Podcast Transcript
Treatment optimization in mCRC: third-line and beyond

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Tonke de Jong (COR2ED)
Treatment of advanced colorectal cancer should be considered a continuum of care and patients should be offered as many life prolonging therapies as possible. Understanding the optimal sequence of available later line therapies and management of treatment related adverse events is key to achieving a maximum response for patients. Keep listening to explore the clinical and real-world data guiding treatment decisions and to hear about the practical management of adverse events and the importance of multidisciplinary collaboration.

Thanks for listening to this podcast episode from COR2ED independent Medical education. So today's topic is all about treatment optimisation for metastatic colorectal cancer third line and beyond. I'm honoured to introduce to you two experts in the field of GI oncology, Dr Thomas Winder, Medical Oncologist, and Dr Mark Lewis, Medical Oncologist. We're very excited to listen to your discussion.

Thomas Winder
So hello and welcome to this podcast where we will be discussing treatment optimisation and metastatic colorectal cancer, third line and beyond, I'm Dr Thomas Winder. I am the head of the Medical Oncology Department at the Academic Teaching Hospital in Feldkirch in Austria, and I'm also the head of the Swiss Tumour Molecular Institute in Zurich in Switzerland, and I'm very pleased to be joined today by our guest, Dr. Mark Lewis.

Thanks for joining me. Mark, would you like to give a brief introduction for our listeners?

Mark Lewis
Yeah, thank you so much, Thomas. It's great to be here. My name is Mark Lewis. I'm a Gastrointestinal Oncologist and I direct a health care system in America based in Salt Lake City, Utah. We cover 7 to 8 states in the US. I'm primarily interested in cancer care delivery. As we're going to discuss today, there's a lot of cutting edge research. I think one under-examined question is how do we actually implement all of these advances in real-world practice? And you and I are going to talk today about a particularly challenging treatment situation.

Thomas Winder
So I think we are now diving directly into the treatment optimisation for refractory metastatic colorectal cancer patients. And we'll discuss a few factors, how we select patients for the treatment and if the points maybe which are helpful to select them. Our listeners will get both perspectives, the US and the EU perspective. I think that's key. And we have seen the treatment landscape for metastatic colorectal cancer in third line and beyond, change a lot during the last years and we have a number of effective treatment options there. But Mark, maybe can you start off with your view on what is the realistic goal of treatment at this stage for these patients?

Mark Lewis
I think it's really important that we talk about endpoints and even more importantly, Thomas, that we make sure that our endpoints are congruent with what matters to our patients. I saw this really eye-opening presentation at ASCO annual meeting in 2019 by a wonderful researcher, Bishal Gyawali, and he said, 'Listen, at the end of the day, what matters the most is overall survival and quality-of-life'. And the fact that I even need to say that, I actually think is telling, because I think we are sometimes not necessarily misled by oncologists, but we get distracted by endpoints that may or may not be good surrogates for those two primary endpoints that matter to our patients. For instance, Dr Gyawali made a very compelling case that we should not extrapolate from progression-free survival to quality-of-life, we should not presume that a longer PFS means a better QoL. And so I think what we're looking at here are, are these agents allowing for durable disease control, and of course within that we may see some response. And are they allowing for maintenance of quality-of-life and performance status. And you know, I've got a palliative care colleague here who often puts it to her patients this way, she says, 'are you having more good days than bad days?' So, number one, we want to enumerate survival. We want to see longer survival. But number two of these increasing number of days, we want to make sure again that there are better days and not worse days. And I think that's what today's discussion comes down to.

Thomas Winder
I totally agree, because with these low response rates we have seen in the third line setting, the disease control rate is the primary goal, that they have a high quality-of-life for a long time. I think that's really key. So now if you think about the available treatment options for these patients and can think about them in terms of molecular selected patients and maybe molecular unselected patients, we have a couple of options. Regorafenib, TAS-102 and we got the data from FRESCO-2 trial with fruquintinib and I think a couple of months ago we got

the SUNLIGHT data and the question is now we have a number of options. So what sort of benefit do these agents offer our patients?

