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US Biopharmaceuticals

KOL Perspective Call Key Quotes and Transcript: Fruzaqla in mCRC

Industry Overview

Response rate not important for 3L+, toxicity matters

KOL comments emphasized that given the low response rates across the board for all mCRC patients in the 3L+ setting, the most differentiating factor when choosing a treatment in clinic is toxicity. Our KOL said that *"**response rate is not that important, mainly in the third or fourth line, because we know that it's hard to have response rate at this point (regorafenib response rate is ~2%). So it's hard to prescribe a treatment. Then saying this can cause a lot of toxicity (is not going to help**)"*. That said, we remind investors that the later-line mCRC patients tend to struggle with other health-related issues, meaning that taking a treatment that can potentially induce further health complications is looked down upon in the clinical setting. We believe that toxicity could matter more in this group of patients as confirmed from our KOL checks.

Fruzaqla seems to be better tolerated compared to comp

Our KOL checks also confirmed that clinician sentiment regarding Fruzaqla safety/tolerability is favorable as seen from the quote "***So it seems that when I compare toxicity again cross-trial comparisons, it seems that fruquintinib is better tolerated compared to the regorafenib*". Our KOL's note that "*regorafenib can cause a lot of Hand-foot syndrome and asthenia and more symptoms, (and) TAS-102 can cause more alterations in blood counts, which is easier to manage*"** also shows that current treatments do indeed struggle with toxicity issues, while some easier to manage than others, still presents hurdles for patient compliance. While our expert currently is lacking real-life toxicity data for Fruzaqla as the drug has only been recently approved, with the lack of a blackbox included on the label (in contrast to regorafenib) we believe that Fruzaqla can become the safest option for late-line mCRC patients.

Fruzaqla dosing favorable for uptake, pricing non-issue

KOL conversation also yielded an important takeaway: once-a-day dosing for Fruzaqla is a huge step forward for patients. Our KOL says that "***I think there's something that is interesting with fruquintinib and that sometimes we forget about, which is the dose. I mean, it's much easier for our patients when we have something that is one step once a day - one tab once a day, for example, instead of regorafenib***". Given that most patients with late-line mCRC are taking close to thousands of pills in the span of couple of months (some medication is for treatment of other symptoms) and the burden on both pharmacists and the patients as a result of that, we see once-a-day dosing potentially alleviating a lot of pressure on the patient and hence diminish hurdles for commercial uptake. Our KOL also comments on pricing for Fruzaqla, quoting ***"(25k pricing) usually is not a big issue. And I'd say probably I have seen less than 5% of those patients will decline maybe treatment because something like that"***. With pricing also not an issue we see the commercial path forward to Fruzaqla, especially with Takeda expertise, quite straightforward.

04 December 2023

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Abbreviations

mCRC: metastatic colorectal cancer
FDA: Food and Drug Administration
PDUFA: Prescription Drug User Fee Act
NSCLC: non-small cell lung cancer
GC: gastric cancer
PoS: probability-of-success
WAC: wholesale acquisition cost
KOL: Key opinion leader

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Timestamp: 04 December 2023 05:30AM EST

Call Transcript

Operator: This call is not for media representatives or BofA Securities' investment bankers or commercial bankers, including corporate and commercial FX. All such individuals are instructed to disconnect now. A replay will be available for BofA Securities' investment bankers and commercial bankers, including corporate and commercial FX. The replay is not available to the media.

Good day, and welcome to the KOL Insight: Fruquintinib approval implications on mCRC market conference call. Today's conference is being recorded. At this time, I would like to turn the conference over to Alec Stranahan. Please go ahead.

Alec Stranahan: Okay, great. Thank you, operator, and thanks, everyone for joining us ahead of next week's holiday break. We're hosting this call to discuss Hutchmed and Takeda's recently approved drug, FRUZAQLA or Fruquintinib for the treatment of metastatic colorectal cancer. My name is Alec Stranahan. I'm a senior analyst here at BofA covering SMID biotech, and my team is on the phone as well. And I want to highlight John Fan from the team, who did a lot of the work on both of our reports and slides, which we'll go through at the end of the call.

I'd also like to thank our colleagues in Japan, Koichi Mamegano and Ritsuo Watanabe, who cover Takeda and have sent us some questions from a Takeda perspective for KOL as well. I also have the pleasure of being joined by Dr. Tiago Biachi de Castria, who is a medical oncologist at Moffitt Cancer Center and Associate Professor at Morsani School of Medicine. Dr. Tiago, are you there?

Tiago Biachi de Castria: Yes. I'm here. Thanks for having me today.

Alec Stranahan: Okay. Great. Yeah. Thanks for joining us. Great to have you on. So the format for today is we'll do a Q&A focusing on the evolving treatment landscape for metastatic CRC, in particular for FRUZAQLA, which was recently approved, including, competitive setup, pricing, payer access, etc. We'll then conclude with slides outlining our analysis of the known launch inputs today and expectations on trajectory. If you need a copy of the slides, feel free to ping either John or I and we can send them over.

There's also going to be an opportunity to ask questions for Dr. Tiago towards the end of the call, or you can email us or hit us up on Bloomberg and we can relay your questions.

So with that, maybe just give us a sense of your background as a practicing oncologist, Dr. Tiago? And then we can dive into the CRC treatment landscape and fruquintinib specifically.

Tiago Biachi de Castria: Sounds good. So as I said, I'm a medical oncologist. I've been doing only GI medical oncology actually for about 11 years now. I was doing medical oncology in Brazil for many years. I came to US. I spent my first year in the US about three years ago at MSK in New York, and then I joined Moffitt at 1.5 year actually ago. And I'm focused on colorectal cancer for clinical and research and liver cancer as well.

Alec Stranahan: Okay. Great. I guess in terms of CRC, specifically, how many patients are under your care typically, and what does the treatment currently look like for newly diagnosed patients in your practice?

