



## CLR 131 - A New Approach in Multiple Myeloma Treatment

CLR 131 is a targeted small-molecule that is being developed for the treatment of myeloma and lymphoma, as well as pediatric and head & neck cancers by [Collectar Biosciences](#). It works by delivering a radioactive, toxic compound directly to tumor cells, while limiting exposure to healthy cells. CLR 131 was granted Orphan Drug designation for the treatment of multiple myeloma by both the U.S. and the European Commission. We are talking to Dr. Sikander Ailawadhi, the lead investigator on several CLR 131 trials, to get his perspective on the potential and future of CLR 131 as an important addition to myeloma treatments.

### Full Transcript:

**Shweta Mishra:** Good morning and welcome. This is Shweta Mishra live from CureTalks. And I wish you all safety and health in these testing times of the coronavirus crisis. Please stay at home and follow social distancing as much as possible unless it is really urgent and try to tune in to curetalks.com on 26th of March at 1:30 PM Eastern to listen to what infectious disease expert Dr. Steven Pergam has to say on where we stand and what to expect in terms of safety for immunocompromised patients during this coronavirus crisis. Today on CureTalks, we are talking about the new small molecule CLR 131, a phospholipid-drug conjugate that is being developed for the treatment of myeloma, lymphoma as well as pediatric and head and neck cancers. And our eminent expert on the show today is none other than Dr. Sikander Ailawadhi. Dr Ailawadhi is an oncologist and an associate professor division of Hematology Oncology at Mayo Clinic Florida, and is also the lead investigator of several clinical trials on CLR 131. Dr Ailawadhi, I welcome you to CureTalks on behalf of the CureTalks team and as well as on behalf of your batch mate and friend and our CEO, Dr. Sharib Khan. He wanted to say hi and has sent his personal regards to you this morning.

**Dr. Sikander Ailawadhi:** Thanks a lot Sharib. But thanks for inviting me to the show. And I'm so glad that I have this. You guys have given me this opportunity to share this information with the myeloma community across the country, across the world. I also want to say I really appreciate your opening the call with kind of wishing everybody's being safe and doing as good as they can in these unprecedented and testing times which is very uncertain, but important.

**Shweta:** Sure. Thank you, pleasure is all ours Dr Ailawadhi to have you on the show and thank you for finding time. On the panel, we have our very knowledgeable myeloma patient experts Gary Petersen, Jack Aiello and Cynthia Chmielewski. Welcome to the show, Gary, Jack and Cindy and thanks for being here today. So without any further delay, I will now hand it over to our co host Gary Petersen to lead the panel today with Dr Ailawadhi. Gary, the floor is all yours now.

**Gary Petersen:** Thank you very much. Welcome, Dr. Ailawadhi. I gotta say that I consider you one of the new Young Guns of the myeloma specialist community, a group of very knowledgeable and up and coming and outstanding myeloma specialists. So thank you for that. Dr. Ailawadhi is an oncologist in the hematology department and CAR-T cell therapy program at Mayo Clinic in Jacksonville, Florida. He specializes in chronic leukemias such as CLL, CML, multiple myeloma and Waldenstroms. Dr. Ailawadhi received his education from the University College of Medical Sciences and the University of Delhi and completed his residency at the University College of Medical Science, University of Delhi and the State University of New York at Buffalo in 2000. He completed his fellowship at Roswell Park and then followed his mentor, Dr. Asher Chanan Khan to work at Mayo Clinic. I wanted to kind of open this and I know that this is about CLR 131. And I know you probably haven't prepared for it, but during these very trying times, really the elephant in the room for all of us is COVID-19 and especially for myeloma patients. Do you have any words of wisdom from the Mayo Clinic and yourself for myeloma patients?

**Dr. Sikander Ailawadhi:** Thanks a lot, Gary, and I really appreciate your time. I know you've reached out to



me several times in the past about discussing the new and upcoming treatments for myeloma and also about CLR 131 specific use and I look forward to discussing today. But I also really appreciate you guys bringing this panel together, for putting this together. So, Gary, I completely understand and second, your thoughts that the elephant in the room is COVID19. I've in the past two days, so Friday, and yesterday, I have spoken over the phone with almost 70-80 patients who were lined up for treatments or follow up visits, etc. And we're trying our best to figure out who needs to get out of their safe zone in their homes and even venture out at all.

The situation with this COVID19 is changing pretty rapidly. And I think the bigger challenge is the amount of information overload that we are getting from TV, from media, from social media. Some of that is very legitimate. But a lot of that is extremely scary, anxiety provoking and may not necessarily be correct. So whatever was applicable to let's say China or South Korea, or Hong Kong or Italy or Spain may not be fully applicable to the US, even for that matter, whatever is applicable to California or New York may not be applicable to Florida. So there's a lot of speculation, there's a lot of concern and I completely understand from a multiple myeloma patient standpoint, that it's very scary. What I can suggest and what the general recommendations that are being talked about is basically what we already know, wash your hands very well. If you have been able to secure some hand sanitizer please use that. But basically this concept of social distancing of trying to stay in a limited safe zone, that is what is extremely important.

