Precision Medicine Podcast, Season 4, Episode 54

Leading Thoracic Oncologist, Dr. Christian Rolfo, Explains How Liquid Biopsies Are Advancing Precision Medicine

February, 2022

Karan Cushman, Producer:

Welcome to season four of the Precision Medicine Podcast, sponsored by Trapelo. This is the podcast where experts come to discuss the problems oncologists, reference labs, and payers face as precision medicine grows and consider solutions for advancing the quality of patient-centered cancer care. Be sure to subscribe at precisionmedicinepodcast.com to get the latest episodes delivered straight to your inbox.

Jerome Madison:

Welcome to the Precision Medicine podcast. I'm Jerome Madison. Today we've got Dr. Christian Rolfo, President of the International Society of Liquid Biopsy and Associate Director for Clinical Research at the Center of Thoracic Oncology at the Tisch Cancer Institute at the Icahn School of Medicine at Mount Sinai in New York City. Dr. Rolfo, thank you so much for being a guest on the podcast.

Dr. Christian Rolfo:

Thank you for the invitation, Jerome. It's a pleasure to be here.

Jerome Madison:

Absolutely. I'm very excited to share this conversation with our listeners today because liquid biopsy, the ability to detect genetic variants from a vial of blood has the potential to absolutely revolutionize healthcare in the practice of precision medicine. From a commercial perspective, the projected market cap for liquid biopsy has been projected to exceed $30 billion by 2030. That's an astronomical number. Depending on what news source you read, and Dr. Rolfo, I feel the need to say this for all of those listeners who are following current events. This may sound like a familiar story, but we are not talking about Theranos.

That's why we've asked Dr. Rolfo—who was the lead author on a paper published in the Journal of Thoracic Oncology this past year, which was titled Liquid Biopsy for Advanced Non-small Lung Cancer, a consensus statement from the International Association for the Study of Lung Cancer—to come on the podcast and share the scientific findings and his perspectives on this topic. Dr. Rolfo, I will tell you reading this paper…and there are others out there that are stuttering various applications of this methodology…it seems that we're only starting to scratch the surface to understand how this can impact the treatment of lung cancer, but also the ability to access genetic information easily and repeatedly can have a huge impact on a number of other diseases.

Jerome Madison:

To begin, can you give us an overview? Because liquid biopsy is kind of an umbrella term, but in the paper and in different papers out there, there's different components of what's referred to as liquid biopsy. Can you talk about those components, and which of these is making the greatest impact in clinical practice today?

Dr. Christian Rolfo:

Sure. That's a very good question. Liquid biopsy is a big family. We have there all the circulating biomarkers that we can find in the blood and in other fluids. It's not only the blood that we are referring to as liquid biopsy. Could be also be pleural effusion or even, for example, CNS fluids or even urine. Generally what we are referring for liquid biopsy in the clinical application is the cell-free DNA or circulating tumor DNA. That's our fragments of DNA that are circulating in the blood.

But also, we have microRNAs that are small components of the blood circulating in the blood as well. Extracellular vesicles for example, that are part in the communication between the cells, circulating tumor cells that were the first ones as well there, but we also can refer into liquid biopsy to proteins or even metabolism that are separating in the blood. It's a big family. In the clinical practice we are using, as I say, separating tumor or separating free-DNA that was this fragment, and was recently approved the use by FDA to not only lung cancer, but also other disease with different specific biomarkers. We are using not only metastatic disease, but also there are several studies now involving earlier stage on minimal residual disease. After the operations for example.

Karan Cushman:

Thank you Dr. Rolfo. Jerome and I, we work really hard to bring the content of the podcast to our patient audience and families. We wanted to start off right from the top by asking you for those patients that are impacted by cancer now, or in the coming years, how will liquid biopsy transform the diagnosis and the treatment of the disease for them?

Dr. Christian Rolfo:

Yeah, this is a big question. Obviously, a liquid biopsy is having several advantages that's compared with the tissue biopsy. I want to start from the very beginning. When we are talking about lung cancer or cancer in general, we are now trying to personalize every single case with different characteristics that the tumor have. Every patient have different treatments according to this molecular profiling or personalized approach that we are doing. We can obtain the information of this tumor in the tissue that is part of that. It is traditional part, that is the tissue biopsy, or we can do also right now with the recent approval and with the technology, we have a very strong and robust data to apply liquid biopsy as well as a tool to obtain this important information.

