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TRANSCRIPT - GR 10 20 23 "Power of Cooperative Groups and Groups that Cooperate: Diffuse Large B-Cell Lymphoma as a Case Study" guest speaker Sonali Smith MD from University of Chicago Medicine

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- Good afternoon, everyone, and welcome to medical grand rounds today. We're really lucky to be hosting the Charles E. Hess's visiting professorship. We are visited by Dr. Sinali Smith from the University of Chicago. She'll be introduced by one of our professors in the division of hematology, oncology. Dr. Michael Williams.
- Thank you very much. I'm glad to see so many people are joining us virtually. I know the residents have an event later today. So, thanks for joining in here. I wanted to do 2 things. One is just to introduce this lectureship and and professorship, and then I'll introduce Dr. Smith. So dr. Charles Hess or Charlie Hess was a longtime faculty member. Here he grew up in Southwest Virginia was an undergrad medical student, and did his training here and ultimately did his fellowship in hematology. Oncology. Here, with Dr. Bird Level, who was one of the giants of early hematology level, and Thorpe was the go-to textbook for a couple of decades and Charlie was a real polymath of classical hematology and malignant hematology. He for years ran a hematopathology conference before we really had him metal pathologists. Here there was an 11 headed scope. We would all gather around and we learned a lot from Dr. Hess in that regard. There are a lot of colorful stories about him which I won't take time to share now, but I can. Later, Mitch Rosner will remember many of those as well.
- So when Charlie passed 10 years ago, his family endowed this professorship, and so every year we bring through an esteemed person in our field to present this, and to visit with our faculty and research staff so past recipients. You can see here include Elaine Jaffe at the Nci. And Nigel Key at Unc. Steve Swordlow another internationally known hematopathologist, Ellen O'connor, and last year Anna case from Dana Farber and I did show here a picture of Dr. Hess and a book that he actually finished after he retired. It's a real tone that he basically hand wrote and pulled images together to sort of reflect kind of all those years of sitting at the microscope. So it's called Hess's Hematology. So our Honoree this year, as you heard, is Dr. Sonali Smith, who's the Elwood Jensen?
- Professor of Medicine and Chief of Hematology, Oncology University, Chicago Pritzker School of medicine. So I've had the privilege to know and work with Doctor Smith for many years, and just a little background. So she's a native of Chicago, and as evidenced by her education and training, she did her undergrad Medical School Residency and Chief Residency at Northwestern University and then went to the South side to University of Chicago for her fellowship, where she developed an interest in lymphoma and joined the faculty there and you know, in the ensuing years, dr. Smith has really become just one of the national and international thought leaders and a true scholar in our field. She's got over 250 publications, almost 200 peer reviewed papers. And a lot of these. She's helped design and lead many of the practice changing studies that we utilize each day, and she's one of those folks that just reminds us how an academic career couldn't have an impact so far beyond our own practice and our own institutions. So it's great to have her here for this. She's been a leader at University of Chicago in a variety of ways as well as with our professional societies, American psycho, hematology, and with the American side of

clinical oncology, she chaired. I mean the Asco meeting every year is the largest and most important oncology meeting in the world, and she chaired the scientific program in 2021, for that has had many other roles with Asco. You'll hear about our US. Cooperative groups in Lymphoma. She's there are 3 of the main groups. She's vice chair for the Southwest group.

- And she's been an esteemed mentor and role model. She's been a very strong advocate for women in medicine has done a lot to advance them in leadership roles and we've had the privilege of serving for many years on the Scientific Advisory Board for the Lymphoma Research Foundation, and in fact, Dr. Smith was the first woman to lead the Scientific Advisory board so really accomplished in so many ways. So today, she's gonna tell us about the power of cooperative groups and groups that cooperate. And she's gonna use diffuse large B cell as A as the paradigm here. But the important keep in mind for any of you who are hard to understand, maybe not going into hematology, oncology. But in any field of medicine where you're doing clinical research, what you're gonna hear will help inform how you think about it, how you approach the field, so it's just an honor, as I said, to welcome her here as the Hess visiting Professor Sony, we have a I won't unbox it, but we have a Jefferson Cup to commemorate your time here and welcome. We look forward to your talk.
- Mike. That was perhaps the kindest, kindest introduction I've ever had, and I will say the groups that cooperate part of this has a lot to do with Lymphoma Research Foundation, which I'm gonna share a little bit at the very end. But Mike and I have known each other for 20 years, and it really is a family within academic oncology, and it's just been an absolute honor to be a part of that, and to work with you.
- I will also throw in that Mike spoke at our twentieth anniversary of the International Chicago, Altman Lymphoma Symposium, along with Elaine Jaffe, and just to hear the story of the discovery of mantle Cell lymphoma in that moment was absolutely spectacular. So I am incredibly humbled to be here. Thank you and thank all of you for for joining us today, both online as well as here in the room. So the title is Power of cooperative groups and groups that cooperate. I'm probably gonna stand to the side of this thing, because if I stand back here nobody will see me at all. Vertically challenged
- And I really wanted to talk about diffuse large V-cell lymphoma for a variety of reasons. I realized that this is an internal medicine audience, and you're going to see a lot of different things on the inpatient and outpatient service. But for the residents Dlbcl is the most common indication for a lymphoma admission, and I think it's important to understand.
- So here are my disclosures. I've cut down on a lot of my consulting, but my spouse is employed by Karis life sciences, and I don't think I have anything that's off-label for today. But if I do, I will be sure to mention it.
- Okay so I always kind of like to start really far out before we move in. And you know, I always ask when I'm on service. At least you know how many new cases of cancer are there in the United States per year, and the answer is almost 2 million in 2,023. That is a lot of people. And although Lymphoma's lymphoma is not the most common. It does currently rank as the seventh, fifth, or sixth, most common cause of cancer in both men and women.
- And we've made a lot of progress. But we still rank in the top 10 causes of cancer mortality.
- If I translate this into numbers, this means about 80,000 people who will be newly diagnosed with non-hodgkin lymphoma, and again, lots of progress, but still about 21,000 people die of this disease every year in the United States alone. So that is a big number.
- But the difference between the incidence and the death rate

