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TRANSCRIPT - GR 09 20 24 ***"Rare, But Not Forgotten: Challenges and Progress in Rare Disease Research - The Case of PTCL"*** guest speaker Enricha Marchi MD, Univesity of Virginia

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Internal Medicine Grand Rounds

- All right. Everyone welcome to medical grand rounds. So we have one of our very special lectures today. The Don Hollands memorial lecture. In just a moment. Dr. Jerry Donowitz, our longtime and distinguished former program director, who was the program director during Dawn's time in Residency, will will introduce this lecture. I'll quickly take us through just some of the changes in claiming Cme. Credit since that is obviously a little bit of a change for us here with grand rounds, and then, after Dr. Donowitz introduces the Don Hollands lecture one of our chief residents, Dr. Shaina Hassan, will introduce Dr. Markey and her lecture. So Dr. Markey has a couple of disclosures that she'll introduce here importantly how to record your attendance again. If this is your 1st grand rounds this academic year.
- So snap a photo of this if you need to. But several convenient ways to claim cme credit. You can use text messaging to record your attendance. Here today. And then today's activity code is right there. It'll come out in an email after the lecture today, you can also register your Cme. And attendance through cloud. Cme.com also very easy. Once you've set that up there's also a cloud. See me app in which to do that as well. So you can snag a photo of this as well. All right. So now that we've done the appropriate disclaimers. We'll bring up Dr. Donowitz to introduce the Don Hollins Memorial lectureship.
- Well, if you see, a name makes retirement look really pretty good. I like that.
- It's a real honor actually to be involved with the Dawn Hollins lecture dawn was actually one of us. She came here in 1,998 from Wake Forest as an intern, and she became quickly known for the quality of clinical care, the breadth of her knowledge, and her patient advocacy.
- What really wasn't known at all was that in her last year of medical school she was diagnosed with breast cancer and before coming to Uva underwent a bone marrow transplant.
- Basically, Don wanted to be known for her clinical performance, not her past medical history. And that's the way it was.
- She finished here very successfully and went to Duke in a pulmonary and critical care fellowship.
- It was in her last year of that fellowship that she developed Aml probably from her previous chemotherapy.
- By that time Don had a daughter Jordan and in order to try to maximize their time with Jordan with the rest of her family, Don chose to undergo another bone marrow transplant at Duke and after really a very long and valiant struggle, Don passed away. October 5th 2004.
- Very soon after the next year the Department decided that there needed to be the Don Hans lecture lectureship really to celebrate Dawn as a student, a teacher, a friend and a colleague and that's how this was formed.