Mark Lewis
So one thing I think is going to be important to note, Thomas, is the mechanistic similarities between the agents that you and I are going to discuss. And I will say that this has been an exciting year. I can't think of a year in recent memory where this particular line in context of treatment has changed quite so much in terms of our thinking.

And so the first thing to talk about is anti-angiogenesis. I mean, for decades now we have been trying to exploit anti-angiogenic properties of these agents for patients with metastatic colorectal cancer. And one thing I think that's interesting is the through line of anti-angiogenesis through consecutive lines of therapy. And we've had reason to believe since sort of the mid 2000s that the continuation of anti-angiogenic drugs makes sense even when we're seeing progression and resistance through earlier lines of therapy. And so I think that's why a lot of the things we're going to talk about today have sort of at their core, an anti-angiogenic mechanism. Now, having said that, there are two sort of main ways to get at anti-angiogenesis. There's the infusion of monoclonal antibodies like bevacizumab and then there are a host of now oral therapies, typically small molecule tyrosine kinase inhibitors with at least some activity against VEGF or VEGFR. And so I think that's going to be the common theme that listeners will hear.

So I'll start by saying this, there's going to be a lot of numbers in my next answer. All I want our listeners to do, Thomas, is to hold in mind this sort of general sense of what these numbers mean and how close they are together. So I'll start with the CORRECT trial. This was looking at regorafenib and it reported a 6.4 month overall survival for regorafenib versus 5.0 months for placebo with a hazard ratio of 0.77. Next we have the RECOURSE trial, which was TAS-102, 7.1 month overall survival for TAS-102 versus 5.3 months for placebo, hazard ratio 0.68. Next, and this is going to be really important for you and I to talk about, SUNLIGHT. TAS-102 plus bevacizumab. Now the overall survival for that combination goes to 10.8 months versus 7.5 months for TAS-102 alone. Hazard ratio of 0.61. And then finally, as you mentioned, the newest player on the scene, fruquintinib with the FRESCO-2 trial, 7.4 month overall survival with fruquintinib versus 4.8 months for placebo, with a hazard ratio of 0.66.

So a lot of numbers to keep in play. I always find these numbers sobering, Thomas, because none of the median overall survivals I just cited are over a year. So that's kind of the space that we're dealing in. Also, you and I are going to maybe come close to the cardinal sin of cross trial comparison. But I do think there are some really salient points that we can draw from, again, keeping these numbers in mind, thinking about the different agents, not just their efficacy, as we'll discuss in a minute, their tolerability as well.

Thomas Winder
So, Mark, you have nicely shown us the similar overall survival rates for regorafenib, TAS-102 and fruquintinib, and we have seen the data on SUNLIGHT recently. And what are your thoughts about that? Would you use now only TAS-102 plus bevacizumab? Or would you say instead TAS-102 alone? And what's the role of regorafenib right now?

Mark Lewis

First of all, having seen the SUNLIGHT data Thomas, it's hard for me to imagine actually using TAS-102 alone. I think SUNLIGHT was nicely set up to show the advantage and perhaps even the synergy of combining TAS-102 with bevacizumab. Again, thinking about how all these different agents work, I think it's mechanistically appealing to be combining TAS-102 with bev, and I think it's largely tolerable for patients. I would say the one disadvantage here, which is important to keep in mind is time toxicity. So especially when we're dealing with people who we know have a finite amount of time remaining in their treatment, I think it's actually reasonable to think, are we tethering them to our clinics, to our infusion centres or not? So obviously with an infusional component, there is that aspect. On the other hand, I think the survival advantage here for the TAS-102 bevacizumab combination is fairly substantial and I personally think worthwhile discussing with patients, 'hey, listen, this is going to be a trade-off. You're going to have to come in and get treated more often. However, this is what I think you get in return'. And again, we've had decades of experience with bevacizumab. We know what the AE profile looks like there. I don't think it's an overly onerous agent. Now with regorafenib, I think regorafenib of all the agents we're discussing today, is probably falling later and later in sequencing because now there are some real competitors for regorafenib in this space. Regorafenib, as you and I know, Thomas has had a troubled history.