- implies that there are over half a million people who are living. So when we start to develop our therapies, I think it's really important for us to think about the short term and the long-term consequences of what we do and how we approach people and survivorship is an increasingly important part of our field.
- Hodgkin and Non Hodgkin lymphoma affect all ages, all races and both genders. And so there is a really large diversity of patients whom we see.
- One of the challenges with approaching non hodgkin lymphomas is that it turns out it's really an umbrella term with about, you know, a dozen broad categories and maybe 100 different subtypes. When you start to really get into the pathology and the biology of this. And so this can make it a little bit inaccessible. When you're first trying to learn about lymphoma for today, I'm just going to look at one slice of the pie, which is diffuse large cell lymphoma. It is the largest slice of the pie, and I'll tell you a little bit more about it and, unlike solid tumors, where a lot of what we do is driven by stage and the extent of disease in lymphomas. The stage is much less relevant. The thing that really matters is the actual histology. We work very closely with our hematopathologists to know what we're treating and then, of course, the intent of therapy, some lymphomas we can cure others. We can simply manage.
- Okay, so diffuse large B cell lymphoma. This is one of those diseases that we want to cure. The goal of treatment. When we meet somebody is remission, and if the remission is durable, then they should be cured.
- There are about 27,000 new cases in the United States per year, and if you look at the incidence rates, the Neon green is the Dlv Cl line, and this had been increasing sort of steadily through the 90 s. Then flattened out. I don't know if the incidence is beginning to go up again or not. But there seems to be a slight suggestion. Then you can see some of the other lymphomas, including mantle cell lymphoma in the dark blue at the very bottom.
- So the neon curve on the right shows you sort of the incidence by age, and there is a population of patients who are in their teens and twenties. So the Aya population lymphoma can occur in that population. But really this is a disease of people as they get older, and the Median age is about 65. So we also have to keep that in mind when we start to think about some of the aggressive therapies in particular, that we address so 27,000 cases. And again, lots of heterogeneity when it comes to the biology. So how do we best study a rare or an uncommon disease in the United States.
- And this is really where the cooperative groups come in. So the National Cancer Institute was founded in 1,937. I think many people are aware that the birth of chemotherapy was an unfortunate byproduct of the chemical warfare that was happening, or at least studying chemicals during World War one and then World War 2. Where an incident off the coast of Bari in Italy led people to observe that all of the lymphatic system, as well as the spleen, would shrink in some of the autopsies that they had done for the sailors who were exposed to nitrogen mustard.
- Well, in order to study this, the nci was developed, and it was originally a very geographically based system, where you would have the Southwest Oncology group, the Eastern Cooperative group. And then there would be some modality based. So like the rtog, was for radiation therapy and this led to a lot of really fantastic work. But what's really important is that in 2,014 the Nct. Was created which consolidated all of these different areas now into groups that really work together and then shared resources at its core. So we now have a central irb, we have a central data system and we have central regulatory mechanisms. So this allows us to conduct research in a slightly more efficient manner.
- The other piece about the cooperative groups is that these are publicly funded. They have extensive breach. There are thousands of practices, both academic and in private practice,

that participate and they are independent, and I think the part that I really appreciate and have come to appreciate even more in my role at swag is that we don't have to have a for profit bottom line, we can. We have the luxury of thinking about different questions and forcing different companies to work together? If we have a question that we want to answer, and one of the trials that is now open, that I had the fortune to work on is one of those where we had to work with 3 different companies to try to get them to collaborate and answer a question in relapse. Refractory diffus, large cell Infoma. okay. So I'm gonna go back to lymphoma for a second, and then I'll come back to the cooperative groups and just exactly how they helped my career. Dr. Williams shared some of that, and I'll just tell you a little bit more about that. So if you will indulge me. This is a little historical tour. But chop chemotherapy. We talked about how you know, chemotherapy was relatively late to the cancer field. I mean, surgery was first, then radiation, then chemo right? And it wasn't until people realize that you could use non cross resistant drugs and eradication of TV, that the concept of combination therapy was really born. And so one of the things that happened in the early Seventys is that people were trying all different kinds of combinations and this particular iconic paper was the one that first showed that simple addition of an anthracy to a Cdp backfall could lead to a phenomenon of a plateau on the curve.

- So this plateau on the curve advanced their, you know, advanced lymphoma, stage 3 and 4, treated with chemotherapy alone led to cure, and I feel like we've been chasing this plateau on the curve for the entire time with diffuse large B cell lymphoma.
- And this led to the birth of chop chemotherapy.
- So of course, the concept then was, if 4 drugs are good, wouldn't more drugs be even better, and the whole thing about more is better and more is better, was really born.
- And this is really one of the first cooperative group studies that I think put to test a couple of concepts. For one thing, the more is better. Approach had been tested in phase, 2 single arm trials through a variety of institutions, and you can see some of the drugs and combinations. So pro-mase cyobom is my favorite, because it's just like such a cool name, and there's so many different agents.
- But this is very, very toxic. But again, the whole hope was, let's maximize what we can do in terms of chemotherapy, and these single arm phase 2 trials when put to the test in a randomized phase, 3 trial done by swag at the time showed a couple of things. One. Yes, we could still cure people. There is a plateau on the curve, but 2 more was not better, and I just kind of shudder to think about what it was like to treat people in the days before anti-emetics, growth factors, anti-microbials, and all the other supportive care we take for granted.
- But this trial, showing that more is not better really sort of put. A squash on further research about adding more chemotherapy for the large part, and becomes the standard of care. And we can tell people we have about a 50% chance of being on that plateau and being cured.
- So it took a long time to get beyond this particular trial, and it turns out that the best way to really improve upon chop was to add immunotherapy and rituximad, contrary to those of you who have read improval maladies. Have you all read that and seen that? So I it's my pet peeve in that book, because he talks about Herceptin as the first monoclonal antibody being used in cancer, and he is wrong. It was retu that beat it by about, I think, 4 to 6 months. But it was the same company.
- But the retoxin that is a is a simple monoclonal antibody. It's a chimeric antibody, against which is a Pan B cell Antigen, and the nice thing about Retoxmab is that it gets rid of every

B cell that expresses C, but leaves intact the pluripotent stem cell that can then remake some normal B-cells over time. And so it's really kind of the perfect target.

