(PLEASE NOTE: Transcribed automatically by Vimeo, mistakes are possible/likely. Our apologies.)

TRANSCRIPT - GR 05 17 24 "***Mantle Cell Lymphoma: Moving from Remission to Cure***"
Michael E. Williams, MD from the University of Virginia

Internal Medicine Grand Rounds

- Hello! Everyone. Welcome to medicine. Grin rounds. It is my honor today to introduce Dr. Mike Williams. Dr. Williams received his ND. From the University of Cincinnati College of Medicine and Master of Science, from the Harvard School of Public Health.
- Following Medical Residency, Chief Residency and Fellowship at Uva, he stayed and joined the Department of Medicine Faculty. Here he has several leadership roles, including past chief of the Hemont division.
- Dr. Williams is highly esteemed for his exceptional patient care and his pioneering research interests which encompass clinical trials and translational science for mantle cell lymphoma. Other non-hodgkin lymphomas and cll his work has a dedicated focus on advanced targeted agents in cutting-edge immeotherapeutics. Reflecting his commitment to innovative treatment strategies and improving patient outcomes.
- He is an emeritus member of the Scientific Advisory Board, and was the inaugural chair of the Mantle Cell consortium of the Lymphoma Research Foundation. A few of his very numerous awards include the inaugural Lrf. Mantle cell lymphoma leadership award in 2021, followed by the establishment of the Dr. Michael Williams. Abstract achievement award which happens annually for Mcl. Research.
- Dr. Williams is a national leader both in lymphoma but also in the Hematology oncology community. He previously was chair of the Hematology, so Specialty Board of abim, and currently serves on Abim's hematology longitudinal Knowledge Assessment Committee, and serves on the editorial Board of Journal of Clinical Oncology, and contributes regularly to National and international programs and research and education for lymphoma and Cl. Despite a very impressive resume, Dr. Williams is also just known for being a very kind and humble human, and is beloved by the residents. Please join me in welcoming Dr. Mike Williams papers.
- Can you hear me? All right?
- Thank you so much for that very, very kind introduction. It's always a treat to present medicine grand rounds and to to just see so much interest in what's going on, not just in our own fields, but across the department. And the yeah, the good fortune we all have as faculty members of working in a an environment where we've got
- colleagues and trainees at all levels, who are very curious and keep you on your toes and thinking, and without question teaching us more than we teach you all.
- So in congrats to the chief residents they're winding down I know that feeling, and then we head off to new things, and then and the new V chiefs will be sliding into the role very soon. So what I wanted to do today as you heard, mantle cell has been a longstanding focus of mine, and what I wanna do is not make you all experts in managing mantle cell lymphoma. But I want you to think about as I go through all of this, how this one subtype of lymphoma can tell us a lot about how we

approach cancer patients these days, people serious blood disease. How we can utilize an understanding of the biology and the advances to really move the field forward and improve outcomes for patients. So so think about it in that direction. These are my disclosures. They were also surrounded by email.

- So just to get everybody sort of oriented here to thinking about lymphoma. So the hemoglobin malignancies are really a complex group of diseases. There's actually probably closer to 100 individual subtypes of non hodgkin lymphoma. And, as you can see, there circled in the red that mental cell is about 6%. So overall in terms of new cases of non hodgkin lymphoma. There's probably about 85,000 a year in the Us. But many of these people, of course, are going to be cured, or they may have an indulant form that may not be curable, but you can manage those patients for years, and indeed decades. So the prevalence of lymphoma, and is really quite high across the population.
- Now, the biology of these really is directly linked to their their normal physiology, and you can see. I won't go through this in detail, but it's been recognized over the last few decades that as a naive B cell coming out of the bone marrow goes into the germinal center and begins to differentiate and expand. If there's antigen stimulation, then they that group expands to make an antibody to fight, say, an invading organism.
- And so, without going through it, you can see that at various stages of differentiation is where these different B-cell lymphomas in particular, will depart from the norm. So they keep some of those phenotypic and genotypic features, but with their acquired mutations, and so with mantle cell. Here they tend to arise in what's called the mantle zone of the normal germinal center. And so that'll be relevant as we as we talk through some of this.
- And then there are other. The Bclls can be pre-germinal center. You can see my myeloma and things here so complicated group. Okay? So here's what we're going to try to talk through and again think about this in terms of of any cancer, not just a lymphoma. But so when we talk about Mantle Cell as opposed to all these other subtypes like, how was that defined? Who figured that like that's different from anything else? So we'll look at a little history. I'm old. We're gonna you'll have to suffer through some history.
- But even within this one subtype there's a real heterogeneity and a spectrum from very slow paced disease. I've got people with mantle Cell that I followed for 1015 years who've never required therapy, and I've got people who progress rapidly like a burget lymphoma. So within a matter of 2 or 3 weeks, they end up with bulky disease so very different. So what what explains that biologically and at a molecular level. So we're gonna talk about, how do we get to cure? And the reason that's relevant here is not just that we like to cure people with a malignancy, but mantle cell, with the exception of using something like Allo stem cell transplant that Dr. Bowen and her crew can provide. That's really the only sure way to cure mantle, cell and Foma. But it's probably 1% of patients who might be able to do that.
- So how do we get to a cure, and and will distinguish a biologic cure which to me means, like, you've destroyed every last lymphoma cell in that person versus a functional cure which may be that they still have some cells left behind but they've gotten a deep enough remission that they're clinically irrelevant, and that patient may be able to live the rest of their lifespan without suffering a relapse.
- So so a functional cure. There are biomarkers I mentioned that will help us adapt, and with all of the tools we have now to treat these patients, we can use some of

the biomarkers that our hematopathology colleagues can provide for us to decide how to treat them.