- Hemingway to Little Jump define courage as Grace under pressure and Don and her entire family really personified that.
- And so the thought was for that reason we wanted to make the Don Hollands Memorial lecture an early grand rounds in the grand rounds season and the reason is, I'm sure you know that across the Us. And every academic medical Center this is a pretty stressful time.
- They're relatively new interns, relatively new fellows, relatively new residents, relatively new attendings and sometimes even relatively new program directors, although not here. And it was the thought that Dawn's legacy, telling Don's story of grace under pressure would make everybody's job just a little bit easier. So thank you.
- So good afternoon, everyone. It's my pleasure to introduce our grand rounds and Dawn Hollins, Memorial lecturer today, Dr. Enrica Markey, she's originally from Italy, attended Medical School and completed her hematology fellowship at the University of Boulogne, where she conducted several clinical trials, investigating various aspects of the common T. Cell lymphoma, and was the 1st to describe the role of gemcitabine in the treatment of patients with T. Cell lymphoma.
- Subsequently she completed her Phd. At Columbia University in clinical and experimental hematology and hematopathology, and she focused her research largely on the translational development of novel rational drug combinations for patients with peripheral T-cell lymphoma. She's an accomplished researcher and has been involved in the discovery of novel therapeutic strategies from the laboratory that have been translated into clinical trials for patients with T-cell lymphomas and because of her expertise she's been named the co-director for the program for T cell lymphoma research at Uva, and she's the deputy director of the global T cell lymphoma consortium.
- So please give me a big welcome for Dr. Markey as she gives us our presentation today.
- Thank you. Everybody. Okay. 1st of all, I would like to thank Doctor without, and the Chief President and all the resident to be here at this lecture that hopefully doesn't become too specific on T cell lymphoma. That gives you some information and data that you can use and translate for everything that is considered rare in medicine.
- So these are my disclosures.
- And 1st of all, what is a rare disease? A rare disease that is also named orphan. When we think about drug development is a medical condition that affects a relatively small number of people when compared to the common disease, and that number changes depending on the country. But when we think about the United States, we think that a rare disease happens in less than 200,000 patients.
- Now, challenges that we have and are uniquely when we consider approaching and treating patients with rare disease are numerous. 1st of all, obviously, we are dealing with a small number of patients, and the 4 is generally difficult to recruit patients into clinical trials. There are oftentimes limited funding that both academic institutions and industry, our desire to invest in in developing research and improving therapy for this disease. There are some regulatory hard roles, and, in fact, the FDA doesn't have clear regulatory pathways to bring a drug to approval. Endpoint changes depending on the time that the FDA is requiring to get drugs into clinical practice for rare disease, and there is oftentimes lack of existing research that therefore determines the lack of understanding of pathogenesis, and then the identification of potential therapeutic targets and then obviously clinical networks

can be lacking or limited and there is truly a substantial need for collaboration that are not only with other academic institutions, but with industry and the patients advocacy group, and these are absolutely mandatory and necessary to successfully improve the field. And then, obviously, as in many other fields, there are ethical consideration about clinical trial, participation and equity and access of patients to novel therapy.

- So when we look at numbers and numbers in cancer, specifically, we know that the most updated numbers in 2,024 predicted there's going to be about 2 million new cancer cases in the United States. We know that the more common one are prostate lung and colon and breast in women, and when we specifically check that number for non-hodgkin lymphoma, we have expected about 80,000 cases this year in the United States of new patients with non-hodgkin lymphomas, and peripheral T-cell. Lymphomas are a type of non-odgkin lymphomas and they do represent about 10% of those cases making that number up to only 10,000 cases in a year of new cases in the States.
- So these are what are peripheral. T. Cell lymphoma. They are a neoplasm of, derived from mature T and Nk. Cells. They are, as I was demonstrating to you, rare. There is a geographic distribution. They're a little bit more common, representing about 20% of non-hodgkin cases diagnosed in Asia, and they are characterized also by a clinical and biological diversity, and the most recent classification, the who classification 2,022, and the Icc. Describes about 30 different subtypes of peripheral T cell lymphoma, as you can see in the lower figure here in the slides, except in a plastic large cell lymphoma, which are depicted with the yellow line. Most of the peripheral T cell lymphoma have a poor prognosis with standard chemotherapy, with an expected overall survival of 5 years of only 15 to 25%. We have got better in approaching and treating these patients because the molecular characterization of this disease has suggested and identified specific, more frequently mutated pathway, and therefore the development of novel, more pathway directive treatment.
- It's not surprising that when we consider 1st line treatment in patients with peripheral T cell lymphoma, we do have data. And we approach these patients with regimen that were developed in B-cell non-hodgkin lymphomas. So our standard of care that is represented by chop chop like therapy that could be more or less intensified are extrapolated from how we treated other non-hodgkin lymphoma, and specifically, the data come from a study that is more than 20 years old. This was a randomized study that aimed to compare more intensive chemotherapy regimen versus standard chop in patients with aggressive lymphoma. It's unclear when you pull this paper from Google, how many patients actually with the T Cell lymphoma were enrolled in this study, but based on this study, we still today use chop as frontline therapy for patients with Ptcl, and not surprisingly, 25% of patients are primary, refractory to 1st line chemotherapy with chop.
- Now, again, when we look at the relapse of factory setting, inadequacy of standard chemotherapy with expected progression, free survival and overall survival of only about 3 months and almost 6 months in patients with this disease we have started to improve, and how we have improved has been with the introduction of some novel agents in the treatment of patients with relapsed refactory disease. And not only and these are data that our group produced when we were back at Columbia, and it was back at Columbia. So we look at more than 20 years retrospective

analysis of patients that were diagnosed and treated at Columbia with preferent T cell lymphoma.