- But what would seem even more impressive is that this addition led to an improvement in survival, and these are not event-free or progression free survival curves. These are actual overall survival curves, and we have raised the bar in both older patients which are the top 2 charts, and then the bottom left is in younger patients, and then the bottom right is a population based analysis from Canada. But really this changed everything, and our chop is now the standard of care as of 2,002.
- So at this point, so I started my faculty position in 2,001. So this is kind of what the world looks like. We were so excited. You know lymphoma's disease learn to be so. Lymphoma is a success story. We cure people. And you know, we keep having all these breakthroughs that are curing a higher portion of patients.
- But the truth was that suffice. Large. B cell lymphoma remained the most, the cause for the largest global lymphoma burden. It's not just in the United States it is all over the world remains the number one cause of lymphoma-related deaths.
- and then, addressing heterogeneity in any kind of precision. Approach had been very, very difficult.
- Before I go back to that whole concept of precision and a little bit about what we did in that area. I wanted to, just for the, for for the the residents, and for others, just to point out that although more was not better in the front line setting.
- we did talk about having a second chance for cure in the second line setting, and that is because there was a concept that when the lymph get the lymphoma came back. If they weren't in that 50% of people who were cured that we could flood the body with more chemotherapy, high dose chemotherapy, rescue them with their own stem cells and actually give them a second chance for cure. And that was based on this very small randomized trial called the Parma Trial, that showed that chemotherapy with high dose, chemotherapy and auto transplant was better than standard chemotherapy. And this gave us a new algorithm front line. You know, chop-based therapy. Second line, high dose therapy with autologous stem cell rescue.
- However, our chop changed the game because all of a sudden, in the frontline setting. We were curing more people. You saw those plateaus go up right. And so now the people who did not have a response to our chop or refractory actually didn't do so well and so stem cell transplant really became sort of a disappointment, if you will, in its inability to cure more people taking it. One step further is this study right here? This is the scholar analysis, and it essentially drives home the point that if a person has had our top and their diffuse large B-cell lymphoma comes back. The outcomes are terrible.
- So if they have primary refractory disease, meaning, it doesn't respond at all to our chop. If they are refractory to second line therapy before a transplant, or if they have a transplant and their disease comes back. Medium survival is 6 months. This is a terminal situation.
- So to summarize where things were at this time, we knew that chop can cure people.
- We knew that more was not better in the front line setting. We knew in the second line setting that transplant could cure some people. But now that our chop has improved, overall survival, second line transplant was doing, much less. The other piece that I won't show you is that everybody was trying to build a better chop or build a better art chop, and there were a number of negative trials. Whether it was giving infusio chemotherapy through epoch R. Whether it was adding on an archop plus X approach, or it was, you know, swapping out for a better antibodies instead of a tuxmab usingab, or whether or not it was looking at the shape of the survival curve and saying, You know what most of the

people who have relapse. It's within the first year or 2. So maybe that's where we should try to do some consolidation.

- All of those approaches, many of those trials were all negative, and in 2,017 we were left with relapse, refractory, real Vcl. Having a Median survival of 6 months and transplant not really salvaging as many of the patients as we wanted.
- So around this time we had a clinical trials planning meeting at the Nci. So this was, you know, the Nci basically saying, we have a problem with lymphoma. We need to revamp the Lymphoma Steering Committee. Let's have a group come together to Bethesda. Let's think about the questions and organize some of our priorities. So Dr. Williams was there as well, and this was a very exciting conversation, certainly for me at the time, too, I was sort of just, you know, an associate professor, and I was really excited to be at the table with all these great people, and they let me be the senior author on this paper. But it was really a a group effort.
- And we kind of came up with a couple of like road rules, if you will. One was that, you know, response rate wasn't something we were gonna settle for, just because something works in the short term doesn't change that plateau on the curve. We started talking about the concept of landmark survival and landmark outcomes. So in other words, if we wanna really shape, we wanna change the shape of the curve, but we wanna improve the curve and elevate as much as possible.
- And then also, you know, we were dealing with the challenges of not having control arms for a lot of the subsets that we're studying again. These are all rare diseases when you start to get down to the subsets.
- So here we are, 2,017, remember, that's where I kind of left that timeline. And this was our approach. We used our chop up front. If that worked that was great. Some people were cured. If it didn't work we would try to give them a salvage therapy. If that worked we go to an auto and that would cure some more people, however, for anybody who did not respond to art shop or had primary refractory chemo resistant disease to second line therapy or relapsed after a transplant. We were sort of stuck, and that clinical trials planning meeting was in some ways a bit frustrating, because we talked about all the things we would like, but really we didn't have much that was going on.
- So that's when everything changed and another leap was made. And this is when car t cell therapy became around. And so a chimeric antigen receptor again. Just kind of taking a little step back is a Receptor That has A Bifunctional Capacity so on the external surface it, can target, whatever You want, to target In This case for Lymphoma It's CD-<unknown>unknown<unknown> and then on the internal side it will have a a stimulatory domain, and this is the surface, the cell surface of the T cell that has been harvested autologously so from the patient themselves.
- So you've got the single chain variable fragment on the external side. You can put it against any antigen you want. You have this hinge region. That's a transmembrane. And then you have cost stimulatory domains which are absolutely essential for these T cells to expand. And there's 2 different costimulatory domains that have been furthest along in lymphomas.
- And that is shown on this slide here. One of them is CD. 28, and the other one is 4 one bb, so these are just different molecules. And people are stacking this up now, too. So you know, we call this car T, and everybody's doing a play on word. So they're supercharged car T cells. There's, you know, all different kinds of ways. You can play on it. But the bottom line is that there were 3 chimeric antigen receptor engineered T cells that were coming along in 2,017 that were being put to the test, and the process was to take patients with the she's large. We sell them form up who were at least in the third line, right? They

got our chop didn't work. They got some second line therapy. Whether it was with or without transplant, didn't work here. They third line meeting survival is 6 months. What do we do? That's the patient. These are the patients who are on these trials.

