Diagnosis and treatment of TRK fusion-positive lung cancer

Brought to you by:
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This NTRK CONNECT programme is supported through an independent educational grant from Bayer. NTRK CONNECT is an initiative of COR2ED

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Caterina Marchió
Welcome everybody, today we are here for this podcast that is going to be covering lung cancer and the detection of *NTRK* gene fusion in lung cancer. I'm welcoming you here on behalf of the NTRK CONNECT group and the podcast will be dealt by a pathologist, I'm the pathologist, and I will be here with a medical oncologist. I'm Caterina Marchiò and I'm a molecular pathologist working at the University of Turin. I work at a cancer Institute, at The Candiolo Cancer Institute in Turin. Today I'm here with Christian Rolfo my co-chair medical oncologist.

Christian Rolfo
Hi Caterina, good afternoon and so I'm Christian Rolfo, I'm a thoracic oncologist at the Center of Thoracic Oncology at Mount Sinai in New York, Icahn School of Medicine and it's a pleasure to discuss today this important topic in lung cancer.

Caterina Marchiò
Good, so I think that here we have the challenge to try to let's say talk a little bit how difficult it is, in our diagnostic practice to identify *NTRK* fusion-positive lung cancer. If I may have a word on this, I would say that it's definitely challenging but not impossible, and I think that in the field of lung cancer, medical oncologists and Christian you are one of the best example of this, I mean medical oncologists in lung cancer are very used to having an eye on the molecular profiling on lung carcinoma so we have seen this for lung

adenocarcinoma but comprehensive profiling is starting to get there. And so, even though *NTRK* gene fusions are rare alterations we have learned these over the past two-three years with a lot of studies, mainly on metastatic cancer patients with the comprehensive genomic profiling, so we got to understand that *NTRK* gene fusion in lung cancer can be detected in a handful, really, of cases.

So when we say rare, I think we need to set the bar and so when I speak about rare alteration for *NTRK* gene fusion lung cancer, I would say really alterations that are found in less than 1% of our population and to be more precise, we would probably set the bar at around 0.3-0.4%.

We need to know, I think, also Christian a little bit about whether there are any clinical pathological correlation that can be useful to identify this fusion and I think that also you participated, to the description of this possible correlation, but we know that really *NTRK* gene fusions can be found in adenocarcinoma, but also in carcinoma of squamous histology and in neuroendocrine carcinoma on the lung so really, we need to think wide in lung cancer.

Christian Rolfo
I think we need to forget a little bit the clinical characteristics of the patients and go for testing everyone so that is something that is still in the brain of several oncologists that we are guided by clinical characteristic but it's time to change that because we don't have guidelines in this specific *NTRK* fusion that is very promiscuous as a gene in fusion partners, I think you raise a good point.

Caterina Marchiò
Yeah and I think that we need to stress once more the fact that *NTRK* gene fusions are an agnostic biomarker and even within lung cancer, they are agnostic with respect to the different histological types, so this is really something that we need to make clear.

We talked about gene fusion, so you know pathologists know a little bit about how to go about gene fusion and lung cancer is a good example, because we have *ALK* translocation, we have *ROS* gene fusions, so I mean we have done a lot of work on that. And we know that we can approach gene fusion at different levels, because you know, gene fusion basically stems from a genetic rearrangement, so you can go about it from a DNA point of view and look for the genetic rearrangement but, of course, then you can look at mRNA levels, so you go to the transcript and you want to see whether the transcript is there. And if the transcript leads to the expression of our functional protein then you can really use the methods that go to the section, so immunohistochemistry.

So we know that we have different ways of going about it. So I don't know about your experience with your pathologists, but I guess that you know in lung cancer one option would be to think about a molecular profiling, because this could be advantageous in this specific set. But we have kind of recommendations that have been drafted over the past

years, so there are many kinds of algorithms that have tried to, you know, to define a strategy in this context, what do you think about it?

Christian Rolfo
I think, is really important. So obviously we are talking today about different countries realities. So, in some countries immunohistochemistry could be a kind of a screening factor, and that is important, but we need to also recommend it to these people that they need to continue with another technique to confirm that.

In our reality in the United States we are trying to do in all the patients the next generation sequencing, because in that case you're able to capture the majority, not only of these fusions but also the co-mutations that we can see across of evolution of the disease. So it's costly but it's cost effective, that is the reality.

Caterina Marchiò
Yeah well, let's try to get a kind of sum up of this point because you've raised two very important points, you know, the differences across countries which are very important. And also the fact that one technique, which is NGS, so that you can get more out of just *NTRK* gene fusions that could be also very relevant for defining the good treatment for each patient. So if you look at their algorithm and we are talking about those tumours in which you have *NTRK* gene fusion with low frequency.