- And we sort of showed that now the introduction of the agents in treatment and enrollment into clinical trial improves survival of these patients, and the updated data presented at the last ash meeting of the Columbia and Cornell University experience in those years kind of confirm that the introduction of novel agents and of stem cell transplant introduced in treatment for these patients again improved survival with numbers that look a little bit better now than the historic 3 months progression-free survival, and 6 months over survival. Now we are about at 5 months of Pfs. With 24 months for some patients of expected survival after 1st relapse.
- So, just to just as happened often. Time in medicine. The understanding of the biology of the disease didn't necessarily preceded the development of drug that actually was were observed to help and benefit some of the patients. And, in fact, here I give you sort of an historical overview of what happened and what is relevant in history, of treatment of peripheral cell lymphoma. From that study that was published on the New England Journal of Medicine in 1,993, that actually established chop as gold standard treatment for patients with old aggressive lymphoma. So we see that at that time there was not even a real understanding and really definition of these entities, clear subtypes on lymphomas. And one of the things I want to point out in this slice is the 1st drug that were specifically approved for patients with peripheral T-cell, lymphomas are rhimidapsin, balino, sodium protrexate. 2 of these drugs are hdac inhibitors. H Doc inhibitors, targets, mechanism the epigenome in the cells, and therefore you notice that the understanding that mutation in epigenetic factors were occurrence in patients with referral lymphoma happen pretty much at the same time in which we were already using these drugs to treat the disease. And then, again, other biologic data that really demonstrated that the presence of mutation in spontaneous mouse model, the Caryet and row a developed disease that looked like Tfh peripheral T cell lymphoma. And now a number of studies that are introduced, and we have been following through that are, add more specific and more attention to specific disease and to specific types of disease. And some study that we're going to review together that actually were designed with the target of a specific Pt cell population that were actually negative, that led to the withdrawaldepsin, for example. And now more and more entity that are getting better described, that by the Who 2022, which actually gets our understanding of the biology better. But obviously our work to try to develop drugs that are working in the disease eventually harder.
- So, as I was saying, the 1st description of recurrent mutation and epigenetic factors was published with the letter in 2,012, on the New England Journal of Medicine, and from that time on there are a number of other pathways that have been identified as frequently mutated and potentially targetable in different subtypes of the disease.
- So, and a number of drugs. Again, I wanted to particularly emphasize drugs that are considered epigenetic agents are the 2 drug that we've source approved. But that is a cytodine that we're using Mds and equimetilating agents.
- And Valematostat is the last kid on the block. That is an ech. 2 inhibitor that is possibly getting approved in the near future for treatment of the disease. And another element that I want to emphasize is that this drug work?

