Podcast: Interpreting real-world evidence in later-line mCRC

Brought to you by:

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Transcript

Tonke de Jong (COR2ED)
Real-world evidence is playing an increasing role in health care decisions. But how can healthcare professionals use this data alongside classical clinical trial data to help inform their clinical decisions? Keep listening to hear more on the utility of real-world evidence, recent real-world data in later-line metastatic colorectal cancer, as well as considerations and challenges related to its use.

Thanks for listening to this podcast episode from COR2ED independent medical education. This episode is supported by an independent educational grant from Bayer. Today's topic is all about how to 'Interpret real-world evidence in later line mCRC'. I'm delighted to introduce to you to two expert Medical Oncologists in the field of GI oncology: Professor Tanios Bekaii-Saab from the Mayo Clinic and Professor Shubham Pant from MD Anderson Cancer Cancer in the United States. We are very excited to listen to your discussion.

Prof. Shubham Pant
Hello and welcome to this podcast. Hi, I'm Dr. Shubham Pant. I'm a professor in GI medical oncology at MD Anderson Cancer Center in Houston, Texas. And I'm truly delighted to be joined today for the discussion by my friend, colleague, and mentor, Tanios Bekaii-Saab. I call him Tony for short. Tony, thanks for joining me today. Can you please introduce yourself to our listeners?

Prof Tanios Bekaii-Saab
Thanks, Shubham. And, you know, we go a long, long way. So I'm Tony Bekaii-Saab. I'm a professor of medical oncology at Mayo Clinic. I lead the GI cancer group across our enterprise, and I also now chair our division of hematology oncology and I'm delighted to join my good friend and colleague, Dr. Pant, Shubham.

Prof. Shubham Pant
Thank you so much, Tony. So Tony, to set the stage, you know, in recent years, we have seen significant treatment developments in later-line treatment setting for a metastatic colorectal cancer patients. You know, however, as you know, there is a lack of comparative trials to help guide the optimal sequence for these patients. So as a result, we are seeing more and more of these real-world evidence trials, which are really trying to fill this gap and to try to answer the questions about, you know, what the optimal sequencing is and the safety profiles. So let's today delve into this world of real-world evidence and kind of discuss how we can use it alongside clinical trial data to really inform our clinical practice. So like, how much does it help? What are the pros and cons of this real-world data? So Tony, first, let's start off with what do we really mean when we say real-world data? Like, what information does this include?

Prof Tanios Bekaii-Saab
Yeah, no, I mean, that's a great segue, a great point here. You know, unfortunately, or maybe in some ways, importantly, we have so many agents that are coming to the clinic, and that's fantastic for our patients. That's helping our patients expand our capability to treat them. But see, you know, in metastatic colorectal cancer and later lines of therapy, we have now three options available to us, and they all seem to be in the same bubble, if I may say. And the biggest question is, how do we prioritise one versus the other? How do we pick the right patient for the right agent or combination of agents? And, you know, when thinking about overall resources, is it a good idea to start comparing these agents to each other? I mean, of course, we need these randomised clinical trials. They're important. But I don't know if I'm interested in a study that compares regorafenib to TAS-102 or TAS-102 to fruquintinib. That doesn't really bring value.

So thankfully, we have, you know, what we call this real-world data. And part of the real-world data can be collected in two ways. One is prospectively through observational studies, meaning, you know, just go to multiple practices and whatever your practice is, just let us collect that data and understand a little bit more how you place this agent, say, regorafenib, in your practice, right? That certainly is one way to do it. These tend to be also a little bit more skewed towards one product or another, because they're sponsored by, say, the company. And so they're really collecting data, say, on regorafenib or TAS-102. There is also the other real-world evidence, real-world data, which, you know, you're looking at healthcare data that's collected from a variety of sources, such as claim insurance data, registries, a number of registries, companies like Flatiron that collects these data from essentially electronic health and medical records, extracts that data, organises it, consumer data. And there is a number of other, you know, elements that go into essentially these what we call real-world data, helping us understand a little bit more clearly about how you, me, and others actually end up practising in the real world and then try to extract outcome data. Now, the caveat with that is, of course, you know, what does that outcome data look like and how do you control for a lot of the factors that otherwise randomise clinical trials?

