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The use of CLR 131 and other targeted radiotherapeutics in pediatric cancers

Many pediatric cancers have very poor overall survival rates once they relapse or if they do not respond to initial standard treatments. Radiotherapy plays an important role in the treatment of these cancers. However, if the cancer has metastasized to many sites, external beam radiotherapy becomes impracticable and too harmful to healthy body tissues.

CLR 131 by [Celleckor Biosciences](#), is a radio iodinated therapeutic that selectively delivers radiation to malignant tumor cells, thus minimizing radiation exposure to normal tissues. It consists of a cancer-targeted small-molecule compound radiolabeled with isotope iodine-131. CLR 131 has demonstrated tumor selective uptake and therapeutic efficacy in various pediatric cancers.

We are talking to Dr. Mario Otto, University of Wisconsin School of Medicine and Public Health and Dr. Daniel Morgenstern, SickKids about use of CLR 131 in pediatric cancers, status on the clinical trials and scope of targeted radiotherapeutics in pediatric cancers.

Full Transcript:

Shweta Mishra: Hello everyone and welcome to Cure Talks innovator series with selector. I'm Shweta Mishra and today we are discussing the use of CLR 131 and other targeted Radiotherapeutics in Pediatric cancers. Joining me on the Patient Advocates panel are Jeremy Pivor and Mark Unger. The featured experts we have with us are Dr. Mario Otto and Dr. Daniel Morgenstern. Dr. Otto is Associate Professor in the Division of Pediatric Hematology, Oncology and Bone Marrow Transplant at the University of Wisconsin School of Medicine and Public Health. Dr. Morgenstern is a Director of New Agent and Innovative Therapy Program (NAIT) and Therapeutic MIBG Program and Co-Director of Neuroblastoma Program at the Department of Hematology/Oncology at SickKids – The Hospital for Sick Children associated with the University of Toronto. I extend a very warm welcome to the panel here and thank you everybody for taking the time to join us on Cure Talks today. Dr. Otto I will start with you, and I request you to begin with by giving us a little bit of background about the drug CLR 131 and help us understand its unique mechanism of action.

Dr. Mario Otto: Thanks Shweta. It's a very nice opportunity to join this panel here and present a little bit more about this drug. These types of drugs that we are now more and more using in Pediatric Oncology. Now CLR 131 is chemically speaking a Radioactively-labeled so-called Phospholipid ether analog also called as PLE and for almost four decades it has been very well known that naturally occurring PLE's selectively accumulate in human cancer cells compared to normal cells and further research on Phospholipid ethers and their derivatives led to the development of PLE analogs which improved Tumor retention and Pharmacokinetic properties and one of which was CLR 1404 which is the parent molecule of the drug CLR 131. The mechanism of how these PLE analogs target Tumor cells is actually quite fascinating. These PLE analogs enter cancer cells so called Lipid rafts and Lipid rafts are specialized plasma membrane micro domains that are rich in Cholesterol, Sphingolipids and Sphingomyelin which organize spatially signaling pathways and regulate cell proliferation and survival. Lipid rafts are much more abundant in Cancer cells than in normal cells likely due to the higher metabolic and signaling requirements in Cancer cells and Lipid

rafts serve therefore as a cellular portal of entry of CLR into Tumors and once CLR 131 is in the Tumor cell or other PLE's as well the drug is rapidly internalized and integrated into cell membranes and into intracellular membranes and because Cancer cells in contrast to normal cells that were relative lack of enzymes that degrade and metabolize these PLE's. There's a high retention of CLR 131 in Cancer cells. In CLR 131 the Radioisotope Iodine-131 is covalently bound to the Phospholipid ether as the cancer targeting weighty and we call this actually a Phospholipid drug conjugate PDC and CLR 131 delivers Iodine-131 to Cancer cells for targeted Radiotherapy with fairly high specificity. The uniqueness of this drug and Friend Rock family is it's almost universal uptake in Cancer cells including Pediatric and Adult Solid tumors, Brain tumors, Cancers of the blood system such as Multiple Myeloma as well and essential for the treatment of Brain tumors is struggling process the Blood-Brain Barrier (BBB) and uptake of the drug has been shown in a variety of Brain cancers.

My lab here in Wisconsin has shown uptake and retention as well as Therapeutic efficacy and Pre-clinical Animal Models of the Pediatric Cancers knew about Stoma, Rhabdomyosarcoma, Ewing's sarcoma and Osteosarcoma and the single dose of CLR 131 lead to a slowing of tumor progression in prolonged survival and these Animal Models while the treatment was overall very well tolerated. Uptake as I mentioned before was also shown for various Brain Tumor cell lines and Xenograft such as Medulloblastoma, glioblastoma and a typical territory Raptor tumor and these pre-clinical data provided the rationale for the ongoing Phase 1 study in Children and Adolescents with Relapsed/Refractory cancers.

