Podcast transcript

Update from ASCO GI 2023: lower GI cancer highlights

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Andrea Sartore-Bianchi
Hello and welcome to this podcast covering highlights of lower GI from the 2023 ASCO Gastrointestinal Symposium in San Francisco. My name is Andrea Sartore-Bianchi. I'm a medical oncologist at Niguarda Cancer Center in Milano and associate professor at the University of Milano. And for this podcast, I'm delighted to be joined by Dr. Shubham Pant. Shubham, would you like to introduce yourself?

Shubham Pant
Yes. Andrea, thank you so much. This is such a pleasure to be on the podcast with you to discuss the latest and greatest in ASCO GI 2023. I'm Shubham Pant. I'm a professor of Medical Oncology in the Department of GI Medical Oncology at MD Anderson Cancer Center in Houston, Texas.

Andrea Sartore-Bianchi
Thanks to you Shubham. So I think we can start commenting on the most relevant news from ASCO GI by touching on the SUNLIGHT trial. Why is that? Because the presentation actually of this trial was eagerly awaited, seen since we had the press release last December announcing the positive results. But I think that it was important to understand the magnitude of the benefit observed.

This is a study that was presented by Joseph Tabernero and involved 492, I think, metastatic cancer patients that were treated after two lines of standard treatment to either trifluridine/tipiracil alone or in combination with bevacizumab. So a phase three trial comparing these two strategies. And the endpoint was overall survival and also a secondary progression-free survival.

So we knew and we saw this result. The study was indeed positive, meeting the primary endpoint. There was an improved median overall survival with the combination of beva and trifluridine/tipiracil. Also, I think that it was nice to see those curves of survival nicely separating early and staying well separate throughout the treatment and follow up.

Also, the subgroup analysis was demonstrating a benefit from all sub-groups and in particular there were also patient who had not been previously treated with bevacizumab. And here there was a kind of a greater benefit with the addition of bevacizumab to TAS-102. But we know actually that this is not the case because most of our patient in clinical practice do receive a bevacizumab in an earlier line.

Overall, three quarters of the patients actually were treated with previous bevacizumab, so just to have an idea and to translate that in clinical practice. Also, I think it was important and it was interesting to note that most of the patients were *RAS* mutated, I think this highlights the unmet need of these patients in getting an effective treatment, because in this trial as high as 70% of patients did display a *RAS* mutation. And, as far as response rate is concerned, this was low, but this was expected: we know that these agents are more likely to control and slow down tumour progression rather than achieving shrinkage.

So I think that, looking at the overall results of SUNLIGHT, this clearly indicated, and this was noted in the Congress, that we have a new standard for third-line treatment. And the good thing is that it's together with other approved drugs in this setting, for example, regorafenib. And as far as TAS-102 is concerned, now we know that the combination should be preferred to monotherapy when feasible for that specific patient. So really I think that this trial is in the context of an enrichment of the continuum of care of patients with metastatic colorectal cancer.

And I don't know Shubham if you have any thoughts about this trial or you agree with me on these points.

Shubham Pant
Yeah. Andrea, thank you so much for that eloquent kind of summary of the trial. I always agree with you on most of the things, so I agree with you here. But just to kind of summarise a few key points of this trial, like you said. First of all we were giving the drug in the third-line setting, you know, after the first and the second line, mostly FOLFOX, FOLFIRI or a combination of them. So I think this was this was important because we really saw very interesting curves which are progression-free survival and overall survival. Obviously, like with everything we have to take it with a pinch of salt though I think there was robust benefit because obviously most of our patients, like you said, do get prior bevacizumab. So where does that fit in? But still, even if you continue the bevacizumab, they really do have that benefit that we see because the benefit was pretty significant that we saw.

The second thing is obviously the adverse events. Again, we saw just like bevacizumab, hypertension, some neutropenia was a little bit elevated in the combination. I do think that for third line, you know, we use the drug by itself, but I think the new standard of care, as you correctly said, would be the combination. If you choose to use this drug, you would probably tend to use it now, if patients can tolerate these in combination rather than single agent, because this is an improvement. The other drugs in this space, you know, regorafenib, again, a tough drug to give at the original 160 milligrams, obviously, we dose adjust that drug. So where does that stand? You know, because this was not compared against regorafenib. Does it improve compared to regorafenib? As we saw in the FRESCO-2

trial? Right? Which was in ESMO last year. Now, where does it stand compared to fruquintinib?