Prof. Shubham Pant
Yeah, you're right, Tony. Great, way to kind of elucidate this content essentially that what are really this real-world data. So, again, what you said, you know, these are all retrospective trials, obviously, looking at registries, consumer data, electronic health records, like you said. So, those come with challenges, right? So, what are some of the considerations and challenges, really challenges when you really look at this data? What should somebody who's reading it, let's say one of our colleagues in the community medicine is kind of reading this, like how do they figure out what the challenges are behind this data?

Prof Tanios Bekaii-Saab
So, let me… here I'm going to actually challenge us a little bit. When we think about randomised clinical trials, we always complain about one thing. What is it we complain about is that this does not look like my patient, right?

Prof. Shubham Pant
You're right. 100%

Prof Tanios Bekaii-Saab
So, it's darn if you do and darn if you don't. You know, we love randomised clinical trials because that's the right way to examine a question, but we also hate it at the same time because it doesn't represent my patient in clinic. So, that's important to keep in mind. Now, scientifically speaking, you know, the rigidity of the randomised clinical trials is important and is probably the best benchmark to understand exactly whether one is better than the other. Now, when we don't have that data, when we don't have the capacity to compare the two, again, let's go back to colorectal cancer, later stages, beyond third line, comparing TAS-102 to rego, we don't have that data. To fruquintinib, we don't have that data. And we're not going to see that data in a randomised trial. So, in that sense, you know, these real-world evidence data, you know, would be helpful.

However, there's so much variability that goes into this. You know, the sources are varied. There's a lot of heterogeneity in the results. There's a lot of subjective. I mean, you know, we know how we practise. We understand how we practise, right? And we call it bias, but it's not bias. It's really what's best for the patient. But you pick it. You pick the right, in your mind, the right option for the patient. If a patient, you know, has a performance status that's borderline, you want to pick the less aggressive treatment or no treatment. If the patient's performance status is stellar, you may want to go even more aggressive. And so, there is this bias that leads to additional variability. How do you pick one agent versus the other? Now, you know, how can you mitigate that bias? It's usually when you randomise and you have, essentially, you don't have a say on where the patient goes. So, that, in real-world data, you don't have that control. And there are other biases that get introduced. So, you have the heterogeneity. You have the bias that gets introduced. And then, and there are a number of other elements, you know, that are particular to specifically what part of the world this data is being extracted from. So, in the United States, where it's the land of the plenty, where you have everything available, when you go, you know, to parts of the world where, you know, you may be limited to one or half an option, you know, outcomes may look a little bit different. And so, you cannot control all these elements with the real-world data.

But at the end of the day, the reason why it's called real-world data, because it, frankly, reflects how you and I do this in actual practice. The only problem with the real-world data is that it doesn't have these rigid, strong, scientifically validated endpoints. So, it remains mostly an observation and not a statistically valid plan for analysis or for design in that sense.

Prof. Shubham Pant
Right. So, what you're saying, Tony, is this is kind of really complementing the information we've gained from clinical trials, right? Kind of an additional layer.

You have the clinical trial, and we look at this, because one of the things, as you were talking, I kind of, you know, I was thinking that really when you look at also these clinical trials, you know, there are a lot of populations which are underrepresented, right?

And we know the minority populations are classically underrepresented. And don't you think like that, you know, that population can show us a little bit, you know, their reaction, their side effects, maybe even their responses, you know, potentially could be a little bit different than, you know, what we see as a very homogeneous population in clinical trials? What do you think about that?

Prof Tanios Bekaii-Saab
Yeah, no, absolutely. I mean, you know, and that has plagued us for many years. Randomised clinical trials actually do not or are not representative of, I would go even more than just saying underrepresented minority populations or overall socioeconomically disadvantaged patients, regardless of race or ethnic background, are underrepresented in clinical trials. And it happens that most or a large proportion of those patients are actually from underrepresented minorities.

So we essentially are not truly, and that could be, depending on how you look at it, that could be a little bit more than 30% of the patient population we treat. So you have a large percent of patients, actually maybe more than that, probably closer to 40%. So a large proportion of the patients that we treat are actually not represented in clinical trials, whether ethnic minorities, underrepresented for different reasons, or socioeconomic disadvantaged patients. And so the real world studies perhaps can provide us with a little bit of representation. In fact, you know, the FDA now has a mandate that, you know, you have to have an equal representation on clinical trials.

