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Programmed Cell Death Ligand 1-Expressing Circulating Tumor Cells: A New Prognostic Biomarker in Non-Small Cell Lung Cancer

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Léa Sinoquet, William Jacot, Ludovic Gauthier, Stéphane Pouderoux, Marie Viala, Laure Cayrefourcq, Xavier Quantin, and Catherine Alix-Panabières.
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Guest: Dr. Catherine Alix Panabieres and Dr. Xavier Quantin are from the University Medical Center of Montpellier and the University of Montpellier in France.

Bob Barrett: This is a podcast from *Clinical Chemistry* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I'm Bob Barrett. Lung cancer, in particular non-small cell lung cancer, is the leading cause of cancer death worldwide. Blocking the programmed cell death-ligand 1 or PD-L1 interaction with its receptor has revolutionized the treatment of these types of cancers.

Tumor PD-L1 expression is one of the well-established predictive biomarkers of response to therapies. However, more than 50% of patients with high PD-L1 expression in tumors do not benefit from first line monoclonal antibody treatment. That may be due to heterogeneity of PD-L1 expression in the tumor, and also by technical differences in the methods used for its detection.

Circulating tumor cells might better reflect the tumor heterogeneity than tissue biopsies, because they arise from different tumor sites. Furthermore, circulating tumor cells are collected using a minimally invasive method by blood sampling. They can be analyzed longitudinally as liquid biopsies, and might provide information on the different mechanisms of resistance to treatment. However, studies regarding concordance between PD-L1 expression in tumor tissue and in circulating tumor cells are not in complete agreement.

A paper appearing in the November 2021 issue of *Clinical Chemistry* may help to address the question regarding the value of estimating PD-L1 in circulating tumor cells. Two of the authors of that paper join us in this podcast to discuss their latest research. They are Dr. Catherine Alix Panabieres and Dr. Xavier Quantin from the University Medical Center of Montpellier and the University of Montpellier in France.

And we'll start with you Dr. Alix Panabieres just so all of our listeners are on the same page, what exactly is a liquid biopsy?

Alix-Panabieres: A liquid biopsy is a non-invasive blood sample where you can really find, detect, isolate, and characterize tumor derived

circulating biomarkers. Of course, the most known one is the circulating tumor cells, and when we clone the liquid biopsy for the first time with Klaus Pantel in 2010, we really thought about the circulating tumor cell; a single cell that you can find in the blood. Of course, today the liquid biopsy definition is more broad, and you can detect more circulating biomarkers like CT DNA, micro RNAs, exosomes, even the immune cells and so on, and not only from blood but also from other body fluids.

And of course, from this liquid biopsy, you have really complementary information compared to the tissue biopsy. And today, it's important to go in that direction to have like, a precision medicine.

Bob Barrett: What technologies did your group use for circulating tumor cell detection in this clinical trial?

Alix-Panabieres: So, when this clinical trial that we led with Xavier Quantin on the lung cancer has been done with the sensor systems. The only FDA-cleared system in USA. The idea was really to use a robust reproducible technology, and to detect CTC the best way.

Bob Barrett: And how did you measure the expression of PD-L1?

Alix-Panabieres: Well, in the last panel of the sensor system, we have an additional channel where you can include an additional biomarker. And of course, we developed for the first time in 2015 the test to detect a single CTC expressing PD-L1. So, we use this free channel I would say in the sensor system to have the PD-L1 expression. So, it was quite interesting to characterize directly in the cell search the expression of PD-L1.

Bob Barrett: Many scientists and clinicians remain confused about the large numbers of circulating biomarkers in these liquid biopsies. What can you tell us about what you suggest might be the most valuable?

Alix-Panabieres: Yes, excellent question. I would like to say that we need to try to combine these different circulating biomarkers, because one is not better than the others. I would say that we have the opportunity with this blood sample to have on one side the plasma, and on the other side the cellular fraction. So, I would say that depending on the cancer type, we need to define some specific algorithms, and to try to combine the best circulating biomarkers, and in lung cancer, it's really what we propose in the future to try to define what is the best combination: CTCs, CTC PD-L1 plus, plus CT DNA or exosomes, PD-L1 plus, and so on. So very important points, but again, not only one, but I'm sure a combination of different circulating biomarkers.

Bob Barrett: Dr. Quantin, I'd like to bring you into this. What exactly is the current place of immunotherapy in the management of non-small cell lung cancers?

Xavier Quantin: Actually, immunotherapy is very important. It is a big change in the landscape of lung cancer treatment. A few years ago, we begin to use immunotherapy since clinical practice six-year that it's very, very important for us. The recent research shows a doubling median of the world survivors for pembrolizumab for example, against chemotherapy with a five-year insight. However, we need the biomarkers to predict who will respond, or not to the treatment.

Bob Barrett: Are the currently available biomarkers sufficiently reliable to guide the use of immunotherapy?

Xavier Quantin: Until now, there is only one clinically useful biomarker is the expression of PD-L1 on tumor cells. Many biomarkers like tumor burden derivative of neutrophil requisite ratio unlike this level had been correlated with immune checkpoint inhibitor outcomes. However, it never benefits in pre-clinical practice. Moreover, the radiological profile of the tumors may evolve and thus the therapeutic pressure on probably liquid biopsy maybe an interesting way to recreate this evolution.

Bob Barrett: So, what is the clinical relevance of PD-L1 in circulating tumor cells? And what is the impact of studies such as yours in clinical practice?

Xavier Quantin: Our study demonstrated feasibility of the determination of year one studies on CTCs, and there is a program cell diflucan one expression in circulating CTC is a button sure alternative to overcome the problem link to tumor we have seen expressing overall heterogeneity. Our study suggests that the presence of year one CTC associated with outcomes especially advancement for cellular cancer.

However, the study was not designed to demonstrate if the PD-L1 CTCs may predict the response to CPI and could be useful to monitor the response to treatment. It is the next step to our research.

Bob Barrett: We'll finally, let us look ahead, give us a glimpse of where this research is going in the future?

Alix-Panabieres: So, this first clinical trial just showed that that you can really detect CTC PD-L1 plus, and they have a clinical relevance, which is very important. And now with the study, we are leading a new clinical trial in the context of immunotherapy.

So, we are including patients with non-small cell lung cancers, and they will receive immunotherapy, so we will get blood sample before the initiation of the treatment, but also during the follow-up, and it will be crucial information to get the CTC count, but also, the CTC PD-L1 plus expression information.

And of course, we will have also a huge bio bank that we will perform in the context of liquid biopsy on one side, the CTCs, on the other side, the plasma for the exosomes, tumor educated platelets, CT DNA, microRNA and so on. So, we put a lot of hope on this new clinical trial, led in the south of France, Montpellier.

Bob Barrett: That was Dr. Catherine Alix-Panabieres from University of Medical Center of Montpellier and the University of Montpellier in France. She was joined by her colleague, Dr. Xavier Quantin in this podcast on measuring the biomarker programmed cell death-ligand 1 in circulating tumor cells.

Their paper on that topic appears in the November 2021 issue of *Clinical Chemistry.* I am Bob Barrett. Thanks for listening.