- What curative tools! How do we know when we've done enough? Have you beaten it down into a deep remission? And can we just stop everything. Do we need to keep going with maintenance? So then, how do we measure a remission?
- And then I'm not going to talk about this at all. But what are the survivorship needs? Of course, there's short and long-term toxicities for many of our treatments. What's the personal stress of going through a treatment or a disease like this. What's the financial stress which is always there?
- So we're not going to cover all of that. But that just gives you the perspective of what we deal with with any malignancy that we're trying to treat. So let's talk about. How did who who figured out what that mantle cell was a thing.
- So this goes back now, actually 50 years. When Carl Leonard, Professor Leonard was at the University of Kiel in Northern Germany, and he developed what became called the keel classification, and one of the entities was something he called centritic lymphoma.
- And we're now 50 years since. Really, the keel classification came out, but he felt like these appeared to be small, clean cells that arose in the mantle zone that I mentioned earlier in a normal lymph node. So we thought it was a malignant version of what of that normal cell counterpart? This was in the very early days when you could even just start to tell a T cell from a B-cell.
- So much of this related to the morphology and these very primitive immunophenotypic tools. So here's Professor Leonard at the blackboard, and you can see he's outlining here. He's outlined his classification. And and it's got this biologic basis. So there's B cell. And you can see T cell subtypes. There's low grade and high grades. We recognize different clinical behaviors of these and then cell of origin. So that's where we get to things like centrasidic right here.
- So. And he was a very meticulous record keeper, pathologist, I always think of as being intensely, you know, data driven and organized. And so here is one draw from his file card file of cases, and this one, that card is patient. K.
- And he called this. This patient had a lymphoma that looked distinct, and he called it Type k, and so that's it was a 78 year old gentleman. With with this lymphoma that he thought was unique from some of the others he was looking at morphologically so that was left out there and then, as things started to evolve back in the late 80 s. Early 90 s. We started having molecular tools we could use in my lab. I was very interested in looking at chromosomal breakpoints that might be associated with certain lymphomas. And again, it was a really metal pathologist who gets a lot of the credit for this, and that's Dr. Steve, Steve Sward, Low. Steve and I were both junior faculty members at the time. He ended up becoming one of the world's best known and metal pathologists. The whbook of hematopoortic classification is sward low through 2 additions. So Steve and I met sort of by chance. He knew I was interested in sort of clonality assessments, and so he sent me 14 frozen tissues from this centroid lymphoma. He had actually spent time in
- keel with Leonard because he was very interested. He thought these were doing things that current classifications didn't, and what we found to make. This story, very short is that I. We showed that they were clonal. They had immunoglobulin rearrangement, but they did not have the usual rearrangements that we knew about in lymphomas, but I had a probe for something called Bcl. One

- That was a breakpoint in what was thought to be Cll. We now know it was leukemic mantle cell, and that breakpoint had been cloned, but there was no gene there, but I knew that there were some correlations in the literature, that lymphomas, that kind of look like centrasidic had this. I happen to have the probe, so I reh hybridize it. I won't won't bore you with the blot, but anyway, found out that 4 of these 14 cases had a clonal rearrangement clearly non-random. So we publish that in blood. And then within just the next 2 or 3 months there were 2 more reports of lymphomas that also turned out to be Mantle Cell. It had the same rearrangement and then we did a second series with additional breakpoint probes that showed that now half of mantle cells, with some additional cases, had this translocation so clearly a non random event. So something about an 1114 translocation and centroidic lymphoma that is somehow driving the development of that cancer. And so, you know, we were on on a track, as were a lot of others to try to figure out what's the gene that's relevant.
- And anyway, all of this led to development of changing the name to mantle cell. And then I got a call one day from Andy Arnold who was an endocrinologist.
- He was interested in parathyroid Adenomas
- and figuring out, are they hyperplastic, or are they actual clonal neoplastic things. So he used, and a parathyroid.
- Gene probe! And he found that a lot of the pathology Adnomus had an in a concentrate, or an inversion in chromosome. 11 that put a breakpoint right next to a gene that had not been identified before, and it turned out. That was the first mammalian G, one cyclin. People have been looking for it. Cyclins are critical pieces of machinery, I mean yeast g one. Cyclins will rescue human cells. I mean, there's that much similarity. So these are fundamental machinery. So I got a call one day. This was, you know, before cell phones and email. I actually had a phone call and Andy Arnold called. He said, we're gonna have a paper out in nature next week. And I think we've got the gene you guys are looking for in lymphoma.
- And so he sent me some probes, and indeed, most of the cases didn't have the earlier breakpoints had one breakpoints, so that kind of sealed the deal. We did some other work that showed that that, indeed, was the relevant gene including looking at the current transportation breakpoints. We just had a call this morning with research collaborators in Barcelona and Elaine, Jaffe and the Barcelona group showed that Mrna. And then we had had the first paper showing that you can have stain for Cyclin d. One, and that's become now a very standard diagnostic test for this.
- So so it's evolved to where, from a morphology standpoint and very limited. immuno phenotypic markers that this entity was defined so I just like I I can't say how much I admire himatopa dollars, because they're really the morphology. They nailed it. I mean, they had it down that this was something unique, and it was up to us to figure it out and just to close the loop. So this is the original patient, K.
- From Carl Leonard from the early 19 seventies going back cutting the section. You can see mantle cell lymphoma, the H. And E. But there's cyclone d. One standing, and there's the 1114. So Leonard first case was, in fact, mantle cell lymphoma by current diagnostic criteria. So what does it do so. You're you all remember this from the cell cycle. So G, one is where cells are sort of in a in a growth phase, not a resting phase and cyclin. D. One is one of the cyclones that triggers through mitogenic signals in the micro environment. It it signals cdk 4, 6. The kinase to bind to cyclin. D. One. It phosphorylates the retinoblastoma gene releases E. 2 F and

retinal blastoma is a tumor suppressor that blocks cells from being in cell cycle all the time.