It is also important to remember that while there will be a lot of individuals who will come in positive with this COVID19 or that's how epidemics work. But the majority will hopefully have a self limited low grade infection. Not everybody will end up in ICU. The biggest concern for myeloma patients are patients who are immunocompromised or have chronic illnesses is that their rate of conversion to that high or burdensome disease or aggressive disease will be a bit higher. So prevention is the best cure in this situation. Please stay limited in your safe zone, do not travel. There are people who are still trying to do gatherings outside just saying hey, we're going to defy this. Please. This is not the time to defy or act that way. Just stay safe. Make sure your contacts are feeling well. And if your contacts are not feeling well, just stay away from them. Unfortunately, a lot of patients that we come across, or individuals, they are not fully transparent about their history. If someone did go on a cruise, did go to Europe, please, please share that information. Don't just sit at home hoping, share that information with your primary care physician. Don't sit at home hoping or I'm going to be fine, nothing's going to go wrong. I think this is a time that we are responsible towards others, we are responsible towards ourselves. Just trying to prevent the situation is going to be the best.

**Gary:** And one follow up and that is previously you said it would come on to us a little bit faster than it might come on to people that aren't immunocompromised. So we have a saying, go to the emergency room at 100.4 or 100.5. Should that change under, if we feel should we go when 99.5 instead because it will get overrun because our body doesn't respond like other people's? And if so, do we go to Mayo and do the tests there?

**Dr. Sikander Ailawadhi:** Excellent question. So, there is no specific guideline for even immunocompromised patients to say that a 99 should be considered equivalent to 100.4 because there is no hard and fast there. But I do agree with you that an immunocompromised patient may not mount the same inflammatory response that an immunocompetent patient does. So some patients who are immunocompromised may not even mount a fever. So how do we know? I think it's a conglomerate of a lot of things. It's a conglomerate of not feeling well. We are still having patients coming in as of yesterday who were influenza positive, who we're still flu positive, so not feeling well, coming in just fatigued, tired, low grade fever or maybe I had 100.4 once, and I have a cough, I have a sore throat whatever is going on, abnormal symptoms.

My concern is yes that on the one hand we need to be tested but at the same time going to the ER would also in a way expose our patients to unnecessary risks. So that's why right now our policy has been if a patient is not needed to come in, they should stay away. In fact, we are applying that policy to our clinical trials also including the CLR 131. If there are possibilities of doing phone visits, we're doing those virtual visits, whoever doesn't need to come in even the clinical trials, the Institutional Review Board IRB, they have made it very, very relaxed. FDA gave guidelines saying hey guys, make it not that strict because these are



trying times. So we are testing here at Mayo. But again we are following the guidelines which have been laid out; it cannot be just although we are setting up drive-thru testing the drive-thru does not mean that anybody can come up and say, Hey, test me.

We're doing this because there are limited resources. So right now the thought is that only patients who meet certain criteria, if someone is positive contact of a patient who has been tested positive, or if someone is showing symptoms, then they can come up and get tested, but they need to meet those criteria. And only then testing can be done. I guess that there are limited resources. So I don't want every myeloma patient with 99 temperature to go into the hospital. But I think it is very reasonable for every patient to check their temperature. The guideline for us as workers, staff is that work, whoever's coming into work; we're actually checking our temperature every day before coming into work. And if somebody has a positive fever like the guideline is 100.4 or 100.5. so above under point four Fahrenheit or above 38 Celsius. If someone has a fever, we're supposed to stop at home, send out an email to our supervisor and say, Hey, I have documented a fever. I'm not going to be coming in.

So it's I think, like I said, monitoring temperature at home is reasonable, but going into the ER immediately may not be. It's a case by case decision. I think this is where the primary care physician comes in very handy because your program is being listened to from people across the country, across the world. The resources and the guidelines are very different in different areas. Rather than following one guideline, that's let's say applicable in Duval County in Florida where I am, that same may not be applicable to like I said, in Los Angeles County where I used to work when I was at USC in Los Angeles. The guidelines are going to be very, very different based on the local resources. So I think it's important to stay in touch with your primary care physician or ask them a question. But also try to figure out if it is really necessary, if you're showing any symptoms, if anybody is showing any symptoms. One can go to the CDC website, a lot of many legitimate resources that everybody can use.

**Gary:** Okay, well, thank you so much for that, that summary. I know that I kind of threw that on you. But you've actually done a great service to all of us. We're very, very concerned, obviously, because of our immunocompromised condition. But let's go on to the subject. And what I'll do is I'll just ask one question, and I see that both Cindy and Jack have put together a series of questions that I just don't want to step on. So we now have a new last chance drug Selinexor for heavily pretreated end stage myeloma patients CLR 131 is another yet to be approved end stage treatment. Can you give us all some background on this drug and the results of the clinical trials? And why do you see this as being very important?

