Podcast transcript
BRAF-mutated colorectal cancer (CRC): testing to treatment

Brought to you by;
Prof. Sebastian Stintzing, Charité Universitaetsmedizin, Berlin, Germany
Dr Thomas Winder, University Teaching Hospital Feldkirch, Austria

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Prof. Sebastian Stintzing
Dear colleagues, welcome to the podcast, testing to treatment of *BRAF* V600E mutant colorectal cancer.

My name is Sebastian Stintzing. I'm a Medical Oncologist from Charité in Berlin and I'm discussing within this podcast important topics, important issues for *BRAF* V600E mutant metastatic colorectal cancer, together with my dear friend Thomas Winder from Austria.

Dr Thomas Winder
Thank you Sebastian, it's a pleasure to join you on this podcast. I'm Thomas Winder, I'm a Medical Oncologist. I'm heading the Department of Hematology and Oncology at the University Teaching Hospital in Feldkirch in Austria. And today, I'm particularly interested in discussing with you the *BRAF* V600E mutant metastatic colorectal cancer and the individualised treatment of these patients. Because I'm also heading the Swiss Tumour Molecular Institute in Zurich, Switzerland.

Prof. Sebastian Stintzing
When we talk about metastatic, when we talk about colorectal cancer, I think we know that this is not a homogeneous disease anymore. It's a heterogeneous disease which you could, you know, subdivide in many, many subpopulations.
But I think when we look into our guidelines, the most important, subtypes of colorectal cancer are of course, the MSI-high, and the MSS. And within the MSS, the *BRAF* V600E mutant, which are a fraction of around about 8 maybe 10% of all metastatic colorectal cancer population. And then of course we have the *RAS* mutant population. Basically, a summary of different *RAS* mutations in the *KRAS* and *NRAS* exons.

So when we look into those three most important subpopulations of colorectal cancer, I think it becomes clear that the worse prognoses have those patients having a tumour bearing a *BRAF* V600E mutation. And when we look into older data, retrospective data, it came clear that for the *BRAF* mutated colorectal cancer population, the median overall survival is probably not exceeding 12 months, which is, I think, really frightening. Because when we look into the double wildtype population, so patients without a *RAS* mutation and without a *BRAF* mutation, we are talking more about like 3 years so 36 months of median overall survival.

And so I think it's quite important having this prognostic data that we start testing or that we test our colorectal cancer patients as soon as possible or as early as possible, because even in stage two and stage three disease, so localised or localised advanced colorectal cancer, those having a *BRAF* V600E mutant cancer have a higher risk of recurrence.
And, I think saying this and looking into our data so far, it really was important that we got the data on the BEACON trial. The BEACON trial was the first trial testing the *BRAF* inhibitor encorafenib together with the EGFR antibody cetuximab and one of the three arms, at least, was also adding binimetinib, a MEK inhibitor to this treatment.

And this was basically compared against a standard of care arm, and I think the data we have seen there was important to understand that we are able to target *BRAF* mutations in a very efficacious way and that we are also able to prolong survival for this worst prognostic subgroup. And we know overall survival was somewhere at nine, nine and a half months, which is good of course,and this was basically almost doubling the overall survival for those patients that were treated with standard of care treatment. And this was a large phase three study, as you know, and those three arms were quite interesting. And Thomas, as you're also, as you said before, specialising on the Molecular Tumour Board and interactions of the different inhibitors, what was the reason to test also the MEK inhibitor, so the triplet and the doublet, and do you see differences in the outcome data? And do you see patients that you may or may not want to treat with the MEK inhibitor?

Dr Thomas Winder
I think that's a very important question, Sebastian. So we have seen in the retrospective data and in the BEACON trial that we may have patient cohort at high risk of progression or recurrence, and we can maybe, dissect this group a little bit. So, one part of this group is a group with a high tumour burden defined as three or more sites were involved. Then we have the patients who have the elevated inflammation. And with respect to the CMS subgroups, maybe the CMS subgroup four is a group who might benefit from the triplet

combination. So the triplet, as you are all aware, is not approved, at least in the EU. If we go a little bit deeper in the genetic backup of these patients, we have seen the patients with high allele frequency of *BRAF* V600E mutations. They may also benefit from more intensive treatment because they have a very, very poor prognosis. And another marker who might help us in defining this high risk population could be the RNF43 mutation. RNF43 is connected to the Wnt signaling pathway. And, this is also a population who might benefit on a triplet combination treatment.

