# Podcast episode title:
# Treatment sequencing in advanced mCRC patients: Third line and beyond

**Brought to you by: Dr Jenny Seligmann, Professor of GI Medical Oncology, University of Leeds UK and Dr Shubham Pant, Professor of GI Medical Oncology, MD Anderson Cancer Center, Houston, TX, USA**

**Jenny Seligmann**
Hello and welcome to this podcast covering treatment sequencing in advanced metastatic colorectal cancer patients in the third line and beyond.

***Tonke de Jong***
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**Jenny Seligmann**
I'm Jenny Seligmann and I'm a professor of GI Medical Oncology based in the University of Leeds in the United Kingdom. Today I'm delighted to be joined on this GI CONNECT podcast by Shubham Pant. Welcome. Can you introduce yourself to our listeners, please?

**Shubham Pant**
Thank you so much, Jenny for the kind introduction. My name is Shubham Pant. I'm a professor of GI Medical Oncology at MD Anderson Cancer Center in Houston, Texas. Great to be on this podcast with you.

**Jenny Seligmann**
I'm delighted that you can join us. So I'm really excited about this podcast for a number of reasons. I think it's very timely to be having this discussion. So our focus is shifting to treatments for metastatic colorectal cancer in the third line and beyond. And of course, we know that a smaller proportion of our patients make it to third line treatments. But still, this is a meaningful and impactful population of patients. So this topic deserves careful consideration, especially as there's been a number of developments in the past year in this treatment space.

So, Shubham just to start off, tell me how you assess a patient ahead of third line treatments. What are the things that you think about?

**Shubham Pant**
You know, third line is a very interesting space in colorectal cancer right now, a lot of newer therapeutics are coming in. So the way I look at it is first of all, look at the *KRAS* mutational status, right. That we have probably done at the beginning when the patient was diagnosed,

that's when we do it. But if they were *KRAS* wildtype and they had an anti EGFR therapy, then I would potentially do a ctDNA testing to see if we could re challenge them with an anti EGFR agent. I would also obviously look at the genomic profile which was done, maybe a somatic mutation, that means mutation on the tumour for our listeners, to see if there were any other targetable mutations that they could go on or any of the clinical trials we could find for these patients in the third line space. So that's where I look at it overall. I look at the standard of care options that we're going to talk about. I look at clinical trials and then I look at any genomically targeted therapeutics that we can put these patients on.

**Jenny Seligmann**
That's really interesting and that then frames our future discussions here really nicely. Some things I think about in the third line are, I suppose, a bit more clinical. So the fitness of the patient, I mean, you're meeting a different patient than you are in the first line. They could have had years of chemotherapy before the third line. On the other hand, you may have a patient who has progressed very quickly through first- and second-line treatment, and I think it's quite important to think about those things. Likewise, their toxicity, how have they found previous treatment, both physically and psychologically, and do they have any ongoing toxicity. Some patients will have ongoing toxicity from their first line or their second line even, things like skin toxicity that may influence decisions. So I suppose it is a bit of a combination of both I would imagine. And thinking along those lines, how do you think treatment goals differ, say, from the first line to the third line? Do you see those being different?

**Shubham Pant**
Yeah, that's a great question, Jenny, and thank you for bringing that up. I think they are very different. I think it's that time that we need to have, you know, not that we don't need to have it before, but you need to have a really serious conversation with the patient and their family about what their goals are. Depending on exactly what you said about performance status, if their poor performance status, we really have to know what they want to do with their life. Do they want to spend time coming into the hospital and to see us? Do they want to have time spending at home? And I think it's very important to have that quality-of-life discussion with the patients about what their values are and what they want. Because, as you know, every patient is different. Some patients come to us and say, we just want to continue and that's what we want to do. And some patients say, you know what, I think I've had enough, I want to maybe just spent time with my family. So I think you're right. It's very important to have that discussion about what the patient really wants to do at this time, because whatever options we have, they're limited unfortunately, at this stage, even with the therapeutics that we have now. So I think that's very important.