Shweta Mishra: Thank you. That was laid out very clearly and comprehensively. I'll move to Dr. Morgenstern now. Dr. Morgenstern it will be great if you could give us an overview about the current standards of care for Pediatric tumors.

Dr. Daniel Morgenstern: Thanks. That's a huge question and a huge topic to take on board and the way to think about it is to just talk about the context in which we are exploring the use of CLR 131 at the moment which is that for most childhood cancers when they first present we already have standard treatment protocols for those diseases which often incorporate combinations of different chemotherapy medicines that might be given intravenously or orally that often incorporate surgery especially of Solid tumors and Brain tumors and may incorporate External Beam Radiotherapy which is when we use X-ray treatment to deliver radiation to the tumor with a Beam shown in from outside the body and then for patients whose disease does not respond to these first line treatments or whose disease wreckers after initial treatment. That's when escalations begin to explore more experimental options and that's when we might begin to talk to families about early phase clinical trials which means testing drugs that are a much earlier stage of development. The first stage of development for new drugs is called a phase 1 study where we're really focusing on the dose and the side effects of the drug on whether it's safe or whether it's terrible to give to patients and that's the stage that we're currently at with CLR 131. So, at the moment the patients for whom this drug would be relevant are really those patients whose disease rather has not responded to the other available standard therapies and for whom really we're looking for novel approaches. I think we're very hopeful that new drugs like CLR 131 will be helpful against Pediatric cancers but it's important to say that the fact that this is a phase 1 study at the moment means that we're just at the beginnings of learning about its use in the clinic and it's really too early to say our this is a drug that works and these are the patients that we should give it for.

Shweta Mishra: Of course, thank you. Dr. Otto let's talk about the clinical trials related to CLR 131. So, what are the results that we are seeing so far in the phase 1 clinical trial study of CLR 131 for Pediatric cancers.

Dr. Mario Otto: Sure, as Dr. Morgenstern just mentioned CLOVER 2 is a phase 1 dose escalation study for children with Relapsed or Refractory extracranial Solid tumors, Lymphomas and Brain tumors. So, because it's an ongoing study the majority of the data has not yet been released however my colleague Dr. ___ presented the first preliminary and safety data on seven patients with Malignant Brain Tumors treated with CLR 131 at the most recent International Society of Pediatric Neuro-Oncology meeting in 2020. These patients received a single dose of 15 mCi/m² or 30 mCi/m² up to 60 mCi/m² and actually one patient received two doses and the median age for those patients was 10 years with a range of 6 to 15 and these

patients had a median prior line of therapy of 2 to the range of 1 to 8 and the diagnosis included Diffuse Intrinsic Pontine Glioma or DIPG, Ependymoma, glioblastoma and naturalist stoma. The most common side effects that were noted or adverse events grade 1 to 2 so lower grade that were reported by patients with fatigue, headaches, nausea and vomiting up to about 50% of the patients. These side effects were all temporary and results spontaneously or with supportive care measures fairly quickly. As expected also from a Radiopharmaceutical the treatment was associated with grade 3 to 4 Neutropenia that means low ANC count or Neutrophil count and also about half of the patients and Thrombocytopenia which means low platelet counts. Also about half of the patients experience that which temporarily required either Platelet transfusions or support of Neutrophils with growth factor. This is in line with the data from adult trials. Recite opinions are the most commonly reported adverse events and however the Data Safety Monitoring Committee being all of these completed those two levels is safe and hence those escalation is ongoing.

Shweta Mishra: Thank you, Dr. Otto. So, could you talk a little bit in more detail about who is eligible to receive this?