- They don't work great, though by themselves, as you can see over response rate. That range from 29 to 45% with Cr complete response rate that are actually lower, and with the specific and exquisite sensitivity of some of these subtypes for the Tfh subgroup of disease.
- So 1st line and advancement.
- This was the 1st example of a study in a rare disease that was conducted in 1st line that they had a specific subtype target population, and, in fact, the echelon. 2 study assessed the role of adding brentaximabidotin. It is an anti CD 30 antibody drug conjugated to the backbone of chop and patients that were selected to be enrolled in this study were patients with CD. 30 positive peripheral T cell lymphoma that were then randomized to receive standard chop versus chp, with addiction, with addition of brentaximabidotin in 1st line treatment what is important to know and to consider when we, when we assess the value of these results is that 70.5% of patients that were enrolled in this study, where patients had an anaplastic, large cell. Lymphoma, anaplastic, large cell lymphoma are disease that are characterized by widespan and significant expression of CD. 30. So because of that biological rationale designing this study. There was a clear intention on having a large amount of patient represented by that specific subtype population, and the study was also not designed statistically to make any sort of conclusion depending on each subtypes. But that's just in the comparison in between every patient's with anaplastic large cell lymphoma versus everybody else.
- So a very successful study with patients that were treated with Bvchp compared to the standard chop chemotherapy that had a progression, free survival of 48% compared to 20% overall survival not reached at the time of initial presentation of this data. And the FDA saying, this is a drug that is a great new drug for this disease for all peripheral tisal lymphoma that express. CD, 30. We know that a number of patients with other subtypes of Ptcl. Also express. CD, 30. Is this something that translated in a true benefit for everybody? This is kind of a little bit of a crowded slide. But actually, when we look at the specific at 5 years, and we go and look into disease, indication and specific response, we see that comparing when we look at the non anaplastic large cell in from a patient there was not really a clear benefit, and when we look at specific subtypes like that, subtypes that carry mutation in epigenetic factors. Aitl, for example, where patients that didn't really do much better would be bchb, so are we using it for some patients that have CD, 30 Ptcl. Yes, because we are desperate to try to improve sometimes. Yes, sometimes not. But the data are not really supporting the use of Bv. In other than anaplastic, large cell lymphoma. That strongly same approach was used with a number of other agents that have some activity for peripheral tissue, lymphoma that were all added to chop, and in person patients were treated, and then most of them didn't do any better. Most of these studies showed that the addition to chop caused increased toxicity, and there was not really a clear, a clear benefit in terms of duration or response.
- And now we look, look at another study that was very much expected in the publication. There was again in 1st line all commerce. So all patients with peripheral T cell lymphoma were able to receive in 1st line, the combination of bromidapsing plus chop compared to patients that were randomized to receive only chop no improvement, no improvement in patients that were treated with addition of the novel agents and pretty much similar results in terms of progression, free

survival response, rate, and overall survival. And these studies specifically led to the FDA withdrew the label for relapsed factory.

- T cell lymphoma for rhomidepsin. Again, what was the caveat? This was an oncomer. This is an analysis that was published. Sorry that. I reported the same reference. But there was another paper that showed this data 5 years after so recently.
- So when they analyzed this data 5 years, and they looked at only patients that enter the study with that specific T follipopular peripheral T cell lymphoma that are those patients that carried a mutation. And there are those patients of which this drug work better. There was actually a pretty statistically significant difference both in progression, free survival, and in duration of response.
- So maybe the design of a study. At that time there was more focus on those specific subtypes that could have benefit, more likely based on the biology of the disease would have not led to the withdrawaldepsilien label for peripheral cell lymphoma.
- Another study that is relevant in in this consideration. In this setting is a study that looked at the role of Azocytabine, that ipometilating agents that I was showing you before that we use in peripheral T. Cell lymphoma. This was performed in the relapsed refractory setting, so Azocytabine was used to treat patients with relapseds at this point. This was a study that was led by the French group that the Lizarc they selected only patients that had those specific subtypes and there was a quite a large difference. I can say statistically significant because because there was also statistical, significant difference. But the problem was that the endpoint and the investigator placed to have this as a positive study was achieving a progression for survival of 12 months with is a cytoline alone. So, even if is a cytodine was superior to any other standard of care that was used. This was a negative study. This was a negative study, and the question is, was this bar too high? Was expecting a progression, free survival of 12 months too much of a high goal and end point to be actually achievable.
- So one thing that I want to mention is also that I continue to discuss the presence of these mutation, but there is none. No study have really shown a specific correlation in between response and presence of mutation. And even if we know that these diseases are more sensitive, the mechanism is probably goes beyond the presence of the mutation and the response to treatment.
- Again, we have looked at pretty small number in terms of order, response rate, and complete response rate, etc. So how the scientific communities have tried to improve this number has been to combine this knowledge together. So there is a number of studies that have been published, and that are still in process that are looking at a number of combinations of novel agents. Most of them have used rhomidepsin as a backbone, because rhomidepsin has been really considered one of the most active single agents per year in peripheral T cell lymphoma. And then the combinations are generally with with other active agents. Other epigenetic agents, other targeted pathways for those specific drugs.
- We have specifically worked for a long time on the combination of azacytidine and rhomidapsin. I just want to give you a couple of background slides to show you why we did that. We did that because we we demonstrated that there was a synergistic interaction in vitro in induction of apoptosis when we use azytidine and rhomidapsin in vitro. We also showed that when we use these 2 drugs together, that was a unique increased number of genes that were modulated by the 2 agents who are using combination after gene expression profiling done on cell lines. And then we