Tiago Biachi de Castria: Yeah, this is a very tough question because - I mean, I have a lot of patients on the way here right now. I would say I have about five - something between five and eight new patients with colorectal cancer. We have something like about 50% to 60% of those patients coming for treatment. They are coming with metastatic disease, unfortunately, probably because we're not screening colorectal cancer properly here in the US.

We do have two main regiments for first-line, of course, FOLFOX/FOLFIRI. I would say about 70% - 60% to 70% of patients here will receive FOLFOX-based chemotherapy in the first-line. We do have data published recently, the PARADIGM trial, that showed that we have improvement in overall survival using Anti-EGFR in first-line for patients with left-sided colorectal cancer.

I don't think we are using as a medical oncologist - from a medical oncologist perspective, I don't think we're using for anti-EGFR for all patients in first-line. So I would say probably we're still doing a lot of FOLFOX plus bevacizumab in first-line. So overall, we have about 50% of patients with RAF mutations. And those patients will receive FOLFOX followed by FOLFIRI or FOLFIRI followed by FOLFOX and or triplet. So with FOLFOXIRI, which is reasonable for a patient with RAF-mutant tumor.

We do have patients with BRAF-mutated tumors. So those patients also will probably they are going to receive triplet in the first-line as well. This is a more aggressive disease. So usually we prefer to use FOLFOXIRI plus bev in the first-line. We don't have many options for targeted therapies like HER2. And in the first-line setting, we have several ongoing studies assessing this subject.

We have about 4% of patients with MSI high disease in metastatic setting, and those patients usually are treated with immunotherapy in the first-line. We have a protocol for pembrolizumab in first-line.

For second-line, as I said, those patients who received FOLFOX, they're going to receive FOLFIRI. Those patients who received FOLFIRI, they're going to receive FOLFOX. So half of our patients with colorectal cancer, we will end up with this discussion that we're going to have today about third-line settings - third line and beyond with our approved options here.

I would say, FOLFOX or FOLFIRI in the first-line, and we do have a quarter of patients receiving FOLFOXIRI.

Alec Stranahan: Okay. Great. That's really helpful. And you mentioned 50% to 60% of your patients entering your clinic with metastatic disease. Could you maybe just elaborate upon the point that you made about detection of CRC in the early stages? And what kind of prior therapies have those patients that are metastatic that come into your practice? Have they been exposed to chemo, anti-VEGF, EGFR, etc.?

Tiago Biachi de Castria: Yeah, this is the interesting. I'm working in an academic center here in the US. So we do have a lot of patients who started treatment outside. So it's a common scenario to see patients receiving two lines of therapy outside. And they're coming to us after the second line. So at that time they will have to receive between clinical trials, TAS-102, regorafenib and now fruquintinib. So - and of course, we have patients coming for first-line.

It's common, for example, for those patients with stage three colorectal cancer, we have for those patients who are having disease recurrence in the future. So depending on risk - I would say high risk stage three we're going to have something like 40% to 50% of recurrence in the future. And of course, those patients who received FOLFOX - adjuvant FOLFOX for stage three, usually they are going to receive FOLFIRI-based chemotherapy in the first-line.

Alec Stranahan: Okay. Got it. And what is the typical prognosis for a metastatic CRC patient that's third line plus? And I guess what - before the fruquintinib approval, what was sort of standard of care in your practice for these patients?

Tiago Biachi de Castria: Yeah. So of course, we have to keep in mind that we're discussing here MSF disease. So those patients with MSI, high these are totally different disease. We use immunotherapy in the first-line maybe in the second-line. And usually, we have a couple of trials with IO combinations for third-line and beyond. So this is a totally different disease.

And - but unfortunately this is only 4% of those patients. And the reason I'm saying this is because the prognosis is also very different. So when we're talking about MSF disease or 96% of patients with colorectal - metastatic colorectal cancer after FOLFOX, FOLFIRI or FOLFOXIRI, we do have two - last week we had two main regimens approved. One is regorafenib and the other one is TAS-102 plus BEV.

So we used to have only TAS-102 or regorafenib. So last year we had the SUNLIGHT trial was published comparing TAS-102 plus BEV. And that trial showed an increase in overall survival. It was 10 versus seven months in overall survival. And since then we started using this combination for those patients without any contraindication for bevacizumab. Usually, this is our preferred third-line.

One of those main reasons is because TAS-102 of course can cause toxicity, but it's more milder toxic compared to for example, regorafenib. Regorafenib can cause a lot of Hand-foot syndrome and asthenia and more symptoms instead of TAS-102 that can cause more alterations in blood counts. So which is usually easier to manage.

So usually TAS-102 is our preferred regimen. And then regorafenib was our preferred regimen for fourth line. Every time that I use regorafenib, usually I started with a lower dose, as was done in the ReDOS trial when they started with two pills per day and checked toxicity. And if the patient can tolerate this two pills per day, then we can increase this to three and then to four pills. So the full dose at the beginning is it's a very toxic regimen. So usually we prefer - I prefer to use this ReDOS regimen.

But for sure until the approval for fruquintinib, our preferred regimen for third-line or fourth-line was TAS-102 plus BEV. I think this is going to stay even with the appropriate approval, mainly because of course we don't have direct comparison. But when we talk - when we take a look at crossfire comparisons, overall survival for our TAS-102 plus BEV was 10 months. So which is higher compared to seven months with FRESCO 2 trial.

So probably we're going to stay using TAS-102 plus BEV even because toxicity as well.

Alec Stranahan: Okay. That's helpful. So just to recap, front-line you've got chemo and then anti-VEGF, maybe an EGFR if it's the patient is RAS wild-type. And then you've got a separate path for MPI high patients with immunotherapy. And then the third-line plus setting you've got regorafenib. You've got TAS-102. But then more importantly you've got TAS-102 plus BRAFF. So that's sort of the setup. And now you've got fruquintinib. My next question is maybe kind of an obvious answer, but I think it's important as we start to talk about the competitive setup and the clinical data between the different third line options.