But I think the take-home message for our listeners for this trial would be that positive results, significant improvement in overall survival and progression-free survival, unmet need for our *RAS* mutant patients, like you said, you know, 70% were *RAS* mutant. And even if they've been prior treated with bevacizumab, this could be an option depending on the toxicities. Now, the other agents which are coming in the third line setting, obviously they'll have to be consideration where does this fit in with the other agents? But I think if you were using this before, this trifluridine/tipiracil combination, if you were using this before now, we would think about using it for bevacizumab. So like I said, I completely agree with you there Andrea.

Andrea Sartore-Bianchi
Great Shubham. So maybe you want to take some points on other presentations?

Shubham Pant
Yeah. So a lot of exciting presentations that we saw at ASCO GI, this was after some time that we saw some really great data, positive data and some really thought-provoking data coming out of this Congress. So coming to the thought-provoking data is what we discussed *ad nauseum*, and what we keep on discussing is where does ctDNA fit in the whole colorectal cancer and other GI malignancies paradigm?

So I'm going to discuss the Kinetics of postoperative circulating cell-free DNA and impact of minimal residual detection rates in patients with resected stage I-III CRC. And this was an important kind of analysis. It was a retrospective analysis. You know, 16,000 patients plus with stage I-III colorectal cancer were analysed. And one of the important points is when do we really measure the ctDNA for it to have some impact?

So as you and I know, your ctDNA positivity any time after your resection, you almost have 100% specificity, all these patients almost relapse. What we really don't know is what do we do with the data? You know, do we go to experimental treatment? Do we give them more chemotherapy? So it's a little bit more challenging. But to put in context for our listeners, this data was done in patients who were resected and it also looked at if cfDNA, you know like circulating free DNA, it's just the DNA which is released from dead cells versus circulating tumour DNA, is there correlation? And when you should really look at the circulating tumour DNA after resection?

So I think what this data showed was that you can measure the circulating tumour DNA any time, two weeks after the surgery, it gets you know, there's a validation there that after two weeks after the surgery, if you're circulating tumour DNA is negative, you have a high chance of cancer not coming back. If your ctDNA is positive, then you have a high chance of the cancer coming back.

Now, the question really is, if you're positive, your outcomes are worse than if you were negative. The next question, obviously, which is being addressed in multiple trials in the U.S. and in Europe, is how do we improve the outcomes of these patients who are circulating

tumour DNA positive? So I think what I took back from this presentation was that after two weeks of surgery, we can use the circulating tumour DNA and feel confident that will impact the future course of relapse or prognosis in these patients. But I think we just need a lot more prospective data to see how we can improve, really improved outcomes of these patients.

So I'm going to punt it back to you, Andrea, about what you thought of these results and where do you think this whole field is headed? You know, that's the, as they say, the million dollar question.

Andrea Sartore-Bianchi
Right Shubham. You already, I think, touched, greatly touched on the most relevant aspect of this abstract. It seems to be kind of a technical question asked by authors, but indeed I think it was important because as you're saying, we have many ongoing trials and the timing, the draw for blood, for assessing ctDNA can matter. Why is that? Because actually the DNA, the half-life of the DNA is very short. So you are supposed not to have any trace of ctDNA just a few hours after surgery. But cfDNA, so the total DNA can be a confounding factor and especially under stress like surgery, you have more ctDNA. So these data clearly indicated that the first week is not optimal. You want to wait at least to the second week. Then, from the second week on until the eighth week, you should be fine. And luckily this is indeed the window that is adopted by many of the ongoing trials that you mention. And from this point of view, I really think that we are reaching exciting times because this biomarker is here to stay.

And actually in 2022 we had the first data from the DYNAMIC trial in stage two. So this is really historically the first stage three trial. And we have some answer in stage two that you can use this approach. But we know that there are many other trials also in stage three and this is , if you think, is even more interesting, assessing whether we can guide our treatment by giving or not giving or escalating treatment according to ctDNA. We are running in Italy the Pegasus trial, for example. And this, I think it's interesting, is a proof of concept because we have also the option of what to do if the ctDNA stays positive after FOLFOX. So here you have another interesting concept of switching to another adjuvant strategy like FOLFIRI based only on micrometastatic disease.

So really exciting times. This is something that technology brought to us and it will be up to good clinical trials that are really running now this year and next year probably to answer and to to give a clinical utility in everyday practice.