- And so once you inactivate that, then cell cycle proceeds Cyclin d. One is normally not expressed at all in B lymphocytes. So having it turned on in these cells you know, short circuits them. Here's the pathogenesis. You start with an early event like the 1114, you go through these very early phases of in sight to mantle Cell, and then the sort of classical one that we typically see, and then some of them evolve, with additional mutations to blastoid and very high grade.
- The the pathway from that first cell becoming malignant to the early phase, is probably 10 to 15 years to get to where it's clinically detectable.
- For some reason these tend to occur more in men than women. They tend to be older. The average age is 63, but a lot of patients are in their seventies or eighties. They tend to present with advanced stage disease. Mammal cell likes to go to extra nodal sites, including gi, I've seen it prostate lung skin and you can have a leukemic phase.
- The blastoid high grade type is is more aggressive. This is a summary from an editorial about 3 years ago, looking at various markers. I'm not gonna read through all of these, except that we can use these to sort of project. How people might do, do they have higher or lower risk disease? But, importantly, none of these factors themselves tell us how we treat an individual patient, the only exception to that being that if you have a mutation in the Tp. 53 gene, then you tend to be chemo resistant from the outset. And so now we would put those patients into a different pathway that would include a targeted drug that we'll talk about.
- Now let's step aside from lymphoma for a second and think about this depth of remission issue, because it's really a relevant thing in, in, not just in lymphoma, but in all cancers. So you hear a lot about liquid biopsies and things like that. And so what that really means is that you can draw blood from a patient. And there's different ways. So a tumor cell, whether it's a colon cancer or a lung tumor or lymphoma that these cells are breaking down. They're and they're releasing small amounts of DNA and material into the circulation. So you can look at circulating free tumor DNA. You can look at circulating tumor cells themselves or exosomes.
- These are all things that you can then actually query at a very sensitive molecular level to find out, you know. Does this patient still have disease? You might be in clinical remission by scans, but you've got detectable you know, Mr. D. So you've got cells somewhere that are releasing this. And you not only can tell that you still got stuff left behind in terms of the disease, but you can actually sequence that circulating DNA and pick out new mutations or clonal evolution of that patient's malignancy. So they're potentially actionable. Not just to tell you it's there or it's not there.
- There's the reason the term measurable residual disease is preferred over minimal residual disease. It is, it really depends what's minimal depends on how you're looking.
- So if you're doing multicolor flow cytometry, you can see there in the middle. You can get down to maybe one cell in a thousand to one in 10,000 malignant cells versus normal, but with current very sensitive. Next, Gen. Sequencing, we can pick out about one malignant cell in a million so pretty good sensitivity level.
- And this is a schematic that I like to again, this is for leukemia. But you can imagine this with almost any cancer. So let's look up here at the top.

- So here's let's say, 3 patients. They all got induction treatment in this case for leukemia, and by looking under the microscope by doing a bone marrow. Maybe by doing standard flow. These they're in remission. You can't find any cells left behind.
- But they have a different path. So if you're measuring MRD.
- Excuse me, some of these patients will have persistent MRD. And they tend to relapse early. So this can be a predictor of people who need sorry allergy season.
- So you see, those patients are destined for early relapse.
- And so this may be actionable, you know, if they're still, Mrd. Positive you check them a couple of times, or the Mr. D. Is increasing, then you probably need to intervene before they have an overt relapse.
- You may get down to where they're Mr. D. Negative. And that may mean they've just got a really deep remission. Remember that functional cure, and maybe they go for months or even years, before that clone expands again, and then they become detectable. Mr. D. And then clinically relapse. Or maybe they're Mr. D. Negative, because you've in fact, extinguished the clone or gotten it down to such a low level that on this line that they'll never relapse. So that's how these sorts of assays can inform our assessment of response. And of course this is it measures a different thing. But it's much more sensitive in a lot of ways than in most ways than, say, a pet scan.
- And this is an example with diffuse large B cell lymphoma. Just to look at the pet versus Mr. D. So here we are on the left side. So if you have an end of treatment, pet scan, which is the standard criteria, let's say, for diffuse large cell lymphoma. If you're pet negative, then you're in remission and you can see that if you're pet negative in the blue line on the left. You see, those patients tend to do well some early relapses, but you can see if you're still pet positive, you tend to relapse, although not always so, probably some false positives. But look at, look at Mr. D.
- If you're MRD. Negative at end of treatment.
- Virtually nobody relapses, whereas if you're Mrd positive, even if you're pet negative, you can see the relapse is not only frequent but early.
- So that's how you can leverage these sorts of tools not just to say, Tell somebody, well, you're in trouble, cause this is probably gonna come back. But we're gonna do something. We're gonna intervene with another therapy that's nonprose, resistant, maybe an immunotherapy so be thinking about that, and how you would again start to channel and model your management of a patient based on this kind of information to enhance the chance of cure. There's been a lot of therapeutic evolution when Mantle Cell was first identified, and you could start to do clinical studies back early in the mid nineties is when that started it was mostly Ritu having chemo, and then we've gone through different generations of novel drugs and targeted drugs. And now we're into the cellular therapy level.
- So coming back to our purpose, here is is mantle cell curable. As I said, there's biologic versus functional cure. But right now an allo transplant is the way to cure mammal cell lymphoma, and we will still offer that to younger fit patients who have very high risk disease, because otherwise their survival tends to be quite short. But there may be ways. Now we can get many more people into these durable remissions, and maybe even biologic cures.
- Some of you heard our our mana, our Lapoma colleague, Dr. Sunali Smith give grand rounds a few months ago, really an outstanding talk on large sell Infoma. But this is a slide from one of her recent papers. This is a partial list of current drug agents and drugs that we're using in lymphoma.