But I guess when you get a third line plus patient into your practice, what is your goal? What kind of outcome do you want for that patient? And how does that influence your choice of therapy?

Tiago Biachi de Castria: Now, this is not that obvious. I mean - and this is a kind of a tough scenario sometimes because of course, we're looking for studies to base our practice showing improvement in overall survival. But depending on what kind of toxicity this kind of treatment can cause, it's hard to keep a patient on a treatment that, of course, can increase overall survival, but it's causing a lot of toxicity without response rate.

Sometimes for us, response rate is not that important, mainly in the setting, the third or fourth line, because we know that it's hard to have response rate at this point. But it is hard to - for example, with regorafenib response rate is very close to zero, so it's about 2%. So it's hard to prescribe a treatment. Then I'm going to say for this patient, well, this can cause a lot of toxicity. It can cause this, this and this and this term is not going to shrink.

So it's kind of a frustrating. And that's why usually at this point if we have any clinical trial available, this is our first choice always. This is another point. I mean, with TAS-102 plus BEV, it seems the response rate is slightly higher compared to regorafenib. And again, probably, I still prefer the TAS-102 plus BEV because of toxicity profile. So usually less issues regarding toxicity with TAS-102 plus BEV.

Now with fruquintinib available, probably I would say fruquintinib will be placed after - at least on my mind in my clinic till we have any kind of direct comparison for fruquintinib is going to stay after TAS-102 and before regorafenib.

Alec Stranahan: Okay. And that's mostly on the OS. The label –

Tiago Biachi de Castria: Yeah, OS and toxicity profile, I'd say. Yeah. As I said, we don't have this direct comparison. But when we compare across trials, overall survival improvement for fruquintinib was about three months, for regorafenib was about 1.5. And it's more toxic. So I have prescribed two patients. They haven't started actually with fruquintinib. So I'm going to have more data for toxicity probably in about one or two weeks.

Alec Stranahan: Okay. Okay, great. Definitely want to get into your choice to prescribe fruquintinib in those two patients. But maybe just the last high level point before we get into fruquintinib specifically is when you look at third line plus patients, we've talked about the available therapies, including fruquintinib. What is sort of the biggest unmet need for these patients in your view? Is it the duration of response influencing survival? Is it the quality of life on the tolerability? What sort of unmet need is still there?

Tiago Biachi de Castria: I think it's response rate. Yeah, response rate. Usually at this point they're very symptomatic. With carcinomatosis, pain because, pelvic lesions, etc. So usually this is the time that they need response, right? So - and it's hard. As I said, response rate is about 2% with the Regorafenib. It's less than 10% with TAS-102. It was 4% if I'm not mistaken, with fruquintinib. So - and this is kind of frustrating for a patient with symptoms and of course with toxicity from the treatment. So I would say, the most important unmet need here would be response rate.

Alec Stranahan: Okay. That makes sense. And maybe turning to fruquintinib specifically, it was approved a couple of weeks ago. How does the label for fruquintinib, I guess, both compared to what we saw from FRESCO and FRESCO 2, as well as the labels for regorafenib and TAS-102?

Tiago Biachi de Castria: What do you mean?

Alec Stranahan: Sorry?

Tiago Biachi de Castria: Sorry, what do you mean?

Alec Stranahan: Yes. The fruquintinib label. Could you maybe just walk us through how that - your view of the label in regards to competing therapies and also the –

Tiago Biachi de Castria: Competing. Yeah. I mean, it's hard because of course we don't have this direct comparison. Of course, same population, refractory disease. This is a kind of a common scenario. I would love to see more biomarker analysis from these kind of studies. I am part of a kind of a study now trying to do. We're trying to do a whole exome sequencing for patients with TAS-102, for example, to see if we have any biomarker to predict response with this kind of therapy.

It's interesting. I would say it's - I was surprised with the benefit of TAS-102 plus BEV versus TAS-102, because remember the all those patients, they have been treated with bevacizumab before. So I was impressed with this benefit. And I was impressed with the benefit with fruquintinib as well because remember this is the first TKI, but it's still anti-EGFR.

So we're still kind of a focus on the same target. So - but of course it's - it was a very good news having more opportunity.

Regarding the treatment landscape, I would say probably we can stay, of course, with the chemotherapy, the first and second line. And then for the third line, we're going to probably pick up our treatment based on toxicity profile. So for a patient with more cytopenias, that patient is struggling with FOLFIRI-FOLFOX with more neutropenia, etc. Probably I would move away from TAS-102 because myelotoxicity diminish with TAS-102.

And probably in that case I would prefer fruquintinib instead of a regorafenib. This is for sure. So it seems that when I compare toxicity again cross-trial comparisons, it seems that fruquintinib is better tolerated compared to the regorafenib. And it says that the dose that was planned for the phase III with regorafenib, it was too high. So I had this kind of discussion several times.

But when we use regorafenib for even combined to chemotherapy etc, with a lower dose, as we have studies from MSK with - for gastric cancer, etc., this is much better tolerated. And it seems that it's still efficient. So we saw a kind of a promising activity with regorafenib combined chemotherapy versus chemotherapy alone.

So it says that the dose was too high. But so I would say for that patient with more myelotoxicity probably I'll prefer fruquintinib in this scenario. And for those patients with more GI toxicities, etc., before or after this second line, probably I would stay with TAS-102 plus BEV.

For that patient who is kind of a declining for IV therapy, which is not common, maybe I'm going to choose this fruquintinib, but this is not that common.

The contraindication for bevacizumab - I mean, you have to keep in mind that fruquintinib is still anti-EGFR. So if you have a patient with a contraindication to bevacizumab, probably it would be a kind of a contraindication to fruquintinib as well. So - but for that patient with a more milder toxicity makes more sense.

Alec Stranahan: Okay, that makes a lot of sense. Yeah. One thing that stood out to us on the label for fruquintinib versus, say, regorafenib, is the lack of a black box. So I think regorafenib has a black box warning for hepatotoxicity. Is that something that precludes use in your clinic, or is that something that you've seen actually in the real world pop up with regorafenib?