**Dr. Sikander Ailawadhi:** Sure, thanks for that question and kind of again, setting the stage for the CNR 131 focus discussion. So I think, Gary, it's important to understand that from a clinician standpoint, for me, the most exciting thing whenever I get a new drug or an option to use for patients is the novel mechanism of action. I think that is what always stands out. Whether it is Selinexor that has a different mechanism from let's say bortezomib or lenalidomide, etc or CLR 131, which has a very different mechanism of action. So I think that is the unique thing that makes us excited in the field to try and target the disease from a different angle using something that the disease has never seen before or is unique.

So when we compare drugs, I would just kind of set the stage by saying when we compare drugs, any drugs, if that discussion comes up, it is important to keep in mind that a myeloma patient would hopefully be able to derive benefit from as many different mechanisms of actions as possible. That said, the mechanism of action of this drug is based on a concept that has been used in cancers before something called a radioisotope. It's been used for thyroid, for solid cancers, for prostate and for lymphomas amongst hematologic malignancies or blood related cancers. But it has not been used before for multiple myeloma, and that's where the CLR 131 comes in as a unique mechanism of action for myeloma. We know that myeloma or the spectrum of plasma cell disorders like plasmacytoma, multiple myeloma, there is a lot of benefit of radiation therapy. Plasma cells are exquisitely radiation sensitive.

That's why if a patient has a solitary plasmacytoma, meaning one site localized myeloma tumor or a plasma cell tumor, and they don't have disease, anywhere else including let's say even in their bone marrow, then



that person could just get radiation at that area and a significant proportion could be cured. Similarly, when multiple myeloma patients have plasmacytomas or plasma cell tumors which are causing pain etc, our go-to treatment is radiation therapy, and that tumor shrinks, those plasma cells die and it helps control the symptoms. With CNR 131, the concept is a little bit different because we cannot provide radiation to the whole of the body by external radiation, I mean.

So the radio isotope concept is that we take a drug, a sort of a chemical, which has a honing capacity to go and seek and attach to cancer cells. And if you add some radiation to that drug, so that the drug hones to the cancer cells, and that's where it delivers its radiation payload, then we have effectively provided radiation across the body to different areas of disease, whether it's in the bone marrow, its plasma cytomas, and by doing that we have effectively utilized radiation therapy to a much more extended area of the body as in basically the whole of the body wherever disease is located without having to go through providing external radiation. Because external radiation is limiting, it cannot be given through the whole of the body, there's only so much of the body that we can radiate before the bone marrow gets significant suppression.

So, the CLR 131 concept is that the drug itself or the carrier, I would say so think of it as a carrier and a payload. The carrier itself has an affinity to the lipid layers, the fat layers in the cell membrane or the cell lining. That is what the CLR goes and attaches to. Now cancer cells depend on those fat molecules to a much larger extent than our regular healthy body. That's what helps the CLR go and attach to those fat molecules in the membrane. The CLR attaches to the cancer cells and that's how it delivers the radiation to it. So that's where the unique mechanism comes.

**Gary:** Okay. Now, one thing I think a lot of people would want to know, is that like a chest X-ray, how much radiation is there? That could be scary to people.

**Dr. Sikander Ailawadhi:** Yeah, I think that's a very good question too, because a lot of myeloma patients may have received radiation therapy previously, and they may have sort of the thought is okay, on the one hand, we're saying that you can radiate the whole body. And if you give radiation to the whole body through a drug, is that too much radiation? I think that's a great question. So the way the study was set up that it started at a very tiny dose – there is a calculation of how much radiation can be given for the person's body surface area. And when we say body surface area that takes into account the person's height and weight. So this clinical trial started at a very low dose and then slowly over the course of the study, the dose has been built up. Now, the way this process works is that every time a patient is identified for it, they see the hematologist. So let's say me, but then they also see a radiation oncologist and consult as a part of the study. The radiation oncologist takes into account all the prior radiation the patient has ever received to their body.

And then it takes into account how much radiation that patient would be getting as part of the clinical trial. So for example, the dose levels that are being used right or that were reported at ASH, and having more uses are what's called 50 milliCurie(mC) – milliCurie is the unit for radiation measurement. So less than 50 mC and 75 mC so and now 100 mC, that's how the doses are developed. So considering the patient's prior radiation exposure, the radiation oncologist calculates, well, how much radiation has been given before to how much body surface area and based on that, do we have enough room to get radiation for CLR 131. I can tell you I've treated a good maybe close to 20 or so patients and the clinical trials over nationally for myeloma and for other related blood disorders have had much higher numbers. We have not come across anybody who has these levels – an average myeloma patient who has been disqualified because they've had too much radiation before. But every patient goes through this safety assessment before we get to the point of treatment.

**Gary:** That sounds very conservative. So that's super. The other thing that well, let's go on to the questions from the panel. Cindy, are you online?

**Cynthia Chmielewski:** Dr. Ailawadhi thank you so much. I am really intrigued by this unique mechanism of action of CLR131. So, I get some of your introduction. I'm trying to understand if this new compound is able



to locate the myeloma cells because of the like layer of fat in the membrane. Is that correct?

