# Recent Updates in Refractory Metastatic Colorectal Cancer Management

[MUSIC PLAYING]

Welcome to this expert brief activity. My name is Dr. Sharlene Gill. I'm a GI medical oncologist based out of BC Cancer in Vancouver and a professor of Medicine at the University of British Columbia and really looking forward to our discussion today. I would like to start by acknowledging that I'm coming to you from the ancestral lands of the Coast Salish people and very grateful that this is where I work, live, and play.
And I'm going to start by introducing our expert panel. Welcome to Dr. Eric Chen. Dr. Chen is a staff physician in the Department of Medical Oncology and Hematology at the Princess Margaret Cancer Centre at the UHN in Toronto and an associate professor of Medicine at-- actually, full professor of Medicine at faculty of at the University of Toronto. His activities focus on the treatment of GI cancers as well as clinical trials, evaluating novel agents for the treatment of GI cancers.
I'd also like to welcome Dr. Petr Kavan. Petr is a medical oncologist and an associate professor at the Department of Oncology in McGill University. He's a medical director of the clinical research program, director of the McGill adolescent and young adult cancer program, and co-director of the GI oncology Rossy Cancer Network in McGill. I also have the pleasure of working with both of these researchers as members of the executive at the GI disease site at CCTG. So they have a very prolific clinical trials experience, which we may also get into. So really excited to have you both here.
So we're here to talk about the treatment of patients with refractory metastatic colorectal cancer. And to put it into the context of the current treatment landscape in Canadian clinical practise, we're going to review some of the contemporary evidence, and then really spend our time having a discussion about what are the current controversies, the opportunities, what's optimal strategy and treatment decision making in this increasingly complex setting, even though we know we have much, much room for improvement.
To kick things off, I'm going to hand off to Dr. Eric Chen, who's going to take us through a high level summary of the recent evidence. Thank you, Eric.
Thank you, Sharlene. So I want to thank oncology education for organizing this event and for providing us with this forum to discuss this very important topic. Here are my disclosures. So I want to start things off by presenting a real patient case. So this is a patient that I saw in clinic a couple of weeks ago. So she's 44 years old right now.
Back in 2018, she was diagnosed of locally advanced rectal cancer. She had the standard of care therapy, concurrent chemo radiation surgery, followed by neoadjuvant FOLFOX. Unfortunately, two years later, she was found to have metastatic disease involving lungs, so her disease is MSR stable KRAS mutated. So over the last three years, she has had FORFOX plus Bev and the experimental therapy, followed by FOLFIRI and bevacizumab [INAUDIBLE].
Despite initial control of her disease, her disease now is progressing. So she is still working full time. And so the question really is that what is our option next? So one of the potential options we have right now is the combination of trifluridine and tipiracil.

So among those two chemicals, trifluridine is actually the active drug. However, it is repeatedly metabolized by submitting phosphorylase. So its half life is only about 20 minutes. Tipiracil is an inhibitor of submitting for phosphorylase. So given together, it stabilizes trifluridine and so that the combination can be given orally and can be given twice a day.

Now, there have been some confusion around 5-FU, S1 and TAS-102. As you can see from this diagram, after administration, they all act through by inhibiting thymidylate synthase, therefore DNA synthesis. However, TAS-102 is actually a class different from 5-FU or S1 so it is not metabolized to DPD so that even for patients who has DPD deficiency that TAS-102 can be used safely.

So the record study randomized patients with refractory colorectal cancer to TAS-102 versus placebo. The median overall survival is 7.1 versus 5.3 masses. However, the response rate is generally low, 1.6% only, and about 44% patients with stable disease on treatment versus 16% on placebo.

Side effects wise, hematological toxicity are common. There's 40% patients may actually develop a grade 3 neutropenia. For non-hematological toxicity GI side effects seems to be common, such as nausea, vomiting, decreased appetite, and diarrhea. But fortunately, grade 3 or 4 events are relatively rare with this drug.

Now, last year that at ASCO GI, the satellite study was presented. So it compared TAS-102 plus bevacizumab versus TAS-102 only. And the medium survival is 10.8 months now versus 7.5 months. Now, you can see that the TAS-102 in both the SUNLIGHT and the [INAUDIBLE] study have similar results, 7.51 in one, 7.1 in the other. So if we look at TAS-102 plus bevacizumab versus placebo, the median overall survival now is 10.8 months versus 5.3 months. Again, the response rate is low, only 6.1%.