Tiago Biachi de Castria: Not that much. I mean, usually, of course we follow this patient really close. So with labs including. So I mean of course we can hold the dose, we can reduce the dose, etc. I would say the main issue with regorafenib is its symptoms like fatigue or Hand-foot syndrome. Hand-foot syndrome, fatigue. It's - they're by far the most common toxicities and those toxicities that sometimes will have to stop treatment because of that.

To be honest with you, I wouldn't say that we would prefer one rather than the other because this black box. I didn't know that there is a black box for hepatotoxicity sorry with the regorafenib. But of course we do see this in clinic. But I mean, it doesn't matter. This black box for our decision making process.

Alec Stranahan: Okay. It sounds like maybe the dose escalation that you've implemented is maybe helping with that.

Tiago Biachi de Castria: Yeah, definitely. And actually - I mean, I have used regorafenib hundreds of times because it's a kind of a common scenario. Those patients - for those patients, for example, with RAS mutant, I mean, we have only FOLFOX-FOLFIRI and then we have this third line decision making process.

So I have used a lot of regorafenib. Every time I use regorafenib, I start with ReDOS regimen. And all those patients that I have seen response, usually I start response with the dose no lower than the food. So usually I remember that I saw at least two, three responses in those patients with the starting dose. So two pills per day. And so it's clear that the dose that was taken to phase III was too high, at least in my mind.

So I'm totally fine with starting with two times per day and then escalating this. They do have some analysis showing that - of course, if we're going to start seeing this kind of analysis for fruquintinib as well. But with regorafenib, they did a couple of analysis showing that those patients with lung mass, they respond better to regorafenib, etc. So I remember that I had a couple of patients with lung mets with cavitation, etc., with response. But usually those patients with lung mets, they are those patients that they don't even need treatment actually. So usually they are asymptomatic.

So we need something that works for those patients with liver mass and with peritoneum. So that's what I said. I mean response rate is important because usually those patients are symptomatic with a peritoneum mass for example.

Alec Stranahan: Okay. That makes sense. And then one more question in terms of concurrent use of chemo with regorafenib or even, I guess, TAS-102. How common is that in your practice? And how much easier would it be to just administer fruquintinib, which I think is one of the first chemo free regiments approved in the past decade or so?

Tiago Biachi de Castria: You mean combined with chemotherapy?

Alec Stranahan: Yes.

Tiago Biachi de Castria: Well, that would be very interesting. Remember, we do have studies that - actually they were negative using ramucirumab for gastric cancer, for example. And this study from MSK, they combined low dose of regorafenib with a FOLFOX. And then the most recent one, this FOLFOX plus REGO was kind of a four or five years ago. And then more recently they used FOLFOFX, regorafenib and nivolumab and was still well tolerated.

So even regorafenib with a lower dose or with a right dose, maybe, it was pretty safe to combine the chemotherapy. Of course, I'm not aware of any data with fruquintinib combined chemotherapy. That will be something interesting to see. Not only combine to chemotherapy, but if we can offer something for maintenance with a reasonable toxicity, that would be great. Remember that those - I said that 70% of those patients are receiving FOLFOX-based chemotherapy in the first line, but after nine, 10 cycles of FOLFOX, we're going to drop oxaliplatin because neuropathy.

And usually those patients they're going to stay with 5-FU based only therapy as maintenance or capecitabine or whatever. And of course this is not an ideal scenario meaning for the patient with high volume disease. So that's why sometimes I prefer for filming first line for a patient with high volume disease and deliver because I can keep on combination for a longer period of time. So it would be interesting to see first data combining fruquintinib plus 5-FU maybe in maintenance scenario after induction with FOLFOX.

And then after that, probably the next step will be trying to combine this with the FOLFOX. FOLFOX is a chemotherapy that we use for the vast majority of our cancers, GI cancers. And it seems that to be at least it was safe to combine with regorafenib. So it would be interesting to see activity of, for example, fruquintinib with FOLFOX, for example. I think it makes a lot of sense, not only for colorectal cancer, but even for other tumors like gastroesophageal cancer.

Alec Stranahan: Okay, great. That's helpful. I think John from the team had a question on TAS-102 specifically in combo. John?

John Fan: Thanks, Alec. Hi, doctor. Thanks for taking my question.

Tiago Biachi de Castria: Hey, John.

John Fan: Just a quick one for me. So we've been talking about monotherapy like regorafenib. Just I'm wondering, how does combo therapy feed into your prescribing decisions? For example, like Lonsurf, Avastin combos, like what goes into your - what feeds into your decisions and choices when you're prescribing monotherapy versus a combo therapy, for example?

Tiago Biachi de Castria: Usually bevacizumab is very well tolerated. So - and usually those patients have received bevacizumab in the past. So this is not a new drug for the vast majority of those patients. So of course we know that can cause some minor bleeding some hypertension. But usually they have been treated with bevacizumab for years sometimes.

So I don't think adding bevacizumab to TAS-102 is a big issue. And then when we have this cross-trial comparisons, it seems that the SUNLIGHT regimen, TAS-102 plus BEV was superior compared to regorafenib. This is one point. And toxicity. So again toxicity here is the main issue.

So the vast majority of those patients - I can talk to my patient and say well we're going to see a lot of issues with your numbers with this pill with TAS-102. And that's fine. I'm going to follow this. I'm going to reduce the dose and you should be okay. But on the other hand, I had a couple of patients in the past who - I started with the regorafenib and they said, well, I prefer my cancer instead of this pill because I'm feeling crap since I started this because toxicities and [inaudible], etc.

And again, those patients are receiving 5-FU. I don't know, maybe that's why we have more [inaudible] syndrome with acne, but I don't know. But those patients are receiving 5-FU for years which can cause Hand-food syndrome as well. So - and this is very debilitating for the - for our patients.