designed, based on that initial phase one and 2 study that again initially enrolled all comers.

- But we were able to show that there was part of an impressive response rate and complete response rate specifically in the population of patients that enter the study with the T cell lymphoma compared to everybody else that led to the expansion of the study in a phase 2 and the other observation that we made was that when patients were treated earlier other than in second, 3, rd or 4th line of treatment responded better, and again, that T follicular helper subtypes that some type that carries mutation actually add further, improve, better response compared to where everybody else. So this has led us and the scientific community in trying to use these drugs also outside clinical trials. So now most of the insurance company actually approved the use of romi outside clinical trials for patients with relapsedies, and we aim to collect the sort of real world experience with the drug. And the difference in this setting was that everybody that had used the drug outside the clinical trial mostly had used it in Angiminoblastic T cell lymphoma tfh the again the overall response rate is convincing, with the complete response rate of 53% and a pretty good progression, free survival that is still just above a year. But these patients were obviously in the real world experience, not patients patients that were sicker, that comorbidity that didn't have access or couldn't access a clinical trial.
- So this is something that Uva is leading. We were awarded then an FDA. r. 1 grant for orphan of her product development in rare disease. And we are running this randomized study with largely FDA funding to compare the combination of Isaromi versus investigator's choice. They're sort of the drug that we use a standard of care to add the label or at the label in patients with Renox and refractory peripheral T. Cell lymphoma. This is again a study that was designed as an old camera peripheral T cell lymphoma.
- And it's still that way. We there are conversations about potentially restricting the subtype of enrollment with obviously the issues of even less even a more limited number of patients.
- Other suggestion that this study and this data in the lab gave was that maybe the way in which this drug worked in peripheral T cell lymphoma was to sensitize the malignant cells to the immune system and make them more visible to the immune system. Therefore we showed that actually there was an increased induction of expression of cancer testis antigen when the drug were used together. So you can see that as a cited in in this expression of the number of cancer tests, Antigen. But really, what you see in this slide was that the combination uniquely affected expression of the induced expression of cancer testes. Antigen. Then it came a second study, a second Iit that has research funding coming from Merck, and they used as always happens there. So with conversation. There weren't, is thereomia. But there were other drugs that have that have some degree of epigenetic activity that we that we are using using products. And we are using the cytobin that as a cytome is, and a community engagement in combination with the embrysma, that is, Pd. One inhibitor in patients with preferred T cell lymphoma preferred T cell lymphoma, including also the cutaneous T cell lymphoma patient. So here our data that we have so far presented and nate Roberts. Part of our faculty has helped a lot in presenting this data, and we have enrolled at this point 25 patients. Few things that go beyond the data itself is this is, these are patients characteristics pretty much 8 different subtypes on study.

