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Investigating Plinabulin as Immune-Modifying Therapy for Non-Small Cell Lung Cancer (NSCLC)

Narrator:
Welcome to ReachMD, and this special edition of Project Oncology, sponsored by BeyondSpring Pharmaceuticals. BeyondSpring: bringing change to cancer care.

Dr. Birnholz:
This is Reach MD, and I am Dr. Matt Birnholz. My guest today is Dr. Alain Mita, Associate Professor of Medicine and Co-Director of Experimental Therapeutics at the Samuel Oschin Comprehensive Cancer Institute of Cedar Sinai Medical Center in Los Angeles. Dr. Mita has served as principal investigator in numerous clinical trials, including a recent phase 2 study for the vascular-disrupting agent Plinabulin, which is the focus of today's discussion Dr. Mita, welcome to the program.

Dr. Mita:
Thank you for having me.

Dr. Birnholz:
It is great to have you with us. So to start, can you share with us your perspective as a medical oncologist and cancer researcher on the scope and burden of non-small cell lung cancer?

Dr. Mita:
Lung cancer continues to be a major health issue. It is the number one killer in the United States. It kills more patients than breast cancer, prostate cancer, and colon cancer combined. We have made some progress for the treatment of lung cancer, but still much remains to be done and therefore any new trial with new drugs that are trying to improve the outcome of these patients is always welcome.

Dr. Birnolz:
Well, on that note, why don't we turn right into those trials and talk about the drug molecule that you've been actively investigating, which is called Plinabulin. I'm curious, how did how you become interested in this molecule in particular and get involved in its lines of investigation?

Dr. Mita:
This is a very interesting story, because I started working with Plinabulin from the very beginning when it reached development in humans in the very first phase 1 study. At that time, we thought that Plinabulin is just a vascular-disrupting agent, and its vascular-disrupting effects are very well documented. We saw some interesting results in the phase 1 study. The drug was safe, well tolerated, and we saw a few patients who had interesting tumor responses, and we thought that this drug is worth developing further. Later, a further research done showed that Plinabulin is not just a vascular-disrupting agent but has very interesting immune-modulating properties and also neutrophil rescuing effects. That means that this old drug now has a new life with some new and interesting mechanisms of action.

Dr. Birnholz:
I'd like to talk about that further because you gave me a sense of what the molecule is. I had a basic idea of how it works now, but where does it fit in this immune therapeutic armamentarium?

Dr. Mita:
It's really a very unique immune-modulating agent. Plinabulin, again, is a drug that binds to the tubulin and by binding to the tubulin, it has vascular-disrupting agents, as mentioned, and can induce direct tumor killing which leads to liberating tumor-specific antigens and

an immune response. Further, later research has demonstrated that after binding to tubulin, Plinabulin can also activate the Jun pathway in the dendritic cells, which leads to the expression on the surface of the dendritic cells of CD80 and CD86, which send co-stimulatory signals which activate the T-cells and further boosts the immune response. Regarding its very unique neutrophil protection properties, it is a very nice example of bench-to-bedside and then back to bench for translational research. In the clinical study that we are going to discuss, we notice that a patient who will receive Plinabulin had less neutropenia and then we went back to the bench to understand why. We realized that activation of the Jun pathway of dendritic cells also leads to production of IL-6 and IL-12, which are well-known factors that protect neutrophils from apoptosis. That is the postulated mechanism of the drug in the neutrophil protection.

Dr. Birnholz:
It seems that there are a number of mechanisms in play here that convey both solo effects and synergistic effects. Are they totally unique in the treatment space? I mean, is there something that you recognize within this molecule based on this research that made it stand out among other treatments out there?

Dr. Mita:
I do believe this is a unique molecule and, again, it is very difficult to understand in a patient which mechanism of action is prevalent. I think that it is important to understand that it is probably a synergy and the immune effects in addition to the vascular-disruption agent and the synergy with other immune modulators are all equally important. I think future research will demonstrate which one of these mechanisms are the most important or better how to exploit all these multifaceted properties of this drug.