Dr. Mario Otto: Let me probably start perhaps with telling a little bit of the trial design. I think that's also very important. So the study is a two-part non-randomized open label study and for the patients that I just mentioned and the studies available at sites here in the US, Canada and Australia. For days what we call the Dose Escalation study with up to approximately 20 patients that will be enrolled and I mentioned also the trial started initially with the first dose or lowest dose of 50 mCi/m² and then subsequent doses will increase by 50 mCi/m² if tolerated and the Data Monitoring Committee feels this is all safe, accelerate to the next dose level and when we get to those levels of 60 mCi/m² above will actually split these stores levels into fractionated doses about 15 days apart and that is based on the experience in adults where the Bone Marrow Suppression is much less when you split the doses into about 14 to 15 days while not affecting the efficacy. Patients who do not experience dose limiting toxicity can be also retreated twice with CLR 131 at the same dose level that they were assigned previously, and we can initiate retreatment by 65 to 125 days after the previous infusion. Now you mentioned the question who is actually eligible to receive the drug? That's way of course important. So the main criteria it has to be patients between 2 and 25 years of age. It is a pediatric trial and the reason why we can't treat patients that are younger than that is a practical one because patients need to be isolated in an MIBG room. It is basically a shielded room, and I would not work with very small infants then of course patients all have to have histologically confirmed Relapsed/Refractory Pediatric Solid Tumors or Lymphoma or Malignant Brain Tumors that without standard treatments options with curative potential. And all patients have to have also an appropriate performance for we call this _____ of 60 or higher. Patients also must meet specific laboratory criteria. They are in the Logical liver function, kidney function for instance and also some patients may have had an Autologous Stem Cell Transplant and in some fewer patients even an Allogeneic Stem Cell Transplant. They have to be at least three months from that transplant before they are eligible for the trial. It is also important that patients must be able to commit and take Thyroid protection its Radioactive Iodine that can also affect the Thyroid Gland and very importantly as well the patient must have an Autologous Stem Cell backup available when receiving those is greater than 30 mCi/m² and we must be able to collect such a backup before starting the treatment. It is also important that female patients of childbearing potential must be not pregnant, practice and effective method of birth control and important also for patients with Solid Tumors and Brain Tumors they must have at least one measurable region with the longest diameter of at least 10 millimeter or centimeter or a PET MIBG evolution that we can follow. There are some Matrix Georgia criterias for instance patients with Neuroblastoma may not have received or would exceed a lifetime dose of 54 mCi/m² of MIBG which is very rare to actually happen. Most patients probably will start qualifying and obviously they can't have a concomitant severe illness for organ dysfunction that won't interfere with each other trial conduct. The other important things are major surgery cannot have happened within 6 weeks of enrollment and any Anti-Tumor therapy or investigational treatment within two weeks of dosing must have stopped two weeks before enrollment and that includes also large area radiation within three months however Palliative Focal Radiations not an exclusion criteria.

Shweta Mishra: Okay.

Dr. Daniel Morgenstern: Maybe I could just highlight a couple of things from what Dr. Otto just said

because I think in some ways this study is a little bit different from other standard Phase 1 studies of anti-cancer drugs because most of those are given by mouth or IV on a continuous rolling basis whereas this is as we've discussed either one infusion or that infusion split in two and so the process is a little bit different in terms of the overall flow of time on study. I think the other things that are really important to understand is this requirement of having available Stem cells before patients are treated can be a challenge because there are some diseases like some Brain Tumors and Neuroblastoma where we would routinely collect the patient's own Stem cells and may have them available in the freezer already and there are many other diseases where we would not have those cells available and so for patients to be treated on study they would need to have their Stem cells mobilized and then harvested before they can be treated. It's a little bit of a different undertaking than joining a drug study and then as we've already mentioned the treatment itself is radiation but actually unlike standard External Beam Radiation, its radiation that then sits inside the body and then needs to come out and comes out over a little bit of time after the treatment which means at least initially patients need to be treated in a special facility. As we have discussed a Lead Lined room which is one of the reasons why the study is only available in limited number of centers.

Shweta Mishra: Thank you Dr. Otto and Dr. Morgenstern. I have one last question before I jump to the panel discussion and invite the Patient Advocates here. Dr. Morgenstern this is for you. So if this treatment gets approved sometimes down the line then would you expect to give the treatment and then still put a patient on maintenance or would you expect to give the treatment and the patient does nothing until they progress.

Dr. Daniel Morgenstern: Yeah, but I think it's a very complicated question and the honest answer is I have no idea. I think we're at a very early stage of developing this drug at the moment. I think we need to wait to see first of all what this safe dose is from the results of the first part of the phase 1 study and then crucially we need to know is this something that will work across multiple cancer types or will there really be specific cancer types that it works better for and then it best to pursue its development in specific cans a or specific kinds of be as compared to at the moment a whole range of different cancers and then beyond that is the question of if it's effective and it's effective in a particular cancer, how does it compare to other standard treatments? A lot of that will depend on a combination of how well it works but also what the burden of treatment is and what the side effects of the treatment are and how that compares to the current standard treatments that we have available. So I think the honest answer is that the moment is that it's too early to say I think most likely the next step will be that we will further test the drug in patients whose disease has not responded to previous standard treatment and we're again trying to test this new treatment and see how well it works once we've established what the safe doses. I just don't think we know that was a long way of saying I don't know.

Shweta Mishra: Thank you. I totally agree. It's too early to say anything. Go ahead Doctor you want to say anything.

Dr. Mario Otto: I just wanted to add also to what Dr. Morgenstern just said we have learned over the last almost 30 years or more than that actually with MIBG that we don't really know at what time also we should use these types of treatments. So of course most Phase 1 studies are done in a setting where there is no other purity option. However these types of treatments could also imagine using them at other times for instance in upfront treatment for patients that do not respond well to our standard treatment. So, there's a lot to learn when to use these types of treatments, at what time and obviously that comes later after we know the side effect profile and the dosing. Obviously they are recommended to dosing for CLR 131 and any of these types of treatments. So as then Daniel pointed out it is very tough to say at this point in time but I'm sure we will learn a lot down the road.