So I would say this decision is based of course on efficacy. Again, we don't have this direct comparison. So cross-trial comparison about efficacy, overall survival was fewer with TAS-102 plus BEV with ten months for the first time, which is impressive in this scenario. And then toxicity.

John Fan: Got it. Thanks, doc.

Tiago Biachi de Castria: I don't think - to be honest with you, I don't think fruquintinib will pass no surplus valve to the third line. So if I was the CEO - Takeda CEO, probably I would try to focus Marsoni and everything, trying to compare fruquintinib with regorafenib. So you can stay for sure in the fourth line for after TAS-102 and then, of course, try to focus on combinations of fruquintinib with something else.

And why not fruquintinib with TAS-102? I mean, we don't have - it seems that we don't have overlapping toxicities. I mean, with TAS-102, it's more myelotoxicity and - but it's still - it is still kind of a flawed permitting. So it would be interesting to see - and then we have this SUNLIGHT data showing benefit adding bevacizumab, which is an anti-VEGF. It would be interesting to see TAS-102 plus fruquintinib maybe. Why not?

John Fan: Got it. Thanks, doctor. That's it for me. Back to you, Alec.

Alec Stranahan: All right. Great. Thanks, doctor. Maybe next, I'd love to dig in a little bit more into the two patients that you plan to prescribe fruquintinib to. Maybe just to start, what is sort of the history of those two patients? What kind of prior therapies have they received, etc.?

Tiago Biachi de Castria: Sure. So one of them is a gentleman with colorectal cancer, a RAS wild-type disease, but a slow growing tumor. And he received a FOLFOX-BEV in the first line. He had a right-sided tumor actually. He received FOLFOX-BEV in the first. FOLFIRI - let me let me try to remember. FOLFIRI-BEV in the second line, because I didn't use it in that case anti-EGFR in the second line because it was slow growing tumor. So I used FOLFIRI-BEV. Then FOLFIRI - then irinotecan and panitumumab in the third line was a RAS wild-type - BRAS wild-type disease, HER2 negative.

So taking panitumumab in the third line. And then he had - actually was - he participated in a clinical trial in the fourth line. But he was taken out of the trial after two months unfortunately. And then last week I had this kind of conversation. And then I mentioned that now we have these three drugs approved. And actually this is a very nice guy who was always interested and clinical trials, etc..

And when I said, well, this is a brand new drug, we don't have this cross-trial. We don't have this direct comparisons. It seems that this one, it seems to be a more efficient in regarding overall survival. But he was really interested and trying something new. And then that's why I said, well we can try this one [inaudible]. He doesn't have any contraindication for bevacizumab as well.

And actually probably - and this is important. But he lives kind of a far from our center. So he would - and here in front we have this. We have a lot of patients driving kind of a three hours to get treatment here at Moffitt. So this is a gentleman who preferred to stay at home and taking only oral therapy. And we can do a Zoom once a month or so. So - and then that's why I decided to go ahead and prescribe fruquintinib. I'm just waiting feedback from insurance, but it should be okay.

And this was the first guy. The second was a lady. I think she's 40-something, high volume disease actually. She has a KRAS-mutated colorectal cancer. I don't remember the sidedness. She had FOLFOXIRI in the first line. She had response, switch this to maintenance. She stayed with the maintenance for a couple of months, but then she progressed improve with the peritoneal retroperitoneal lymph nodes and more liver lesions. We tried to do - actually at that first I resumed chemotherapy with FOLFIRI. She had some response and she was very symptomatic with a couple of liver lesions.

We did some y90, very focused y90 in a couple of lesions. Was good for her, actually. That was good for her. And after that, yeah, she received TAS-102 plus BEV in the third line or second line maybe. She progressed really quick to TAS-102. She was not eligible for any clinical trial. And she has a very kind of rapidly progressive disease.

And then I saw her probably I think it was one week after FDA approval. And she was interesting, and trying this new therapy. I have discussed with her in the past about regorafenib, maybe because my opinion about regorafenib, she was not so excited with that maybe. So she decided to go ahead and start with fruquintinib. So - actually she was my first patient that I prescribed, so I'm still waiting for the approval. That should be back by Monday or Tuesday next week hopefully.

Alec Stranahan: Okay. That's really helpful. I know it's still early. It was just – fruquintinib was just approved a couple of weeks ago. But have you encountered any challenges with adopting fruquintinib in your clinic or any hurdles to either get it on hand to administer or reimbursement, etc?

Tiago Biachi de Castria: I'll see this approval by insurance, but usually it's not a big issue once this FDA approved. I think there's something that is interesting with fruquintinib and that sometimes we forget about, which is the dose. I mean, it's much easier for our patients when we have something that is one step once a day - one tab once a day, for example, instead of regorafenib.

As I said, I like the ReDOS regimen right for regorafenib, but it's hard for the patient taking thousands of medications to be aware of how many pills he has to take today, when we're going to increase this dose? I mean - and it's even for the pharmacists sometimes it's hard to be on top of all our patients on oral therapy. So which is kind of becoming more and more common.

So it's much easier for the patient that this medication is only one tab once a day for three weeks on [inaudible]. So the dose is something that is very helpful for our patients.

Alec Stranahan: Okay. Great. That's really helpful. Maybe, operator, we could see if there's any questions from anyone on the line. Could you read the instructions for asking a question?

Operator: Yes. Thank you. If you would like to ask a question, please signal by pressing star one on your telephone keypad. If you're using a speakerphone, please make sure your mute function is turned off to allow your signal to reach our equipment. A voice prompt on the phone line will indicate when your line is open. Please state your name before posing your question. Again, please press star one to ask a question. We'll pause for just a moment.

Alec Stranahan: Okay, while we wait for questions to come in, one that I received via email. It's relating to price of fruquintinib. I think they've set a price of 25,000 for the 5 mg for a month, which is maybe slightly higher than what we see for regorafenib or TAS-102. I guess how big a hurdle is price for these patients? How much do they pay out of pocket, if anything at this point?