The algorithm suggests to go let's say to look for a molecular approach if you already have set that in place at your institution, and this would let's say go to NGS as you were saying. And, of course, if you have a molecular platform at your institution, it would be wise to just, you know, say double check that the panel, the target of panel that you've chosen is actually picking up *NTRK* gene fusions with the good sensitivity and specificity and go for it. Because, as you were saying, and this is a very important point on the top of *NTRK* gene fusion we would also detect all the other genetic alterations that may be relevant for the patient.

But, of course, if you don't have this option, *NTRK* gene fusion detection can be approached by another method that is screening with immunohistochemistry and then, very importantly, as you were saying always confirming at the molecular level, whether the fusion is present or not in all cases that have been scored as positive by the pathologist.

Christian Rolfo
Some of the cases that are using some PCR or technologies as well need to be confirmed, so this is important because sometimes I see some confusion and that's I want to ask you as a pathologist is what is your opinion, because sometimes oncologists I saw recently against that they are confusing PCR positive that is really not confirming this.

Caterina Marchiò
Yeah well let's say that a PCR test has a limited reference range by definition. So I mean the PCR has the problem that you have to design a specific primer first of all, you always look

with the PCR at something that is known. So it's a test that can be used, but with a lot of you know, with a pinch of salt, you need to be very careful in screening with the PCR test.

And one thing that in the diagnostic setting is still a little bit unknown, I think, is the approach by liquid biopsy. When we drafted, for instance, that recommendation, we had very little information, actually no information about studies addressing *NTRK* gene fusion by liquid biopsy but I know that you have done a lot of work so it would be very beneficial, I think, for our audience to know a little bit more about it.

Christian Rolfo
Yeah, liquid biopsy obviously is a great tool for not only for the detection, but also for the monitoring of patients in general with target therapies. So we did an experiment on 39 patients, that is, obviously, we know that this is very difficult to collect this kind of patients in a trial, we did an experiment on 39 patients including nine different diseases and, at the time that we collected the samples, and the results, it was only *NTRK1* fusions available for liquid biopsy. And why is that? Because as you say, *NTRK* is treating with different fusion so it's very difficult to get a methodology that is covering all the fusion possibilities with a deeper coverage in only one test. So nowadays we have these technologies, and that is recently. But there are not still larger studies focusing on that. So what we saw in this series of cases that we published recently in British Journal of Cancer is that the concordance was very high actually 88% of the patients who have tissue confirm that were fine in the liquid biopsy so is a really a big concordance. And we also were able not only to that identify the fusions, but also the mutations in mechanism of resistance in some patients and actually some of the cases were really, I would say were very good for education, for example, EGFR patients with *NTRK* fusions during the course of their resistance were found. So it's really interesting to see how we can apply these, and me and you, we will work together in a liquid biopsy project that we will launch for this kind of answer these questions that are very really important not only for the detection, but also as I say, monitoring and see how the allelic fraction variation and the dynamics is reducing during time and that will be a surrogate like another target of progression free survival and overall survival. We need to know a lot about co-mutations as well and liquid biopsy could be in a good tool for understanding clonal evolution of these patients.

Caterina Marchiò
Yes, definitely, we need to push this forward and to get more data about it because I think it would be really relevant for medical oncologist to know how they can use this strategy for, as you were saying for monitoring.

Good. So after we have put a lot of effort on, you know, finding the right way to address the diagnostic issue, I think, especially pathologists really need to know how impressive are the results of the studies. When I see the results, I really feel that I am contributing a lot to the success of this therapy for this patient, so I do think that this is a team work and once we have signed out a case as positive, we know you will talk us through how impressive these could be for the single patient.

Christian Rolfo
Yeah actually I think this is a very nice example how precision oncology or personalised medicine can arrive in these specific alterations we have several drugs, very good news for patients that are having these alterations.

The first two drugs that we know in this setting are larotrectinib and entrectinib, and both of the drugs are showing impressive results in these kinds of tumours. I will say tumours because it's across different tumours and across adult and paediatric patients. And also a very important activity of these drugs was demonstrated in the brain, so that they are able to cross the hematoencephalic barrier perfectly. And, in some cases, even with primary tumours in the brain they're able to have a very good response. Was impressive also to see in kids, for example, in the paediatric oncology, that the reduction of the mutilating surgeries in some patients was achieved with these drugs, and that is, a very good news and we need to continue with that.

