Video Podcast transcript

BRAF-mutated NSCLC: Testing to treatment of *BRAF*-mutant metastatic NSCLC

Brought to you by;
Prof. David Planchard, Gustave Roussy, France
Dr Federico Cappuzzo, National Cancer Institute Regina Elena, Italy

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Dr Federico Cappuzzo
Dear colleagues, on behalf of LUNG CONNECT it's a great pleasure to introduce this podcast on testing to treatment of *BRAF*-mutant metastatic non-small cell lung cancer.

My name is Federico Cappuzzo. I'm the Director of Medical Oncology at the National Cancer Institute Regina Elena in Rome, Italy.

And today I'll discuss this topic together with a friend and a great expert in the field of lung cancer, David Planchard.

So, David, please.

Prof. David Planchard

Thank you, Federico. It's a pleasure to be on this podcast with you and have this discussion on *BRAF* non-small cell lung cancer.

So, I'm a Thoracic Oncologist, I'm leading the thoracic committee at Gustave Roussy in France and mainly employed in early phase, phase 1, but also phase 2 and phase 3 trials in non-small cell lung cancer.

Thanks so much Federico and happy to be with you today.

Dr Federico Cappuzzo
So, the topic we are discussing today is very, very exciting because we have new options and new therapies for a molecular event, *BRAF*-mutation that is present in approximately 1 to 2% of patients with non-small cell lung cancer.

Now, we know that these patients present some specific characteristics. In general, we are talking about a never smoker, a female with an aggressive histological type and we have a different option and also different controversy in the treatment because formerly *BRAF*-mutant patients were included in all trials with chemoimmunotherapy.

So chemoimmunotherapy for some people is considered also an option in frontline setting. But we have a target therapy showing probably higher efficacy than chemo in chemoimmunotherapy.

So, David, which *BRAF*-mutations are we testing for and how and when are you testing your patients?

Prof. David Planchard
This is something important and I think and nowadays we have different *BRAF*-mutations. The most important is to identify what we call the *BRAF* class I mutation, which are the *BRAF* V600E. So that means located on amino acid position 600 and this activity, it's clearly an oncogenic driver alteration in non-small cell lung cancer but also in other tumour types. So this mutation is located on exon 15 of the *BRAF* gene.

On the other side we have other mutations of *BRAF*, what we call the class II. They have, generally, a lower kinase activity and we have the class III which generally have low kinase activity or no kinase activity.

So, the deal is to identify the class I *BRAF* V600E, we have different ways to identify this mutation. The most simple is to look by immunohistochemistry. We have some specific antibody that can identify this population. But clearly, it's not the recommendation, because you will identify only the *BRAF* V600 mutation. You will not identify the other mutations. And clearly you are not looking to the other molecular alterations in non-small cell lung cancer. After, you have the PCR which is probably one of the recommendations.

But same for the PCR, depending on which PCR you use, you will particularly focus on the *BRAF*. You can look on the *EGFR*, you can look on the *KRAS*, but generally you don't look and have a whole picture of the non-small cell lung cancer molecular

alterations. And finally, you may lose time, you may lose tissue, and so nowadays, and I think we can have discussion, and this is to look by next generation sequencing, DNA sequencing, RNA sequencing, for which you will focus on the *BRAF* V600E mutation, but also on the other types of *BRAF* mutation, which are also important because we can discuss the strategy in the non-classical mutation and there is new *BRAF* inhibitor ongoing in clinical trial. And also you will look at the co-mutation that might be important. And you will look also the other types of actionable genomic alterations to have the best decision upfront for this population.

Tissue? Yes, this is the standard of care. You can think about the liquid {biopsy}. And more and more we are looking also for the *BRAF* mutation on the liquid and clearly sensitivity, specificity are becoming better. Just keep in mind that sensitivity is not completely perfect. And by using liquid biopsy, you might lose around 30% of patients for which you will not capture ctDNA. So, the recommendation for me is tissue next generation sequencing. Liquid biopsy might help, particularly if you don't have any sufficient tissue biopsy at baseline. And sometimes if you can, you can do both. And clearly you will improve the probability to capture this population with a *BRAF*-mutation.