Dr. Christian Rolfo:

Which information is that is obviously related with the opportunity to the patient to have some special biomarkers that we are targeting with medications. We have right now, new target

therapies that are approved. We can start treatment without going to the traditional chemotherapy or chemotherapy and immunotherapy. We can go directly to targeted therapies that are covering this alterations. Liquid biopsy is an important tool. One of the advantage that have also compared with the tissue is capacity to capture heterogeneity, and that means, just to make a clear example, I will try to make it very easy to understand, but when you have a cake, this cake that have different flavors, and I give you only the part of the chocolate, that is for example one biopsy, is a small part of the cake. You can say or you can find that this cake is only chocolate. But if I show you the complete picture, you can see also the flavors and that is what's happening with liquid biopsy.

Dr. Christian Rolfo:

We are to capture clones of the disease that are not only in the primary tumor, but also in some metastatic patients for example. This information is also coming from the site of the metastasis. This is a very important information. We are now also using, not only for the detection of these alterations. Fortunately with all the therapies approved, we have completely different opportunities for patients who are harboring some alterations because the response to the drugs and the opportunities to enter in this special pathway of treatment is giving more opportunities to treat, I will say for these patients.

But also, we are using the liquid biopsy to monitoring the response to these treatments and to understand not only how is the treatment responding, but also the resistant mechanism that are involved in case that the drugs are not working. It's a plethora of opportunities with liquid biopsy, because it's a very dynamic compared with a biopsy. You cannot repeat tissue biopsy every time, but you can repeat liquid biopsy very frequently, because what we are doing is just a blood draw. It's minimally invasive, and we can have in real-time data for monitoring the disease.

Jerome Madison:

Very comprehensive. Dr. Rolfo you're a thoracic oncologist and in this paper, it was a real eye-opener to me that was reported that as few as 18% of non-small lung cancer patients have adequate tumor specimen for complete tissue genotyping. That was defined as eight biomarkers. That's stunning to me because there's a lot of data out there that shows the lack of testing in non-small cell lung cancer, or the slow rate of adoption of full genotyping. But there's not enough talk about this, that there's simply not enough tissue. That's stunning. Can you talk more about it?

Dr. Christian Rolfo:

Yeah. The data that there and you're referring is based on some real-world data that are coming, for example, from the NILE study that was in a study collecting data from real-world patients, and you have there in clinical practice and is referring it specifically to the aids guidelines and recommended biomarkers that we are using. Having a complete testing for all this biomarkers is very limited sometimes in tissue. Obviously, that depends on the quality of tissue, the quantity of tissue and the kind of biopsy that is performed. If we are doing a cytology that is collecting some cells, obviously that is very difficult to get a complete information of the molecular profiling because the techniques that we are using to obtain that, that they call next-generation sequencing or high-throughput sequencing is a big number of genes that we are analyzing is difficult to accomplish with a small quantity of tissue.

Dr. Christian Rolfo:

It's true that in recent also presentations, for example in ASCO this year was a very nice presentation coming from the Milan Consortium that is a consortium of community doctors working in lung cancer. They showed that only 50% of the patients in lung cancer are tested in this big population. If we see, for example, what was happening in the rates over the time, the overall population of this study from April 2018 that was 33% to October or March, 2020, we increased a little bit to 45%. It's minimal increase on testing. If we put together also the disparities there, there was another study percent also in ASCO this year that showed that only 39% of some groups of disparities like the African American population was tested.

Dr. Christian Rolfo:

This means that when we are talking about the big approvals and the fast approval of FDA, that was doing a tremendous job in the last two years to approve different drugs, we are doing something wrong to not test these patients. We need to make this happen very quickly in all the patients because we have the technology it's reimbursed, it's approved. I don't understand why we are not having big rates of testing because it's changing completely the course of the disease in patients. It's important, and I will say it's mandatory, and it's not ethical to don't have this information before we start any treatment.

Jerome Madison:

Yeah. You mentioned the NILE study, and I don't have that data citation right in front of me. For those listeners who want more information that go to the landing page on precisionmedicinepodcast.com for this episode, and we'll have it there. But one of the findings of the NILE study, the tissue-first approach. 67% of patients had an actionable finding, but with liquid biopsy reflex, 33% more patients were discovered to have an actionable finding. I think Dr. Rolfo, that centers the question on tissue versus plasma, which do you do first? What were the recommendations of the IASLC of when to perform plasma testing or liquid biopsy versus a tissue biopsy, and then testing the tissue for non-small cell lung cancer patients?