I think when the CORRECT trial was first published, again, it was a relatively novel entrant into this particular space, to the third line space. And I think we learned and unfortunately patients learned, that it could be a very toxic agent. One of the investigators I worked with on regorafenib called it son of sorafenib, which I thought was a very apt descriptor because I think we saw with it a lot, unfortunately, of the AEs that we sort of associate classically with small molecule TKIs that may not have a very tight target. And I think regorafenib's promiscuity, if you will, going after multiple receptors, unfortunately also results in a lot of different toxicity, quite a lot of hand foot syndrome, a lot of diarrhoea, a lot of fatigue, and sometimes even treatment refractory hypertension. The other key point, Thomas, I think, is just how quickly side effects emerge with regorafenib. I saw regorafenib AEs emerge easily the fastest of any of the agents that we are discussing today and typically within the first month of usage.

Now you might argue, okay, well that gives you the opportunity to dose adjust. But again, remember, there are a finite number of months remaining in these patients' lives. And if we're taking even one month and making them frankly miserable as we try to dose optimise regorafenib, I'm not entirely sure it's the best use of their time. So the long answer I have to your question is that I think regorafenib falls later in the sequence and I think that the TAS-102 bev combination becomes much more appealing.

I'll point out also that the NCCN guidelines here in America, which I suspect will yet be updated, the last update, I believe, in March of this year, 2023, already suggests that it's preferred to combine TAS-102 and bevacizumab, and presumably for the reasons that I stated. Thomas, what's the situation in Europe and what's your stance?

Thomas Winder
I think the situation in Europe is pretty much the same. We had the ESMO virtual guidelines updated a couple of weeks ago and they state also that TAS-102 plus bevacizumab has a 1A recommendation. So they are highly recommended and I think the point you raised about the infusional agent of bevacizumab is surely one point we need to think about in daily clinical practice because our outpatient clinics, they are full and we need to think a little bit on patient comfort as well.

So I think that's a key point you raised. And another point is, I think the combination which was tested in the SUNLIGHT so TAS-102 and bevacizumab is I think nowadays the standard combination maybe for patients which have a hypertension uncontrolled or a high bleeding risk. I think that's the group we should select and maybe that's the group who should get TAS-102 as a single agent. And I totally agree with you as well that the regorafenib will step back a little bit in the next line of treatment.

And now we have to challenge, we have to determine the optimal treatment sequence of these patients. And I think there are several factors we need to keep in mind. So we had heard maybe ECOG performance status, tumour volume may be a selection factor, age, sidedness, prior therapies. So what is, in your daily clinical practice Mark, how do you select these treatments? We have discussed previously with the same overall survival benefit, how do you select your patients for each of these treatments?

Mark Lewis
There are so many factors in the calculus, right Thomas? Lots of things we can consider. And it's interesting, you may remember this there was a time in the Journal of Clinical Oncology where what is now the Art of Oncology column was called, 'When the Tumour is not the Target'. And I loved that title because I think what you and I are getting into is, we spend so much time, so much time measuring objectively the size and nature of the cancer. It's actually surprisingly, almost worryingly easy to forget about the patient, the host, if you will, for these tumours. So you have to think about their age, performance status, you have to think about the prior treatments they've been through. To me, one of the great advantages of a longitudinal therapeutic relationship with the patient is, of course, you get to know them as people, but you also get a sense of what they can and can't tolerate. And you and I both know that the first and second lines of treatment that get them to this point may have not been that easy for them to take. So that is absolutely going to be top of my mind for each and every patient with whom I'm making this decision.