So upfront for sure, I don't know, Federico, what are you doing in clinical practice? Are you doing this mutation NGS testing panel for all patients at baseline with non-small cell lung cancer?

Dr Federico Cappuzzo
Yes, absolutely. This is what we are doing.

I mean, we offer NGS testing to all our patients and we test not only the metastatic patients. We test all patients the first time that we see the patient in the clinic, regardless of the stage, regardless also of histology. So, this is what we are doing routinely in our center. Fortunately, we are a reference center for the entire region here in Italy. So, we have all the facility support for performing a very extensive NGS panel in all of our patients.

I think that NGS is now the gold standard for testing, because we have so many genes that we need to assess in lung cancer that we cannot perform a test gene by gene. It is absolutely not convenient from the economical point of view, but also is, we waste a lot of time and tissue for performing the test, so NGS is much more useful. And it is important, of course, to test the patient as soon as possible. Because once we need to treat the patients, we need to understand exactly what are the characteristics of the patient. So, if we don't know exactly what is the profile, the molecular profile of the patients, there is a risk that we cannot guarantee to the patient the best approach. And now, for these patients, we know that we have targeted therapies that we can offer specifically in the field of *BRAF* inhibitors, we have different clinical trials. David was the person running the majority of these clinical trials.

The first agents that we used were dabrafenib or vemurafenib, so, what we can call first generation *BRAF* inhibitors, and these are agents that showed efficacy in the field of *BRAF* mutant, even if the combo {combination} with other agents is much more effective. But with a single agent we still have a signal of efficacy, and also an

acceptable toxicity profile. Also, with this approach, of course, the problem is that the response rate was limited to a fraction of patients and quickly mechanism of resistance could occur.

So, David, I think that, by using a single agent, probably we understood that *BRAF* is an important target. But of course, we absolutely need to improve the results. So, you are the person running the majority of clinical trials. So, in which way was the research moving towards overcoming the problem of resistance?

Prof. David Planchard
It's particularly for this *BRAF* population and particularly cell lines with *BRAF* mutation. This is the first time for which we are able to anticipate potentially the mechanism of resistance. Because what we learned if you block *BRAF,* you have a quick activation of the downstream pathway and particularly MEK and HER activation. And so that's why the next stage was to make a combination of *BRAF* inhibitors in combination with specific MEK1 and MEK2 inhibitor like trametinib or binimetinib to anticipate finally the resistance. And this is what has been shown in different phase 2 trials.

The first combination that had been tested was dabrafenib and trametinib in these populations, first-line or previously treated. We have around 65% response rate, median PFS around 11 months. So, you nearly double the response rate, and also, in terms of progression free survival, when you start upfront with the combination dabrafenib + trametinib.

We have nowadays a new combination with encorafenib and binimetinib. Two nice trials, a US trial, the PHAROS trial and the French trial, the ENCO-BRAF (IFCT-1904) trial. And this trial also showed particularly really nice data in first-line of treatment with the response rate of 65 to 75%. And in terms of median progression free survival in the PHAROS trial, median progression free survival reached 30 months, which is really impressive in first-line for this population. So clearly nowadays, this is a standard of care. And this is in all the guidelines, NCCN guidelines – recommendation, ESMO guidelines – recommendation to start upfront dabrafenib + trametinib or encorafenib + binimetinib are highly efficient. After safety issue, I would say generally tolerability are quite fine. Most predominant toxicity is the digestive toxicity in terms of nausea, vomiting and some diarrhoea, around 50% for the dabrafenib + trametinib, around 30% for encorafenib + binimetinib. You have some asthenia, you have some retinal toxicity you have to follow, particularly with encorafenib + binimetinib, and particularly of interest for the patient, pyrexia. Pyrexia in nearly 50% of patients have been observed with dabrafenib + trametinib, which can have a consequence for the quality of life for the patient and this pyrexia is not found or is really exceptional with encorafenib + binimetinib. That might probably favour this combination in terms of tolerability.

And the last thing and something important in characteristics of all the patients that have been included in this trial with the *BRAF* V600E mutation, it was mainly adenocarcinoma. And you have only one third of patients, never smoker. And two thirds of patients were current or former smoker. You can find a *BRAF* mutation whatever the smoking history which increases the way we need to test all the patients that we had discussed previously.