- Most of the patients had quite advanced disease when they were diagnosed. Most patients are pretty heavily pretreated with the median number of prior line of 3, with a range from one to 6, so kind of like the characteristics of patients with relapsed refractory, peripheral cell lymphoma, incutase of T cell lymphoma. We have shown that this, these different combinations. It's a 3 arm study are fairly safe. We have identified a maximum tolerated dose and a recommended face to dose, and we have closed 2 of the arm in which patients are being treated with prala and pembolism and the cytobin pembolism, and we are currently enrolled and trying to complete enrollment in the next 4 or 5 months of the triplet arm is effective, mostly patients that got into this study at a cutaneous tsal lymphoma. 53% of those patients have cutaneous tsal lymphoma. Some patients are on study also for prolonged period of time, which means almost a year a year and a half over. Response rate is still low, because mostly the normal disease. We have not seen a lot of activity and but there is a quite significant disease, controlling rate and clinical benefit in these patients. And when I say that, and you look at 30% you might not be very convinced. I'll show you a guy with one of our patients, dear patients that have a cutaneous distal lymphoma with a lot of tumor stage MF. On the skin, and we can probably see that we have described this in a case record that one of our medical students has actually published recently.
- And what we can see here is that this patient had a flare. So these tumor really got much swollen right after the infusion of a Pembrolizumab. And then, once the inflammation resolved. Actually, those tumor lesions slowly were flattening out, seeing that you know, there could be a role of these agents also, mostly incutaneous T-cell lymphoma, and these, I thought, was a nice example to show you that might give you a sense of also in other subtypes. That group of group of disease that we deal with that are pretty challenging.
- A lot is new and coming up for peripheral T cell lymphoma. We are doing too well in B cell and lymphomas. But we really desperately need agent for these patients. A lot of pathways, a lot of study going on and not a lot of still very, very effective job on the horizon. Again. At Uva we do have now a new, a couple of studies that are 1st in human study, with novel agents for patients, with cell lymphoma. And this is a novel target that was identified. Byo is a CD. 94. Dr. Loggerns and Dr. Phil worked a lot to also try to look into the expression of CD. 94 in patients with Lg and leukemia, which is another type of you know by definition, T cell lymphoma. And they saw that actually, CD 94 is expressed more in patients in in the cells, in patients with Lgl leukemia and on lgl cells, and also Nk. Cells of patients that carry the disease compared to the regular to the healthy cytotoxic CD, 8 positive cells and Nk cells.
- So there was an antibody, a monoclonal antibody. That was, that is Dr. 0 1 that was designed and built in the lab, and that showed to be very with very high affinity, actually binding both the normal human and monkey and gl cells. So this this drug is, there's no data. There's no clinical data published yet that will be presented in next ash meeting. So the data are confidential. But they're quite a bit of excitement about it, because it's a naked antibody. And there's a significant number of responses of this patient. One reason because I brought up this is because it's new, but it's also one of those examples that are really rare in the field and in the clinical trial landscape, because these patients are the rare of the rare. When we look at the CD. 8 positive and KT. Cell lymphoma, we are really and extra nodal antitsa lymphoma, saponicolytic primacutaneous epitosplenic, gammadan, fatisseal

lymphoma middle. We are looking at a very heterogeneous and very rare group of patients. So it's kind of a an exception that we have such a study. This study is open in 3 continents.