Shubham Pant
What I found fascinating what this field is, Andrea, that you can use this way to deescalate care, really showing more and more of that so that people don't get the neuropathy and with whom can you really deescalate the care, decrease the toxicity from the adjuvant therapy that we give. Now the escalating care, that's I think where it's going to be more challenging. Like the Pegasus trial and everything I think will be great in telling us that, does a delay just delay recurrence if you give something? Or does it truly lead to that cure? Right? That's what we're leading to for patients. Or just gives them stress saying I'm ctDNA positive, I'm going to relapse sometime there's really nothing we can do about it. Right?

Andrea Sartore-Bianchi
Right. We need these answers soon and I'm really optimistic that this tool will be in clinical practice very soon because this trial is really recruiting well.

Shubham Pant
I love your optimism, Andrea, so I'm going to give it back to you to discuss the next abstract.

Andrea Sartore-Bianchi
Right. Thank you. And I thought it was interesting to touch now on another study that was presented. The study with botensilimab and balstilimab. This is a phase 1a/1b study with these two immune checkpoint inhibitors in metastatic colorectal cancer. Now, what is interesting is that here investigators look at MSS tumours, and we know indeed very well that immune checkpoint blockade is strikingly effective in MSI-high tumours but studies available are really clearly indicated that in MSS tumours you have very disappointing results. And we know that this is the vast majority of our patients, 95% in the metastatic setting.

So now it seems that there is something with this combination that is changing the state of things and because why is that? It can be possibly related to the mechanism of action of one of the two monoclonal antibodies. Possibly that botensilimab because actually botensilimab if it's used together with balstilimab might be advantageous because it seems that they can prime better T-cells, enhancing activation and memory formation. And also there is this Fc-enhancing fragment that possibly also can promote the depletion of intra-tumoural TREG. And we know the TREG are actually kind of nasty in precluding response to the MSS tumours.

So now here in this trial, we have this 23% overall response rate. And this is way more than expected in MSS tumours. And on top of this, there was also a lot of control of disease. So more than 50% of all stable disease. So it's not only tumour shrinkage, but it's also controlling tumour growth. So I think really these results are interesting. And in terms of reasoning on data, we cannot mention the difference that investigators saw quite consistently over time in terms of liver involvement. So it turns out that if you have active liver metastases, you don't have a response. So all that 22% was achieved in patients without active liver metastasis. And what is I think very interesting is that we don't know. We don't know why. So there is a biologic possibly underlying this, but we have to investigate more and have more insight. Why is that? But this seems to be consistently observed in this trial, but also in other trials.

So as an overall picture, I think that this combination can have a role. The results should be confirmed, but can have a future also in this tough setting for immunotherapy of MSS tumour, possibly in only liver so-called liver excluded, patients without liver involvement. Shubham, what's your take on this data?

Shubham Pant
Lots of thoughts on this. So first, I wish they would make antibodies that you can pronounce a little bit better. So I'm just going to call it BOT, BOTEN, you know, but again, you know, what you're seeing is very relevant. So I cannot tell you how many negative and you know

this how many negative phase one trials we've run in combining one checkpoint inhibitors with something else in microsatellite stable colorectal cancer.

Shubham Pant
And we've had multiple tumour microenvironment agents, agents which are decreasing TREGS, deregulatory cells that we need lower, you know, given the immune desert microenvironment that we call it. So this was really exciting. I think so. I think it was interesting and I think this is really exciting that we really saw these results in these patients with MSS colorectal cancer.

I think the caveats you mentioned, as they say, the devil is in the details. Right? So the caveats that you really mentioned were first of all, these were patients who did not have liver metastases. But I think that's very interesting. It probably gives a different tumour biology. There are some preclinical data on if you have liver metastases, maybe it enhances the TREGS and does not make the drug more effective. So really, I would love to see the next steps in this drug. Right? The thoughtful drug development, learning from the phase one, taking it all the way to phase three, which could be in, as you know, quite a few patients do have not liver metastases. So I think there is a patient population there.

The second thing is it's interesting to see if both checkpoint inhibitors, but one which is a CTLA-4 inhibitor because of the different construct maybe is active in this setting.

But the third one that I would like to point out is I think this agent is very active and we know that from the colitis, you had about 20% of patients had grade three colitis. And as you and I know that is a significant side effect. So I think we have to really look at how the colitis can be controlled, maybe with dose adjustments versus the efficacy. So interested and excited to see the next steps in the story of combining these agents, because we really do need something for MSS colorectal, that's a high unmet need, as you know.

Andrea Sartore-Bianchi
Thank you, Shubham. And now, do want to touch on some more data?