- So that's a pretty big toolbox.
- Excuse me.
- And so, looking back to the early days of treatment with Ratu Sam and Chop, or other regiments so chop VR. Cap. Our back. I always remind the students
- that much of oncology is a search for vowels. Because it really helps us with our regimens, you know. Eat etobicide huge get. I mean, I lost some mind very big. So so keep, you know, there's a lot that we have to deal with, you can see. So, anyway so you can see that the response. Rates are pretty high. So Mandal cell will respond to treatment. But look at the progression, free survival. So how long does does that response last? And you can see it's a little over a year to 2 years with more intensive regimens it can be longer. So most of these patients will relapse, meaning that even though they're in remission, say, by a pet, you know, they've got disease, and it's gonna come back within usually a year or 2.
- So what do we do for initial therapy from back, you know, 20 years ago the Median survival is probably a little under 3 years now. It's well over 10 years. Patients can live a very long time now, even with more aggressive forms, there is this indolent subset that we will observe without treatment, like we do with other indolent lymphomas for let's say we've got a younger fit patients under 70. Then we use a chemotherapy regimen like Ben Domestine or Tuximab with without a targeted agent. Dr. Portel has led Us. Cooperative group studies looking at testing some of these novel combinations, or the standard has been recently for young people to use a high dose like terabyte regimen, followed by an auto transplant consolidation and maintenance. But so that's a big hammer. You're really pounding down on this clonal population with chemo immunotherapy, and then high dose therapy in a transplant. But what if there? There's somebody who just had very sensitive disease, and they've already achieved a deeper mission. The transplant is not helping them at all. It's giving them risk without benefit. And what about is there something we can do to decrease or eliminate the need for a transplant by leveraging some of our targeted therapies like Ibrutinib.
- So the triangle study, which was just fully published about a week ago. We'll talk about that.
- So here's without going through too many of the details. Here's a regimen again. You see, the vowel got dhap here, so only 4 cycles, and then a consolidation auto transplant after intensive therapy. And then this study done by the French was to decide, is there any benefit, since we know even the transplant doesn't cure them about doing 3 years of maintenance or toxin. Have get a dose every couple of months, or you just observe them.
- And what that showed is that you can see in the red line. If you get 3 years of maintenance retux, you do pretty well. I mean, you go out. Most of these patients, probably 80% are still in remission at 5 to 6 years, whereas even if you didn't get it. You see the relapse there in blue. Now, these curves are still pretty good when you think about historic mantle cell data, but still room for improvement. So with this maintenance, Retoxomab became a standard after chemo and after transplant for mantle cell and then with longer follow up, now going out to 10 years. You can see a lot of these people are still doing pretty well in their first remission. The benefit from survival is not significant, but there's still a trend therenow. So this is all pretty happy news. But here's you have to mine through this. And look, look at this carefully, but not everybody is doing well.

- There's a subset of patients, even though they're getting that intensive chemo. They're getting a transplant. They're on maintenance retuks. There's still a proportion of these people that relapse within 2 years of starting treatment. So it's progression of disease 24 POD. 24, which turns out to be valuable in a lot of lymphomas, but in mental cell you can see that those patients do miserably. So they relapse early, and you can see that the the 7 year overall survival is around 10% for people with that early relapse. Whereas if you didn't, if you relapse later.
- 7 year overall survival is closer to 90%, 85, 90%. So there's a subset of people that we need to do better. Who are they? How do we recognize them. How do we modify our therapy to improve their outcomes?
- Now, here's a a a study that we have open here. We've approved a lot of patients to it. In fact, Dr. Balan just put a patient on the study this week. So this is asking in the question, can we use Mr. D. To tell us who needs a transplant and who can maybe have it avoided. So to make a long story short, we use nextgen sequencing. You take a patient who got any induction therapy.
- And then, if they've got a marker that's informative. And about 99% of people do have a next gen sequencing marker.
- If you're still Mrd, positive, then everybody goes to an auto transplant maintenance. But if you're Mr. D. Negative, then that's the experimental part here, and those patients get randomized to either a standard auto and maintenance or just maintenance alone. So it's asking if you've already gotten to a deep remission does giving does high dose therapy and a transplant add benefit. So this study is almost completed accrual probably will finish this year and it'll be very interesting to see, you know whether we can use Mr. D. To risk adapt therapy for these patients?
- Now, here's the triangle study that I mentioned. So this is from the European mantle network. They've done these. It's like 1213 countries with over 600 sites and they've done a lot of the big phase, 3 trials that have established care. So here's what they're doing, and I'll go through this fairly quickly. So it's 870 patients previously untreated.
- Most. There's the male predominance. And this is these are all in European countries. So 98% white. So if you're from a different ethnic group or racial group can't say that this is how what's gotta be your be your experience with it. So we're trying to focus on that in all of our clinical research these days. To make sure we have representative patients in studies. But here's what they're doing. So arm a is auto transmit standard. Our shop. Our dhap was their regimen transplant, and then observation or the same regimen with a brutanib a Btk inhibitor. I'll show you more about that in a minute given there and then with maintenance.
- Or here's the other experimental arm. Can you just give chemo with Ibrutinib 2 years of maintenance, and then observe them skip the transplant, so can a Brutnib do well enough in getting a deep permission that you don't have to do transplant.
- And about half the patients got Rhetaxim, in addition to Ibrutin maintenance, is the point that I'm making there at the end. So here's what they found.
- This is the data that was published last week. So the transplant group is here in red. So again, that's about what we saw in the previous study that I just showed you so pretty good outcome. But if they got a transplant plus ibrutinib, you can see they actually did significantly better.
- This one has not reached significance in part because of patient numbers. But here is the auto transplant group, same curve. Here are people getting no transplant, just chemo and ibrutinib and you can see the trend is certainly in favor of those patients