- So these 3 agents were all tested through these trials that were listed here and the results were really unbelievable. Instead of a Median survival of 6 months, we still had a very big drop off. But you'll notice that not you know that that previous curve I showed you where the Median survival was 6 months. Essentially there are very few long-term survivors in the single digits. And now, all of a sudden, we have 40, and it was consistent across the 3 different products that were being tested.
- So there's a plateau on the curve, and between these 3 CD. 19, directed car T. Cell now has 34, 30 to 40% durable remissions in the third line setting. And this was just an absolute, huge step.
- Just to put the case in point, I just want to share one of my patients so, and maybe the the details are just really that he was young and healthy, but he had one of the worst lymphomas I had ever seen so he was 50 years old when I first met him in November of 2,013. He had just, you know, what looked like a diffuse large Esl and Fomo without any super high risk features. But it just didn't respond to anything he got. Art shop didn't work rice. Esha had an auto transplant and then progressed again, he went on to several clinical trials cell in Xor brutalitamide. And then what you can see here on the Ct. Scan is this like almost 20 cm mass, and what you can't appreciate on the on the scan is externally what it looked like was a gigantic open wound that was just seeping and his wife and his daughter would just change the dressings, you know, 6 to 10 times a day, and you know, he was just getting more and more debilitated. We ended up radiating this right. But radiation is wonderful, but it only works for you and your being. So. We radiated his his ingrinal mask which responded, and unfortunately, he then had progression in the lungs, developed multiple pulmonary mess.
- So this is a man again, 50 years old, you know, really prime of his life.
- He ended up being the first patient in the State of Illinois to get car T. Cell went onto the Novartis Trial University of Chicago. We've had a really strong car T cell program, led by Mike Bishop, we were first to have all 3 commercial products and currently have every commercial product available and have our own Gmp facility where we're making some tri-specific car T's, which is kind of fun, too.
- But anyway, so for him. This is him. 7 years later.
- He did go on. His children got married. He's now a grandfather, and you know, this is like, when you look at these survival curves, this is what I wanna think about. And he has given permission for this. He is all over our, you know, website and everything. But he was my patient, and still. He text me from Notre Dame's football field every year because he lives in South Bend, and he's like, I'm still here, and it's awesome.
- So here we are now, 2,017, and this is what Car T cell does compared to, you know, the control or there was no control but historical control. So a little leap forward now, of course, car T does not come free of cost. There are 2 major toxicity, Cytokine, release syndrome as well as immune cell associated neurotoxicity, syndrome or icans and this can be sometimes very mild, sometimes very severe. I just put the 3 products that were, FDA approved in the third line setting with the expected free release syndrome and neurotoxicity, I'll say also, for again, we have more survivors now. So survivorship kind of comes in and we do have to think about long term effects of the carte cell approaches, which include Cynias, hypogamic anemia, and sort of a lifelong risk for infections.
- So November 2,017. Axi cell was approved, followed soon by the other 2 products.

- So our algorithm has now improved and we have car T available in several different areas. But there were still some questions remaining. This includes, do we really need to get to car T, can we cure more people in the front line setting? What are the options. If car T. Doesn't work, what can we offer people if they're not eligible for car T car, T is expensive, it's limited to academic institutions, and not everybody can get to where they are being delivered. And even though we're working on outpatient community based car Ti think we still have a long ways to go.
- The other question was, Can we move car T earlier in the algorithm? And here people kind of took a step back and said, Well, why is it that carte works for that 40% which is phenomenal? I mean, really, I don't want to understate how important that is. But that means 60% of people don't benefit from carte. So what are the reasons? And there's a number of different reasons. This is just a very simple cartoon. But in general there can be loss of CD. 19,
- there can be host or tumor factors, and there can be some T cell specific factors as well. So to talk about the T cell specific factors, you know, typically, when you have a T cell, if there's an antigenic stimulation in this case, cancer. It will expand and try to eradicate the malignancy and eventually develop a team memory phenotype.
- And that is what gives you sort of this long, lasting immunity. The problem with refractory cancers is that it's the bottom half here. There's persistent antigenic stimulation. The T cells end up acquiring all of these features like P. Lag. 3. Digit and Ctla, 4. Expression just to name a few, and those T cells become exhausted and essentially dysfunctional. So trying to do car T cell. When people have been very, very heavily pre-treated, you know. Might mean that you're not really getting the best T cells to do the job that you want to do.
- So. There's a lot of data again. This is just another cartoon, just sort of suggesting different points along the way that T cells might be affected by some of the treatments that we do. But I think the bottom line is that cancer is an inflammatory state, and these T cells are, you know, driven to a point of dysfunction and exhaustion.
- and a lot of the treatment that we give, particularly for lymphomas are actually lympho phoenix. So bender musty, which is a very commonly used chemotherapy is extremely T cell suppressive and trying to harvest health and T cells. After that can be very, very difficult.
- So with these concepts in mind, the question was, Can we move car t cell earlier in the process? And I told you, house stem cell transplant has been the standard of care in the second line setting, even though we don't think it's as good of a standard. So the question is, can we replace transplant with car T, and at ash of 2,021 there were 3 presentations. This was really just an unbelievable year, including one of the plenary session by Fred Lock, who was one of our former fellows.
- And Manali Condar, who's part of my swag family, and Michael Bishop was at the University of Chicago. So this was a huge year for lymphomas, and really it was a randomized phase, 2 trial car t cell therapy against salvage, therapy and auto transplant, which was the standard of care, and patients had to relapse within 12 months. They had to be or be refractory to their first line treatment.
- and just to summarize a lot of work into one slide. What this showed is that moving car T cell up to the second line setting 2 out of 3 studies were positive. So Axi cell as well as license cell were positive. There was an improvement in progression, free and overall or progression, free survival. And also now for license cell, I believe there's a small survival advantage as well.