And when it's not possible on the actual randomised clinical trial, then you have to follow that up with an observational study that focuses specifically on these patients. Because we really need to understand the pharmacogenetics of patients may be different. We know that there are major differences, for example, you know, with the oral tyrosine kinase inhibitors between, you know, Western-based populations and Asian-based populations. So we know that there are differences of how you tolerate the drug and ultimately how much it works. And specifically when you're starting to look at toxicities that are long-term, sometimes some of the less common toxicities perhaps may be manifested more in underrepresented patient populations versus others.

So I think this is one of the values of these real-world evidence or real-world data, is it actually, it truly can be more representative, more representative of the clinical practice.

Prof. Shubham Pant
Right, complemented and maybe make our clinical practice whole, right? Because how many times, you know, we are working with fellows and be like, hey, pull that paper, and they go, man, this patient does not look like anything.

Prof Tanios Bekaii-Saab
It's not my patient. I can't find my patient in that demographic. Right. No, you're exactly right. It's always a challenge.

Prof. Shubham Pant
So I think it's a great kind of segue into our next step, Tony, in which let's talk about what you already alluded to is in metastatic colorectal cancer patients in the later lines of therapy, you talked about regorafenib, TAS-102, TAS-102 / bev, fruquintinib, you know, could you talk a little bit about these therapies? You know, what would they compare to really, but they were not compared to each other, right, in a way like direct comparison?

Prof Tanios Bekaii-Saab

No, so we have, right now, we have three agents, actually, that are available to our patients beyond, so three lines and beyond. In fact, you know, for some patients, it's second line and beyond. If a patient goes on FOLFOXIRI and their RAS, they have a RAS mutation and no other alterations that are targetable, second line, we actually are thinking about one of these options, TAS-102 plus/minus bev, regorafenib, or fruquintinib. So it's pretty complex, and it's getting closer and closer to the second line, but mostly it's a third line question for most community practitioners.

So we have three agents, regorafenib was the first that made it into the market more than 10 years ago, based on the CORRECT trial at 160 milligrams, pretty rough, you know, a lot of us, you know, found an incredibly tough time, or a lot of patients have a really tough time with it. Its toxicities happen early, their worst is early, so there were a lot of iterations in practices, you know, "my favourite dose is 80, my favourite dose is 120, I don't like to go above that." So there was a lot of confusion about how to use it, so we went back, looked at a study called ReDOS, which optimised the dose of regorafenib by using an approach where you go to 80 to 120 to 160 on a weekly basis, as tolerated by the patient, and that study actually did show that the dose escalation strategy is superior to the 160 that was established with CORRECT, and so that became more of a standard on both on the NCCN and ESMO guidelines, so that changed a lot the way we use regorafenib. Survival was better [numerically longer], I mean, it wasn't just that it hit its primary endpoint, but survival was better [numerically longer], although a secondary endpoint, with regorafenib as an optimised dose versus 160 milligrams. So that dose escalation strategy seems to work well, and frankly, I think it did set the stage for us in the world of using these tyrosine kinase inhibitors to consider similar strategies across the board, because we all know that we have issues with these TKIs.

Then came TAS-102, and TAS-102 came first based on a study called RECOURSE, and then further with CONCUR. Again, looked very similar to regorafenib at 160.

And then came the SUNLIGHT Study, and the SUNLIGHT Study essentially looked at TAS-102 plus minus bevacizumab, and did show that adding bevacizumab to TAS-102 in the third line did better than TAS-102. But there was a little bit of a design flaw in that study that needs to be mentioned. One, 28% of the patients who received TAS-102 plus bevacizumab, or TAS-102 that were entered into the study, were not pre-exposed to bevacizumab. That's not our practice in the United States, and in most of Western Europe. The other thing is that, again, a large proportion of patients did not even receive bevacizumab in the first line, a bit unlike our practice, or received it in the first two lines before they got the third line.