Interestingly, adding bevacizumab to TAS-102 does not increase hematological or non-hematological side effects except hypertension. About 10% of patients in the study developed hypertension, including about 6% with grade 3 or 4 hypertension, which is really not surprising given that we know the mechanism of action of bevacizumab.

Another potential option is fruquintinib, which is an oral TKI. It binds to all three subforms of VEGF receptors. So the fiscal study is a phase 3 study randomized patients to fruquintinib at 5 milligrams daily, three weeks on, one week off versus a placebo. The study was only conducted in China. Phase 2 is of the same design, but the study was conducted internationally.

Looking at the medium overall survival, you can see that the hazard ratio is essentially the same, 0.65 in one and 0.66 in the other. Looking at the absolute numbers, so the medium overall survival is 9.3 versus 6.57 in FRESCO, and 7.4 versus 4.8 in the FRESCO-2. Again, response rate is low, about 2% to 5%. Most patients has stable disease or treatment.

So why is the difference between FRESCO and FRESCO-2? If we look at the patients enroled in this studies, it seems that patients enroled in the FRESCO study are more likely to be KRAS wild type. They received less treatment. And only 30% patients in the FRESCO study received anti-EGFR therapy versus 70% in FRESCO-2.

So generally speaking, patients enroled in FRESCO studies seems to be less treated, has a better prognosis. I think that those explained why we are seeing the difference in the median overall survival.

Side effects wise hypertension is the most common. And this is really not surprising that including about 30% of patients will develop hypertension on treatment, including about 10% patients will have grade 3 or 4 hypertension.

Now, before I close, I just want to hopefully discuss why the treatment in refractory colorectal cancer has been so limited and progress is so painfully slow. I think we, GI medical oncologists, all look at our colleagues who treated lung cancer with envy like they have made so much progress in lung cancer. And the progress in colorectal cancer has been so painfully slow in the last 10, 15 years.

So this is taken from the clinicaltrials.gov website. So between 2010 to 2023, 75 phase 2, phase 3 trials in advanced colorectal cancer were terminated or withdrawn. 41 of them in the second line or letter setting, and 19 in third line or letter setting. And the agents included immune checkpoint inhibitors anti-EGFR and anti-VEGF agents. So reasons for withdrawal or early termination are lack of efficacy and enrolment.

So I think that we all know that compared to lung cancer, we still do not have comprehensive biomarker testing in colorectal cancer. So far, that only limited panel testing is funded in most provinces in Canada. We do not have looting access to ctDNA testing.

And frankly, we do not understand the tumour biology in colorectal cancer very well. We still talking about right versus left-sided colorectal cancer instead of actual rare tumour biology. We're still we actually teaching our residents and the trainees about the why right colon cancer is different from left-sided colon cancer.

And even when we have options, we do not have timely approval and funding for new drugs. And there's a lot of barriers for us to participate in clinical trials that include excessive regulatory requirements and the costing of participating in clinical trials is going up and up, and this general lack of awareness as well.

I just want to show an example of the benefit of participating in clinical trials. So this is a patient of mine who was diagnosed of metastatic colon cancer in 2018. So he had resection of his primary disease and liver [INAUDIBLE]. And he had adjuvant FOLFOX. But six months after completion of adjuvant FOLFOX, he was found to have metastatic disease, let's say in April of 2019.

His tumour is stable, but he has BRAF V600E mutation. So he participated in a clinical trial, and he completed that two years of therapy. So his treatment completed in May of 2021. As you can see that in May of 2024, three years after discontinuation of all treatment, he has no evidence of disease. So it is important for us to participate in those trials.

And finally, I think that as a community, we are not as active in advocacy as in some other tumour sites. Colorectal cancer is a common disease, and we are a very large community. I think that we need to engage with our patients, our patients' families, their caregivers, and together, that we need to advocate more by only doing so that we can have timely access to those new agents and improve outcome of our patients. Back to you, Sharlene.

Thank you so much, Eric, for not only presenting the evidence, but putting it into the bigger context of how do we apply this in the real world challenges of what our patients are experiencing. So that's all very important. I might start by asking Doctor Kavan. We're talking about refractory metastatic colorectal cancer. And sometimes, refractory is a bit of an ambiguous term. How do you define refractory disease in your practise?

Thanks, Sharlene. Yeah, and let me just congratulate you, Eric. I think Eric, you really did an amazing job. And how you try to highlight the unmet needs, it's amazing. The only thing I would add is age. Because not only we are talking about left, right only, and we don't really talk that much about biomarkers. We even don't take age in consideration, and we know that the age is a factor as well. They have genotypically different disease, young patients.