Prof. Sebastian Stintzing
Talking about triplet versus doublet, do you see a difference like in toxicity?

Dr Thomas Winder
Yes. I think that's an important point. We have seen more toxicity in this patient cohort with the triplet combination, but we have not seen more efficacy regarding overall survival and progression free survival. Maybe with regard to response, we see a little bit more efficacy, but not in overall survival and progression free survival. And the toxicity is more because of the MEK inhibition. And therefore I think this is just for the subgroup I tried to define previously.

Prof. Sebastian Stintzing
As I said before, a *BRAF* mutation is not only in the metastatic setting, but also in the adjuvant setting a worse prognostic or bad prognostic factor. Then into the BEACON study was a second-line trial of course. So today we are using FOLFOX, FOLFIRI or FOLFOXIRI in first-line. So what is your choice? I mean, we have the initial data of the TRIBE saying, giving us some data that FOLFOXIRI so the triplet plus bevacizumab may be the best treatment of choice for those patients, but what are your thoughts?

Dr Thomas Winder
So, since the TRIBE trial we have seen a meta-analysis from Chiara Cremolini which showed that patients may not have the best benefit from the triplet chemotherapy combination plus bevacizumab. They have more toxicity but the efficacy is maybe the same. And in 2022, we have seen a European consortium, who presented the data as well at ESMO showing the same picture. So, there is right now, as far as I can say, no point for the triplet chemotherapy plus bevacizumab, for this patient cohort, because of toxicity and efficacy, I think the best we can do for them in first-line today is the doublet plus bevacizumab. But we are looking forward to targeted treatment combined with chemotherapy in first-line. Hopefully soon.

Prof. Sebastian Stintzing
Absolutely. What was your doublet of choice for those patients, either FOLFIRI or FOLFOX?

Dr Thomas Winder
FOLFOX.

Prof. Sebastian Stintzing
Yeah. Me too. Absolutely. I also think the data we had seen in in the TRIBE2 study, which was basically a FOLFOX backbone, also I think are very convincing that probably FOLFOX is

the right choice there. We have talked a lot about the *BRAF* mutation and the prognostic impact. When do you test? And when we look into the test systems that are available. I mean, starting from immunohistochemistry, going up to comprehensive NGS profiling of the tumour. So just, when I asked my pathologist, my molecular pathologist, what should I expect? What kind of testing system do you prefer, or do you think would be seen as standard of care?

Dr Thomas Winder
So I would dissect this question into three parts. So when to test, what to test and how to test. And I think when to test, we should test as early as possible. You mentioned the data in the early-stage, stage three where we see that *BRAF* mutants and microsatellite stable, they have a very, very poor prognosis. So far we do not have the data for targeted treatment in early-stage setting, but we know that they have a poor prognosis and maybe they need an earlier follow up. So that could be the reason for early testing. But that's not in daily clinical practice so far. In the metastatic setting, I think we need to test upfront. In Europe we have a good testing rate of about 90%, but that's not the usual case. So we need to test, that's the first statement. And then if we need to test, I think sequencing out of tissue is the gold standard so far. If we have no tissue available then liquid biopsy and *BRAF* sequencing has a high concordance rate with tissue, and that's another additional option. When we are discussing about immunohistochemistry, and that's always a point because in melanoma they did they did at the beginning immunohistochemistry. That's not proven for colorectal cancer. So I think immunohistochemistry is no option for patients with metastatic colorectal cancer because of different antibodies used, heterogeneous staining. And with the sequencing we get the yes and the no answer and therefore for me sequencing is gold standard in the metastatic setting, an NGS where we have multiple molecular alterations and microsatellite or mismatch repair deficiency. We can maybe have two molecular alterations and then we can identify these patients.