**Dr. Sikander Ailawadhi:** Cindy, thanks for that question. And yes, we can hear you very clearly. So it's basically the target is what's called phospholipid ether phospholipid ethers or fat molecules that have this phosphate kind of moiety on them. These phospholipid ethers are the target, or the target that the CLR molecule binds to. These phospholipid ethers can be present in the healthy body cells also but are much, much more concentrated in cancer cells. In fact, in the preclinical studies that were done and also other clinical trials and solid tumors, this has been tested the preclinical studies which is in animal models, etc, it clearly showed that the CLR would go and isolate itself much more in cancer cells because of the abundance of these phosphates in the ethers in the cancer cells. When the CLR attaches to these phospholipid ethers, that's how it delivers that radioisotope, the radioiodine, which is the payload, the I131. That's how the name CLR I 131 goes. So this I131 is delivered in those cancer cells, because the CLR has attached to this phospholipids ether.

**Cindy:** Okay, so, would it go after any cancer cells, I mean, it's not specific to myeloma or...

**Dr. Sikander Ailawadhi:** Cindy, that's an excellent question, too. So this actually has activity in a lot of cancers, it is not specific to myeloma. In fact, the initial studies were done in solid tumors in lung cancer, for example, benefit was noted, but later on, it was found out that for some reason, myeloma cells have even a higher concentration of those phospholipid ethers and that's why the studies were done in animal models first, where plasmacytomas were created, these myeloma tumors were created, and they responded very well. So you're right, it's not specific to myeloma. In fact, the two studies that we have going on over here, one of them is myeloma specific, but the second one is actually enrolling a lot of different diagnoses across what's called lymphoid hematologic malignancies, or cancers in the family or the cell lineage where myeloma comes from. So lymphoid cells typically convert to plasma cells, so lymphoid plasma cell cancers, including non-Hodgkin lymphoma, Waldenstrom's macroglobulinemia, certain cancers associated with chronic leukemia, lymphocytic leukemia, and of course, myeloma. So, these cancers have an abundance of these phospholipid ethers. And it so happened that myeloma is one of the ones that has an exquisite higher number.

**Cindy:** Okay, so I kind of like relating things to things I already understand. We have antibody drug conjugates, where the antibody attaches to the surface of a myeloma cell. And then a drug is inserted with the drug. Is this considered a drug conjugate because it targets the myeloma cell by looking up the radiation or considered a radiation therapy or something different?

**Dr. Sikander Ailawadhi:** Yeah, no, you're absolutely right in saying that this is considered a drug conjugate. When we say drug conjugate, what does that mean? The conjugate is basically two different things combined together. So over here is the combination is between the drug which is the carrier and this payload of the I131. So it's the carrier and the payload put together makes it a drug conjugate. Now, your comparison with let's say, other antibody drug conjugates. Let's take the example of Belantamab that is an antibody drug conjugate against what's called BCMA or B cell maturation antigen, again, something that is not FDA approved but has shown promising results and is currently being reviewed by the FDA. So the concept over there is also that the drug is specifically against a target. In that case, the BCMA, and it has a payload attached to it. Similarly over here, the drug is against the phospholipid ether the carrier is against the phospholipid ether, and it has a payload which is the radio iodine or I131.

**Cindy:** Okay, make sense now. I read it's given in 2 doses, is that correct?

**Dr. Sikander Ailawadhi:** So yes, actually different dosing schedules have been evaluated. Initially, the trial was that it was given in only one dose, those were at lower doses. Now for quite some time, considering the safety profile and also data that I had presented at the American Society of Hematology annual meeting in December 2019 in Orlando, right now the drug is being given in what's called a fractionated dose in which the calculated dose for the patient is split into two portions, and those two portions are given one week apart. And while the clinical trial say, well, the patients get these fractionated dose, so I would, I'm using the term



fractionated, you'll notice because I'm not saying two doses, because then patients may think that hey, am I getting double the amount of radiation they were giving us before no, it's the same calculated dose, but it's split into two portions one week apart.

And then these patients do have an opportunity to get another set of that fractionated dose a few months down the road once they have recovered or their bone marrow has recovered, etc. So patients may feel well, am I supposed to get only this one week apart two fractionated dose? Yes, that is how the phase two clinical trial is being run. But all those patients who get the fractionated one week apart dose can get another set of that fractionated one week apart dose down the road, if they meet all the criteria, their bone marrow is recovered, etc, etc. I think that's important to understand.

**Cindy:** So you go to the radiation person who says what the dose for your specific body would be. And then that dose is divided at this point over two infusions. And if you need another one, several weeks down the line, that same process happens again.

**Dr. Sikander Ailawadhi:** Yes, that can possibly happen again, of course you meet with a radiation oncology, the calculations are made all over again. And yes, that is possible to do. That is a second portion is an optional portion. So we're actually offering it to patients who have recovered, I have patients who are going through that second set of dose with the fractionated one week apart. I've had patients who've gone through that, because they tolerated the first one very well, had some blood counts go down, but those blood counts recovered. And now they had a significant improvement in the first go around and the thought was okay, can we get you a second one and hopefully it'll build upon the first one. So we offer it to the patients but it's not mandated by the study and we are doing it on a case by case basis.