- This study was a negative trial. We could talk more about that. But what I would just say is that both the zoom, a 7 and transform study, have now allowed us to bring carte into the second line setting and again benefit more people.
- So a lot of people will say, All right. So then, why are we doing any auto transplants? Is it completely off the table? And I would just say that. And I was part of this paper with Mehdi Hamadani. Is that transplant does still work for some people, but usually for the late relapses and not for the early relapses.
- But despite that evidence that auto transplant still helps people. See Ibm Tr data, which is the international bone marrow transplant registry, you know, which catalogs all of the transplants done in around the world shows that people are choosing not to do auto transplant and car. T has really taken over and almost eliminated other types of transplant like Allo as well so as of 2,022. Because of those trials that we're done, we have a new standard of care, which is that if patients have relapse or refractory diffuse large B cell lymphoma. We look at 2 different things. We look whether or not it's an early relapse or late relapse, and we look at the fitness, and if it's a late relapse, yes, maybe transplant has a role. But if it's an early relapse, or if they're unfit they can get car T, and you might say, car T. Sounds a lot more aggressive than a transplant. Why would an unfit person be eligible for car T, but not for an auto transplant. And the answer is that in order to do an auto transplant, you have to be able to collect stem cells they have to respond to chemotherapy, and they have to be able to tolerate high dose chemotherapy, whereas for car T cells, because we're not relying on intensive therapy, we're relying on the t cells to do the work, you actually get away with a lower intensity of treatment. And older patients, even up to the age of 90, can go through that you also don't have to be in remission for car T to work so lots of advantages there.
- Alright, but like I said, car T is not available for everybody. So what do we do for them? I won't go through all of these in detail, because there's a lot of data out there, but I will just say that the field has just I mean, I look back at that 2015 meeting at the Nci. None of this existed like it wasn't even on the horizon, really. And we now have antibody drug conjugates which are a Trojan horse mechanism of delivering cytotoxic payloads. We have Selenxor, which is a first and classic sport and inhibitor, we have anti CD, 19. So CD, 19 turns out to be a pretty exciting target as you saw car T cells take advantage of this. But there's now non-cart T approaches, including tafacidomab, which is an enhanced anti CD 19 monoclonal antibody as Well, As, A, new Antibody, drug, Conjugate, Lonka, Stuxnet, that can Attack, CD-<unknown>unknown<unknown> so if Car, T. Is not, available These are some of The Agents, That, are out there.
- One of the downsides to those regiments is that they are purely palliative.
- But I will say, and this little curve right here kind of triggered interest in Tacitimad, which was that anti CD. 19 monoclonal antibody with Lenolitamide.
- The fact that if people have a CR. To this it can be very durable really sort of piqued our interest within swag and led to a trial that is, on this next slide. But just to to say, some people will say, well, if You're, targeting CD-<unknown>unknown<unknown> with these Antibodies does That mean you can't do Car T. Later, and I think that question is still out there. I don't really know the answer to that.
- But looking at that curve for tuff acid amad and lenolitamide, saying, Okay, here's a non car T approach. There's some people who will do really, really well. Is there anything we can do in this particular setting? And so through swag? This is a study. Where I'm one of the national pis along with
- Patrick Regan and Jennifer Amingwall, where we're looking at relapse, refractory large B cell. Lymphoma. We're doing a safety run in. But the eventually we will have a randomized

space to where we add one of 2 different agents. We have 3 companies actually 4 companies, because 2 of the companies that got bought out. So it took a long time to get this up and going, but it is up and going now, and we are hopeful that for people who cannot get car T, that's this will be an option, and hope other people will open it.

- The other new kid on the block that came around just in the last few years is by specific antibody. So I talked About Retuxmab being sort, of a simple quote Unquote, naked Antibody, it, is A Antibody, just against CD-<unknown>unknown<unknown> It Eliminates, all The positive cells, and That's, kind of it.
- By specific antibodies, as the name implies, has 2 different targets, and the ones that have been the most successful are the ones that are targeted against CD 3, which is a Pan T cell Antigen, and then brings it in proximity. We think I don't know, you know mechanistically, how exactly they come together. But you target CD, 3 on T cells and then pick an antigen on D cells, which is C in this case it activates the T cells so you could think about it as an off the shelf kind of T cell therapy. It's exciting all the T cells.
- And there are a lot of different by specific antibodies that have been in evaluation. Some of them are engineered, for example, here with Gloufetumab, there's an extra capturing A Component.
- so you have 2 areas that will look, for as the antigen and one that looks for CD-<unknown>unknown<unknown> and there are others that have been engineered for persistence as well, and within the last 6 months we now have 2 new antibodies that are approved by specific antibodies for diffuse large B cell lymphoma, and I'm just sharing the waterfall plot here, as well as the duration of response in the progression, free Survival. When you look at who went on to these trials. It is pretty impressive. These are patients who have refractory disease. A lot of them have had prior car t cell therapy, and yet they are getting this off the shelf. T cell. Engaging treatment that can be given in the clinic, not in the hospital necessarily, although the first dose does need to be given in the hospital because of potential Cytokine release syndrome. Very little icans, and there are some durable remission. So I think this is very exciting glitamab was just approved while we were in Lugano, Switzerland this year, so we had a big month meeting, and everybody's there, and all of a sudden we'll fit him up, got improved, and it was very exciting for a lot of people.
- And again, you know, this is another patient population where 86% were refractory to their most recent therapy. 30% had prior car T and the complete response rate was 39%. So again, you know, maybe not a cure. But for those people who do respond. The duration of response can be several years, certainly better than the 6 months that the scholar trial would have predicted for us.
- So last little can we speak for 2 2 pieces real quick? One is, you know, I talked about frontline therapy, and you know, back again in 2,015 everything was like, well, should it be our chop plus x, should it be our chop, followed by ex, you know, response adapted our chop, and we just have these series of negative trials. It was actually very, very discouraging at the trot at the time. And what? The only positive study that has come out has been the application of an antibody drug conjugate, called pullatusumavidotin which is again a Trojan horse mechanism against a protein on these cells, when added to our chop in a head to head comparison shows that there is a modest improvement in progression, free survival, for by about 6% no difference in overall survival just yet. And I think whether or not this becomes the new standard of care is something that you know. We will probably maybe even be determined by insurance companies more than you know the clinician. But it's an expensive addition, but certainly looks, you know, promising.