doing very well, and re keep in mind now, these patients on the plateau out here on these Kaplan Myers, so they finish their 2 years of maintenance. So they're in remission off treatment and then down at the bottom is overall survival, which is not significantly different. But you can see it's trending that the abruttum containing arms are gonna outperform in terms of overall survival in this group. Now, what about some of these biologic subsets. So at the top A and B, so one of the things that our pathology colleagues will help us with is the is the prolifer proliferation index. So A. KI. 67 score. And if you're above 30, that's a higher risk for recurrence. So if you look here at the lower risk less than 30%. You can see that they they do it better with a brutnive on board.

- But if you can see if you've got a higher, prolifer proliferation index. You do worse in both arms, but still it trends better for the abrotid. Now I mentioned this, p. 53. Mutation, so that correlates with poorer outcomes for a lot of different reasons.
- And so in this case they did not use the molecular mutation testing. They did just, p. 53 immunostating, which I think is about 80% correlate with mutation. And so if your p. 53, low expression, not much difference, a little trend. But look here for the people who are p. 53, mutated or over, expressing, likely mutated, you can see there you really don't do well some do, but most fail quickly. And if they got auto transplant only, whereas if you got a brutnib they didn't much better. So again, we can start to with this information, start to risk adapt treatment for these patients.
- So here's their their conclusions from the the paper. So the added value is that it confirms a superior efficacy by adding a Brutnib to standard treatment in younger, transplantable patients. Auto transplant without a Brutnib is not superior. That was the way the statistically, the design was, it's not superior compared with adding the the fixed duration of a Brutnip. And so their conclusion is that
- Brutnib should become part of first line treatment in younger cell employment patients, and whether the transplant adds efficacy to the just chemo ibrutinib only will need some some longer follow up. But you can see our management is starting to evolve. And so now you can take an oral once a day. Pill abrutnip potentially instead of high dose therapy in a stem cell transplant with the short and long-term toxicities of that. And maybe it's going to be that there are still some patients who will benefit from that high dose, therapy and finite treatment or we may change treatment altogether. So we've talked about a brooded. But let's look into other approaches in this disease. Mantle cell has turned out to be a really good model for testing new drugs. That target the B-cell receptor pathway which led to multiple FDA approvals that then have applied to other diseases.
- So here is a study that we took part in here about a decade ago. Now, looking at Brutnib in relapse, refractory mantle cell lymphoma always like to point out that the senior author on this Christy Bloom, was a Uva resident. She and her husband. Bill, who's she's a superstar in lymphoma there at Emory now he's in acute leukemia but they were both sort of graduates, we you know, who have done very well indeed in the field. So here's the study looking at Ibrutin, single agent in heavily pre-treated patients. So 111 patients bore. Tesamib is a proteasome inhibitor that has proved in mantel cell. And so some people that had it, some hadn't 560. So it's 4 capsules a day once a day, and you can see a median of 3 prior therapies and most of these people had high risk prognostic scores. So so this is a really tough group of patients to treat. And I'd like to show this case example. This was the first patient at Uva that went on this study. She was a lady who had had just a year and a half earlier. She presented with mantle cell. She got intensive therapy with red

number called hyper cvad plus Methotrexate hydroc, and then an auto transplant, and a year and a half later she relapsed and she relapsed in a lot of extra nodal sites, including disease, around her orbits, or she had a lot of diplopia related to that.

- And so here is her baseline scan. Now the way the study worked is. She came in. We got her on the study, and she took her first dose of aroot to be in the clinic, and then she had to come back 24 h later, so we could recheck labs and make sure. Then she can go ahead and take the next dose was not a lot of experience with this, and what was interesting is when she came back the next morning, she said, you know, it was really strange. When I woke up this morning my double vision was gone and you could tell, on exam looking at her and feeling her notes, they had already shrunk with a single dose.
- So that's a powerful drug.
- So it's really hitting its target. And here she is at 60 days. You can see on the bottom, where this disease in the in the sinus and soft tissue there has gone and she stayed in remission for about 2 years so longer than she did with with a single agent longer than she did with the original therapy. But then, as we learned in using this drug, that some patients not only relapse. They kind of explode when the Btk stops working, the disease is kind of kicked into a higher gear, and she had a full minute progression and and passed away from her disease. Now we have second, third, fourth line things we can use for patients like her.
- So here's the progression. Free survival curves for this. And if you just look at the orange line, that's all patients. And then we published this, follow up with 2 years. That showed that that about 40% of patients still remained in remission. So again, you can start to query that population base and say, Well who are the patients who did really? Well, who are the people who didn't respond at all or failed early. So you can start to biologically sort through and personalize what the approach would be. One of the patients is, I'll bore you with one other anecdote, and that is.
- we got a call from a patient in Washington, DC. Who's a retired Navy pilot.
- and he had mantle cell. Lymphoma probably had about a month live. He had been through every single therapy and combination that was available at the time, and was progressing on it.
- He got in touch with us. We saw him, you know, a few days later, and he was eligible for the study, and he was the last person in the Us. He took the last spot in this study, so he was the last patient accrued to it, and a month later he was back, fishing and out. He was in remission, and his remission, after being resistant to everything else, he he went just under 10 years with a Brutnib living a normal life. And so it just shows you the power of these sorts of drugs. And then he progressed.
- Craig is managing him, and now he's on. He switched over to Bonetta Clacks and on other things. So you know, he survived long enough to benefit from the other next generation thing. So it shows you the value of doing these studies and offering these drugs, because for a lot of diseases, you know, a clinical trial is your best option. You get the standard of care, or you get a novel agent. So it really just invigorates and motivates our work, and you can imagine all the patients who weren't the last patient of the study, who who died within a few weeks and didn't get this chance. So it's very motivating to do what we do every day for these patients. So here's a cartoon that I like to show. So this is the B-cell receptor pathway which is activated in most all