**Cindy:** And this is an infusion?

**Dr. Sikander Ailawadhi:** Yes. This is an infusion. The other interesting portion that sometimes may cause confusion to patients that, well, you're talking about radiation and you're talking about an infusion. What does that mean? So remember, I said that this is a drug conjugate. So there's the carrier and the radiation attached to it. So it is given as an IV infusion, takes about 30 minutes or less on every occasion that the patient gets it. This is administered not in the chemo units, etc, where normally all the drugs are. This is administered by radiation oncology. They are the ones who handle this. So I have my radiation oncology counterparts, and the patient sees them. We arranged for the dose to be administered, the sponsor of the study selected out, they confirmed that the dose is available and when they can deliver those, that dose is delivered. Radiation Oncology brings in the patient in kind of bedside rooms which when radiation treatments are given.

Patient is given the infusion, their radiation level is checked and once their radiation level is appropriate, which happens very fast, the same day they go home. And then the patients are kind of monitored. The next week they come in, they get them a second portion of dose, again in radiation oncology in that Medline room, and they're sent home and then beyond that, we just start monitoring their labs and how they do. So the treatment itself involves these two, one week-apart infusion, which may be repeated down the road, but the primary portion is this one week-apart, divided dose.

**Cindy:** Who is the target audience/population for this? I heard it may be used as bridging therapy and or they'll teach patients who may not want to consider this?

**Dr. Sikander Ailawadhi:** That's again, a very good question. So okay, so what I would say is that this term bridging therapy, I think I had also used this term when I was presenting at the American Society of Hematology meeting. The reason I used this term then or we have a lot of views about this drug are because a lot of times patients will be in need of response to something and we also have to remember that any drug that is given or that is tested in clinical trials is first tested in very advanced patients. So advanced as in patients who have failed a lot of treatments, are very heavily pretreated and that's where drug development starts.



So when patients have a lot of disease, and we have seen that a lot of patients who are given treatment with this, there is a need to control the disease right away. And sometimes when the disease can be controlled, that patient can go on to other treatments that may be available whenever in future the disease progresses. And in that setting, there is this concept or term of bridging therapy, because you got to know that this is unusual, because we're giving this treatment – two infusions one week apart. And so patients are more used to getting treatment every week, every three weeks, every day, whatever the drugs may be. So you get the treatment and if you have a disease response, the next time the disease grows, because the clinical trial let's say you're done with this treatment with the CLR 131, the next time the disease grows, you may have an opportunity to get something else.

That's where I think the biggest advantage so far has been, and of course, this is talking about very heavily pretreated patients. I was kind of reminding myself of the data, that majority of the patients. So the multiple myeloma data that we had represented about 50% of the patients met in multiple myeloma who got this treatment, met the criteria of what's called quad-refractory meaning four or more drugs refractory, which typically includes bortezomib, lenalidomide, pomalidomide, carfilzomib, Daratumumab, these are the more common drugs which are used. The average number of prior lines of therapy were five, anywhere from two to 17. But the average number of prior lines of therapy was five lines of treatment. When we talk about that much of heavy pretreatment patients, getting that response, so that the patient actually may be able to even get to something else – that is phenomenal and that's where this term bridging therapy has come.

So when you ask Cindy what is the best population – I think the myeloma relapsed – patients who have relapsed or refractory multiple myeloma, we know it's a heterogeneous group. Patients can have progression based on just their labs. They can have rapid progression based on lots of tumors. They can have rapid progression based on these multiple tumors or just kind of disease growing very fast. So I think the important thing to consider is if we are able to use this drug in selected patients, let's say who are just progressing biochemically or based on labs, I think the benefit may be different than for example, if we have patients who have large tumors or plasmacytomas and they are rapidly progressing, and something is being used just as a last ditch effort, I think the benefit would be different. So that portion is still being worked out. But I think what has been very exciting for me and the community as a whole is that we have been able to see responses in a lot of different patients across these different subgroups. So patients who have very advanced disease, patients who have disease that is biochemically progressing, I think we still need to figure out exactly where the niche or the maximum benefit would be. But so far, we have seen responses across the board.

**Cindy:** Wonderful. One last quick question and then Jack could ask all his questions. Just thinking about people that have a high tumor burden and this is only in two doses, the question pops to my mind – Is there anything showing for like a tumor lysis syndrome or editing release syndrome like that your cancer is dying so fast that you have to worry about it or not with this type of treatment?

**Dr. Sikander Ailawadhi:** So, so far, Cindy, I think that's again, a very good question. So far we have not seen that sort of a tumor lysis syndrome situation in any of the patients. In fact, it's been used I personally used it in a patient in quite a few patients with large bulky disease. Now, whether I have the same amount of benefit or not is questionable because I don't think we have large enough numbers in all of these different subgroups to say who benefits more who benefits less but tumor lysis syndrome so far we have not seen.