Dr. Christian Rolfo:

Yeah. In 2019, when we published the first version of this statement, we recommended that time to have a sequential approach. That means when we are using tissue, and we don't have sufficient analysis or sufficient tissue to do the analysis, we can go for liquid biopsy as a second place in case that we are not able to get more tissue. We was using in case that patients have, for example, some biomarkers already discover, identified, and treated with TKIs, using kinase inhibitors for this or these targeted therapies we call and they progress. Liquid biopsy was used as a first approach for discovery, which kind of mechanism-resistance was involved with. In the recent version, we are talking about older approach.

Dr. Christian Rolfo:

Beside the sequential, we are talking about the complementary approach that is opportunity to do liquid and tissue. As you say, was demonstrated in this study Nile, but also in other studies that the complement of liquid biopsy can increase the number of detection or the rate of detections in the patients. Also, it's given a good baseline for later on follow up the patients, because when the patients are on treatment, if we want to see if these biomarkers are having a clearance, so it's a non-detectable during the treatment, you cannot do a biopsy. You need to use liquid biopsy to do that. Also, given the opportunity to do as I said before, a real-time information. There is also the blood-first approach, and that could happen in some patients that unfortunately we don't have any

opportunity to get biopsies. That sounds weird, but it is not uncommon in a clinical practice, because sometimes you don't have at the moment of recurrence or when the patient is having a disease that is really difficult to get with a needle.

Dr. Christian Rolfo:

Liquid biopsy could be a first approach. Obviously, there is something that we need to remember that there are some patients that are [inaudible], so patients that could be not having any detection in liquid biopsy. That is a very minimal situation but could happen. In that patient, we need to have the rebiopsy. It is unfortunately that cases happen, but fortunately are very minimal now with the new technology that we have.

Jerome Madison:

Precision medicine podcasts will continue right after this.

Karan Cushman:

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Jerome Madison:

Lung cancer seems to be outpacing a lot of other cancer types, Dr. Rolfo in its use of NGS testing in broad-based molecular profiling. But the paper also addresses the limitations and the potential of liquid biopsy in what you call non-oncogene addicted non-small cell lung cancer. Can you describe this patient type, and where the opportunities may be for the use of liquid biopsy?

Dr. Christian Rolfo:

Yeah. There are patients, obviously the biomarkers that we are referring that could be the oncogene biomarkers, like EGFR, BRAF, V-RAF, MEF and other biomarkers that have currently read, for example, in drug that have currently a treatment. There are patients that are not falling in this category. We are using in these patients, obviously some other treatments, including chemotherapy, immunotherapy, or the combination of chemotherapy and immunotherapy, or the combination of immunotherapies as well. In this population, liquid biopsy is doing tremendous efforts to try to also find biomarkers to predict the response, and the response rates and the overall survival in these patients. For example, what we are doing in immunotherapy is obviously part of the research. It's not still in the clinical practice, but we are doing for example, dynamics of DNA.

Dr. Christian Rolfo:

Patients that are, like I said before in the baseline, we do a determination. We see the quantity of DNA that is present in this sample and then we see there is a decrease or increase that what we

call dynamics during the treatment. That is an of the response of the patients in some studies. There are also other things that we can do is to calculate the number of mutations. Even if the patient doesn't have mutations that are druggable, we can also have patients who have an important number of mutations, and we calculate this number of mutations that we call tumor mutational burden. This is also object of a study since was applying several studies.

Dr. Christian Rolfo:

Still is not clear the application. There are also opportunities to check in liquid biopsy co-mutations. Some mutations that are not really drug able but can impact in the activity of the drugs. That is all part of the research. We are using this liquid biopsy to try to explain not only the response, but also to explain mechanism resistance, or why patients are not responding even if they have, for example a tissue PD-L1 that is one of the biomarkers that we are using for immunotherapy positive.

Jerome Madison:

Thanks for that. Because patients can be tested for mutations more frequently with liquid biopsy, clinicians have seemed to have a huge wave of genomic data crashing over them more frequently Dr. Rolfo. The IASLC also recommended routine molecular tumor boards to help with the appropriate interpretation of this wave of data. Can you share why that's important?

Dr. Christian Rolfo:

That's a crucial point, I would say because this kind of forum of discussions that are multidisciplinary with experts of different approach of the genomic application in clinical practice, and that includes not only oncologists, but also biologists, genetics nursing counselors. There are a big number of people that is experts in this area with different point of view. We are meeting regularly to discuss case by case and to try to give to the patient the best opportunity to treatment. We are using for that some level of evidence that there are some publications regarding to that.