And when you start adjusting for a lot of these factors, the delta goes from very clinically meaningful to somewhat clinically meaningful, still favouring adding bevacizumab to TAS-102, but not to the same degree that the study without the subgroup analysis did show. So where's the good news here? The good news is that we're showing that bevacizumab added to TAS-102 enhances outcomes.

And then the new kid on the block, fruquintinib, another tyrosine kinase inhibitor, very focused on VEGF receptor inhibition. FRESCO-2 study, FRESCO first in China, led to its approval in China, FRESCO-2 global study showing improvement versus placebo, very nice numbers. Again, relatively well tolerated. Fruquintinib is also another option and seems to preserve its activity, relative activity, post-TAS-102 and post-regorafenib and post both. And so now we have all these agents available to us in the same bucket.

Prof. Shubham Pant

In the same bucket, you're right. So that brings us to ASCO GI 2024. I think we had a lot of real-world analysis in ASCO GI 2024. I was actually surprised by the number of real-world analyses that were done, which points to the fact of we need better drugs, more kind of more home runs like the MSI in the small patient population, some drugs like that.

I feel like the HER2 is also an emerging area with some of the ADCs where we can improve outcomes in a more exponential manner. However, we are where we are.

So maybe we can discuss some of the real-world evidence which was presented in ASCO GI in 2024. So I know there was a regorafenib study, a number of kind of studies with regorafenib and TAS-102 that were presented, Tony.

Prof. Tanios Bekaii-Saab
Yes. So there were a number of studies that were looked at, but that to your point, that again tells you that we just, and we won't have those randomised clinical trials. And maybe one other point that is important to keep in mind is that the best strategy for our patients would be to have a targeted strategy, biomarker driven strategy that only happens in 15% of our patients with colon cancer. So 85% of our patients today don't have a specific biomarker when they fail chemotherapy. This is what we're thinking about. And that's why it's so important to have these.

A study that essentially looked at real-world use and outcomes with regorafenib, this actually looked at a ReDOS-like strategy. And another strategy was a dose adjusted strategy. So not necessarily ReDOS, but flexible dosing. And then patients who actually received, you know, the 160. And when you look at all these numbers, and again, understanding, like we discussed that there are a lot of limitations to real-world evidence, but here's the interesting part in this study. In this situation, those patients who actually went on the ReDOS-like, actually were the patients that were less performant and they had poor performance status. They were the patients who had more adverse alterations, such as KRAS and NRAS. So they had a poor performance status, more adverse KRAS / NRAS proportion than the standard dosing regimens. And yet, the dose adjusted and the ReDOS like population performed better [stayed on treatment longer]. So here, the bias is, was essentially, you know, the patient who's not doing as well is going to go on this dose adjusted, dose optimised strategy. And the patient who has a better performance status, strong, I'm going to just throw the 160 directly at them. Well, guess what happened? The dose adjusted, the flexible dosing actually showed at least historically that it's better than the 160. So that actually is, I think in my viewpoint, at least for regorafenib, this was one of the most interesting real-world studies that was presented at ASCO GI 2024.

Prof. Shubham Pant
And I saw another one, which was the real-world study for regorafenib, again, in metastatic colorectal cancer patients who had long-term responses to regorafenib in the USA. And they looked at patients, you know, who were these long-term responders and what were the unique characteristics? So looked at patients more than four months or five months, long-term responses. And they kind of saw things that we would think that we would see in this group, that the patients who had typically had favourable long-term response had better ECOG, you know, PS at rego initiation, less advanced disease at diagnosis. And the majority, you know, had received prior bev, which is very common in our patient population.

But Tony, one of the, obviously, the burning question, what everybody wants to know is which one should we use first? Like if we use rego first and then TAS-102 plus or minus bev, or TAS-102 plus or minus bev first, and then rego second, like, is it better or not?

And, you know, I saw a couple of studies, you know, one was the OSERO study, which essentially looked at if you did rego, TAS-102 plus bev or TAS-102 before, and then followed by, you know, rego or, you know, TAS-102 or TAS-102 bev, is there any difference? And they really showed that the overall survival was comparable [REGO vs TAS-102 +BEV], you know, regardless of whether, with whatever is administered first, right?