So that brings me to toxicity. I think toxicity is perhaps the key consideration here in terms of quality-of-life trade-offs, because earlier when I was citing the survivals for placebo, there are very few of the options that you and I are discussing today that offer more than a few extra months of median overall survival beyond placebo, which means these drugs really have to be worth it. We have a saying here in America, I don't know if this idiom is going to translate. Is the juice worth the squeeze? Meaning is what you're getting out of the drug, is that actually a worthwhile trade-off for these patients? I think in a lot of the cases, if you actually ask them point blank, the answer would be no.

One really interesting and I think a fairly novel metric I've seen emerge out of this entire discussion. In fact, I first encountered it in the discussion of TAS-102 as a single agent is called TWiST. And TWiST is a metric. You may be familiar with it already, time without symptoms of disease or toxicity. And basically investigators were smart enough to say, hey, listen, sometimes quality-of-life decrement is because of disease progression. Sometimes quality-of-life decrement is because of something you and I do, an iatrogenic effect, an adverse event from treatment. And what they were interested in sussing out was, well, what about the time where neither one of those things is happening? What about good quality of time where the patients are neither impaired by disease progression nor by the drugs themselves?

What I found really compelling when I first learned about TAS-102 as a single agent is out of the roughly two extra months of median overall survival that that agent was garnering in RECOURSE, almost the entirety of those two months were deemed to be quality time based on this TWiST metric. And those are the kind of things I think we should start thinking about, because when we get down to this point, when unfortunately we are not curing patients, we're not even adding years to their life, it really, really matters that that remaining time is good time, what I call legacy building time.

And that's where you and I need to talk to them very frankly about these toxicity profiles. How about you, Thomas? How would you make these treatment recommendations to your patients in Europe?

Thomas Winder
I can totally agree with your points and I learn something new. So TWiST. I love it. I already love it. I think that the time without symptoms, that's a key endpoint for third line treatment.

There may be some real-world data also out there to select TAS-102 or regorafinib. Maybe the sidedness is one which has shown that the left sided tumours may benefit a little more and we prefer to give, to start with regorafinib. But I think a key study we need to mention here, when we discussed previously a little bit the side effects, is the ReDOS study. The ReDOS study was a phase two trial which may help us or which helps us, so in daily clinical practice to reduce the symptoms, the side effects of regorafenib treatment by the same efficacy we may get. So we start with 80mg of the dose we increase each week from 40mg until we get in the third week to 120mg of regorafenib. And if in between there are some side effects, we go a step back maybe when we are at 120mg and there are side effects we go back to 80mg. And I think that's very, very helpful for our patients in daily clinical practice to manage them by keeping the efficacy of this drug. I think that's key. For the side effects, hand foot skin reaction, I think that's something which is very key in daily clinical practice and there we need close together with the multi-disciplinary team, with our dermatologists. We may have troubles with diarrhoea and may need the help of our gastroenterologists. I think interdisciplinary management with the team is very helpful there.

So I think there are some real-world data out and I mentioned one of these real-world data for the for the location and maybe we can prefer for the left side of the regorafenib. Do you

think, Mark, in the US., do you use this real-world data for sequencing of the treatments we have?

Mark Lewis
You know, it's hard to have rigorous sort of prospective trials that are going to have multiple arms looking at all these different agents Thomas. I mean, the math, as you know, immediately becomes staggering when you get into various combinations and permutations.

I actually think real-world data are quite important. While I do practice in the US., I think the largest data set that may be relevant here actually comes from our colleagues in Japan. There is a really interesting real-world evidence study presented from the Japanese group earlier this year where they looked at claims from a national registry there, I think it accrued between 2014 and 2021. What that allowed them to do in this particular line of treatment was look at sort of outcomes, a variety of the sort of drugs and combinations that you and I are talking about today. What was really interesting is, again, TAS-102 plus bev sort of rose above a propensity score matched cohort that included TAS-102 alone and also regorafenib and again, I think that the takeaway was the combination, like you said, aside from, you know, some select patients with issues with hard to control blood pressure or some bleeding concerns, TAS-102 bev really rose above TAS-102 monotherapy and it rose above regorafenib monotherapy in this real-world setting. I found that quite compelling.