Tiago Biachi de Castria: Yeah, I would say the - for the vast majority of those patients, it is not a big issue. I have seen a couple of patients who declined, actually. Well, when you start talking about how much benefit they're going to have with this kind of therapy. We're talking about with regorafenib, we're talking about 1.5 months, etc.

I have to say a couple of patients who declined because they're out of pocket cost. This is not common. So - and usually from our side, usually we don't take this into account, to be honest with you. I mean, I just had this kind of a conversation with teaching, for example, to discuss NALIRIFOX versus FOLFIRINOX in the first line setting.

And I would say, well, I mean, of course, we understand that NALIRIFOX, which is more expensive compared to FOLFIRINOX, but we're looking for something better for our patients. So it doesn't matter the cost. At the end of the day, we're looking for something that is better for our patient. So - but of course, we're talking about sometimes an oral therapy, which is more common to see out of the pocket cost.

So I'd say this is usually is not a big issue. And I'd say probably I have seen less than 5% of those patients will decline maybe treatment because something like that.

Alec Stranahan: Okay. Okay. That's helpful. And then another question that came in from a Takeda perspective, who's going to be marketing fruquintinib in the US. Have you had any interactions with Takeda's oncology sales force, either in the past or specifically for fruquintinib?

Tiago Biachi de Castria: This is very interesting. I got an email yesterday actually, and I scheduled a meeting next week I think on Wednesday. So this will be probably - I'm trying to recall here, but this probably will be the first interaction.

Alec Stranahan: Okay. And that was that email was specifically on introducing you to fruquintinib? Sorry, can you say that again?

Tiago Biachi de Castria: Yes, it was.

Alec Stranahan: Okay. Very helpful. Operator. Any questions on the line?

Operator: Not at this time.

Alec Stranahan: Okay, one more question that I got via email, doctor. It's more of a high level question, maybe looking beyond what's currently approved, which has been the focus of our conversation here. But do you see any other treatments coming up the pipeline in clinical studies for advanced metastatic colorectal cancer patients that has caught your attention, or maybe something you're excited about?

Tiago Biachi de Castria: Well, we do have a couple of studies with IO combinations. And this is a very hot topic actually in colorectal cancer because, for example, we had a couple of negative studies combining TKIs and immunotherapy, like regorafenib plus nivo, regorafenib plus nivo-ipilimumab. And more recently we had a study with [inaudible] combination, the [inaudible] combination which is kind of a promising even for colorectal cancer. The main issue for all those studies are - is that those patients with liver mets, they did not have any benefit with the combo.

So - and again, and I had this kind of discussion with people from many companies. We have - we need something that works for liver mets in colorectal cancer. So it doesn't matter if we bring it up a new combo for a patient with lung mets because they are symptomatic. They don't need sometimes any treatment.

So it's unlikely that those combinations will be moving forward. In this scenario if they cannot prove any benefit for patients with liver mets. And then we have a couple of studies trying to combine IO therapies with liver direct therapy. So this is a kind of a promising scenario.

So combining y90 for example, or any kind of - or SBRT or any kind of a local therapy for the liver, plus IO combination. So IO of course is a very hot topic in solid tumor oncology. Unfortunately, works really well for - only for those patients with MSI high disease. But we're trying to identify a subgroup of patients or maybe kind of a different approach for patients with colorectal cancer, MSS disease, maybe using some combination with local therapies for the liver.

I don't know, maybe in the future we're going to see combos with fruquintinib, maybe with IOs, which is something that will be interesting to see because we do have this kind of –

Speaker: Approaching a railroad crossing.

Tiago Biachi de Castria: Sorry. We do have this kind of combination with another tumors, with anti-VEGF and immunotherapy like HEC[?], etc.

Alec Stranahan: Okay. That's helpful. Yeah, I know fruquintinib is in studies, at least in China, combining with sintilimab. And –

Tiago Biachi de Castria: This is the next step. Yeah, actually, I mean, this not only with fruquintinib. All those TKIs we have tried to combine to IO. And we got some good results, actually. For example, with the lenvatinib, we get - we got this approval for endometrial cancer combining lenvatinib and pembrolizumab. I think for renal cell cancer as well. So it seems because this TKIs they can modulate tumor microenvironment.

So it makes a lot of sense. I mean I don't know if for kidney it would be so different compared to regorafenib for modulating the tumor microenvironment. So - but I mean we will need more studies to take a look a little bit deeper on this.

Alec Stranahan: Okay. One last question that I got over email. Going back to the payer access and reimbursement. I guess these are probably still coming online for fruquintinib, but in terms of regorafenib and TAS-102, would you say the majority of patients that come into your clinic, their insurance covers these therapies, or is there maybe some pockets where patients –

Tiago Biachi de Castria: No, no. Sometimes there is some co-pay, but usually it's not a big deal. 99% of those patients insurance covers because it's FDA approved and it's on the NCCN guidelines, which is helpful to get approval by insurance as well. And this is a very unmet need. So usually we don't have any issues with that.

Alec Stranahan: Okay. That's great. Operator, any questions from the line? Otherwise, we'll switch over to the slides that we have.

Operator: There are no questions at this time.

Alec Stranahan: Okay, great. Well, thank you, Dr. Tiago, for your time. That is very, very helpful conversation. We're going to run through some slides now.

Tiago Biachi de Castria: Of course.

Alec Stranahan: You can feel free to drop or stick around if you want to hear our analysis of fruquintinib. But again, really appreciate your time.

Tiago Biachi de Castria: Of course. Thank you.

Alec Stranahan: Okay. Thank you.

Tiago Biachi de Castria: Bye-bye.

Alec Stranahan: So opening up the slides and let us know if you need a copy of these. We can send them over. But flipping to slide two just high level background on fruquintinib. I won't dwell too much here. I think we covered it pretty extensively with Dr. Tiago. But it was based on both the FRESCO 2 and FRESCO data, which is interesting in our view.