Prof. Sebastian Stintzing
I think talking about sequencing, I mean, you know, you start basically with Sanger sequencing, which has sensitivity that is probably not good enough, or for me, actually, I would say it's probably not good enough. But then, of course, you can do nested PCR and so on. And I think today most of the pathologists have at least a more specific, more sensitive, *BRAF* mutation analysis. So sequencing, I think it's really important. What I would also like to see is basically, how good was the DNA extraction out of FFPE tissue? Also, what was the tumour fraction versus the normal fraction of cells? I think that's it's also important. So I think within the pathologic report, we really should have some of those quality parameters knowing, okay, there really was tumour on the slide that they investigated. And then you get a good result in the end to really be sure. But sequencing, as we all know, I mean, I know that you have been doing sequencing a lot, me too, we all know we are not only looking into the V600E. So you have, you know, some nucleotides before or some after this. I had also seen and I think many of us have seen those reports where maybe in *BRAF* 598 mutation or 601 was reported. What should the oncology make out of this information, is this valid information? Do we need this? And what are you doing with those patients?

Dr Thomas Winder
That's a point that you should take from this podcast. We have three classes of *BRAF* mutations. So not just the V600E, but the V600E is the most important for us at the moment in daily clinical practice. Why are we differentiating these three classes of mutation? Because they go with a different activation of the tyrosine kinase. And so far we know that the *BRAF* V600E mutation has the poorest prognosis and response to targeted treatment. For the non-*BRAF* V600E mutations, we know that they have pretty much the same prognosis as the *BRAF* wildtype and we have no targeted treatment so far. So therefore we need to identify the *BRAF* V600E patients, to get them early on the targeted treatment. So that's a very important point we need to keep in mind when we get the reports back from the molecular pathologist, to interpret these results correctly and draw the conclusion, which are patients for the targeted treatment, and which are the patients for the standard of care.

Prof. Sebastian Stintzing
Yeah, absolutely. And talking a little bit more about testing. In the beginning we talked, you know, we need to MSI-high, MSS. We need *RAS* and *BRAF* mutations. We know that *RAS* and *BRAF* V600E mutations are usually mutually exclusive.
But what about microsatellite instability? So MSI-high tumours or mismatch repair deficient tumours? There is some overlapping. How should we treat those? I mean, in first-line we don't have the BRAF inhibition available so far, but are they treated differently in second-line in your opinion, or what is your approach to those patients having an MSI-high *BRAF* V600E mutated tumour?

Dr Thomas Winder
Yeah, we have seen there is an overlap between MSI-high and *BRAF* V600E mutations also in clinical trials like the KEYNOTE-177 who set the stage for first-line immunotherapy, microsatellite instable metastatic colorectal cancer, but also in CheckMate 142. And we have seen in the subgroup analysis of these trials that patients with *BRAF* V600E mutation do respond to immunotherapy. So right now I think they get at first-line, MSI-high *BRAF* mutants, the immunotherapy and in second-line the targeted treatment options. But we are looking forward to the SEAMARK trial who is combining immunotherapy and targeted treatment in the first-line setting and we will see if this improves efficacy.

Prof. Sebastian Stintzing
It will be interesting but those patients are difficult to find, I can tell you.
So yeah. When we talk about the *BRAF* inhibition in second-line, as done in the BEACON trial, encorafenib + cetuximab in second-line in *BRAF* V600E mutant tumour, pretreated with or without immune checkpoint inhibition, do you see a problem treating those with encorafenib and cetuximab? Or what's the data on this subgroup who are in second-line, failed first-line and now in second-line, you want to give them cetuximab and encorafenib?

Dr Thomas Winder
Okay. If they are MSI-high and in second-line. So, I think that's a good option. So, that's what we should do in second-line for these patients. So we should give them targeted treatment option in second-line and we can set the stage for that. So that is efficacious and better than the chemotherapy. And we know that we lose these patients, during the lines of treatment,

the *BRAF* mutants, for example, in the second-line were 50% then in the third-line, maybe 30%. And when they progress on targeted treatment I think the best option we have seen in the retrospective analysis, is chemo plus bevacizumab, maybe not lonsurf (trifluridine and tipiracil) or regorafenib in this setting.