So I think there are lots of options for molecularly unselected patients, if you'll allow the expression Thomas. But I think the other place that you and I need to kind of move the conversation is, we are seeing more and more identification of novel biomarkers and then some treatments that are sort of sculpted in that setting for these later-line patients. What biomarkers do you think are relevant for this group? And then with that, Thomas, what targeted treatments, if you will, do you sort of pair to those biomarkers?

Thomas Winder
I think you raise a very, very important question because we need to select these patients who have a driver. And I think *HER2* is a very, very relevant target. And here I want to mention just three studies.

On the one hand, the HERACLES trial, it's a couple of years ago. It showed the combination of trastuzumab plus lapatinib, it was active and well-tolerated in heavily pretreated patients with *HER2* over-expression. I think that's a key study we need to keep in mind and we need to test *HER2*. Another study, which is the MOUNTAINEER study with tucatinib in combination with trastuzumab. They produced a durable response for these patients in previously treated *HER2* positive metastatic colorectal cancer patients. And then couple of months ago, we have the DESTINY-colorectal02 study with trastuzumab deruxtecan with also promising antitumour activity in patients with *HER2* over-expressing tumours, even if they are pretreated with TKIs. I think that's key and for these patients who were heavily pretreated, that's a very, very good option. And I think a couple of weeks ago at the ESMO meeting we got the data from the CODEBREAK 300 study, a combination of sotorasib, so a selective *KRAS* G12C inhibitor in combination with panitumumab versus TAS-102. And we have seen these data and I think they have a promising response, but overall response profile, they have a promising data on progression-free survival.

And I think we need to select the patients with *KRAS* G12C mutation, so this specific mutation, and we need to discuss with these patients all we mentioned previously, and we need to offer them the combination treatment. And then maybe two other targeted treatments we may have. That's microsatellite instable patient if they didn't get the treatment previously in first line.

I think all over the world, I think that's the same with you in the US. as with us in the EU. We treat these patients in earlier lines, but if they haven't had immunotherapy, they should get it. And pretty much the same is with the *BRAF* V600E mutant colorectal cancer patient, if they have not had targeted treatment options, they should get that at least in later line. So I think that's the key targets we have and we need to keep in mind in third line setting.

Mark Lewis
So well said Thomas. One of the phrases I've heard here in the US, at least, is we're trying to make every cancer a rare cancer. And I think what that statement means is, yes, each one of the molecular subsets you just mentioned may have a prevalence in the single digit percentage range, but we only find what we look for.

And then once we find these things, we can absolutely therapeutically exploit a lot of these biomarkers for the patients. And so it becomes quite advantageous. So clearly molecular status remains relevant in the later line setting. You mentioned earlier the role of the molecular tumour board. Do you still pursue molecular testing at this stage in treatment? And how do you work with your molecular tumour board to guide treatment decisions?

Thomas Winder
I think the molecular tumour board is a key instrument in later line setting. So after third, maybe fourth line setting. Now when we have patients who are in very good performance status who have a life expectancy for more than six months, where we do a broad molecular characterisation, and I think then we need to sit together with our geneticists, with molecular biologists and discuss these results, maybe for an off-label use of drugs for patients who qualify for that.

I think that's for the molecular tumour board. But we are always also discussing a little bit EGFR re-challenge. So there was also that broad discussion of clonal selection and maybe the switch of *KRAS* mutant status to *KRAS* wildtype status. I think that steps back also a little bit with the new treatment option we have in Europe.

So how do you implement these tests in daily clinical practice? Did you say you are doing liquid biopsy and if the *KRAS* data switches, do you offer them to the anti-EGFR antibodies?

Mark Lewis
Yes, we are Thomas and I'm really glad that you brought up the sort of dynamism of this. I think we are incorrect to think of cancer as something static.