- B-cell malignancies with the, you know. Membrane embedded antibody up there on the top, the B cell receptor. And then now I I won't read through all these. Here's the Btk inhibitors. It's second and third generation drugs.
- Mtor inhibitors, the proteasome inhibitors and Vanetta clacts, which is a Bcl. 2 appetosis inducing molecule. So that's a limited set of what we actually is being tested. Now, some of these, many of these are, FDA approved. And so now the strategy is to look at. How do we put them together?
- And I'll I'll say more about that in the last few minutes. So here's if you look on the top here. These are some of the first gener or first generation of targeted drugs, immunomatory drugs, and proteasome inhibitors, etc. And then here we are. You can see that the overall response rates in relapse patients is about, you know, 70 to 80% for most of them. And if you start using combinations, you get higher responses. So a very powerful group, I'm not gonna go through you know, all of these per se. But just to mention that W. again, that we're looking at combinations of drugs and our group Dr. Portal and our translational group have done work as well as several other centers in the in the Us. And in Australia, showing their synergy between Ibru and Vanetta claks so that giving them together makes sense. there was a a multi center study led by Dr. Portel out of Uva that was recently published. But here's a study looking at.
- You don't see many placebo controlled studies in cancer. But this is one. It was 2 oral drugs. So it's a brutal plus bonettax versus a Brutnib and placebo, and you know it shows that it's a positive study. So there was, in fact, benefit. But you can still see this relapse setting. Most of these patients are still relapsing within about 2 to 3 years. So does this mean, this is better than seeing how they do on Apr. Or Btk inhibitor, and then giving the banana flaxes the next. So you know, there's a lot of ways to look at this, but this study will probably be fully published soon and, in fact, here's the current United States Inter group study, but led by alliance, our our cooperative group. Ecag will also be part of this, but this is looking a completely chemo free approach for older patients, so previously untreated males, so older, defined, as I think, above 65, or younger, but with comorbidities that preclude chemo or intensive therapy. So they're gonna get single agent zanner, or they're gonna get xanabrutinib a Btk inhibitor plus ritu ad they get a remission. Then they get randomized to either maintenance or just take them off treatment and observe, so this is gonna explore in a multi center way, whether we can avoid chemotherapy and get adequate control for these patients.
- So let's talk about a little bit now, just to close with the fourth generation, which are chemo free regimens. We just went over those. And now the cellular immunotherapy approaches. So many of you have been up on on the unit and seen our patients coming in for car T. So Chinook, Antigen receptor T-cell is where you take a patient's autologous T-cells. They are sent to a central lab facility, where they are genetically transformed, transfected to to make their T-cells armed to recognize the Olympicoma antigen. Usually CD, 19. They expand those in vitro. They put them in a bag like a transfusion, and then they ship them back to us, and we infusion to the patients where it becomes sort of some people call a living drug because it gets in there proliferates binds to the residual lymphoma cells. But it comes with a lot of toxicity. Cytokine release, syndrome, neurotoxicity, and others.
- So a very powerful but fairly complex therapy to give again, here's an anecdote. This is one of the first patients treated at Uva 5 years ago.
- So high grade lymphomas refractory therapy.

- He got his car t cell. And then here is his baseline scan showing a pet scan, showing disease that's very widespread. And then here is a scan at 60 days, showing that you can those of you who are keen on during the lunch hour of reading, imaging. You can see that the previous sites of disease and the chest have gone away. You see, he's got an infractomy, so only the right kidney is showing up, and you'll notice that this bladder looks abnormal. And indeed that wasn't lymphoma. He turned out to have a concomitant bladder cancer, uithelial malignancy that was subsequently treated. So he was several years out at last, follow up still in remission from his lymphoma. So cartese a powerful tool.
- So here's a study in mantle Cell that called Brexit cabbage gene looking at patients with relapse disease. And just briefly, here's the response rate. So heavily pre-treated patients, 93% response rate.
- And in the light blue 2 thirds of those are complete remissions by Pet scanned. You can see most, everybody responded, and the duration of response in the early follow up looked quite good. Some early progressors, and then a plateau. But over time these tend to be coming down. So it's unclear that anybody's going to be cured by a car T or mantle cell.
- And then, just very recently, within the past month, this is a different car called Lysoscell, or Lysocaby Gene. It's got different signaling molecules. I won't go to the details, but it makes it seems to have a lot less side effects and toxicity than the previous one I showed you, and you can see the capital Meer curves over on the right for the outcomes, and again sort of a steady progression rate. But some of them are reasonably durable.
- The exciting thing about this study to me was that again, the response rate was over 80%. These were heavily pre treated, multiply resistant patients. But here, the complete remission rate was 72%. And you can see that that bad group with p. 53, mutation 11 out of 19 got a complete remission blastoid the high grade version 1117 out of 27. And this is really key. So patients that have central nervous system progression that one. We don't have great answers for for most of these people. But here 6 out of 7, with central nervous system, mantle cell achieved a remission so high responses, poor risk patients. The toxicity looks more favorable. This drug was just approved 2 days ago, I believe, for follicular lymphoma. It'll probably have a mantle cell indication soon, so I suspect we'll be doing more of this one.
- But I'll try to remember to say this at the end. But if you're all
- sticking with me on. How do you leverage this stuff? So imagine with these kind of responses, if you've got a really high risk. Mantle cell. P. 53 mutated. They didn't get a remission from the first. Go around. Maybe we can. Instead of doing a transplant, we will be doing a car for those high risk patients, or Mrd positive, for example, that we can go after them before they have that clinical progression.
- Now, there are other ways to go after these, immunologically. This is.
- I won't go through. We have lots of immunotherapeutic tools. Some of them act to turn on your immune system. Some of them have a drug attached to them that gets internalized so kind of a smart bomb. But what we're talking about now are by specific antibodies. So these are antibodies that are engineered so that 1 one side of them it binds to a B cell target like CD 19, the other one binds to CD. 3. So you're basically instead of making a car a T cell that goes and finds the lymphoma, you're using an antibody to bring the effect or T cell and juxtapose it with the lymphoma cell.