Shweta Mishra: Absolutely, thank you doctor. With that I will not keep the patient panel waiting anymore and I will now invite Mark Unger to join the discussion. Mark is board member, Band of Parents, a nonprofit organization that funds innovative research and clinical trials for Neuroblastoma. Marks son was diagnosed with stage 4 Neuroblastoma at the age of 3. Mark please go ahead and ask your questions.

Mark Unger: Thank you Shweta. So we're someone the Band of parents. We've been an organization that

started by parents and the Band of parents make sure if you're aware of us as an organization. But we've supported clinical trials for Neuroblastoma of more than 10 million over the last about 12 years in various different organizations and the primary one being Sloan Kettering where many of the children were treated. The reason that I'm interested in this treatment and wanted to find out more about it because my son was diagnosed in 2000 at stage 4 and did well. We were firstly at Yale then we went to Sloan Kettering where we received the eight protocols which included the antibodies that Sloan developed. It was a reason that we went there in 2003 a year later he was clear cancer and then about 6 months later he relapsed with a Brain Tumor and at that time the standard of care was essentially Resection and Radiation and we were told by the lead doctor, Dr. Chung at the time that there was really no cure for a Brain Tumor Relapse of Neuroblastoma. Fortunately with some work on my excited rate in terms of looking for alternatives we were able to locate one directly slow and actually run by the Pediatric team that used radio labeled antibodies that were administered intrathecally. In other words if you put a hole in my son's head with a port and then that was delivered but he did not have any more Solid Tumor, the tumor was removed. He did have Leptomeninges spread at the time so he was not doing very well and they did it again the radio, the same antibodies are used in his body which clears cancer there, were designed and with this I-131 the same I assume was similar isotope, and they also used an 8H9 which is a little different one. And the theory was that the antibodies would wash the brain attached to whatever is floating around Cancer cells and I'm not a doctor or laymen and then those antibodies once they were attached with least the radiation kill Cancer cells and that is all this radiation would actually flush out of the Brain Spinal Fluid within 24 hours and not have a major impact like Beam Radiation did which he had as well. And so, he was the first child to survive this relapse and he now is the standard of care at Sloan Kettering and actually Why Maps – which is a publicly traded Bio Pharma Company and is trying to get this program approved by the FDA as well for treatment. So, I always think that there's probably other treatments may be because this one doesn't have to be invasive to the brain in terms that goes to the Blood-Brain Barrier that you don't need to have the myoport, and all that my son still has today. He's 23 now, so I do have a couple of questions that I wanted to ask. You can ask those Shweta or do you want me to ask these specifically for what you wrote here to me?

Shweta Mishra: No, go ahead. Feel free to ask.

Mark Unger: I'm relatively dangerous when it comes to medical information so I may not be 100% on point but in order for this treatment to be used, do you need to reset the whole tumor? Because my son's tumor was about a golf ball size and so that means that whatever you're using the transportation vehicle as well as in the radiation. Is that able to actually remove the tumor and kill the tumor over a period of short period of time? Where's the reset needed?

Dr. Daniel Morgenstern: Thanks so much for the question and the background I think just allows your question but just to clarify the background because I think it is really useful in a way there are now multiple products or multiple drugs that use the same type of technique to try and deliver targeted Radiotherapy and one of those that you've mentioned is, which is tagging the radiation onto an antibody. Then there's CLR 131 which is tagging the radiation onto this PLE and then there's MIBG therapy which is tagging the 131 ID in the radiation onto MIBG another molecule so in a way actually the business end of it is the same for all of these which is Radioactive Iodine. It's just about differences in the molecule to attach it to the cancer cells. I think the answer again is going to be to your specific question about whether we need to reset the disease? We don't know in the specific instance of CLR131. I think what I would say is that what we know from MIBG therapy in your Blastoma is that the therapy works much better for disease in the Bone and the Bone Marrow than it does for large soft tissue masses of tumor which is probably to do with the extent to which the MIBG is able to penetrate into the Tumor and I wouldn't be surprised if similar things are true for CLR 131. Although on the other hand, I think don't we've got data now suggesting that the CLR 131 does get into the middle of tumors at least on the basis of Imaging. I think specifically for the patients whose Neuroblastoma comes back in the brain which is a relatively unusual circumstance but definitely one that needs particular treatment. It is intriguing that CLR 131 crosses the Blood-Brain Barrier and so could be given into the blood and yet still potentially treat disease in the brain. I'll let my colleague add to it.

Dr. Mario Otto: Daniel I totally agree. I think we don't know how this will be panning out and whether we will need to remove first tumor but again what we know from most Solid Tumors is that as much as normally you

can remove initially the better it is for treatment but we don't really know this for sure, for targeted video therapies that may be actually a reason to not remove everything or leave it actually the way it is just because of cross-firing effect where the radioactivity can actually treat from one cell across many cells actually a cell that's further away and so we don't really know that for most other treatments like Immunotherapies or Chemotherapies we try to remove large tumors when we can get to them safely.