And really, the real-world data that was presented in ASCO GI this year, you know, a couple of studies really did not show that really sequencing. So you've got to look at the patient characteristics, actually, the patient in front of you and see which one would be better for the patient. But either way, there's no bad option essentially here, right? Both are kind of good options, but we need better options with biomarker-driven kind of, you know, more biomarker-driven options.

So, you know, Tony, coming to TAS-102, I caught some of these other real-world evidence. So one was actually from Joleen Hubbard, in which she looked at the real-world analysis of patients who were receiving TAS-102 versus TAS-102 plus bev in a real-world setting, right? So kind of the SUNLIGHT study, but in a real-world setting. And she kind of found similar things, which was, it did support, you know, TAS-102 plus bev seemed to be a little bit better than TAS-102. Really, there was no difference in healthcare resource use. That means, though patients came maybe more times to clinic for TAS-102 plus bev they had the similar amount of ER admissions and other things. So that did not change.

Prof. Tanios Bekaii-Saab
I mean, I think, frankly, the totality of the real-world evidence data fits essentially where you would expect it to fit. Meaning, one, that the real-world data does suggest that patients, the toxicity profile from these agents is very similar whether you look at the real-world evidence databases versus what was observed in clinical trials.

Two, that, you know, perhaps bevacizumab added to TAS-102 is a better option than TAS-102. That's good to see. That just, you know, confirms what we've seen with the clinical trials. Also, you know, suggestion that the flexibility in the dose of regorafenib improves overall outcomes over the standard dose, 160 milligrams, that we've seen.

And again, you know, still, at this point of time, other than the FRESCO2, we don't have a lot of real-world evidence with fruquintinib. But the good news is that the FRESCO2 did show that frequintinib is active regardless of how much you get pre-exposed. So those patients who received rego and followed by TAS or whatever sequence still benefitted the same from fruquintinib. So at least we know it's good salvage regimen and perhaps at some point, you know, start thinking about where to move it in a different line.

And I think the sum of all this is the real-world data is a powerful dataset with all the limitations that we discussed, whether heterogeneity, whether, you know, biases that get introduced here and there.

But overall, the real-world evidence is confirming a lot of the data that we've seen here and there. And when you start comparing things in the real world, what the conclusion ends up being is, well, all these agents work about the same. And it doesn't matter how you sequence them, you're going

to do well for the patient who's going to do well, and maybe not as well, unfortunately, for some of the patients.

But overall, you know, to say that one is superior to the other would be a misstatement, unless we compare them in randomised clinical trials, there's no place for this argument. The only argument that can be made is try your best to expose patients to these therapies sequentially as you feel fit for your patient. So if you start with rego first, I think you're right. If you start with TAS-102 and bev first, you're also right.

Prof. Shubham Pant
I mean, if you do TAS-102 also by itself, maybe then you're also right, right? I mean, the comparison was there in randomised, but again, as you pointed out, 30-28% did not get prior bev, which is a huge, you know, it's a huge factor in maybe driving that response, right? So there are some nuances to every trial. But I think what you're trying to say, Tony, here is that the future is kind of bright. You know, the real-world evidence, I think the use will be more and more. And I think you're right. I think we do need real-world evidence studies as these data sets mature. Because really, do you want to see a randomised study of rego versus TAS-102 versus fruquintinib? Because I mean, what is that? How is that going to move a field forward? It's just a lot of patient resources for no good. So it's better to kind of, you know, classify them according to, you know, RAS status. We have these RAS inhibitors coming out now and really trying to move forward, you know, the field forward with that.

So, Tony, I want to really thank you again. This is always awesome. You know, whenever we both get together, we kind of have a long chat, but, you know, I really appreciate you sharing your insights, and I really want to thank our listeners, we hope you found our discussion useful because really, we think this is a very important discussion to have, kind of, understanding what real-world data is, and importantly, how you can use it in treating your patients. Thank you so much, thank you Tony.

Prof. Tanios Bekaii-Saab
Thank you Shubham, this was great, thank you.

Tonke de Jong
Thank you so much for sharing your insights Professor Bekaii-Saab and Professor Pant.

We've learned a lot from your discussion on interpreting real-world evidence in later line mCRC.

If you liked this episode and want to find out more on GI oncology, then look on the "Oncology Medical Conversation Podcast" under the account of COR2ED medical education for other interesting episodes.

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