- So there's a bunch of these now we use an all but the top. 3 here, actually all but the and next to mad, those are all FDA approved for lymphoma indications. Blenna is approved for Al, and it's likely I'm told that that Audrey, and next to Mab will be approved later this year. So let's look at just one of these. There's a huge amount of data. This is a glow Fitimab in a report that came out a couple of years ago, and I won't bore you with the the swimmers plot here, but you can see the long lines mean people with durable ongoing remissions. But if you look over here, and this study, like many in the last 5 years, you can imagine the interpretation is complicated by the fact that we were in the Covid era, and these are very, you know, suppressed people. So a lot of these studies had patient mortality due to covid infection. So it it makes it a little harder to pick up what the overall survival signals gonna be. But here's one thing that you can pull out of this is that the overall response rate in these patients the complete rate response rate was 50% overall was 73%. But what's interesting? This is finite therapy. So they didn't stay on this indefinitely. But for people who were in remission at the end of the planned treatment. None of those patients have relapsed thus far.
- So again. Now this is not making a car. T, and, by the way, car T is what 400,000 or something to generate it and give it or just generate it. But these aren't cheap, but but it's off the shelf. You don't have to delay while you're making the car. So maybe the buy specifics are, gonna be a good way to say, clean up residual. Mr. D. Get a deeper remission.
- And here this is from I put this together last fall, but without going through it you can see that. Where are things going now. There's over 150 trials right now, going on in Mantle Cell just in mantle cell. And they're looking at ways to either. Add one of these targeted drugs. To chemo. But here you can see, these are all basically just immunotherapy and targeted drug. Only. So I think when this wave of trials matures and gets out there. You can see how much treatment a mantle cell has evolved in the last 10 to 15 years, and that is, gonna continue at a rapid pace.
- So improving where we going in the next few years, I think it's gonna be very much risk adapted. So separating indolent from TP. 53. Mutated. We're gonna be using Mrd status to determine maybe duration of therapy, or, you know, adding therapy, we're gonna use. I think, Mrd driven endpoints. You saw that for the the ones transplant trial, I think the the use of cytotoxic chemo and high dose therapy and stem cell is gonna be decreasing, or maybe even eliminated for a lot of patients. And we'll be using different immunotherapies or cellular therapies instead.
- We need to do as much as we can to optimize these combinations and figuring out how to sequence. There's new therapeutic targets. Dr. Tau is here, and he and the Translational Research group are looking at other new targets that we could be be testing. And then I've mentioned the the use of these potent immunotherapies for the high risk patients, maybe, rather than an allo transplant.
- At least you could do this first and save the Allo and to make really optimize these. We're in the early days. We need to understand the mechanisms of how resistance to these occurs, whether it's a car or a buy specific. And to that end, Dru, really spearheaded, a, a, a critically important study, in my view. Not just because I'm
- I play a small part in the study. But this is a synergistic team. Science award from the Leukemia Lymphoma Society. These are very competitive. They give 2 internationally. One of them is here in the last. Go around. And so this is a collaboration that Dr. Tau is leading with our center, looking at improving car T. Efficacy.

- And then Michael Wong and his group at MD. Anderson, and then Marco and Steve Shuster at University of Pennsylvania, are the other centers. So this is a 4 year, Grant, and we're gonna be looking at ways to potentiate improve these therapies. So that's all I wanna say about mantle cell. I didn't want to finish by just acknowledging that it's been a while since they did my first grand rounds. I was chief resident at the end of that year. So you all have yours next week. But you know, I've I've been fortunate to spend my career at Uva. I've had colleagues, mentors, role models that just really made such a difference our research staff. The people that have collaborated over the years our patients and their families. We have just superb nursing and clinical support staff. We've had very generous folks who supported our research we learn a lot from each other, and that's certainly been true for me. And then I've had just terrific support from family and friends. In fact, my wife had to sit through. Talk here with me today. So thank you for that.
- I should say my wife Becky is here today. Thank you, Dr. Williams. That was a great talk. If there are other questions in the audience, please feel free to come up, and I can get us started. So I guess in a disease like mental cell, where we could have some patients living 10 years out now with therapy and having multiple lines of effective therapies.
- What's your thought on surrogate endpoints and sort of using those for sequencing where with the triangle study, we saw failure, free survival improved. But overall survival. There was a significant difference. Yeah, it. It's a great point. And I think that's where we have to go in the field. So you know, one of the I sort of put my info slide up again. But one of the things was, you know, when when have we done enough?
- And so knowing when to stop, so you can spare toxicity.
- For people who've already gotten where you need them to be versus recognizing those who are not going to do well and have that early progression.
- So I think the Mrd is going to be one way to do it, and probably the most powerful way we. I didn't show the data. But in multiple studies, especially from the European Mammal Cell group they've shown that Mrd is the single biggest predictor of outcome in mantle cell lymphoma. So end of treatment. Mr. D. If you are still positive then you tend to have a progression within a year in the vast majority, whereas if you're Mr. Negative, it correlates with much longer. So the question is you know, what do you? What? How do you know what to use in those patients. And is it gonna be an immunotherapy? Should we just maybe via Brutnib or nowadays we use different Btk inhibitors that we just know that they need to be on maintenance therapy. You saw that Ritu Lab gave benefit, so no doubt all of those patients had disease left behind, and by getting Ritu lab it suppressed and cleaned up that clone. Maybe it took it down another log or 2, so that remember those curves on recurrence that it just seemed a longer time to come back up and progress. So I think we'll be able to use MRD.
- And it may even start to replace things like pet at some point as certainly we don't need to do serial pets. I'm always happy not to image a lot of people so we'll be using Mrd, and then we may be also using things like, not just do they have detectable tumor cell DNA. But can we sequence it? And which mutations do they have? Have? They? Is there a. P. 53. Mutation in that clone? And therefore it's like, okay, well, then, we need a targeted drug. Maybe in addition to their immunotherapy. So we can really get very specific for that patient's biology to improve their chance of cure.