We are using level of evidence for categorize these alterations in order to give to the patient opportunities or in the standard of care, or even allocating the patients in clinical trials that are available in the region for different patients. This is, I think it's a very important opportunity for patients, but especially for patients, but also for physicians and healthcare team. Because as you say, this is a tsunami of genetic information that we need to have the help of others to understand a little bit better, what we can do with this, how we can interpret that and help the patients. That's the meaning of all this.

Jerome Madison:

Yeah. With you being at a renowned cancer center and being a specialist in lung cancer, you guys have the staff or the expertise in house, but the vast majority of cancer patients in the U.S. are treated in the community. What about community centers who don't have that expertise? How are they to facilitate these molecular tumor boards?

Dr. Christian Rolfo:

Yeah, generally the small centers they can associate with the center of reference for this. We have referral centers and we have here, for example, in tumor boards people that is from other

hospitals or community practice that they can show the case. Also, if there are opportunities within societies for example, ask of the American Society of Clinical Oncology, also offering molecular tumors boards for discussion of patients.

I think it's just the opportunity that we need to try to find, looking for networking. Nowadays is difficult to think that one doctor can give all the answers to the patients because we need a team and that is important to have this discussion. If you are a cancer patient treated in a community hospital, that doesn't mean that your doctor will not be connected with big centers to discuss your case. It's important that we, as a doctor, as a patient as well, try to find if that is happening the cases, because it's really interesting.

Jerome Madison:

Yeah. As we wrap this up, Dr. Rolfo, you've given us so much to think about and there seems to be so much more depth to this specific methodology of testing. Just in these last few minutes, you've given us the ability of circulating tumor cells for genotyping, for non-small cell lung cancer, to be able to track response to therapy, minimal residual disease. We recently had a conversation with LUNGevity, which is a patient advocacy group for lung cancer you may be familiar with. For that group and for a number of other tumors, early detection just seems like the holy grail. In fact, there was a seminal book published in 2010, titled The Emperor of All Maladies by Siddhartha Mukherjee, which earned the Pulitzer prize and is on Time Magazine's top 100 nonfiction books of all time. If you have not heard of it, please go check that out.

Jerome Madison:

But it's an essentially a biography of cancer from the earliest documented understandings of cancers to the conclusion of that book, when it was written in 2000, zeros. The future pointed to state-of-the-art hopes for the future that included The Cancer Genome Atlas and gene-editing technology, which 10 years later, 11 years later we have today. Dr. Rolfo, could the capability of liquid biopsy be the missing link to win the war on cancer? I know I'm reaching there, but what do you think?

Dr. Christian Rolfo:

Yeah. Early detection, obviously, as you say is a big opportunity for cure patients for increased the survival rates of our patients. Liquid biopsy is doing an important advance there in the technology and in the knowledge. We have nowadays some technologies that are in almost in the commerce. It's not still completely approved, but we have, for example, methylation, that is one of the technologies of DNA. Obviously, the percentage patients that we are capturing with these technologies, it's not still 100%. We have still and gaps there that we need to solve. Certainly there are several new technologies, including collaboration with, for example, images. If we are willing to increase the rates of the screening programs, for example, lung cancer. I think in the future methods like radiomics, for example, integrated with a liquid biopsy can be helping these populations to be detected easily.

We don't have still the technology to be in 100% patients, but there is important progress on that. The same has happened with minimal residual disease. That is another big topic when we are doing surgery to patients with early stage. We want to know how these patients with recurrence or when these patients with recurrence liquid biopsy is involved, but in all these studies. Actually, we are waiting for some results of this studies to apply this in a clinical practice in the future. But

I'm really sure and confident that we will have good results in a very short time. Will have opportunity to change this in the near future. That's my hope for this year as well.

Jerome Madison:

Fascinating. Dr. Christian Rolfo. Oh, go ahead.

Karan Cushman:

I was just going to say, we're already set up for part two here.

Dr. Christian Rolfo:

Yeah. I'm happy to do it when you invite me again.

Jerome Madison:

Absolutely.

Karan Cushman:

Great.

Jerome Madison:

If we can fit it into your busy schedule, thank you so much for taking time, Dr. Christian Rolfo, president of the International Society of Liquid Biopsy and associate director of clinical research at the Center for Thoracic Oncology at the Tisch Cancer Institute at Mount Sinai, New York City. Before we get you out of here, for those who want to connect with you on Twitter or your social media, where can they reach you?