So we have in the setting of lung cancer obviously the frequency, as you say, in these diseases is limited, but when we find these kind of patients, we need to treat with this kind of inhibitor because the responses are very good and actually larotrectinib shows an important activity in brain and recently in a presentation in World Lung Cancer with the data of larotrectinib showed that there was important activity, not only in the systemic but in the brain with overall response rate in general, around 87% so even complete response included, and what is impressive on these two drugs, especially in the data that they presented on larotrectinib it's confirmed that the median time to response is very short, so the patients are starting to respond in a very short time, so after 1.8 months they're starting to have activity of these drugs in reduction. And obviously it's an impact in progression free survival and overall survival, that is there. The other drug that is entrectinib, entrectinib has an interesting history behind. It was designed especially for the brain. And the activity in the brain is also important in this drug. The data presented in ESMO this year confirms that the response rates are high, including in lung cancer in these 22 patients included the cohort were responding in a very well way and actually the response rates in these patients are 63 or 64% of the patients with a duration of response of around 20 months. So, it's impressive results and also we're confirming the activity in the brain with an intracranial response rate that is around 60%. And that's more or less the news for these two drugs that I think is very important.
Obviously, we need to discuss about toxicity that is something important and several of the toxicities that we see in these patients are related to the physiological activity of *NTRK*. So *NTRK* is involved in proprioception, in weight control so when we are blocking *NTRK*, we have some of these alterations, so patients that are increasing the weight, patients that are also having some psychiatric response or difficulties that could be also seen and also importantly to remember that these patients can also have some other toxicities like muscular pain, myalgia, constipation, diarrhoea could be also important, increase of liver enzymes and that is more or less the relevant, but the majority of the toxicities are grade one or minimal grade two and grade three so it's really well tolerated.

Caterina Marchiò
Good, so you have spoken mostly about the first generation TRK inhibitors right. So do we have any interesting data that we should talk about the second generation TRK inhibitors?

Christian Rolfo
Yeah there are new drugs coming, and one of the drugs that was in development for a long time is selitrectinib, that is called LOXO-195, and this is also an inhibitor for the TRK. Actually there are clinical trials confirming activity in the brain in the preclinical. There are also other drugs coming, like repotrectinib. Reprotrectinib showed already activity in TRK *in vitro* and *in vivo* and there are several trials, now there is the TRIDENT trial that there are some preliminary data of this. And also this drug is not only an *NTRK* fusion inhibitor but it's also a *ROS-1* inhibitor like in the case of entrectinib. That's the difference, for example, with larotrectinib that is only a TRK inhibitor. And there are new compounds like taletrectinib that is in Phase one. Actually, we saw some results in these patients as well, and this is also a trial that is including metastatic patients with different tumour types. So it's really brilliant, I will say the research in this field, and we will have several other new drugs coming in, and obviously we will have questions about sequence, what we need to use first, what combinations, are these patients responding later on to immunotherapy or not? We don't know that so there are different things that we need to discuss and see in time. It's very important that when we have patients and we discover even in them mechanisms of resistance we are addressing them properly and also notifying or trying to make a publication because it's very important that we learn from every case, because this is a very rare disease.

Caterina Marchiò
Well. These are always impressive data, you know when we talk about TRK inhibition I'm always impressed, and if I have to, you know, to take something back home for pathologists, I would just say that I would like to be part of this, you know, this new way of dealing with targeted therapies and this new pathology that we are witnessing, I think we are really experiencing a new era for pathologists, that is really much closer to patients than it was before, so that would be my take home message for pathologists I would say. What would be your take on it for oncologists?

Christian Rolfo
I will say that, first of all, we have options for patients and we need to serve to the patient, and we want to find the patients. So, my message is test your patients doing the proper tests to try to accomplish that. If you don't have in your institution the possibility to do that, you can contact always a centre of reference that they can do that. But if you are entering in this pathway for a patient you can change completely the reality of that patient. So it's really important and we saw it's not only lung cancer so it's important that we test several of these patients.

Caterina Marchiò
Right, I totally agree, I think that our expertise as pathologists as you were saying, if we do not have the ability to do it ourselves, our expertise about knowing about *NTRK* gene fusion is also to address to the right lab, so that's a very important message overall.

Christian Rolfo
And we need to have a very good communication between pathologists and oncologists to make this a team to work together in these patients.

Caterina Marchiò
Absolutely. Well, good. So what do you think Christian, I hope that the lung podcast that we are managing is going to be useful for our colleagues and from my side I would like to thank you for this nice conversation.