**Cindy:** Okay, great. Thank you so much for your time.

**Gary:** Jack you online?

**Jack Aiello:** Dr. Ailawadhi. How are you doing?

**Dr. Sikander Ailawadhi:** Hey Jack, how are you doing? So good to hear you over the phone. I hope you guys are feeling well, especially in California with all the craziness going on across the country.



**Jack:** I want to follow up on some of the questions and answers that you had with Cindy there. You mentioned you've seen responses across the board. So the first obvious question I ask is how durable had those responses been?

**Dr. Sikander Ailawadhi:** So, Jack, I think you're asking a very good question. How durable have these responses been? So I know in my lower case, response is something that we look at very quickly and we sometimes can get that benefit. But do these responses last? Now we have seen responses last in the myeloma group for at least a few months. I think the number of patients is relatively small, but I've had responses lasting 3/4/5 even longer duration of time, months, sorry. I think the response rate in my assessment, the duration of response happens depending on how much was the disease before how fast it was going, etc. So, in that three month follow up period, which actually the study requires the three month follow up is where the study kind of stops the intensive follow up, and then patients go to long term follow up, etc.

We have not seen any of the patients progress through that time. Patients do progress down the road, if they do, but at the same time, I think patients who have had just that small amount of biochemical progression, that is where we've seen longer durations of response, that's where we've seen much longer and better and durable responses. I think this is not yet at the point of me saying, hey, the median response, progression free survival is eight months or nine months. But I think the biggest advantage of this has been that almost across the board, a lot of patients, the overall response rate is somewhere close to 45%. So about half the patients, nearly half the patients have a significant improvement. And even those who do not meet that response criteria, a lot of patients meet what's called the stable disease criteria. And in fact, all of the patients that were reported, even at ASH, none of the patients had in the average fifth sixth line of treatment, none of the patients had disease progression during that initial three-month follow-up. So it almost seems I know it's not right to maybe use that analogy, but we have seen that flattening or improvement in the curve within that three-month follow-up period, which kind of gives every patient that significant breathing room of disease control.

**Gary:** Jack, just a point, that's kind of interesting, is that Daratumumab when it was first used as a single agent had a progression free survival, well, it had an overall response rate of 26% and a progression free survival of 1.9 months. So if he says, it might be eight months or six months, that's like three to four times better than what we saw with Daratumumab and Daratumumab has turned into quite the star, when you use it earlier in the disease progression. So it's to me, that's what is kind of amazing.

**Dr. Sikander Ailawadhi:** Yeah, so Gary, I would add there that the assessment in the patients who got less than 50 mC dose which is not a dose we're using anymore because the dose has been increased. The median progression free survival was about three and a half months. But in the 50 and the 75, and now actually we've gone up to the 100 mC is what we're getting to, in those dose assessments, this median progression preterm is still ongoing, but I can tell you that the responses have been better and longer than the one with the lower doses. So the number is going to be higher than that three and a half months, but I don't have that specific number to share with you right now.

**Jack:** Okay, thank you. Let's all talk about side effects as well. I got a chance to look at the poster from IMW19. And there were only four patients involved. But they all showed pretty significant hematological side effects. Half of them experienced anemia, neutropenia, and all of them experienced thrombocytopenia of grade 3 or more. Is that concerning? Are they manageable? What are you seeing as in more patients now that you've expanded the trials?

**Dr. Sikander Ailawadhi:** Thanks, Jack. I think that's an extremely important question again, because while we talk about the benefits, the efficacy, the improvement, responses and progression free survival, well, at what cost? What are the side effects? How is the patient going to tolerate it? So the side effect profile in my mind is relatively clean. When I say clean, I'm not saying that there are no side effects, but my thought is that side effects are predictable. And even at higher doses, we have seen that the side effects are mostly confined to hematologic or blood related side effects. So the thrombocytopenia or low platelets, the white cell



count decrease overall and the neutropenia which is decreasing the good immune fighting neutrophils, those are typically the side effects that we have seen. Now has grade 4 happened? Yes.

So even significant decrease in counts have happened in some cases in myeloma patients and in lymphoma Waldenstrom patients, but they tend to be very predictable. And in fact, there was a card that I had presented at ASH in December, which kind of looked at the trajectory of decreasing counts in these patients. And it seems that trajectory is very, very predictable. And when I see the patients, I kind of explained to them, hey, about three to four weeks after the treatment, your counts are going to start going down and about seven to eight weeks after the treatment, they are going to start coming up. So there is this in between 3-4 week period when the counts go down, and then they start coming up, somewhere about 2-2.5 weeks is when we start seeing the dip both in platelets, neutrophils and anemia. So that's what brings in mind this term called the cleaner side effect profile, because I think it is very predictable and hence manageable.

Now, there are a lot of factors which are taken into account. So for example, if a person is 70 years old or 80 years old, their bone marrow reserve is going to be smaller as compared to someone who's four years old. If someone has 80% or 90% bone marrow involvement, they are going to have; so, if the patient has 80 90% involvement in the bone marrow, their disease control will be very, very different as compared to if they are or their side effect profile is going to be different as compared to what they have if they have 20% involvement. So that's kind of I'm sorry, I'm actually getting paged in between about something. So that's why I'm having to break or you're hearing the tone in the background. So that's where I think the side effect profile is different.