Dr. Christian Rolfo:

Yeah. I have my Twitter that is Christian Rolfo. It's easy to find. I have also LinkedIn that is my complete name. It was a pleasure to be here and thank you very much for the invitation.

Jerome Madison:

Absolutely.

Karan Cushman:

Thanks for being with us.

Jerome Madison:

We learned that you're a big opera fan in New York city. The Broadway has been closed down. You have a beautiful voice, Dr. Rolfo, are you the singer at all?

Dr. Christian Rolfo:

No, not at all. I'm enjoying the singers, but I am not.

Karan Cushman:

I know Jerome, I bet Dr. Rolfo's shower has a different answer to that question. Just saying.

Jerome Madison:

We all sound great in the shower.

Dr. Christian Rolfo:

I'm not an opera... An opera lover, but not an opera singer. You're right here in New York, we have a lot of opportunities. Also, you can access to that by virtually now with all this pandemic was also giving the opportunity to get also access with the technology to the art as well and that was a positive thing of all this difficult time.

Jerome Madison:

Yeah, absolutely. Do you have a favorite show that's on Broadway now?

Dr. Christian Rolfo:

Not really. I need to take time for that. I was in the opera recently seeing the magic [inaudible 00:29:24] and was a gorgeous presentation, but I need to have a little more time to Broadway. I hope with this numbers of COVID that are going down in the future when all the people get vaccinated, and we come back to the normal life and enjoying cities like New York.

Jerome Madison:

Absolutely. Dr. Rolfo, we can't thank you enough for taking the time out of your busy schedule to talk to us about the utility and the potential of liquid biopsy. Thank you for being a guest on the Precision Medicine Podcast.

Dr. Christian Rolfo:

Thank you.

Karan Cushman:

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About Our Guest

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Christian Rolfo, MD, PhD, MBA, Dr.hc. is Professor of Medicine (Hematology and Medical Oncology) and Associate Director for Clinical Research in the Center for Thoracic Oncology at The Tisch Cancer Institute. Dr. Rolfo's clinical and research focus is on drug development, lung cancer and other thoracic malignancies, biomarkers, resistant mechanisms discovery, and liquid biopsies. Dr. Rolfo has held academic appointments at numerous institutions, including the University of Cordoba, Argentina; University of Antwerp, Belgium; University of Palermo, Italy, and the University of Maryland and Greenbaum Comprehensive Cancer Center where he was Director of Thoracic Medical Oncology and Director of Early Clinical Trials. Dr. Rolfo earned his MD at the University of Cordoba School of Medicine, his PhD and Doctor Europaeus in Clinical and Experimental Oncology Research at University of Palermo, Italy, and an MBA in Hospital and Health Services Management and Organization at Polytechnic University of Valencia, Spain. He completed residency training in Medical Oncology at the National Cancer Institute in Milan (University of Milan, Italy).

Dr. Rolfo is President of the International Society of Liquid Biopsy (ISLB) and Chair of the Education Committee at the International Association for Study of Lung Cancer (IASLC). Dr. Rolfo served as member of the Drug Approval & First in Human Commission at the Ministry of Health in Belgium during his time as Phase I Director at Antwerp University.

Dr. Rolfo is actively working on drug development and lung cancer and mesothelioma treatment. His research is focused in molecular oncology, targeted therapies and Immunotherapy in thoracic oncology using new techniques in liquid biopsies, specifically in extracellular vesicles and circulating free tumor DNA. His research group identified ALK translocation in exosomes in NSCLC patients, and showed, for the first time, the videos of labeled EVs uptake by living lung cancer cells. He is currently working on the identification of new biomarkers involved in immunotherapy and TKI drug-resistance and early detection of lung cancer with liquid biopsy. Dr. Rolfo has contributed to the development of several compounds including Erlotinib, and the pharmacokinetics of Olaparib, Entrectinib, Selpercatinib, Trastuzumab Duocarmazine, among others.

Dr. Rolfo has authored more than 250 scientific articles, has made several contributions to book chapters, and has served as a book editor. He has published extensively in peer-reviewed journals including *New England Journal of Medicine, Lancet Oncology, Cancer Discovery, Nature Clinical Reviews in Oncology, Journal of Thoracic Oncology, Nature Nanotechnology, Clinical Cancer Research, Annals of Oncology*, and *Lung Cance*r among others. Dr. Rolfo is Editor in Chief of *Critical Review in Oncology Hematology* and Associate Editor at *ESMO Open*.