Mark Unger: Thank you and I did want to mention that I'm so thankful for you doctors out there that are trying to do the impossible and find new play barriers to save our children. I know it's not an easy job but on the technical side, I didn't watch that little one and a half minute YouTube video which was pretty cool. It's a simple way to understand the technology and could you explain again how does the PLE and these Lipid Rafts actually find this part of the cancer cell that's unique and bind to. Is it a man-made thing that look pretty man-made on the video? But was it a naturally occurring. How does that actually work in layman's terms?

Dr. Daniel Morgenstern: Yeah, that point of entry these sort of Lipid Rafts are actually on pretty much every cell however in tumor cells they are in higher express too much higher extent and the Lipid Rafts are part of the cell membrane and they are composed of a high amount of single lipids in cholesterol and are naturally already an entry point for a variety of types of fatty acids and in essence PLE is a long chain fatty acid mimetics and tumor cells when they grow, when they get particular, when they get more aggressive they undergo a metabolic shift and that increase their needs for lipids and cholesterol molecules that can produce energy, help them build new cell membranes because they divide so quickly and they also serve as basically an island of signaling and PLE's are therefore transported into the cell via some active and passive transport mechanisms like Pumps we call them Flip Aces and then what happens is actually they go inside the cell and then they bind pretty quickly and integrate themselves into the cell membrane and other intracellular structures. Basically like a brick into a wall and there they sit and they don't actually disappear very quickly. They sit there really like a brick in the wall and since they carry the Radioactive Iodine that radioactive iodine is not going to be released at all, it's just sitting with that molecule and because it is so close to the DNA in the cell nucleus where damage needs to happen to kill a cell. This is how basically it works. They're just sitting there radiating the nucleus of that tumor cell as well as surrounding tumor cells. Does that make sense?

Mark Unger: Yeah. It does actually.

Dr. Daniel Morgenstern: Radiation in general, ionizing radiation breaks up DNA what we call Double strands and causes double-stranded breaks in the DNA and that is often not repairable by a cell and the cell needs to die then.

Mark Unger: So the actual PLE's is almost like food for the cancer cells acting exactly.

Dr. Daniel Morgenstern: It's a basically an analog of naturally occurring building block of cell membranes.

Mark Unger: But do we know much about how it varies between different cancers. How much of the PLE they take up? How much rough they have?

Dr. Daniel Morgenstern: Yeah, they are so their difference is at least in Vitro in the test we can see that there are different amounts of Lipid Rafts in cancer cells. However, we had looked at Pediatric cancers and we were actually surprised that not always does the amount of Lipid Rafts is expressed in different cancer cell types correlate with the uptake. So there may be other ways that some other active pumps that are there in cancer cells transport this besides Lipid Rafts. So, besides being located in Lipid Rafts. I think Lipid Rafts are probably not the entire answer to that possible.

Mark Unger: So, have you this Phase 1 clinical trial does that include Neuroblastoma patients.

Dr. Mario Otto: So, Neuroblastoma patients are eligible for the trial and to my knowledge though I'm not sure whether we have actually currently actively involved a patient with neuroblastoma. We treated a patient

here and I think the challenge for enrolling Neuroblastoma patients is that MIBG therapy which is as we've mentioned another form of Radionucleotide treatment so very similar has been around for a long time and has obviously got a very long and reasonably good track record in Neuroblastoma and so in terms of the pathway of decision making for a patient, if there is patient who's suitable for MIBG therapy it's probably difficult at the moment to recommend CLR 131 as an alternative because that is at the stage of learning about the dose where the MIBG is at the stage of having a dose and knowing much more about it. And so really it's more likely to be relevant for Neuroblastoma patients who have disease that doesn't take up MIBG because then potentially might take up the CLR 131.

Mark Unger: What primary Pediatric Cancers have you had on the trial and how long the trial lasted? What have been its results so far?

Dr. Mario Otto: Again. I think this is an ongoing trial so results on the efficacy of the drug haven't been released yet. So, even we as investigators don't know really how other patients at other institutions fair and it's too early to say because we are also still in that dose finding phase where we increase the dose with every patient forward and so efficacy hopefully will also go up. The more radioactivity you can actually inject in, the more is tolerated with the patients but there were a variety of patients with Brain Tumors as I mentioned DIPG Medulloblastoma and a couple of other Brain Tumors and variety of Solid Tumors such as Urine Sarcoma and some very rare Sarcomas as well.

Mark Unger: How many total patients across all the sites have been on the treatment or on the trial so far?

Dr. Mario Otto: That is a good question. I assume it's probably by now about 12 or 13. Daniel?

Dr. Daniel Morgenstern: I would say it's probably something like that. I don't know the exact number.

Mark Unger: Alright, then you said there have been minor side effects or what side effects have you had so far besides fever, nausea?

Dr. Mario Otto: Yeah I think high fevers or Daniel you go ahead.