- It's open in, I think, 20 sites in the Us. In Australia, in Asia. It's opening in Europe, and within 2 years it's opening now and on this sites. But in 2 years we've had about 45 patients around this study. So nothing comparing the field of oncology to breast cancer, lung cancer.
- Another novelty which we will still see where it goes in terms of how active it is, etc. It's a new class of drug. These are our protein degrader. So these proteins are iter by functional protein that are actually binding the ubiquitin protosome system and target for degradation. Proteins that are known, otherwise targetable with, for example, with small molecules, inhibitors and the Kt. 333 is important, highly selective atrobifunctional molecule that targets. Stat. 3. Stat. 3 very, very highly. Jack Stat. Pathway, very highly recurrently mutated in peripheral t cell lymphoma, and cutaneously cell lymphoma and allergia leukemia. And again, we are also part of this study that is enrolling. In this case all cameras was enrolling all cameras and we will have some of the updated data presented at ash.
- Lastly, another effort that we're trying to be part of and sort of also lead is a T cell consortium petal consortium. In this case that is going to aim to collect prospectively this time, genomic data, clinical data, quality of life data in patients that are highly diagnosed or with relapsifactory disease stepping into our clinic. So this is an effort that is largely led by mass. General, there are a number of sites in the Us. That are part of this, we are in the process of potentially getting part of this. The idea is to collect all these clinical and genomic data on patients, biopsy and to use a machine learning also approach to try to figure out and tailor better treatment along with getting more information of patients with peripheral T cell lymphoma.
- So, lastly, in conclusion, I hope I sort of gave you an idea that the rarity of peripheral tisal lymphoma has really contributed, and slower the pace of research and limited. Truly, the amount of high quality evidence-based data that we use when we make therapeutic decision, our improved understanding of the pathogenesis and key, affected pathway should actually guide the design of clinical trial with the specific attention to the target population the trial design, and also the endpoint that we choose, because as long as we believe in our drug, we shouldn't put endpoints that are maybe not really realistic.
- Despite the rarity we're kind of looking into trying to move from one size fits all for Ptcl, we know they're not the same disease. We know they're rare. Those are the challenges.
- Epigenetic agents showed clear activity. A single agent that is present when used by a single agent, but obviously is enhancing combination. There are a number of novel targets, and I didn't really focus much attention. But there are car T cell therapy that are being developed for peripheral T cell lymphoma have been even more challenging than in the B-cell malignancies real. But there are studies open in which we are trying to recruit patients. And obviously the only way that we have to advance the field is to collaborate nationally, internationally, and in partnership with industry that tend to have a little bit more funding and resources that might not be invested so happily in rare disease, but is absolutely necessary and with this I would like to thank a lot of people. I hope I didn't forget anybody. I want to give a shout out to Dr. Cropney that I work with in clinic that is essential for our cutaneously lymphoma clinic helping on many of these clinical trials and helping,

obviously managing these challenging patients and everybody else in the department. The Lymphoma group, the clinical research team that without which this would not be possible, and everybody in the lab that is also contributed significantly to produce some of this data and help us figure out what to do and thank you for your attention.

- I'm happy to take question. I'm don't get offended if there's no question fine but
- I'll ask a very general question. You highlighted a lot of really important lessons. When thinking about rare diseases, and obviously not everyone here is going to go into hematology and oncology. But among the things that you pointed out. What would you say might be some of the more important ones. When you think about fields like cardiology or endocrinology, or other fields where there are rare diseases. There, too.
- As we've got young people here who might be thinking about a research career.
- I think probably one of the most important thing. Is the and I hope I was clear in showing you is that trial designs the aspects of the research of making sure that you are setting a realistic bar for your drug or your approach, and you are designing the study rationally in terms of the population. And what's your expectation is the other thing is that
- I've been a big supporter of having you know, biological rationale to develop a drug or a combination of drug or therapeutic approach for patients.
- History proves that sometimes an observation is something that it's not really an expected result can help, as how development of a lot of approaches in medicine. So keep your eyes open if you see something interesting, even if you don't. Even if there is not that biological rationale behind. Maybe it's interesting to go and explore a little bit further.
- you know, it seems like a lot of drugs. It seems like a lot of combination, a lot of trials. These patients don't have a lot of options when you know when they relapse and they don't respond. Well, they go through it whatever is approved very quickly.
- What is approved is like at this point 2 drugs because the 3rd one and the label with that was withdrawn, so is not a lot.
- There is. So the other important aspects of it is you know, the patients don't really have equal access into clinical trials into big centers and try to look at how you can develop treatment that are accessible and how to expand the aspects of research that gives access to patients. And you know these are the institution, and probably are all doing that. But in a rare disease it's even worse. And I think it's something that we need to really try to put more effort into.
- Thanks for a great talk. Especially with these rare diseases. You start to see some incremental pro progress. And then you also see, with some of your results or the results you presented while they're statistically very significant, they may not be the most clinically, apparently significant, especially when you're comparing, like
- Pfs of 4 months versus 6 months. How do you go about? I guess educating potential prospective patients about. You know the benefits and potential results. You may see.
- I generally say that you know, in in the lifespan of a disease that might kill you within 22 and a half years, 6 months are relevant that there is a lot of research coming up pass not as fast as research open time is not really, really relevant the pace of it for that single patient you always have that missed drug that is about to come out, that maybe with a benefit. But sequencing treatment and having those 6 months of progression for survival in which the patient is maybe getting back on is also, you