Shubham Pant
Sure. Going from metastatic or advanced to localised rectal cancer. So I'm going to discuss as our last abstract the long-term results from NRG-GI002, which was a phase two trial. It was a platform trial for TNT, total neoadjuvant therapy, in locally advanced rectal cancer. So essentially what the authors tried to do was create a platform designed so we can really add on agents to the existing standard of care. So the existing standard of care, as you know, with the high risk locally advanced rectal cancer is chemo, maybe followed by long course chemo radiation followed by surgery. So what they did was, they used that backbone of using FOLFOX, eight doses of FOLFOX, followed by long course radiation and capecitabine followed by surgery. But the other arm was combining the veliparib, which was considered as a PARP inhibitor. I'm going to call it PARPish inhibitor or non-PARP inhibitor now. But when the study was designed, obviously this was meant to enhance the radiation induced synthetic lethality that was shown in smaller studies. Right? That this can potentially in preclinical model, that this can potentially do that.

The second one was to combine the capecitabine and the radiation with pembrolizumab. And the scientific thought was that radiation can really enhance the antitumour immunogenicity, reduce the neoantigens, change the cold tumour to a hot tumour maybe, and then utilise that to bring in the checkpoint inhibitor to improve the outcomes. It was a great effort by the group and by the authors and by the cooperative group.

The main takeaway points from this, was that neither veliparib nor pembrolizumab significantly improved the short-term outcomes in unselected patients when compared to TNT and what they really were looking for was this new adjuvant rectal score, NAR was the primary endpoint, so really did not change that. They also looked at pathology, path CR, complete CR rates, overall survival and disease-free survival. Interestingly, you know, pembrolizumab did improve the three year overall survival, but really did not have a significant improvement in the neoadjuvant rectal score or disease-free survival. So interesting. But I really don't know exactly what to do with that data. I think I agree with the authors when they presented it that this trial at least gives us some idea of benchmarking for future looking, advanced rectal trials, so gives us some benchmarks of survival outcomes in these trials. And then we'll see what the subgroup analysis says.

So interesting data, but I think just it's more of... that we'll use it for benchmarking or filing LAR for locally advanced rectal cancer trials rather than really change our standard of care currently. So I don't think it really changes the standard of care, just provides some more interesting data. What do you think about it, Andrea?

Andrea Sartore-Bianchi
Yes, that's true. I think you really described all the strengths and the weaknesses of this approach. And if you think about it historically it's such a difficult setting, the preoperative treatment of rectal cancer. If you remember also those big trials with negative data by adding oxaliplatin during the radiation. Therefore there is kind of a balance that you have to put in place in, and total neoadjuvant at the end is the mainstay now, but it's chemo. If you try to add something different, target treatment or immune therapy, we saw that it's difficult. Maybe because we lack a biomarker to select and this is possibly really the case for PARP inhibitor or for all agents working on DDR because here we are really in colorectal cancer, we don't have so far a good biomarker for using olaparib or other PARP inhibitors, but we know that the DDR is important in these tumour types. But it's so complex that you need to have more than one biomarker probably.

So I really agree with you as far as the outcome is concerned. Given that it is pembrolizumab, so given that it is an immune checkpoint inhibitor, having that prolongation later on in overall survival, it can be difficult to interpret. But when you deal with immune therapy there might be something because we know that the earlier you give the immune therapy, maybe the better you can have in terms of results, even with few administration and on the long course. But this is something that possibly we will see with other trials and also with a longer follow-up.

Shubham Pant
And Andrea, one of the things is, you know, how many of them were MSI High, right? So I didn't really see that. But the question is, if you have 10% MSI high, they could have pushed that survival forward, as we know from multiple trials now that we probably just need to use a checkpoint in these patients and they got a great response, so...

Andrea Sartore-Bianchi
Right, maybe a few patients that are more than enough for or having got that prolonged advantage, yeah right.

Shubham Pant
It was great discussing these articles with you, Andrea. Any final words?

Andrea Sartore-Bianchi
I think really we discussed the abstracts most relevant in the colorectal cancer space. Of course, we have to say that there were many other interesting data, not only colorectal but really interesting it was to see also other tumour types, for example, in high GI location and biliary, hepatocellular. So it was a great Congress. And I think that we really had our discussion, at least of the most relevant presentations for colorectal.

So I would like to thank all the listeners for their attention. Thanks also for Shubham of course for this great discussion.

Shubham Pant
Thank you, Andrea.