So refractory cancer, so we all know it's basically cancer not responding to systemic treatment. And the problem is, that we have primary, secondary, and additional resistance. And the resistance is responsible for the disease progression or new lesion.

So, it could be sometimes clinically difficult to decide if this is like progressing to disease, refractory to treatment or not, because of different treatment options. So I'm always careful when it comes to certain drugs, such as IO drugs or drug like regorafenib, because there are some specific radiological findings which can be falsely interpreted as progression. But when we are making the decision, this is not responding disease, and we have to change treatment. We take in consideration not only radiological picture, but biomarkers, biochemistry as well, and the patient condition.

Yeah, and I think also the conventional definition of refractory in colorectal cancer has been 5-FU, oxaliplatin, or irinotecan, Bev, and EGFR, if eligible, if RAS wild type. But we know, and certainly in the studies, Eric, that you reviewed that the eligibility really did change over time compared to the earlier studies, like correct in the original recourse trial where it was that more conventional definition.

So in that timeline, we then had introduction of BRAF targeted therapy for patients with BRAF mutated disease. Some discussions about EGFR rechallenge like does that make sense if you're using EGFR in earlier lines of therapy? So the patient population does change. And maybe, Eric, I might come back to you and ask you a little bit about in the trials that you highlighted both with SUNLIGHT and FRESCO. FRESCO-2 permitted prior trifluridine/tipiracil therapy. Like half of the patients in FRESCO-2 had prior trifluridine/tipiracil therapy. Does that matter? Do those eligibility criteria help you, let's say, if all these options were available in selecting patients? Or how would you decide? Would you use the conventional definition of refractory, or would you use the definition as defined in the trial?

So that's a very good question. And I think that we struggle with that daily in our practise. So I think that we-- traditionally, we define as refractory to all kind of chemo or funded therapy. Now, the matter of the fact is that this therapy that is not funded, that most patients do not have access to. So conventionally, right now, I would think that any patients who have exhausted any funded therapy, they are refractory to me.

But getting to your point about the changing the eligibility, changing the landscape, certainly, that's what we see. So that with patients getting more prior treatment that as a benefit gets smaller.

So maybe, Petr, so as many of the listeners know, in Canada, even now at this time, we don't have funded access in most provinces to trifluridine/tipiracil and still awaiting final negotiations for trifluridine/tipiracil, and Bev for the SUNLIGHT regimen, although there's some optimism that will happen with the positive CATF decision.

But in Quebec, the access has been-- [INAUDIBLE] has had approved the access to trifluridine/tipiracil to Brazil. So I think compared to my practise, you probably have much more experience with this. So how do you think about when you're now seeing sequencing, are you offering SUNLIGHT to your patients? Maybe you can share a little bit about how you're fitting trifluridine/tipiracil in your practise.

It was a huge improvement from our perspective when access to TAS-102 was guaranteed in Quebec. And it actually goes back to your comment, about the lines of therapy when, historically, we were more reluctant to change line of therapy because we have basically only two lines of therapy, or maybe three, not very effective.

So it's true that you don't want to keep patients on ineffective treatment and toxic treatment on [INAUDIBLE] too long because then you are probably losing benefit, and patient maybe won't be fit to