Dr. Daniel Morgenstern: All right I think from my experience here the actual infusion itself is extremely well tolerated with minimal side effects if any. The biggest challenge is the effect on the Bone Marrow after especially as we get into the higher doses because one of the challenge of Radionucleotide therapy is you're putting radiation into the body and what you're relying on is, you're targeting to take the radiation to where you want it to go which is the cancer and for it not to go elsewhere in the body which is the Bone Marrow especially but if the cancer is close to the Bone Marrow or if the cancer is actually in the Bone Marrow then it's very difficult and so I think for us the main toxicity we've had is the effect on the blood counts, the low Neutrophil count and the low platelet count after the treatment rather than actually any challenges at the time of administering it.

Dr. Mario Otto: I think the other part to that story is also that many of these drugs and particularly CLR 131 is fairly highly bound by proteins in the blood before it's actually taken up into the cell so It actually circulates for a couple of days in the bloodstream and while it's doing that it also bypasses the Bone Marrow and so although there may be patients who do not even have a Bone Marrow involvement of the cancer, it still will bypass and travel alongside the Bone Marrow just because Bone Marrow is way full of blood and will radiate the Bone Marrow and then you will have the effects as Dr. Morgenstern mentioned.

Mark Unger: Do you find that it couldn't matter if the dose gets into the brain or is it like or sort of whatever the percentage is in the body is also found in the brain of the PLE's.

Dr. Mario Otto: So that's what we call and this is also fantastic question. There is a part of this study that we didn't talk about because it's rather technical part of this study so some patients will actually qualify to take part in Dosimetry study and Dosimetry what that means is we want to know how much of the injected dose of radioactive compound actually goes to the tumor and which one does not and eventually is going to

decay and is excreted, that's part of the Dosimetry study and that will actually exactly tell us how much goes to let's say a brain tumor or tumor that's located somewhere else in the body, in the abdominal cavity or metastases in the lung for instance. But we don't have that data yet at least not in Pediatrics.

Mark Unger: Understood. Thank you.

Shweta Mishra: Thank you, Mark. Next up on the panel we have Jeremy Pivor. Jeremy was diagnosed with brain tumor at the age of 12 with a recurrence at age 23 and he is undergoing experimental treatments for the new tumor growth due to the rare molecular makeup of his tumor and he advocates for brain tumor and young adult cancer communities through writing, speaking, fundraising and lobbying. Jeremy, please go ahead.

Jeremy Pivor: Thank you Shweta for having me and thank you all of you Dr. Morgenstern, Dr. Otto and also Mark for all the work you do. Yeah, just to sort of outline a little bit of my history but just to give a clear picture. I was diagnosed with Angiolipomas back in 2004 when I was 12 years old and that time the standard of care was as you said Resection/Radiation but we really didn't want to pursue radiation because of potential long-term side effects which shall bring into one of my questions in a little bit. But then I was great for 10 years after having resection. But then in 2014, when I was 23 I had a recurrence and spot that time standard care was now Temodar and rather than standard radiation I did proton beam radiation and I did it at medical school and nine months into then I had another recurrence and this time back when I was 23 surgery wasn't actually an option because the tumor was in the motor sensory cortex and so it was too dangerous to operate there but then when I had my recurrence when I was 27 in 2018, there was a part that I could resect and ___brain surgery once they did the pathology on that and genetic testing they saw that it had advanced to __glioma and given the life history and also unique molecular characteristics which I won't go into. Now I wasn't really qualified for lots of classical clinical trials and so we had to pursue completely different experimental course and try Precision therapy with IDH targeted like a therapy that were approved for other cancers but did off label which didn't end up working on its own. So then we did another round of radiation this time just standard radiation along with Immunotherapy which I continue on those treatments until today. But of course, I was going through this trying to stay up to date on the next clinical trials because it's not an if I get another recurrence, it's about when and so a lot of my questions will have some about the molecular topics are the medical topics we have discussed. I do have some just general questions about consideration for clinical trials and so my first one is to Dr. Otto what are the considerations especially with a child when parents are the direct decision-makers that parents should consider but also when you are child I was 12 years old and while I was still a kid I really wanted to be part of that decision-making process. So what considerations should patients when they're old enough but also parents take when they decide to do this treatment option or if they thought of considering this clinical trial verse another treatment round?