- So you'll notice that in all of this I haven't talked about the biology of lymphoma at all. I've just been talking about it as if it's like one clinical entity like, where did the biology go?
- Well, turns out that it's a little bit more complicated because there is significant heterogeneity. And you know this snapshot from the who back, in 2,017 highlights 2 concepts that were emerging, you know, at the time, or at least had been actually more than emerging. The cell of Origin concept had been around for about since 2,001, and it essentially tells us that even though things might look one way underneath the microscope, if we dig deeper with fish testing or with gene expression profiling, there's 2 buckets of biologic abnormalities that that really underlie a lot of the heterogeneity. So let me talk about that for a second.
- The first was, and this is really going back to 2,000 is looking at gene expression, profiling of diffuse large. We sell lymphoma. And remember at the time it was 50% cure, right? So when people come to clinic, half are cured half or not, how do you distinguish who falls into which bucket and gene expression profiling use frozen material at the time to look at the pattern of messenger Rna to see which genes were turned on and turned off and it turns out that there are at least 2 different patterns, one which looks like germinal center B cells and the other one which looks like non-germinal center B cells.
- And this is not just important biologically but prognostically. So, the people who have, you know, the germinal center type do much better than the patients who have the non germinal center type. And this really sort of got everybody really excited. And there was another decade or 15 years of trying to say, All right, we know these 2 biologic subgroups exists. Can we exploit this therapeutically?
- And you know there were many reasons to do that. They had different genes that were turned on and off. Maybe you could target them.
- And unfortunately, after 20 years of trying to exploit cell of origin, as you know, trying to look at which targets we could go to. They have all turned out negative and I think you know, I took out some of the slides just in the interest of time, but it turns out that there's probably a lot of biologic overlap. So even though these gene expression profiles are distinct, there is enough overlap and probably deeper genomic differences.
- So at the Nci in loose stouts group. This is just one example. There's also other labs around the country like Margaret Chip and others. What they did was, they said, All right. Well, let's rethink biologic heterogeneity. We know these gene expression subgroups exist the germinal center, and then the ABC or Non Germinal center. And when they go deeper and look at the actual genome, turns out that there are many groups.
- And so this is probably why our inability to target cell of origin you know, is true. It's because of all of this underlying heterogeneity. So now we start to get into really small groups. Right? Remember, we said, 27,000 cases of Dl Bcl. And now we have, like 7 or 8 genetic subgroups. And it is getting even smaller and smaller, but I do think that it will help us get towards precision medicine, particularly if we understand the biology that's there.
- So that was one was the cell of origin, the other part about diffuse large B cell lymphoma. That has been an evolution is the concept of double hit, and this is something that I think as residents, you may see, you know, on the floors quite a bit. You know what is double hit, lymphoma. What are these high grade v. Cell lymphomas?
- And essentially it started out with the observation that the Mick rearrangement, which is, you know, diagnostic for birket lymphoma, remember, with the starry sky and the tangible body, macrophages, and all of that Mick is the driver for Birket lymphoma, but it also exists into piece. Large B-cell lymphoma, and, more importantly, when it occurs into piece large B cell lymphoma, 75% of the time it is co rearranged with Vcl, 2.

- So Nic is a driver. It causes these cells to grow. Vcl. 2 is an anti-apoptotic gene, and protein keeps these cells alive so that phenotype is very drug resistant and leads to this concept of double hit lymphoma.
- So this was something that we started to have trials that were for double hit lymphoma.
- But of course things continue to evolve. And it turns out that if you add in modern techniques to, you know, with gene expression profiling to the double hit lymphoma, you come up with something called the double hit signature, where it picks up by whole genome, sequencing double hit lymphomas that were not captured by fluorescent insight to hybridization. You know where you look for the actual break apart probes and the gene rearrangements. So adding gene expression, profiling, deepened our ability to identify the highest risk patients at a biologic level.
- What's even more exciting, I think, and I call it yep is this paper that was published by Laura Hilton just a few months ago. And by the group in Vancouver, is that this double hit signature that we were just talking about isn't restricted to piece large vsel lymphoma. It also applies to Birket lymphoma, and for a group of germinal center diffuse large vsel lymphomas that you can't otherwise classify.
- And so they said, you know, rather than saying, this is a subtype of Dlv. Cl, let's lump all of them together and call this the dark zone signature. And so this was, you know, just it's kind of a newer concept. But you can see the frequency. 100% of Birket lymphomas have the dark zone signature, all of the classically defined double hit lymphomas 77% of them have the dark zone signature, and then there's a portion of other lymphomas that have it.
- And so they should really be lumped together, and our chop is just not enough for that group. So I think this is kind of an evolving entity.
- The other piece, and this is where I did misspell Laura Hilton's last name. But if you have a chance. And you're interested in lymphom biology. This was published in Jco. Just like 4 or 5 months ago, and is just, I think, a really fantastic sort of conceptual shift, if you will, and how we think about lymphomas, particularly in the relapse, refractory setting.
- So you know, we talked about how you know transplant. If our chop didn't work, or if chop didn't work, transplant was great. If our chop doesn't work, transplant isn't as good unless people recur late, then maybe it is good. And so to sort of explore this a little bit further with the group in Vancouver, did David Scott is the and Ryan Moran are the 2 senior people.
- Is that you know this is just one simple cartoon, but they have a hypothesis that is supported by their data that those patients with primary refractory disease, essentially you treat them and the clone from the original. Lymphoma, that is resistant or refractory persists.
- And then out grows, and there's a lot of overlap in that refractory patient in that lymphoma, in terms of the number of mutations and the types of mutations. So both the spectrum and the number of mutations are very significantly overlap. And so getting more chemotherapy in that setting doesn't really make a lot of sense, because the shared mutations that led to resistance are still there.
- On the other hand, if you have late relapse, there's probably a common progenitor cell, and so when you treat patients, you eliminate that. But that common progenitor cell survives and has a second relapse if you will, or second, you know, evolution to Dlv. Cl. And here, when you look at the spectrum and the number of mutations, there's almost no overlap. So they really are 2 different diseases defined by a difference in time.
- So this is kind of early and exciting. I wouldn't say this is definitive just yet, because this was done on this. You know, relatively small number of patients. I think it was like 160 or something like that.