Dr. Birnholz:
And just to clarify, Dr. Mita, is this drug that we are talking about intended to be used as a solo treatment or is it to be used in combination with existing therapies?

Dr. Mita:
If I had to make a guess based on its mechanism of action, I think its full potential will be reached in combination, either with chemotherapy drugs or with other immune modulators. Time will tell.

Dr. Birnholz:
Excellent. Now you had talked about the neutropenia benefit as one of these interesting immune effects that might have been unanticipated but was observed. Just to get a sense of what that means or translates into as far as clinical outcomes for patients, does that essentially translate into being able to keep a patient at the right chemo dose without having to interrupt it?

Dr. Mita:
Absolutely. I hope we are going to talk a little bit more about the study, but very briefly in the study that was recently presented in Orlando for the ASCO meeting, patients who received docetaxel alone had an expected rate of neutropenia or about 30%. Now patients who receive the combination of docetaxel with Plinabulin had a much lower rate of grade 4 neutropenia, which was in single digit percents of 3-5%, and that was again coming as a surprise and now we try to understand then, I explained a little bit of postulated mechanism for that happening. The bottom line is that in patients who received the combination, no patient had infections or sepsis on treatment and the dose reductions on the combinations are much less frequent.

Dr. Birnholz:
On that note, I want to turn now to some of the phase 2 data that you did present at ASCO IO. Maybe you can give us a preface with some of the key findings that you shared and how they were received by your peers at the conference.

Dr. Mita:
The study that was presented was initially a very straightforward study. A phase 2 randomized trial in patients with lung cancer as a second or third-line treatment. In patients who were randomized to receive either docetaxel alone in the standard dose 75 mg square meters or a combination of the same dose of docetaxel with Plinabulin 30 mg square meters, later on, in order to mitigate some of the side effects with Plinabulin in combination, another cohort was opened with a combination of docetaxel 75 mg square meters and the lower dose of Plinabulin at 20 mg square meters. The results were quite interesting. The primary endpoint of the study was overall survival and secondary objectives were time to progression, response rate, and safety. In terms of primary endpoint, the overall survival, although it was numerically higher in the combination arm at about 8.7 months versus 7.5 months with docetaxel alone, this did not reach a clinical statistical significance. However, some very interesting data were seen looking at the duration of response. The median duration of responders on the combination arm was significantly higher than with docetaxel alone. Patients receiving docetaxel alone had time to progression to approximately 1.5 months versus 12 months in patients who received the combination. That was statistically significant and very intriguing. Additionally, very interesting and intriguing results were seen in a sub-group analysis of patients with measurable lung disease. In these patients who have large, bulky measurable lung disease, patients who received the combination of the Plinabulin and docetaxel lived an average 4.6 months longer than the patients who received docetaxel alone. That

was 11.2 months versus 6.7 months with docetaxel alone. This did not reach statistical significance due to the low numbers, but it was definitely intriguing. Again, duration of response was higher; overall response rate was almost doubled in patients receiving combination – 10% with docetaxel versus 18% with the combination of docetaxel and Plinabulin. All these results looked promising and value the next phase 3 study that is ongoing.

Dr. Birnholz:
Dr. Mita, were there also quality of life measures that were monitored with this study? I imagine respiratory relief, fatigue, those elements would be of special interest to this patient population.

Dr. Mita:
This is an excellent question. The quality of life was not formally measured in this study; however, the side effects and the safety were very carefully monitored. We did notice that in patients who received the combination of Plinabulin with docetaxel there was a slightly higher incidence of nausea, fatigue, and diarrhea; however, when the dose was reduced from 30 to 20 mg of Plinabulin, these side effects were much less and there was not any significant difference between the patients receiving docetaxel alone versus the combination. A very interesting side effect that we see with Plinabulin is high blood pressure, but this is a very different high blood pressure than what we see with other vascular-targeting agents. The high blood pressure generally occurs acutely in the hours following the infusion and it is very short lasting – only a few hours – after that it resolves and it never returns and there have been no sequelae in any of these patients that had high blood pressure. Additionally, the dose reduction from 30 to 20 mg of Plinabulin led to a significant decrease of the incidence of the high blood pressure and mainly the grade-3 high blood pressure, which is the one that is worrying the clinicians. Now on the flip side, we have seen that the patients who received the combination of Plinabulin with docetaxel had less incidence of asthenia or fatigue and also, as mentioned, less neutropenia. That led to the fact that patients with the combination had just as good if not better quality of life as the patients who received the single agent, docetaxel.