And in fact, you and I as oncologists may actually be part of the drivers of evolution. Right? Hopefully we don't encounter resistance, but I think we can certainly see the impact that our

treatments have at literally the DNA level on the cancer. So absolutely, I think retesting is worthwhile. Having said that, we need to walk before we run.

What I mean by that is you mentioned earlier making absolutely sure that every single patient who is a candidate for immunotherapy receives immunotherapy. We recently did a real-world study here in the US, just to see if patients were having adequate testing for mismatch repair deficiency or microsatellite status and a staggering one third of patients in the metastatic setting were not receiving testing for MSI or MMR, which is completely unacceptable, we need to bring that number up to 100. The other thing I'll point out is, and I don't think we mentioned this yet, is what do we make of tumour mutational burden? I think TMB is an incredibly difficult target to nail down. You know, here in the United States, I think we were all fairly surprised several years ago when our governing agency, the FDA, the Food and Drug Administration, said that if you've exhausted all other treatment options and your TMB is above ten mutations per mega base, then you get access to immunotherapy. I don't think it necessarily holds for every single cancer. And I also know we can endlessly debate the bifurcation of a continuous variable. But my own sense is this, number one, I think for colorectal cancer, I think the threshold for TMB is probably higher. I don't think it's ten. And number two, I think that that number too Thomas can evolve over time.
So what's interesting for me is to measure TMB at the very beginning of treatment and then measure it later after several lines. And the trend I usually discern is to see the TMB rising. And what I think is interesting is, you know, we almost always, of course, are getting platinums in the first or at least the second line treatment. Not alkylating exactly, but I suspect that the platinums in and of themselves have the ability to drive up TMB. And my point is some patients, not many, but some patients actually become candidates for immunotherapy in later lines even if they weren't at the beginning. So I think that that's how some of us approach in the US. Number one, everybody has to be tested for immunotherapy candidacy at some point. Number two, this is an evolving treatment landscape in the individual patient and you and I, our job is to survey it from time to time and catch those changes.

Thomas Winder
So great. Well, thanks, Mark. I've really enjoyed the discussion, but we should probably start to wrap up a little bit. So if I was to summarise our discussion, I think the key points are we need to focus a little bit on endpoints. And I think in the third line setting, the endpoints are very key. Quality-of-life, overall survival, and, I got it, TWiST. TWiST is also very important.

Mark Lewis
That's right.

Thomas Winder
I think we need to keep in mind a little bit real-world data for sequencing these treatment options we have. So maybe we need to think about location. We need to think about REDOS to lower a little bit the toxicity profile of these new treatment options we have. I think that's very key. And then you raised a very important point for molecular selected and molecular unselected. For selected I think the patient's individual factors are very key for the sequencing. For the molecular selected we mentioned *HER2*, we mentioned *BRAF*, MSI, tumour mutational burden, maybe with a higher cutoff than ten. I think that's very key to

select these patients and to offer them these treatment options and maybe for the later, later line we have the molecular tumour board where we do a broad molecular characterisation, where we discuss it in a molecular tumour board, and we offer these patients a new treatment option.

And Mark, anything you would like to add in terms of the points I raised here?

Mark Lewis
No, this is a fantastic conversation Thomas. I learned a lot of from you and also how things might look in the EU versus the US. But I think what's globally true is, listen, our patients unfortunately in this particular line of treatment have a finite amount of time remaining and it's how we make the best use of that time.

Again, I go back to what my colleague here says, are they having more good days than bad? You and I do our very, very best to add to the number of days. I think it's also incumbent upon us that we not be inflicting harm and we try to make those days as good and as meaningful as possible. Things have to be tolerable before they can be effective.

Thomas Winder
Great. Well, thanks again and thank you to our listeners. We hope you found our discussion useful. Thank you very much and have a good day.

Tonke de Jong
Thank you so much for sharing your insights Dr. Winder and Dr. Lewis. We've learned a lot from your discussion on treatment optimisation for metastatic colorectal cancer, third line and beyond.

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