**Jenny Seligmann**
Yeah. And I think the other important thing is for the patients who do want to pursue third line options, I think we need to be realistic. I mean, we're going to discuss the data, but we have to be realistic about where they are in the treatment pathway. And think about other elements such as integrated palliative care. And actually some of the trials we'll talk about have very nicely integrated that within their trial design.

So one more question just to push you before we talk about some of the options and the data. When you're looking at all of the trials in the third line and beyond, what do you think is the most meaningful clinical end point?

**Shubham Pant**
Thank you for the easy question, Jenny! I think clinical meaningful end point, you know, beauty is in the eyes of the beholder as they say. So the clinical endpoints, you know, for some patients, it's like, what's my survival? How long did this give overall survival to our patients? Some patients say, hey, what are the side effects? How do they feel like when they were on it? Were they getting admitted? Were they not getting admitted? Like how did patients feel on it? So it's really for me and I'm sure for a number of our listeners, it's more patient driven. We give them the options and they see what they want to pursue, but it just depends a lot on patient factors, as we discussed.

**Jenny Seligmann**
I think that's very fair. I think it's very fair. But again, I think things like response rate have a lesser place than, as you say, overall survival and quality of life do.

So going back to your first point about mutation status and that being one of the main things that may drive decisions. Just out of interest, if a patient was coming to see you routinely in this setting, would you be re-biopsying or doing ctDNA? And I'll start out by taking the pressure of always asking you the questions, by saying in my own practice we wouldn't routinely, at the moment, do that. So we wouldn't have access to ctDNA as standard. And most patients are not interested in being re-biopsied. And for quite a lot of our treatments it probably wouldn't change the management anyway, but of course that's in Europe. What would be your standard at MD Anderson?

**Shubham Pant**
Yeah, so normally not a re-biopsy unless we're doing it for some kind of clinical trial specifically. Mostly it would be ctDNA because we would have had a whole Next-Gen sequencing panel early in the patient's journey. So I concur with you there that we would not, you know, we would not regularly, unless it was in the context of a clinical trial, just re-biopsy them. It wouldn't be the norm.

**Jenny Seligmann**
I wonder if it be good to just start with the approved and available agents for third line metastatic colorectal cancer. So these would obviously be TAS-102 and regorafenib. So one question that's always unclear to me is if you're going to use these agents in a molecularly unselected population, which one would you choose first and what kind of things come into your decision making process?

**Shubham Pant**
And I want to ask that question back to you, Jenny, after this! But I look at the side effects, the toxicity profile, I think they're a little different. I think regorafenib, being a tyrosine kinase inhibitor, just has more toxicities, like more fatigue and diarrhoea and others. I think the ReDOS strategy about starting low and going a little bit higher is what we do, kind of

start at the lower end and then escalating the dose to see how they're tolerated. And I've seen patients do differently, different patients do differently on that. Then with the TAS-102, obviously more haem toxicities. So just in look at how their marrow is doing and everything, what they're counts are, that would be one of the considerations and because the data is fairly similar, in a way you can't cross compare but it is fairly similar. So I kind of look at the, you know, again, like you said, any lingering toxicities, you know what it is and how we can overcome that. So I'll ask you, Jenny, so what do you guys do? Do you guys do ReDOS? What are you doing across the pond?

**Jenny Seligmann**
So across the pond, yeah, we do that and I think that's been very helpful data in terms of tolerability. But again, even at the 160 mg dose you often do have to go back down to 120 mg and that's okay for some patients. The decision of what to do first I think is more complex. I mean, we have some data for TAS-102 that patients who have previously progressed through first- and second-line chemotherapy are the ones who benefit less from TAS-102 and that's certainly something that I consider.

On the other hand, we have some data suggesting that regorafenib may not be as helpful in *KRAS* mutant patients. But again, that's from, you know, small subgroup analysis. And I think you have to be quite careful when you're considering that, particularly in this *RAS* mutant group who have limited treatment options anyway. And again, we'll come to that when we discuss molecularly targeted agents.