know, treatment that is not too toxic, and patients can recover. Clinical performance might give them access to an allogenic stem cell transplant, that at this point, despite all the drugs we have, is still the only curative. So consider curative options for a patient that relapse disease. You say you're, gonna you know, be cured from this, maybe very small amount. Only if you go to the transplant, that means that you're gonna have to achieve at least a very near complete remission. So if you have a drug that gives you a chance to get that I think, is has been worth trying it for me, and I guess

- I convinced my patients that it was worth it. Well great talking, Rika. Always complicated to get through all the T cell things. And and you. You do a very good job of that. We're very lucky to have you here.
- The question I have is is based on the I think it was the the Drenbile study, where they really are taking this very rare subtype of Nk. Cytotoxic T cell lymphomas and expanding it and and using the drug in this this subtype. That's very rare. But to do so, they're having to open it in many different, essentially the entire world.
- To get a few patients. Do you see that as the strategy to to bring things forward to these exceedingly rare subtypes of lymphoma?
- Knowing the cost and how that's probably going to relate to the drug cost, and if it does get approved hard question. Thank you, Greg, for that Jambio. The Jambio study is an exception, it's a really big exception. The other interesting thinking about the drug bio study is that it was really designed with the thought it was going to be extremely active in allergia leukemia which is a group of patients. And I apologize. No drugs that really work. You know, there are a number of patients have also an indolent disease. But when they start becoming cytopenic, and there's really not much out there. And there's not even that 3 drugs that give you access to 15% complete response rate. So and that's and that might be working in those patients. But it's less clear than we would expect. So that study is going to teach a lot. I think that those are really the Libra within the Ptcl. We recently worked on a review that was published on blood that, you know, looked at the studies out there for those disease, and when we say rare, I say a hundred 30, 40 cases presented retrospectively in 15 years across. You know. Obviously, patients are not all listed in this registry, but very, very little.
- So the global effort for other subtypes of Ptcl. And I'm not sure I'm answering your question. But the subtypes has been actually broaded and study needs to come and then be designed with that specific target. I think, you know, adding together, Ptcl nos, that are not clear, it's not gonna it's not gonna help. So even if it's very hard and makes it even harder to run trials. I think there has to be a it's subtype specific which might not mean that we have zebra. But the broad group. I think that the study, the data that we are acquiring now, genomic information, are maybe going to help us to figure out. If mutation actually describe, not really the response to treatment, like group of disease that might respond better. So once we're going to be able to also access more information about the genetic of this disease, and maybe on the large scale, some of information correlating with risk these drugs that they might be more sensitive to, is going to maybe make it easier, easier instead of a pathologic disease.
- Yeah, it's potentially like, because also you know, I hope I didn't give you too much the day. The idea of homogen, you know, being a uniform and homogeneous. But those CD 8 positive cytotoxic are completely one of the question is, what is the FDA gonna ask to approve this drug, because these are very, very heterogeneous type

of disease. Some of them don't have any nodal involvement. Just livers splint and bone marrow. So are we gonna measure the responses. Okay? You can see if the spleen shrinks or there are disease that only stays pretty much in the bowel wall. How are you going to measure if the patient is responding? Are we using Lugano? So measuring? Lymph nodes, is not going to be so even just that sort of there's been a lot of conversation on. How are we going to take all this group of patients? Which are you can start dividing there. You're gonna have 10 patients like.

- And even being able to say, Okay, us response was not assessed homogeneously in this. So, but there is no way that we can get drugs like and monoclonal antibody without having that target. Via thank you.