- Peter. Oh, yeah, Mike, thanks so much for such a stimulating talk. Yeah. So I'm just wondering whether we really understand the biology of these cancers.
- Because it looks from all these therapies that you have outlined that these cells can proliferate just by turning on their Bcr and then you mentioned earlier that the main abnormality is the C one d. You know the cycling? D. One.
- That it kind of. It's an autonomous. So on one side. So if it is something autonomous where the cyclin D one is turned on. Why would it be influenced by the B cell receptor? You know this is the normal physiology of of B cells. So I'm just wondering whether we need to spend more time understanding the biology.
- And and then the second point I was trying to I was thinking is you indicated that based on the DNA work, that there are so cells sitting around you know, and then they surface up. And I was wondering whether we can have ways of stimulating these cells to bring them up.
- Okay, because it looks as though our immune system does not take care of this few sales. So so this helps for some reason, our resistant to our regular and whether you can bring them up earlier and in their activated state, then get rid of them. Yeah. So all good questions. The. So there's probably it's not just cyclone d one in by itself, if you like over express cyclone d. One In and early B-cells. You don't get mantle cell lymphoma. You have to have other mutations, so some of those may be in the B-cell receptor pathway, where they've got constitutive activation of CD. 79 or other molecules that are driving it. So. And interestingly, one of the early thoughts, you know, 20 years ago was, well, let's inhibit cyclin d. One. And we can really treat this cancer doesn't work at all, because what happens is, they almost immediately upregulate Cyclin d. 2 and cyclin d. 3. So they just bypass you and go right around it. So there's virtually no effect of that at all in terms of you know. How do we manipulate those residual cells to make them more vulnerable?
- That's not something. I think, that people have thought much about with mantle Cell. I know some years ago, in acute myeloid leukemia, before we had all the targeted drugs. Now some people were saying, Well, maybe you should give a Cytokine like Gcsf or Gmcsf.
- To drive those cells back into cell cycle and then hit them again with chemotherapy like hydrocyabine. Again didn't work so well. But that's the idea. I think. You know, one of the one of the things that we know about these cells that can make them resistant is that they've got these apitosis inhibitors and some of the work that we've done and others have done. You know, there are blockages like Bcl 2 and others that keep cells from going into an ipatic program and cell death.
- And one of the things that happens in Mantle cell is, you get Bcl Xl up regulated. And so there are ways now to try to get at that. They're they're hard molecules to target because there's such a critical part of our normal cellular machinery that you can get a lot of toxicity by knocking down some of these molecules. So.
- but all good questions. Yeah, Dr. Nobos, I'll let you have the last question. Oh, thank you. I could say even Briefly, after all these years I still very much enjoy your talks. Thank you my question, and I don't follow the mental cell literature much is. My recollection is that there was thought to be a portion of patients who could be potentially cured by auto transplants. Is that debunks? No, I mean, there are. You're you're quite right. There are people with therapies we're doing now, including auto transplant what I mean. You saw a lot of those patients now from the the Lima study and others that you know they're in remission at 8 or 9 years, and so what? Whether they're cured, and they'll if they live to be 100. They'll never

relapse, or you know, as Jim Armitage, famous old you know. Lymphoma Doci said, well, if they if you keep them in remission and they dive an MI. Then we cared them because they didn't. They didn't relapse and die of their lymphoma. So so that's one way to look at it. But yeah, I think there are. No, there's no doubt there are. There's a cohort of people who will have very, very durable responses, and and are functionally cured because they'll never relapse from their disease in their in their lifetime.

- Make it hard if you're young, in terms of those sequencing right? Because if you could get to a point where you're really it's gone and especially if you added a brutnip now, potentially to that pathway again, it it might make it that you don't want to minimize cytotoxic and auto for everybody.
- No, I agree with that completely. I think the there still may be populations of patients who do really well with that finite therapy. It's intensive and stuff to go through. But but you know, being on 2 or 3 years with a Btk inhibitor.
- It's not. You have symptoms from that, and there's risk and side effects, afib and bleeding and other things. So they're they're not chemo, but they're not non toxic, and the financial toxicity is extreme. They're very, very expensive agents to use.
- So yeah, I think we I don't know that we're gonna abandon it altogether. But I think we'll be using it in a more targeted way. Certainly. I think people, for example, with p. 53, mutation and stuff. I think that auto transplant has been shown not to really benefit those patients.
- So I think a a different strategy, maybe a car, an allo, we certainly, that's what those are the patients that will take to an allo transplant, younger with very aggressive p. 53. Mutated disease, and and manage them that way.