- And you know this needs to be validated. But if this is true, then I think this really gives us a clue as to how we can tailor our therapies going forward.
- So who's left behind? I would say, this is another place. The cooperative groups really can have an edge, and that is that when you look at Dlbcl, one thing I didn't. Highlight is that almost everybody on these trials was under the age of 60, and the Median age of lymphoma is 65. And, in fact, in the United States 50% of patients are over 65 and 30 are over 75. So we are leaving a lot of people behind. And if we just want to look at Kaplan, Meyer curves. If we look at the Goya trial, where people were about 60, they have a 70% 3 years of Pfs. If they are closer to 70 that drops down by to 57. And if they're over 80, it's 47%.
- So there is a big drop off that goes with age. And those were just the trial eligible patients. So the fittest of the older frail people.
- So we designed this trial through swag. And again, this is something running with Liz Bram, and we decided to look at treatment. Naive piece, large B cell lymphoma. And then, based on the rationale, that hyper methylation increases as people get older within their Dlbcl, we're using a hyper methylating agent called Asocytidine, and this is our Mini chop, with or without oral asocytidine, and this has gone through the safety run, and it is now, in the randomized phase, 2 portion, and is occurring really nicely, so hopefully we can get this done sometime soon.
- So precision approaches are still very challenging, matching patients to the best treatment. And capitalizing on the genomic and transcriptomic features is still, I think, pretty far off in the clinic at least.
- And We also have a number of populations with unmet needs. I just talked about the older patients. But there are patients who have Cns involvement patients with comorbidities like the average person in the United States has a lot of comorbidities and can't go through a lot of this treatment.
- And then, of course, there is the whole issue of equity, and you know, if any of you were at the plenary session at Ash when Fred Lock presented. I don't know if you remember, there was a man who stood up in the audience, and he said, and he's a Nigerian American person from Indiana named Renew, and he had trained at Hopkins, and now he works there. He runs something called the Indie team group and he and his daughter, you know, published this paper about ensuring equity, because what? He raised his hand in a roomful of 5,000 people said, How come on this pivotal trial that establishes car T for second-line therapy? There were no African American patients like none and it was just like the room was kind of taken aback, you know, who speaks up at the plenary right? But anyway, he wrote this very nice paper, which I think is a nice roadmap for thinking about diversity in our trials so lots of exciting days ahead. Since that 2,017 mark, we've had a number of new therapies and I just wanted to end with a bit of a personal note. which is, you know, I talked about. You know, the power of cooperative groups, and I told you a little bit about the background.
- For me personally, being part of the Nci. Cooperative groups was life changing, and I shared my story with the fellows this morning, but you know, for a variety of reasons. When I finished my fellowship in 2,001.
- There was no lymphoma program at the University of Chicago, you know, just long, long story. But everybody who had done lymphoma had left, and I was there as a brand new instructor trying to figure out how I was going to build a career in lymphoma when there wasn't a program. There was no mentor, etc., and one of our leukemia doctors said I should go to the Clgb. And introduce myself, which was beyond scary, because I was so tiny little instructor, and I walk in, and I see all these giants. And but I did, and I offered to

write up any of the negative trials, you know. Just be at the table just kept showing up and sale Gb. Ended up now, called Alliance ended up having, or the people who were there have turned out to be some of my closest friends and it really kind of helped, you know, form a Lymphoma family, if you will. It also opened the door for me to become part of Asco and ash and in 2,004 I gave my first patient education session for the Lymphoma Research Foundation on Mantle Cell lymphoma. Actually, I think there were 5 people in the room. But this is like a long time, because nobody knew you know what it was, and you know, it was a really uncertain time for Mccl.

- But I then went on to be the co-chair of the Lymphoma working group for the C. Ibm. Tr. For 5 years, where I really learned a lot about transplant a lot about statistics working with a very good friend, Mehdi Hamadani, who's just brilliant. And when I was giving an educational lecture at Swag one year, Jonathan Friedberg, who is now the head of the Swag Lymphoma Committee. He's also the editor in chief for our highest journal. Jco had heard me give an educational lecture and you know we had known each other through sort of all these circles, but he invited me to be a vice chair of the Swag Lymphoma Committee, and over the last 10 years we have worked really hard to make it a very inclusive committee. Try to develop some really exciting trials, promote our junior faculty, and be able to talk lymphoma, which is so much fun because there is so much going on.
- It led to being part of the Lymphoma steering committee for the Nci, and then the women in Lymphoma group. I just wanna mention this is this is actually a really interesting group that started in 2,019 at Lugano, which is, you know, one of our big lymphoma meetings is in Lugano, Switzerland, and Judith Trotman, who is a lymphoma investigator from Australia
- Saw an expert in flicular lymphoma panel, and every single person there was a man, and she's like, Are there no women lymphoma experts? And so she sent an email. This man'll, you know, started everything. And so she sent an email to 12 of us. II happened to be one of them and within 48 h we had 72 women saying, we need to form a women and lymphoma group.
- We now have 1,500 members from around the world. It is headquartered. In Australia. We have a free educational series that occurs quarterly and we talk about different areas. So II actually was fortunate enough to give the very first lecture on Dlv. Cl. When we started back in 20 19. And it's just been amazing carla Casullo, who is at Rochester, is now the president of women in lymphoma. We also have our male champions of change, and Mike is part of that. And it's just been a lot of fun, you know, to like, get to know people from every country around the world. It's really been amazing.
- I did get to be a program chair, and then I would say, the highlight of everything I have ever done is through the Lymphoma Research Foundation, and Mike sort of, you know, mentioned this. But the Lr is an advocacy group, and they have a scientific Advisory board. That is selected by your peers. And this this has been, you know. Talk about working together. We. We work on grants you know, have given out almost 50 million dollars worth of grant money over the last, you know. 20 years. But certainly over the last 3 years. When I was there we gave out about 18 million dollars worth of grants and have a training program and a mentoring program and it's just been an absolutely unbelievable source of joy and friendship and camaraderie.
- So I have this incredible village of people who are like my closest friends and confidants that I've met along the way and I wanted to say that Mike and I have known each other for 20 years haven't even remember exactly when we met. But I remember multiple conversations when you're you know, when your son was expecting and when Lulu was born, when Owen was born. And you know it's just been a wonderful friendship. And you

are just such a statesman in the lymphoma world. So it is an honor to be here. I wanna thank you for inviting me. Truly, this is like the warmth of this group and of Uva has been incredible. So thank you for that.

