest of the space.

Dr. Eichenbaum:
Thank you, Charlie for the opportunity to work with you on this program.

Dr. Wykoff:
What a privilege. Thanks, David.

Announcer:
You've been listening to CME on ReachMD. This activity is provided by MedEdicus LLC and is supported by an independent education grant from Genentech Incorporated. To receive your free CME credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.