Putting all patients together, you're right platelets do go down, even below 50,000 in the 20,000-30,000 range, but we're able to transfuse and almost universally all the patients come up, even neutrophils and platelets and hemoglobin does improve. That is exactly the reason why this fractionated dosing came by. So when the drug was being given as the single dose, one dose, it was causing more dip in the counts. Now when we fractionated the dose and divided it and gave it over to separate infusions one week apart the side effect profile changed because the dip in the counts was not as profound and we were actually able to increase the total dose delivered. So I think that is where the side effect profile is different but the hematologic side effects are very, very specifically the only side effects we've seen. We haven't seen any other significant issues like diarrhea, vomiting, nausea, hair loss, eye side effects, rashes, fatigue, etc. Fatigue could come from anemia, but nothing that is independent of it. So that's, I think, where the clean side effect profile comes, counts go down, we support, they come up.

**Jack:** That's good. Thank you. I'm going to use myself as an example here. I know you talked about mC and computing the dosage amounts and such but if a patient like me, had prior radiation for plasmacytoma, as well as total body radiation, you think that would already be a limitation to using CLR?

**Dr. Sikander Ailawadhi:** So, I think Jack again, that's a very good question. Having radiations for plasmacytomas so far, in my opinion has not been an elimination, no patient has been eliminated because they've had too much radiation. But again, it's important for us to figure out what is safe and what's not. So, total body radiation, like you mentioned, which can be sometimes used for pre transplant conditioning is something that is not usually used for transplants. There are some cases but it won't be across the board. I don't think I want to speak for my radiation oncology counterparts or the dosimetry calculation. But what my thought is that while a patient who's received quite a bit of radiation in the past may not be able to get that second set of treatment 3-4 months down the road, but may still be able to get the fractionated dose the first time around, which is what the primary goal of the clinical trials is so far.

So I don't think I want anybody to assume that, hey, I've had X amount of radiation, so I may not be eligible. I think that's where if somebody seeks out this clinical trial or has availability, I think it's very reasonable to have the discussion with the hematologist. Typically, we are able to easily pick up the phone call, our radiation oncology counterparts and say that, hey, this is the radiation history for the patient. Do you think they are eligible to get the 75 mC or the 100 mC, whatever dose may be going on for the trial, and the radiation oncologist can actually do that calculation pretty quickly and get back to us. I think it's okay to seek



out the trial or at least consider it. And if for some reason it is not safe, the patient will not be given treatment, we do want to make sure that it's safe for patients.

**Jack:** Okay. And then one last question put on, look into your crystal ball. If this treatment gets approved, sometime down the road, 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? What do you think is going to happen?

**Dr. Sikander Ailawadhi:** Yeah. So I think again, Jack, that's an excellent question. I'm going to try to shine my crystal ball a little bit better, to get you the right answer. So I think we still need to understand how this drug behaves and what kind of efficacy and safety data continues to emerge. And what is the optimal dose and optimal schedule, let's say the second treatment round, how many patients get it and how safe it is, but the way I look at it, I don't think that the single dose is it. I think that what CLR 131 does for us is that it kind of opens the gates. I started by saying a new mechanism of action for myeloma. We have so far not seen any combination with any other drugs. But there is a role for that. I mean, we know that for example, bortezomib, carfilzomib, they can be given as with radiation. And in fact, historically, there has been a thought that they can in some way be even radio sensitizers or help radiation work better.

How that works in actual clinical trials is yet to be seen. So I'm not saying that that's the way but combinations are one thing. Repeated doses are already being tested. So that would be an important part. The third important thing which I'll be very frank, I'm most excited about or where I want this drug to go or clinical trial to go is before for transplant. We know that there is significant improvement for MRD negative patients, so whoever is MRD negative is going to have a significantly better progression free survival outcome. So just imagine if a patient comes for transplant evaluation, we do a bone marrow biopsy, they have leftover disease or are actually MRD positive. And we go ahead and give them a single dose of CLR 131. I would say even we increase the dose and give them the best possible dose. So imagine where TBI was used in your case.

And now we have converted that patient to MRD negativity. The only side effect we are concerned about is low counts. But guess what this patient is going to get their transplants or their stem cells have already been collected and they're going to get their conditioning melphalan or whatever, and the stem cells are gonna come back. So I am actually most excited about where we might be able to use this – the benefit of the disease eradication and not have the fear of local counts, because the stem cells are going to come back and are going to take care of the counts anyways. So I think it opens up a lot of possibilities of things that we can do. This initial trial is telling us that we know what the safety profile is. And we know that we can actually give it a second go around and build upon the benefit from the first time around. And now let's try to figure out how we can combine, how we can use it with some maintenance down the road and side effect profiles like Jack rightly mentioned, have to be first defined, studied and then kind of figured out how that has to be done. What happens when you combine this with others? We don't know yet. But a lot of these opportunities are now opening because we know how the safety and emission benefit from this drug is.