The FRESCO study is a randomized global study, whereas FRESCO was actually a China-only study. And it's interesting that the FDA did take both of these studies into consideration and maybe signal some increasing openness, at least as a secondary endpoint to look at non-US data. It's approved in third line or fourth line metastatic CRC. And the approval did come 20 days ahead of the PDUFA. No AdComm, no black box on the label as opposed to regorafenib which was touched on with Dr. Tiago.

And I thought it's interesting that the language included on the label, no requirement to have prior exposure to TAS-102 or regorafenib, which I think was baked into the study designs intentionally. And it does put fruquintinib essentially head to head, competing on level ground with TAS-102 and regorafenib monotherapy. Again, there's some combos that have entered standard of care that Dr. Tiago mentioned. But I do think the use of that varies on depending on each physician's practice and preferences.

And just looking at the label overall survival, it is competitive or slightly superior, particularly against regorafenib, but also TAS-102 both on OS and PFS. Despite a slightly more advanced patient population. Overall safety, pretty much what you would expect with the class hypertension and hand-foot reactions were the most frequent grade three or four AEs, but nothing that would really deter use in our view.

Slide three. Just looking at the market size. CRC is a - it's a large market and underserved, 153,000 patients with CRC in the US, of which 53,000 died in 2023. So even a seven, eight, nine-month extension in survival could be quite meaningful for these patients. And Takeda, they're also pursuing authorization in the EU and Japan, which you can see here on the slide represents a pretty large expansion on TAM[?], if approved.

Our estimates, 25% of CRC patients end up progressing to third line. Plus this could be higher as well. I think Dr. Tiago mentioned 50% to 60% of patients are metastatic by the time they enter his practice. And regorafenib, TAS-102, sales are still gaining momentum, as you can see from the IQVIA sales volume data that we've included on the slide.

On pricing, slide four. And I'd say this is probably the most important slide that we put together. And this is feedback we've gotten directly from Takeda IR post-approval. So the list price of FRUZAQLA is about 25,000 for a 28-day supply and 66,000 - sorry, 6,300 for 1 mg dose. And in Takeda's view around pricing, this reflects its potential as the first novel chemotherapy-free treatment option for biomarker, regardless of biomarker status in the US, which, based on our conversation with Dr. Tiago, that could impact sort of the risk benefit profile for many patients in terms of tolerability, given the monotherapy activity.

The exact cost, I mean, this is pretty standard, but it will depend on a few different factors. So it sounds like they're in ongoing negotiations with payers currently. So the actual price that the insurance companies pay, it sounds like not a ton of the burden of cost is on the patient shoulders. But our expectation is most insurance companies, if not all will cover FRUZAQLA probably in the next six to nine months. And they're currently working with payers to obtain coverage in the US.

And just lastly on slide five and I'll end the call a little bit early, is just a screenshot of our latest model. Ask us if you want a copy of that in terms of the revenue build for fruquintinib in the US, EU and Japan. And I think even though it's maybe 20%, let's say blended royalties to Hutchmed, it's still a pretty meaningful opportunity with very low effort on Hutchmed part. It could be maybe 300,000 at peak. So still a meaningful opportunity.

Obviously, Takeda is well incentivized to support the launch, a strong launch in the US and gain approvals in EU and Japan. And we think this does add another leg to the investment thesis for Hutchmed as well.

So I'll end there. Let us know if you need a copy of anything we've discussed. And thank you so much for joining and have a great Thanksgiving holiday next week. Thank you.

Operator: This does conclude today's conference call. Thank you for your participation. You may now disconnect.

Price objective basis& risk

HUTCHMED (HCM, C-1-9, $18.56)

Our PO of $29 is derived from a probability-adjusted net present value (NPV) analysis, including $7/share for savolitinib, $10/share for fruquintinib, $4/share for surufatinib, $1/share for amdizalisib, $1/share for sovleplenib, -$2/share for other pipeline assets,

$3/share for the commercial platform and $5/share for net cash. We use a weighted-average cost of capital (WACC) value ranging from 7% (commercial platform) to 11% (future pipeline) and terminal value ranging from -5% (legacy business) to 2% (future pipeline).

Downside risks to our price objective are 1) unfavorable efficacy and/or safety data for savolitinib, fruquintinib and surufatinib in clinical trials, 2) weaker-than-expected revenue for commercial platform, and 3) earlier-than-expected or more-than-expected competition for the above-mentioned three leading clinical assets.

Analyst Certification

I, Alec W. Stranahan, hereby certify that the views expressed in this research report accurately reflect my personal views about the subject securities and issuers. I also certify that no part of my compensation was, is, or will be, directly or indirectly, related to the specific recommendations or view expressed in this research report.