For TAS-102 there seems to be less variation in outcome by molecular status. There is data as well that it shouldn't be one or the other choice, and that actually patients who have had both actually do well. So it's quite reasonable to give one and if a patient is still fit for treatment and would like to have more, it looks to be a reasonable thing to then use the other agent.

So I'm glad that you find that as challenging as I do and I agree with you, it's an individual patient conversation. So moving on to some of the more recent data, so we've obviously got the SUNLIGHT data that was presented at GI ASCO which was looking at TAS-102 plus or minus bevacizumab. Of course, this isn't brand new data because there is a phase two trial in Denmark that showed promising data previously looking at TAS-102 plus bevacizumab. Of course, most of the patients were recruited in Europe and Asia, so I am very interested on the US take on this.

**Shubham Pant**
The SUNLIGHT trial was patients who received TAS-102 plus bevacizumab versus TAS-102, and they essentially received it in the third line setting. And the patients had to have had previous regular therapies, platinum, irinotecan, which when this is molecularly unselected patients. An interesting thing that I thought was that about 76% had received treatment with a prior VEGF, 72% with prior bevacizumab. And we saw progression free survival and overall survival benefit and they talked about a few quality-of-life parameters also.

The interesting thing was when I looked at the subgroup analysis, even the patients who had received prior bevacizumab, they did tend to get benefit in progression free survival. That was a big question for me because I don't know how it in England, but you know, out here a majority of our patients, if they're eligible to get bevacizumab, would have received bevacizumab or an anti-VEGF essentially. So that was a pretty good point for me. There were like only 25% patients and I was just wondering where they accrued these patients from. So maybe places where it was not available, it would be a rarity for our practice for them not to have been exposed to an anti-VEGF. But I do think even in the presence of anti-VEGF, those data stood. And I think it's a viable option for the patients. What about you, Jenny?

**Jenny Seligmann**
Well, it's interesting you say that. So across Europe, I think that there's most countries patients will have been exposed to bevacizumab before the third line, but not in all countries, and that includes the UK. And that's mainly based upon things like health economic thresholds for approvals and actually I think this is probably the most convincing data that's ever been shown with the addition of bevacizumab to a chemotherapy agent in terms of efficacy endpoints.

But again, scientifically, I thought it was really interesting because it really provides proof of concept that bevacizumab is effective despite progression, which has always been a bit unclear to me. So I agree with you that was probably the most notable thing of the analysis.

Will this then change the balance between regorafenib versus TAS-102 plus bevacizumab? For me, yes it would. Again, as you said beforehand, there was not much to go between with regorafenib and TAS-102. Whereas actually the addition of bevacizumab really made the data much stronger. So I think there is a meaningful difference, which would mean I would sequence the TAS-102 plus bevacizumab ahead of the regorafenib in this situation.

**Shubham Pant**
Yeah. So I think if they've never had a VEGF, that's a slam dunk. As far as the patients who received prior VEGF, it's still coming back to the toxicities, you know, what they have received before, if they're really, you know, have had myelosuppression with the previous therapies and everything, I would still discuss with them, you know, options, especially, like I said, majority of our patients have had VEGF prior. So I think it kind of differs again. But yes, if they have never had prior VEGF, that's a no brainer to add TAS-102 with bevacizumab on the SUNLIGHT trial.

**Jenny Seligmann**
Great. So I suppose the other trial that has been of interest last year is FRESCO-2, which was presented at ESMO, which was of course building on FRESCO-1. So this is looking at fruquintinib. Any thoughts about this trial?

**Shubham Pant**
Yes. I think that's more like a fourth line regimen. Essentially the patients who came on had to have prior oxaliplatin, irinotecan, anti-VEGF if they were eligible, anti-EGFR if they were eligible. Also progression or intolerance on TAS-102 and regorafenib. So more of a fourth

line, I think regimen though quite a few patients had received at least one or both essentially. And you know, there was a median overall survival difference of 2.6 months. So I think that's definitely an area, but I think I would slot it right now to more of my fourth line kind of option.