Dr. Mario Otto: Jeremy, it's a very good question. Thanks for sharing your story. I would say gladly nowadays we have numerous new options for the treatment of Relapse and Refractory Solid Tumors and Brain Tumors and there are also many phases 1 studies as you mentioned out there. I think it's difficult because there are many individual criteria that you have to consider when choosing treatment options for a particular patient with a relapsed cancer and frankly we take a lot of time to discuss all the pros and cons of available studies with families and that means really parents and patients and also be considered their quality of life which is also very important. Cure is not always achievable but if it is then you also want to consider quality of life when you decide on different treatments. Now, I would say one important consideration parents and patients should consider when you choose CLR 131 is probably a couple of things. First you need to adhere to radiation safety practices and the initially necessary patient isolation and sometimes the younger child that's particularly anxious and clingy may have really a difficult time with the limited contact to Mom or Dad. It might not be really just for that purpose a good candidate for that type of treatment. Another one is having obviously a pregnant primary caregiver which proposed a similar problem and then of course what Dr. Morgenstern already mentioned previously was the ability to collect stem cells prior to the treatment may be a technical challenge particularly in the very heavily pretreated patients which our patient population with solid tumors very often is. Now on the other hand, I would say the treatment itself is relatively straightforward and has limited in patient time compared to some other treatments and CLR 131 is radiation therapy and not chemotherapy and many relapse tumors and cancers are fairly resistant to a lot

of chemotherapies we already gave. So targeted radiation therapy such as CLR 131 could have a distinct advantage over some of these other treatments. But it is a very difficult decision we spend a lot of time in talking to families and patients and obviously you have to talk appropriately to your patients and explain what's going to happen with any type of treatment. But I can say that I'm always very humbled and very impressed about how adamant patience even young kids can be about their treatment and what they would like to have and also being very open to say what they don't want to do and so this all has to be put in consideration when you recommend or when you discuss treatments with patients.

Jeremy Pivor: Thank you for that Dr. Otto and my next question is part of one of these considerations and something I had to consider especially when I did my second round of radiation are about the long-term side effects of radiation and one of the reasons I didn't do radiation was 12 years old as my parents and doctors were concerned about especially with children the amount of time you have after treatment, the long-term side effects that I can develop whether that's disabilities, physical disabilities, but also secondary malignancies and what do we know about CLR 131 and this potential considerations if any? It is directed to Dr. Morgenstern.

Dr. Daniel Morgenstern: So again it's a great and very important question. I think the honest answer is we just don't know at the moment because our total duration of experience of this drug in Pediatrics is only a year or two at most. So we'd be pretending we knew something that we didn't. If we said we knew exactly what the late effects were. I think we know from MIBG therapy in patients with Neuroblastoma that there is an increased risk of second malignancy in patients who have MIBG therapy although it's difficult to separate that out from the increased risk that comes from all of the other components of the treatment and from having had a childhood cancer at all and in terms of the radiation and especially for brain development we know as you've highlighted that there are challenges with neuro development especially in young children especially under the age of 3 who have external beam radiation to the developing brain. I think honestly we don't know what the impacts of this will be. I think you could argue that hopefully the impact of this will be less because potentially it's more targeted that the radiation is more focused on the tumor but I just honestly think we don't know that at the moment. I think it's something we've got to be aware of and I think unfortunately is one of the challenges of how we develop new drugs is that honestly at the moment are focused for the study is on short-term toxicity because if we try to have the long-term toxicity as the outcome measure of the trial it would never get finished. But on the other hand clearly it's very important that is borne in mind in the future development of the drug.

Jeremy Pivor: That makes a lot of sense Dr. Morgenstern as follow up when used for brain cancers you might not know this yet just because of the two year time scale. But often times even on a short term scale these radiations can cause inflammation and that's something to be considered in the brain, depending on where it is like for me that's the biggest consideration because it's in motor sensory cortex and so when I had my radiation I got lots of seizures especially right after so is that found with this or does that cause inflammation?

Dr. Daniel Morgenstern: I think that's a great question. From my personal experience I don't think we've seen that as a challenge so far. Dr. Otto if you can remember from the central data whether they've been patients who've needed steroids post therapy because of radiation induced inflammation, or not.

Dr. Mario Otto: Yeah, no I'm not aware of that at this point in time but it is entirely possible that when we reach higher doses that this may be important tool consider and give patients steroids. But at this point of time we don't know that yet.

Jeremy Pivor: Thanks and my next question is more related to roadmaps because often times with once you get to this decision-making in clinical trials or experimental treatments you are just focusing on. Okay, what's just my next treatment? But you have different treatment options here thinking about down the road too and sometimes certain treatments prevent you from considering other treatments in the future for example, it was in 2018 recurrence it's a long history I ended up not doing the next standard chemotherapy. One because of the molecular part of my tumor that would make me not as likely respond to it but to because if I want to do Immunotherapy would affect the efficacy of the next treatment option I wanted to do.

Do you know what this treatment how it might affect the efficacy of other treatments down the road and also about the ability of participants built to participate in clinical trials of other types of drugs in the future and is there a consideration you tell patients. It's for Dr. Otto personally and maybe Dr. Morgenstern feel something to contribute?