US - Biopharmaceuticals Coverage Cluster

Investment rating	Company	BofA Ticker	Bloomberg symbol	Analyst
BUY				
	89bio, Inc	ETNB	ETNB US	Geoff Meacham
	Acumen Pharma	ABOS	ABOS US	Geoff Meacham
	Agios Pharmaceuticals	AGIO	AGIO US	Greg Harrison, CFA
	AlloVir, Inc.	ALVR	ALVR US	Jason Zemansky
	Amylyx Pharmaceuticals	AMLX	AMLX US	Geoff Meacham
	Beam Therapeutics	BEAM	BEAM US	Greg Harrison, CFA
	BioMarin	BMRN	BMRN US	Geoff Meacham
	BioXcel Therapeutics	BTAI	BTAI US	Greg Harrison, CFA
	BridgeBio Pharma	BBIO	BBIO US	Greg Harrison, CFA
	Bristol-Myers Squibb	BMY	BMY US	Geoff Meacham
	Caribou	CRBU	CRBU US	Geoff Meacham
	CRISPR Therapeutics	CRSP	CRSP US	Geoff Meacham
	Eli Lilly and Company	LLY	LLY US	Geoff Meacham
	Erasca	ERAS	ERAS US	Alec W. Stranahan
	Esperion	ESPR	ESPR US	Jason Zemansky
	Exscientia	EXAI	EXAI US	Alec W. Stranahan
	Gilead Sciences Inc.	GILD	GILD US	Geoff Meacham
	HUTCHMED	HCM	HCM US	Alec W. Stranahan
	IGM Biosciences	IGMS	IGMS US	Greg Harrison, CFA
	Immatics	IMTX	IMTX US	Alec W. Stranahan
	Insmed Incorporated	INSM	INSM US	Jason Zemansky
	Intellia Therapeutics	NTLA	NTLA US	Greg Harrison, CFA
	Janux Therapeutics	JANX	JANX US	Geoff Meacham
	Keros	KROS	KROS US	Greg Harrison, CFA
	Kiniksa Pharmaceuticals, Ltd.	KNSA	KNSA US	Geoff Meacham
	Krystal Biotech	KRYS	KRYS US	Alec W. Stranahan
	Kura Oncology	KURA	KURA US	Jason Zemansky
	Kymera Therapeutics	KYMR	KYMR US	Geoff Meacham
	LianBio	LIAN	LIAN US	Geoff Meacham
	Liquidia Corporation	LQDA	LQDA US	Greg Harrison, CFA
	Lyell Immunopharma	LYEL	LYEL US	Geoff Meacham
	MeiraGTx	MGTX	MGTX US	Alec W. Stranahan
	Merck & Co.	MRK	MRK US	Geoff Meacham
	Mineralys Therapeutics	MLYS	MLYS US	Greg Harrison, CFA
	Neumora Therapeutics	NMRA	NMRA US	Geoff Meacham
	Rani Therapeutics	RANI	RANI US	Geoff Meacham
	Regenxbio, Inc.	RGNX	RGNX US	Alec W. Stranahan
	Reneo Pharmaceuticals	RPHM	RPHM US	Jason Zemansky
	Rocket Pharmaceuticals, Inc.	RCKT	RCKT US	Greg Harrison, CFA
	Royalty Pharma	RPRX	RPRX US	Geoff Meacham
	Sana Biotechnology	SANA	SANA US	Geoff Meacham
	SpringWorks	SWTX	SWTX US	Alec W. Stranahan
	Syndax Pharmaceuticals	SNDX	SNDX US	Jason Zemansky
	Travere Therapeutics Inc	TVTX	TVTX US	Greg Harrison, CFA
	Turnstone Biologics	TSBX	TSBX US	Geoff Meacham
	Tyra Biosciences	TYRA	TYRA US	Greg Harrison, CFA
	Vertex Pharmaceuticals Inc.	VRTX	VRTX US	Geoff Meacham
	Werewolf Therapeutics	HOWL	HOWL US	Jason Zemansky
	Xencor	XNCR	XNCR US	Alec W. Stranahan
NEUTRAL				
	AbbVie	ABBV	ABBV US	Geoff Meacham
	Alector, Inc	ALEC	ALEC US	Greg Harrison, CFA
	Amgen Inc.	AMGN	AMGN US	Geoff Meacham
	Arcus Biosciences	RCUS	RCUS US	Jason Zemansky
	Biogen Inc.	BIIB	BIIB US	Geoff Meacham
	Cytokinetics, Incorporated	CYTK	CYTK US	Jason Zemansky
	Editas Medicine	EDIT	EDIT US	Greg Harrison, CFA
	Johnson & Johnson	JNJ	JNJ US	Geoff Meacham
	Moderna	MRNA	MRNA US	Geoff Meacham
	Pfizer	PFE	PFE US	Geoff Meacham
	Recursion Pharmaceuticals, Inc.	RXRX	RXRX US	Alec W. Stranahan
	Revolution Medicines	RVMD	RVMD US	Alec W. Stranahan
	Vir	VIR	VIR US	Geoff Meacham

US - Biopharmaceuticals Coverage Cluster

Investment rating	Company	BofA Ticker	Bloomberg symbol	Analyst
	Y-mAbs Therapeutics, Inc	YMAB	YMAB US	Alec W. Stranahan
UNDERPERFORM				
	CureVac	CVAC	CVAC US	Geoff Meacham
	Day One Biopharmaceuticals	DAWN	DAWN US	Alec W. Stranahan
	Novavax	NVAX	NVAX US	Alec W. Stranahan
	Regeneron Pharmaceuticals Inc.	REGN	REGN US	Geoff Meacham
	TG Therapeutics	TGTX	TGTX US	Alec W. Stranahan
	United Therapeutics Corporation	UTHR	UTHR US	Greg Harrison, CFA

Disclosures

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Hutchmed China Ltd (HCM) Price Chart

B: Buy, N: Neutral, U: Underperform, PO: Price Objective, NA: No longer valid, NR: No Rating

The Investment Opinion System is contained at the end of the report under the heading "Fundamental Equity Opinion Key". Dark grey shading indicates the security is restricted with the opinion suspended. Medium grey shading indicates the security is under review with the opinion withdrawn. Light grey shading indicates the security is not covered. Chart is current as of a date no more than one trading day prior to the date of the report.

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Buy	233	60.21%	Buy	113	48.50%
Hold	83	21.45%	Hold	33	39.76%
Sell	71	18.35%	Sell	25	35.21%

Equity Investment Rating Distribution: Global Group (as of 30 Sep 2023)

Coverage Universe	Count	Percent	Inv. Banking Relationships [R1]	Count	Percent
Buy	1869	53.48%	Buy	1046	55.97%
Hold	828	23.69%	Hold	461	55.68%
Sell	798	22.83%	Sell	370	46.37%

[R1] Issuers that were investment banking clients of BofA Securities or one of its affiliates within the past 12 months. For purposes of this Investment Rating Distribution, the coverage universe includes only stocks. A stock rated Neutral is included as a Hold, and a stock rated Underperform is included as a Sell.

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