Dr. Birnholz:
That is excellent. Dr. Mita, I want to spend a few minutes now talking about the phase 3 study and development that I referred to earlier because it seems to be catching a lot of momentum. Tell me, what is this trial seeking to find and which patients are being recruited?

Dr. Mita:
This is a trial that is hoping to replicate the promising results that were seen in the phase 2 in a larger patient population. It is a randomized phase 3 study, a second or third-line chemotherapy with docetaxel plus or minus Plinabulin at the lower dose, 30 mg, which was shown to be better tolerated in patients with non-small cell lung cancer and they have to have at least one measurable lung lesion, because these were the patients who were deriving the most benefit in the phase 2 study. The study is called the Dublin 3 study and it is open worldwide and I strongly encourage any investigators who are interested in this study to research it and to join.

Dr. Birnholz:
That is great. Is this study also accommodating patients who have failed other therapies such as immune checkpoint inhibitors?

Dr. Mita:
The study is really meant for a second or third-line treatment, but patients who may have received first or second-line immunotherapy are allowed to enroll.

Dr. Birnholz:
And, Dr. Mita, just to help me understand in case I'm a little naïve on this point, but I understand that Plinabulin here is being studied in combination with both chemo and immune checkpoint inhibitors, respectively. Why study both in this case?

Dr. Mita:
That is a very good question actually. I guess the answer is that we are still learning about this drug and we are trying to understand its full potential and therefore based on the phase 2 data, the data was compelling enough to justify this larger phase 3 study to confirm the promising results, but also based on the preclinical work done showing the synergistic activity with PD-1 inhibitors as well as with CTLA-4 inhibitors, just based on this novel immune mechanism of action of Plinabulin, clearly immune therapy combinations are justified as well and there are a couple of investigating initiated clinical trials that are either planned or ongoing combining Plinabulin with other checkpoint inhibitors.

Dr. Birnholz:
Let me ask you then since we are on this subject of the global phase 3 trial, I think the big question in the room is, how can oncologists who are treating patients with non-small cell lung cancer potentially get involved in the clinical trial directly? Can you talk about that?

Dr. Mita:
As I mentioned, the trial is open globally, both in the United States and Europe and it is listed under clinicaltrial.gov; again, it is the

Dublin 3 Study of Plinabulin and docetaxel combination. Any investigator who is interested in participating can contact the sponsor and the organizing sites and join the study. It is going to be a global effort. It is going to require a lot of patients, so any help on this study is welcome.

Dr. Birnholz:
Well, with those parting comments, I do want to thank my guest, Dr. Alain Mita, for joining me to discuss this new player in the immune oncology therapeutic landscape. Dr. Mita, it was great having you on the program today.

Dr. Mita:
Thank you so much for having me. It was a pleasure.

Dr. Birnholz:
For access to this and other episodes focusing on lung cancer therapies, join us at ReachMD.com where you can be part of the knowledge. Thank you for joining us.

Narrator:
The preceding program has been a special edition of Project Oncology, sponsored by BeyondSpring Pharmaceuticals. Thank you for watching.

BeyondSpring is a global clinical stage biopharmaceutical company developing innovative immuno-oncology cancer therapies, with a robust pipeline from internal development and from a collaboration with the Fred Hutchinson Cancer Research Center and University of Washington. BeyondSpring's lead asset, Plinabulin, is in a Phase 3 clinical trial as a direct anticancer agent in non-small cell lung cancer and Phase 2/3 trial in the prevention of chemotherapy-induced neutropenia. For more information on this clinical trial, please contact BeyondSpring Pharmaceuticals at general@beyondspringpharma.com, or visit www.beyondspringpharma.com.