**Jenny Seligmann**
Yeah. I mean, I suspect that approval will be sought maybe fourth line and beyond because really that is where the data is. And I can't see a trial going entirely head-to-head between all three of these. So I think we'll probably have more questions than answers in this space in the next few years. But again, it was showing that it was relatively tolerable and as you say, associated with another overall survival gain despite this pre-treatment. So again, it's just pushing these patients out. We don't have a huge amount of information about subgroups. Maybe more data will follow in time.

Shall we move on to molecularly targeted patients? We've got a couple of groups to consider, so we've got the *KRAS*, the *RAS* wild type patients. And then again, recent data from the MOUNTAINEER trial from last year in HER2 positive patients and even now in *KRAS*-12C patients as well. So again, the refractory setting is really very busy nowadays.

**Shubham Pant**
So, like we said, we really in the third line you have the options, currently you have TAS-102, regorafenib. You obviously have the other options of looking at molecular targeted agents and one of the ones in the MOUNTAINEER trial that you mentioned was a combination of trastuzumab, we've used it forever with tucatinib, which was a tyrosine kinase inhibitor for HER2. Main side effect is diarrhoea. These patients in this MOUNTAINEER trial had about three prior lines of therapy. So exactly what we are talking about. We talked about two, but it's, you know, could be three. And patients did have a response rate of about 38% with a duration of response, that means if they responded it was about 12 months. So that's fairly significant, I think, for the patients.

But I'm really excited that HER2 has moved from breast cancer forever now to GI cancers and it's really exciting to see it in gastric, to see it as a valid target in colorectal cancer. So super excited about the data.

What are your thoughts about NTRK fusion and really targeting that in patients with colorectal cancer, super rare like needle in haystacks.

**Jenny Seligmann**
Needle in a haystack, but worthwhile looking for. When we were talking about response rates there, NTRK targeting agents in patients who have a fusion, off the top of my head I think over half of patients had a response in the very refractory setting and not only did they have a response, but they had durable benefit from it. So again, you're absolutely right. If you can find this alteration then it's really important.

So thinking about EGFR re-challenge, I mean, this seems like a really exciting area. Again, just using our comparator of say TAS-102 or regorafenib. So we started out with data from the

CRICKET trial. This is obviously quite old now. This is, I think, nearly ten years old, which was looking at re challenging patients who had previously had a response to anti-EGFR who were obviously *RAS* wild type and then re-challenging them after a further line of treatment. And in an unselected patient, the response rate was approximately 20%. And then things have got more interesting and a bit more precise with the CHRONOS trial, which looked at trying to identify the patients who would most benefit from this approach by testing their ctDNA following progression on their second line chemotherapy. And actually using this approach, it was even more successful. So patients that remained wild type on their ctDNA, their response rates were even higher. So again, this feels like a really obvious thing to do. Is this something you're doing in your routine practice?

**Shubham Pant**
Yeah, we tend to do the ctDNA and we do think about an EGFR re challenge. That's right, Jenny. So I think it's important that, you know, that these patients might get that mutation and that now they could be re-challenged if they regain their wildtype status. So I think it would be something that we would consider here definitely.

But Jenny, I know we've had a really interesting, wide, far-ranging discussion of both clinical practice and how practices differ or they're similar across different continents. So maybe I'll give you the opportunity to summarise and give us some take home messages.

**Jenny Seligmann**
Sure. So, yes, thank you. I've really enjoyed this discussion and I hope that our listeners have enjoyed it too. I think our main points is that you really need to assess patients in the third line quite carefully. We've talked about both patient and molecular factors that you should take into account when making treatment decisions. We've discussed the currently approved options and some of the decision-making processes that you may have when deciding which approach to take first. And we've talked about molecularly targeted options, which for some of our listeners will be things that they can do in the clinic tomorrow. And for some of our listeners, it will be things that we are hoping that we'll see in our own practice very soon.

So I'll finish up there by saying thank you, thank you for joining me today. Thank you to GI CONNECT for the podcast and if you've enjoyed this podcast, then there are plenty of others on wide reaching topics on the GI CONNECT website. So thank you for joining us and I hope that you'll join another podcast soon. Thanks very much.

***Tonke de Jong***
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