So, the next step, probably we have these two combinations. Any recommendations for you, Federico, finally, which treatment and what might be your practice tomorrow for this population with the *BRAF* V600E mutation in first-line?

Dr Federico Cappuzzo
Well, this is of course a very, I can say, difficult question because clearly we have two combinations that we can use, dabrafenib + trametinib or encorafenib + binimetinib, and these two combinations certainly are effective. There are some small differences in terms of the toxicity profile. Honestly, I think that the data presented this year were very impressive for the combination encorafenib + binimetinib. These are probably the best data that we have in the field of *BRAF* mutant. Of course, we don't have a formally any clinical trial comparing these two combinations with dabrafenib + trametinib, so, we can not conclude that one, based on the evidence, based on clinical data, that one combination is better than the other one, but certainly the data with encorafenib + binimetinib are, at the present, the best data ever presented in the field of *BRAF* mutant non-small cell lung cancer. So, based on the current evidence this is the combination for which we have much more evidence of efficacy.

Prof. David Planchard
I totally agree. We've never had any head-to-head comparisons. So, I think both options will be the recommendation. Clearly the fact we have this quite impressive PFS first-line with encorafenib + binimetinib clearly push for this combination, and the fact also to not have this pyrexia that might impact the quality of life of the patient is also clearly probably in favour of this combination. So, hope to get access quickly for this combination, particularly in Europe, for example, for our patients in first-line of treatment. And just keep in mind, it's only currently for the patient with a classical mutation, class I, the *BRAF* V600E mutation. But the other type of *BRAF* mutation currently it's still research, and generally this combination have a low activity and particular generally no activity for the class III. They might have some activity for the class II. But we need to discuss, case by case, particularly in a molecular tumour board.

Dr Federico Cappuzzo
So, David, in some way, do you select patients to one therapy, to the other one. There is some selection you are doing? And what do you offer at the time of failure? Because unfortunately, these patients at some point develop resistance.

Prof. David Planchard
This is what we try to look. So that mean probably the fact, not only to look at the *BRAF* mutation but also all these co-mutations because we perform large NGS. So, testing for all the patient DNA sequencing, RNA sequencing. We'll try to identify if we can have a better selection of the patient depending on the co-mutation. Can we anticipate which combo {combination} is better for which patient? So, I think this is still in research and particularly the next step. What are the mechanism of resistance for this combination? Does the mechanism of resistance differ between dabrafenib + trametinib and encorafenib + binimetinib? It's one of the questions.

So that's why we need to re-biopsy the patients, liquid biopsy, tissue biopsy to better understand and probably hope in the near future to have new recommendations and probably better selection for this population. And the real question is what to do, and as you asked, what to do when the patient progresses on targeted treatment? Nowadays we don't have a new generation of *BRAF* inhibitors. We don't understand exactly the mechanism of escape. It's quite complex. We have some *MEK* mutation, *HER* mutation, *NRAS* mutation, *PIK3CA* activation, also it's really complex for the *BRAF* when to escape to this double inhibition in first-line.

So, I would say nowadays the standard of care should be some chemotherapy plus immunotherapy. So, this is what we do and this population might respond, particularly to the combo {combination} and particularly when you have a patient with this mutation who is a former or current smoker patient. And this is what has been shown. If you have a smoking history, *BRAF* mutation, you may have a better efficiency of immune treatment. I would be prudent. I would probably not treat this patient with immunotherapy monotherapy, despite that there might be, in a lot of cases, i.e. PD-L1 positive. So, I would keep the chemotherapy and immunotherapy as we do for the other molecular alteration because generally they might fail with immunotherapy monotherapy. So, probably best combination chemotherapy plus immunotherapy in second-line of treatment in case of disease progression. And of course, I will always try to push for new tissue biopsy to try to identify any mechanism of resistance, to try to better adapt the treatment in this population.