**Jack:** Dr. It was nice talking with you. I wish you and your family, great health and thank you so much for being available today.

**Dr. Sikander Ailawadhi:** Thanks a lot. I really appreciate it.

**Gary:** Thank you, Jack. I know you're getting a lot of messages. Do you have time for a few questions from the audience?

**Dr. Sikander Ailawadhi:** Yeah, I think it should be okay. I think we still have a few minutes. Sure.

**Gary:** It seemed like you're pretty darn busy. So Shweta could you please ask those questions?

**Shweta:** Sure. Thank you very much. Thank you so much, Gary, Jack and Cindy for a great discussion so



far. And Dr. Ailawadhi, we have a couple of questions from the audience. And the first one says how does CLR 131's 43% response rate as sixth line therapy compare to on market drugs? I'm guessing you'll have touched a bit upon this, but could you answer the question?

**Dr. Sikander Ailawadhi:** I think this is a very good question again, how does this compare to other drugs that are already available. So just merely look at the response rates, this 43% ish 42.8-43% response rate, and also the others achieving almost everybody getting at least stable disease, meaning that the disease did not progress during that three months follow up period. That is really encouraging. Now I'll be very frank, I don't think I'll ever use the term saying hey, this drug is better than that drug, etc. Because my concept is always how can I get the maximum amount of benefit to my patients from all the available treatments. So I'm not going to say hey, this is better than Pom or this is better than Carfilzomib or this is better than that. I think that's not a fair statement because the way we use the on-market drugs is very different. I think what's unique and different is that right now we're using this just by itself, patients get that divided dose and then we just monitor.

So that concept which used to be talked about one time in the past, with transplant of treatment free interval that the patients are not actually getting active treatment for myeloma, and all they're doing is monitoring labs and supporting, I think that is a huge advantage which CLR 131 is bringing back because now with transplant even we go to maintenance, there is no treatment free interval that typically happens. But this drug is actually bringing that concept back. Now how it gets combined with other agents, what's going to, I think best define that competitive strategy with other drugs on the market.

**Shweta:** Thank you, doctor. And I believe this is a follow up from the same person and he asks, how does this data compare to the anti BCMA therapeutics currently in clinical trials and other drugs for multiple myeloma, which might be easier to administer logistically than a radiopharmaceutical?

**Dr. Sikander Ailawadhi:** I really appreciate that question from whoever came from the audience. Thanks for asking that. No, I should say that BCMA targeted drugs are very exciting because that is also a very, very exciting target for myeloma. Right now, there is no BCMA drug that is FDA approved, but like I said, there is at least one with the FDA, actually two with the FDA right now. And a lot of the CAR-T cells are also against BCMA. So, BCMA targeted drugs are across the board. There is not one drug to compare with. But if I was to pick one drug, let's say Belantamab, which is an antibody drug conjugate, and it has been reported in combination as well as by itself. The response rates with CLR131 are actually slightly higher when compared to single agent, some of the anti BCMA drugs and I completely understand the logistic challenges of getting it administered in a radiation oncology area, etc etc.

But think about it this way that with any of the antibody drug conjugates or BCMA targeted drugs, whether it's bispecifics etc, that also brings with itself repeated treatments, kind of have to go ahead with treatment by treatment every two weeks, every three weeks or whatever the schedule may be every week sometimes. That is where the logistic simplicity is. Plus also think if a patient has to get radiation therapy, for myeloma patients unfortunately, radiation therapy needs to be given from time to time then that radiation oncology suite can be or has to be utilized anyways. So I'm not saying that this drug is going to be available at your neighborhood radiation oncologist tomorrow, but I'm saying that the logistics for administering this radioisotope are already in place. There are a couple of radio isotopes that are used in the past for heme malignancies of lung related cancer. So I think that's where I think it may not be as big of a logistic challenge as we think it may be.

**Shweta:** Okay, thank you so much for that answer, Dr and we don't want to keep you holding here any longer. Thank you so much for your time. So I'll just wrap it up now. Ladies and gentlemen, we were listening to Dr. Sikander Ailawadhi of MayoClinic and patient advocates Gary Petersen, Jack Aiello and Cynthia Chmielewski discuss about the potential of CLR 131 small molecule which was granted orphan drug designation for the treatment of multiple myeloma by both the US and the European Commission. We hope that this yet-to-be approved end stage treatment comes out as a relief for the myeloma patients who have already tried multiple treatments. Dr Ailawadhi, I thank you very much for your time and all the information



that you shared with us today. Gary, Jack and Cindy and the audience, I thank you for your insightful questions that brought out an informative discussion in the last hour. The talk will be available on [curetalks.com](http://curetalks.com). So please visit our website for more details on our upcoming talks. And stay safe everyone and keep in mind as Dr. Ailawadhi said, prevention is the best cure in the situation with the corona virus around. So stay indoors and make sure all your contacts are feeling well. So until next time, everyone, thank you and have a great day.

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