continue treatment and get all lines of therapy available. So that definitely impacted our practise. We are more willing to discontinue chemotherapy if patients wasn't benefiting.
You can put patients on TAS-102 as a preferable drug. The main reason is because the drug is effective, their efficacy is limited. However, it's effective drug. For some patients, and it's clearly clinically less toxic than regorafenib, which was already available in Quebec. And despite the fact, we always dose reduce regorafenib, modify the dose.
And we are very careful with dosing, still, there is a toxicity, which is substantial. So our experience was very positive. And the only side effect really, you can expect, is neutropenia, which is very easy to treat with G-CSF, which is guaranteed in Quebec, is reimbursed in Quebec.
So you don't end up with febrile neutropenia requiring admission. So it was very positive experience. And of course, now, when we have SUNLIGHT trial data, the efficacy can be enhanced by adding VEGF inhibition, such as bevacizumab.
The drug combination is not approved and officially reimbursed in Quebec. However, there is a general agreement that it's an effective drug combination, and we should be doing it. So to my knowledge, pretty much all larger hospitals in Quebec agreed that they will cover these drugs from their budget. And there are ongoing negotiations with [INAUDIBLE] and Aramco about that. But, yes, we are inclined to use drug combination rather than [INAUDIBLE] single agent.
Yeah. And so building on the comment you made earlier about sometimes when we're thinking about choice in this setting like regorafenib or and trifluridine/tipiracil, and then probably next year, we'll be talking about SUNLIGHT and fruquintinib. Fruquintinib, when those become potentially available.
Maybe Eric, I wanted to come back to you and get your opinion a bit on some data that was presented by Professor Ducreux at ESMO-GI. And it was kind of a study trying to look at this question of sequencing. and the study was designed to look at, compare trifluridine/tipiracil to regorafenib in refractory disease versus the alternate sequence of starting with regorafenib and then going to trifluridine/tipiracil.
The study was closed early because the SUNLIGHT data had come out. But they had managed to accrue almost 240 patients. And I think, if you know what they had suggested was that based on being able to go on to both lines of treatment, to Petr's point about accessing all available therapies, and even from a toxicity standpoint, the trifluridine/tipiracil to rego sequence seemed to be more favorable. I wonder if you think that is aligned with what you would have expected in clinical practise. Is that how you think about sequencing currently?
I think that as Petr mentioned already that the side effects from certain drugs certainly is more harder to tolerate. It is possible that if you give patients a more toxic drug that their quality of life may deteriorate. You are not able to go in to give them subsequent lines of therapy. So I think that goes to what we talked about, that try to preserve their quality of life, try to preserve their functional status. so that they get all lines of therapy. I think it's an important consideration for us.
That's a safe answer that covers-- I'm going to pin you down here as we close because-- I think and this question is open to either of you. And then I'll share what my thoughts are. when we are in it going to be in a state. And I anticipate this will happen where we are going to have access to SUNLIGHT. We now have that regimen, probably that 10-month survival is really appealing and median survival. And then we'll potentially have fruquintinib. How will you sequence those when you're seeing a patient with refractory disease, assuming they're both available?

Well, I mean, so I just started to use for fruquintinib. And my first patient's experience is actually quite positive, that the patients-- again, is a young woman and tolerated treatment very well. CA have dropped from $5,000 to 1,000 within two months. And her pain control got better.
So, to answer your question, I don't know, but I have a feeling that we probably more likely going to use TAS-102 and Bev in the third line setting and then if they progress.
It'll obviously depend on patient factors like-- Petr, what do you think about that response?
Yeah, I agree with Eric. And we cannot completely dismiss that quality of life aspect as well. I do feel that TAS-102 and Bev probably has preferable toxicity profile still. We need more experience with fruquintinib. We are just at the beginning, but the data for sure are appealing.
There is another aspect, Sharlene, we don't know well because we don't understand certain biomarkers and certain drugs. But there seems to be some logic with 5-FU base or [INAUDIBLE] based chemotherapy in combination with strong VEGF inhibition such as Bev. And, there is data, that it really work, and it's effective. And when you discontinue Bev, there is a risk, which was never well documented in colon cancer, but well documented in brain tumour patient population that is a rebound effect.
So let's say Eric had patients previously on first, second line, chemotherapy with Bev. And you continue. It makes sense as well. So I would probably take that aspect in consideration as well. And to me, it makes more sense to continue with this TAS-102 strong VEGF inhibition and then go to VEGF inhibition and other pathways and kinase is a different toxicity profile. And then it depends on the approval, how really fruquintinib is going to be approved and reimbursed in Quebec and in Canada. We don't know yet, I guess.
Yeah. Thank you. I mean, this is where you guys are the experts. But these are very nuanced considerations when we think about sequencing. And I would agree with you. I think that would be how I would envision mapping it up out but barring any contraindications to trifluridine/tipiracil.
So I want to thank you all for your insights. Thank you, Eric, for a really great overview. And I think huge unmet need in this space with patients who, as Petr noted, are increasingly younger, when they're presenting in our practise. But there is some hope and optimism that we are having. There are more options that are available. And now, we have the good challenge of trying to figure out how best to sequence it. But it's good that we have these choices for our patients.
And I just want to close by highlighting what Eric had commented about the importance of really thinking big picture, making sure we have optimal biomarker testing, and thinking of clinical trials whenever available. Because obviously, we need to continue to push the needle in this space. So thank you so much. I really enjoyed discussing this with you, and this will bring our discussion to a close. Thank you. Thank you.
[AUDIO LOGO]