Dr Federico Cappuzzo
So, David, we routinely perform NGS testing in our patients. Sometimes we detect the mutation, the primary driver, but also, we detect the co-mutations. You already, discussed a little bit about co-mutations. So, I think there is a huge difference if we detect another potential driver, for example, a *BRAF* mutation together with, I don't know, a *KRAS* G12C mutation, or it's completely different if we detect a *BRAF* mutation together with a co-mutation, but for which the role as a driver is not really established, for example, a *TP53* mutation, or some other mutation.

So, what is your approach? What are the implications for you? I mean, if you detect that at the same time, it's very rare, *BRAF* and *KRAS*. Honestly, I don't remember any of my cases, but potentially could happen. So, what is the option that you can offer to a patient in which you have a *BRAF* mutation together with another potential driver? And what are the implications if you detect, for example, a *TP53* mutation that is much more frequent?

Prof. David Planchard
I would say probably the more we are performing large NGS testing, the more we are identifying this population, so some co-mutations where we don't know exactly what to do. And this is something that have been done in the PHAROS trial. They have detected quite a lot of co-mutations, but that does not seem to change the response to encorafenib + binimetinib.

In my experience, and with dabrafenib + trametinib we had some patient with *NRAS* mutation or *PIK3CA* mutation and these population have the shorter duration of response to the combination. So, probably I might anticipate that some co-mutations might have some bypass pathway, co-activation or downstream pathway activation.

And probably in this case, we might be much more prudent in these patients because they might have a shorter duration of response. So, this is something we try to look at. And probably we might imagine in the future if you have another *KRAS* mutation, or in some patients sometimes you have some uncommon *EGFR* mutations or something like this, why not to make a combination to triple inhibition for *BRAF* or *NRAS* in combination with a *BRAF* and MEK inhibitor? That might be something that could be discussed. But I would say nowadays in clinical practice, there is no specific recommendation. But we need to learn about this population.

Dr Federico Cappuzzo
I totally agree. Sometimes when we detect the co-mutation its important, exactly to understand what are the options that we can offer and what is the best strategy? I totally agree that in any case, presence of a co-mutation represents a complication.

Prof. David Planchard
Exactly a more intelligent disease. If you have only the *BRAF* you are quite confident, and generally this patient will have a really prolonged duration of response. And in case of multiple co-mutations, be prudent because this patient may have a shorter duration of response. So probably perform more regularly CT scan evaluation to be sure that the patient will not have an early relapse with the targeted treatment.

Dr Federico Cappuzzo
So, we are at the end of this very, very nice discussion, David. So today David and I have had a great discussion exploring *BRAF* mutant metastatic non-small cell lung cancer. We have considered its significance, the testing method and the current treatment strategy.

I think that the most important messages that we have from this podcast are that clearly, we need to test all patients with the non-small cell lung cancer, regardless of the stage or regardless of the histology, because it is extremely important to detect all patients with a molecular event for offering an important therapy that has clearly an impact in terms of duration and quality of life. If we avoid chemotherapy to our patient, this is something that our patients are certainly they want, they ask. So, it's important also to use a test. Next generation sequencing is certainly the gold standard for ensuring that all patients are properly tested and is the best way in which we can detect all cases and importantly, the way in which we don't miss any of our patients and we know that we have discussed with David today, that we have important therapies available, and particularly the combination of a BRAF and MEK inhibitors represented the best option we can offer today in frontline setting for treating *BRAF* mutant, specifically the V600E mutant metastatic non-small cell lung cancer and also the toxicity profile of this combination is certainly acceptable.

I think we are at the end, I don't know, David, if you have any other final considerations for this discussion today?

Prof. David Planchard
So, we completely changed the landscape of the non-small cell lung cancer by testing. So clearly, we need to test all the patients, whatever the histological type, whatever the smoking history. Tissue testing, liquid biopsy. The more we are testing

the more we identify specific oncology driver alterations, including the *BRAF* and clearly, we change the prognostic of this patient because nowadays, I would say we have quite magic targeted treatment, particularly with this combination. Don't waste time. Upfront testing. I completely agree, NGS. And after try to identify this population to be the right population for the right treatment and we improve the PFS, we improve the OS. And that might be completely a magic answer.
Really happy to have these discussions with you, Federico.

Dr Federico Cappuzzo
Thank you again, David. And thanks to our listeners. And of course, we hope you have found our discussion useful today.

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