Prof. Sebastian Stintzing
But I think we just need to make clear, as you said, don't wait with targeted treatment for further lines. If the patient is in second-line use the options we have before really waiting for them because, as you said, we are losing patients. It's a bad prognostic subgroup anyhow. So, I think it's really important if it's an MSI-high *BRAF* V600E mutant tumour in second-line, encorafenib + cetuximab would be my regimen of choice. We talked a lot about now, about chemo, about the combination of chemo plus encorafenib cetuximab and you also mentioned the BREAKWATER trial. Maybe you want to talk a little bit about the BREAKWATER trial? What data do we have so far? Is it toxic?

Dr Thomas Winder
So, we have seen the safety lead-in data from the BREAKWATER study a couple of weeks ago at ESMO meeting this year in Barcelona. The BREAKWATER study is a randomised phase three trial investigating encorafenib plus cetuximab with or without chemotherapy. And the results of the safety lead-in, so the preliminary data, the safety lead-in data was that the combination of targeted treatment, so encorafenib cetuximab plus chemotherapy. That it has a manageable safety profile for daily clinical practice. The antitumor activity with regard to response is high up to 80%. And the efficacy is also high regarding overall survival. And the key point in this study was when we are looking, the inclusion was you can include upfront or patients in second-line, and what we have seen there is that the median overall survival is higher in first-line setting. So, meaning again we need to get these patients with poor prognosis as soon as anyhow possible on targeted treatment.

Prof. Sebastian Stintzing
Well, I mean we are all very excited about the data we have seen so far. And of course, we want to see the full data as soon as possible. Opening up an option for those patients for precision oncology in first-line and not waiting until second-line, I think that's really important. I was quite impressed by the outcome data we have seen so far. It's small patient population. I mean, it's just like 30 patients, right? So we have to be very cautious about the data. But with the response rate in first-line of those 12 patients of 80%, this is quite something. Nothing that I would have expected for the FOLFIRI + encorafenib + cetuximab group. And also, as you said, the median OS and the median PFS is really exceeding what I had expected at least. So if this data is really validated in the full data set, I think this will really change our treatment approach to those patients in first-line, making it even more important to having them tested for *BRAF* mutation as soon as possible. So, I think that will be really nice data we will see.

Prof. Sebastian Stintzing
So when you think about the future of *BRAF* V600E colorectal cancer, not only metastatic but colorectal cancer as a whole, what do you expect? What are your hopes?

Dr Thomas Winder

So I'm looking forward to getting the data from the SEAMARK trial I mentioned previously. Microsatellite instable BRAF mutant patients for the combination immunotherapy targeted treatment also in the first-line setting. And there is an initiative also for the early-stage setting. But, I think you can better comment on this initiative.

Prof. Sebastian Stintzing
Well, yes, of course. I mean, moving from second-line where precision oncology is standard of care for *BRAF* mutant metastatic colorectal cancer. We are now with the BREAKWATER, we hope to move this in first-line. And so, there are several initiatives in the adjuvant setting to also, demonstrate efficacy in stage three disease. Liquid biopsy plays a crucial role in those trial initiatives. So basically the patients who are treated with standard of care, FOLFOX/CAPOX treatment for three months then a liquid biopsy would test whether they are still ctDNA and if there is ctDNA, a treatment for the *BRAF* V600E mutant cases with encorafenib + cetuximab would be started and with the SAGITTARIUS trial initiative, which is a Horizon 2020 funded project. But there are also other projects, for example, from the British FOxTROT trial group and also the UNICORN basket trial from the Italian GONO Group. So I think, a lot of research is going on and we can still wait and be excited about what we will see within the next years. I want to thank you for this nice and good conversation and discussion of this important patient group.
So, Thomas, thank you so much.

Dr Thomas Winder
Thank you. Sebastian, it was a pleasure.

Tonke
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