- And I will say I do have another village. Which is my parents. My dad came from India in 1,964. Really happy, he decided, and my mom agreed to come here. I was born in Chicago. I've been married for 30 years to a guy from South Dakota and we have 4 kids. And that's also been another really huge source of support. So with that I will thank you. We are building a brand new cancer building. It'll be the first of its kind in the State of Illinois, and the first in the Midwest, outside of the James, that it will open in 2,027. So we are hiring, and anybody wants to go and tell on apology. Thank you very much.
- Pass it around. Yeah.
- Sony. That was just outstanding and just an inspiring. I have to say. It's amazing what you've gotten done. I'm glad I was gonna actually make the point that in addition to all you've done professional, your mother or 4. And so you've done all of this while keeping, you know so much going on. So it's just really, really phenomenal and congrats on all success and thanks for shoutouts. I was glad to see a number of Uva folks rolling through your presentation. Patrick Reagan, who's a Uva resident chief resident a few years ago now but Rochester Christie Bloom, who was one of our residents, as was her husband.
- Bill Bloom, both the stars in the field, and Christy. Of course, in lymphoma. Mike, the question I have is sort of the practical one that we all struggle with in lymphoma, and I'm sure it's true. Across other disciplines. We've got rare diseases and people that are really sick when they hit the door. A lot of our high grade lymphomas, you know that you have to come in. You have to be eligible to get on the study. There's paperwork. You may need another biopsy.
- And so some people are just too sick. They can't wait 3, 4, 5 weeks to get onto the study. So how do we? And then you've got a misrepresentation of the outcomes for that new regimen. So how do you? As a leader in the cooperative groups? How do we deal with capturing that population, whether they're older or other reasons, they're frail or unfit. How do we? How do we do that?
- Yeah. And that's a really important question. II often wonder if that original swag trial that was chopped versus the intensified regimens. If we had taken that approach, if the results might have been a little different. So what Mike is alluding to is that we have this inadvertent selection bias, you know, when we enroll people onto a clinical trial because they have to be stable enough to wait several weeks to get, you know, consented registered, randomized, and then treated.

  And so, really the sickest patients never make it on, and it probably explains some of our phase, 3 trials being negative. And there is data from Mayo clinic that the time from diagnosis to the time to starting treatment is actually sort of a poor man's way of saying, is there any selection bias? Because people who can wait inherently have better risk or disease.

- I think the way the cooperative groups should approach it, and many trials should approach it is to allow one cycle of treatment to be given before people get entered onto the trial. So you know, while you're trying to get everything together, it makes it a little bit messy because you don't always get your scans in time. You know. Sometimes the biopsies may or may not be sufficient, but II truly think if we wanna get rid of that inadvertent selection bias that we're gonna have to allow some pre therapy in our elderly

study that we have it. There is the ability to give pre phase steroids in fact, it's mandated that everybody gets pre phase steroids, and that should give them at least a week or 10 days. But II agree, I think our sickest patients are not gonna go on the other piece we're doing in that study is that we're doing a frailty assessment. We're using an Italian tool that was developed. And it's web-based. Where you can really sort of figure out if people are fit, unfit or frail. And I have a feeling we're not gonna have any of the frail people on there, and so it'll be another point to make when, when the studies done. I prosecute. Take questions. Chemical target therapy. And now we're talking gear without the cars.

- So target service that prime you this patient with that kind of therapy, this patient. Give another small molecule dying. Prime this patient to another cars. And what's your comment about this kind of precision? Yeah, no, I think so. So that is an unmet area for us is to be able to apply that precision therapy and cure more people upfront. So if we know upfront who's gonna have that resistant disease that would spare everybody so much? But the challenge is that we we don't have a good tool upfront to do that. I think this dark zone signature, if that gets validated and it becomes a routine part of himatic pathology to say, Does this person have dark zone, you know phenotype? Then maybe they wouldn't get our chop or pull up our chip, they would get something totally different.
- But I don't see that happening anytime like it'll probably be in the next couple of years, I would guess, if that's even there. The other challenge is that and II didn't emphasize it because I was talking about relapse, refractory disease. But a lot of people are cured.
- And so when you have a treatment. Naive population. The bar, to show an improvement in outcome is very, very high, and it requires a lot of patients, you know, to enroll on the trial. So I agree with you. I think we need better tools. Upfront cell of origin. Is not it double hit? Is not it maybe dark zone, is it?
- But maybe there's something else. Yeah.
- Great talk. Thank you so much. This might not be an answerable question, but I wondered if you have specific study questions, you think can be answered better with cooperative group compared to pharmaceutical, sponsored trials and vice versa. And how you think about that. Yeah, yeah, no, that's a great question. We sometimes like in our group. We'll sit there and we'll come up with clinical trial questions. And they're like, you know, what pharmace gonna do that they're gonna do it faster. And they're gonna do it.
- You know, in a way that you know, we get certain types of information. So we do try to say, what are the questions that Pharma won't ask. You know whether it's a quality of life question whether it is, you know, validating a a tool, you know, like in the mantle cell. And Fomo, you know, looking at Mrd, you know.
- partnering with some of the smaller biotech firms, or even like this one where it's like multiple companies. They're never gonna work together. They don't wanna know if their drug is not as good as the other. Right? So those are the kinds of questions we think about. We also have a much more robust pro aspect, I think, than I mean. II great like they. They have a role, right? They have resources, and they have the ability to do certain things. But they won't ask those questions that are comparative or powered for survival. For example. You know, because they time is money. They want the quickest answer the quickest readout and not that we don't. But that's not our bottom line. So yeah, I think it's a. It's a great, that's something that's really fun to talk about within the yeah, thank you so much. Think what's coming.
- Fantastic, really? Good, really. Good.
- I wouldn't want this.
- Thank you.