Dr. Mario Otto: Sure. So excellent questions Jeremy and I guess in general as is the case with most phase one studies patients while they are on study cannot receive in parallel other forms of cancer directed treatment it just simply because you would interfere with the safety aspect of the study where you don't know which drug would cause a safety issue. For CLR 131 the only exception is probably focal radiation to a progressive tumor spot in the body so large radiation and large area radiation is not allowed but a spot variation would be allowed. Now, that being said parents and patients can always change their mind about Trial participation and if a patient experiences progression while on study there is a clearly always the way to say. The patient goes off study receives a different form of treatment. Now whether they're eligible at that time for that particular treatment depends a little bit on that particular treatment in the eligibility criteria for it. The observation period from a former clinical trials perspective of the CLR 131 study is a total of 75 days. So after that patients are always free to pursue something else down the road if a tumor of course, progresses or if there's any other reason that a patient wants to have some form of a maintenance therapy, just not doing these in 75 days of observation period that's for the safety perspective. It's very difficult to say I would not anticipate for the majority of trials that this could be interfering with eligibility for them unless it is in a time frame that saw earlier that they're still radioactivity on board so that may preclude also just for radio safety purposes that may preclude participation or at least postpone it until the radio activity is completely gone. Does that answer your question?

Jeremy Pivor: I think higher dose is that other thing to take into consideration is the blood counts and the most phase 1 already.

Dr. Mario Otto: Correct. Yeah and I felt levels and so it may be the patients have to wait for their accounts to recover to that threshold to be eligible for subsequent study.

Jeremy Pivor: That's right, very important one. Thank you and then my final question maybe Dr. Morgenstern or Dr. Otto I like both you to answer is zooming out a bit just from CLR 131 what would you say to a parent who is concerned about having their child participate in experimental treatment and also what would you say to the child as well.

Dr. Daniel Morgenstern: What a wonderful and interesting question, but I think it's thing. I spend a lot of time thinking and worrying about and I think I see my role as mainly to make sure that I honestly share the information that I have available. I think it's very important that patients/parents and as much as possible depending on the age appropriateness the child know what they're getting into and the level of confidence that we as the clinician have as to whether it will work on. There are some things that we offer that a clinical trials but actually it's only a clinical trial in name but realistically we have a very strong expectation that it's going to work and will be a benefit therapeutically and there are other trials that at the other end of the spectrum when it's a very new type of treatment and we have to be honest with families and say we just don't know whether this will work or not. We have no previous information from patients with this disease of this working. I'm offering this to you because I can't offer you a better option and I think that finding that balance about giving the information and being realistic about the likelihood of benefit I personally find really important and then I try and help the family depending on what they want to work through the decision-making process and I think as it were the bad old days of medicine the doctor knew best and the doctor told the patient what to do. I think the pendulum swung very much towards patient empowerment which I think is absolutely appropriate. I sometimes worried swing so much that it sort of the medical team washing their hands and saying well we don't know what to do, you decide what to do. So first, I think we have to find a balance and it varies from family to family. I think as to how much guidance they want and clearly ultimately enrolling in a clinical trial is the family decision and our responsibility is to make sure they have as much information and I think from the patient perspective it really depends on the age and the experience of the patient. In a lot of the patients that I talked to for early phase trials have been through years and years of treatment and actually super expert on everything even if they're ten, nine, twelve years old and completely

different from taking a nine-year-old patient off the street who's had no interactions with hospitals. I think it just comes down to the individual, try and personalized the discussion.

Jeremy Pivor: Dr. Otto do you have anything to add?

Dr. Mario Otto: Yeah, I mean everything that Dr. Morgenstern said is exactly what my experience is as well and also my personal goal when I talked to families and one part is really the important one we are the experts, it is what it is so we have to also take that responsibility and expertly educate our families and also dive into new treatments that have come up in and sometimes also dive in the preclinical data and make up our own minds that we feel comfortable offering a certain study to families. That is our responsibility. That's what we go to school for a long time and that's what parents and families should expect from us. That's one part. The other side of the matter is of course that all standard care treatments that we used to cure kids with cancer, once started as an experimental therapy we have to be as open to that as well and they all started as the majority of those started as early stage clinical trials and so it's the nature of these experimental treatments that we don't know yet all the potential side effects and whether all patients will benefit from the treatment or any patient actually benefits from treatment. So, we just have to be very clear to families about that and if treatments show promise in preclinical work and in the test tube in animal experiments, we hope that this show benefits in patients as well and that they are safe and well tolerated and have an acceptable side effect profile. So that's in essence what I explained also to families when they have to make this decision: do I want my child to participate in or us as a family participate in an experimental treatment?

Jeremy Pivor: Thank you both for all the work that you are doing. Thanks for answering my questions.

Dr. Morgenstern: Thanks so much.

Shweta Mishra: Thanks Jeremy for your questions. Thank you, Dr. Otto and Dr. Morgenstern. It was a great session and thanks for all the information shared. We hope CLR 131 proves to be instrumental in improving the prognosis and survival rates for Pediatric cancer patients in the coming years and Mark and Jeremy thank you for your time and your questions. It's been a very informative discussion and it was a pleasure talking to all of you. This talk will be available on Cure Talks and Selector websites and YouTube channels. Until next time, thank you everybody and have a great day. Stay safe.