Podcast transcript

Update from ASCO GI 2023: upper GI cancer highlights

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This programme is supported through an independent educational grant from Bayer and is an initiative of COR2ED.

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Tonke de Jong
Welcome and thank you for listening to this podcast, where in this episode you will learn more about the exciting updates from ASCO GI Conference 2023, which took place in San Francisco. I am Tonke de Jong and on behalf of COR2ED Independent Medical Education I'm happy to introduce to you today's experts, Dr Dotan and Dr Uboha.

Dr Dotan is an oncologist and chief of the Division of Gastrointestinal Medical Oncology at Fox Chase Cancer Center. Dr Uboha is an oncologist and an Associate Professor of Medicine at the University of Wisconsin. Welcome to you both.

Dr Efrat Dotan
Thank you for having us

Dr Nataliya Uboha
Thank you for having us. It's a pleasure to be here.

Tonke de Jong
ASCO GI is the key conference for updates on potentially clinically changing practices in the field of GI cancers. And in this update we will go through the key upper GI studies presented at the conference and I'm very excited to learn more from today's experts. So welcome again and perhaps, Dr Uboha, you can take us through the first abstract that you have selected to discuss today and tell us why this abstract is of interest.

Dr Nataliya Uboha
Good day, everybody, and thank you for inviting me to discuss some of this new and exciting data from GI ASCO. I will be talking about the Phase 3 SPOTLIGHT trial. SPOTLIGHT trial was a trial that looked at the activity of a novel agent, zolbetuximab in patients with untreated advanced gastroesophageal adenocarcinoma.

Before I go into what zolbetuximab is, let me tell you what it targets, and it targets the proteins called claudins. Claudin 18.2 in particular is a tight junction protein, which is typically expressed in normal gastric mucosa and in many epithelial cells, and its expression is altered in gastric cancer cells. And so zolbetuximab is a first-in-class chimeric IgG1 monoclonal antibody that targets claudin 18.2.

Previously there was a Phase 2 called FAST Study that looked at the activity of this drug in gastroesophageal adenocarcinoma and showed some promising activity. And so at this prior ASCO GI meeting, we saw the results of the next study, SPOTLIGHT study, which was a Phase 3 study looking at the activity of this protein in patients with advanced gastroesophageal cancer.

And so this was a global study. It enrolled close to 550 patients. And patients that were enrolled in this study were randomized to either chemotherapy alone or chemotherapy plus zolbetuximab. And patients that were eligible for participation had to have tumours that had high expression of claudin 18.2. And this was based on the results of the prior phase 2 study that showed that the activity of this molecule was primarily seen in patients with tumours that had high expression of this protein. Claudin 18.2 high expression was defined as moderate or strong, claudin 18 staining in more than 75% of tumour cells. Patients that were eligible for participation also had tumours that had no HER2 expression.

And so the enrolled patients were randomized into 1 to 1 fashion to the chemo or chemo plus zolbetuximab. And the study looked at progression-free survival and overall survival. And this was a very positive study in favour of experimental arm. Overall survival and progression-free survival was significantly improved. Overall survival in particular was improved by about three months, 18.2 months versus 15.5 months. 18.2 months, I think, is the highest overall survival that we've seen in patients with this disease in Phase 3 study. And so was progression-free survival, this was improved as well. Interestingly, response rates stayed about the same in both arms.

And then in terms of toxicity, it's important to note that zolbetuximab has GI toxicity. GI toxicity is seen because this protein is also expressed in normal gastric cells. A significant percentage of patients had nausea, vomiting, decreased appetite in the experimental arm. But other toxicities were as expected as the toxicities that you would see from chemotherapy. And so I anticipate that zolbetuximab will likely gain approval by the FDA for the treatment of this disease.

Tonke de Jong
Yeah, that sounds very interesting. Very impressive results, right?

Dr Nataliya Uboha
I believe so, yes.

Tonke de Jong
Yeah. Could you tell me a bit more about if you think that these findings will impact your patient management now that you go back to the clinic?

Dr Nataliya Uboha
I think absolutely, once the drug gets approved, we will be using this agent in the treatment of patients with this disease. It's also encouraging to know that there was a press release about the partner study called GLOW, which used capecitabine and oxaliplatin as a chemotherapy backbone. And this study appears to have a positive readout as well. We are waiting for the final results, but I believe that's another evidence that this is an active agent that will be utilized.

I think the bigger question will be how do we incorporate this drug into the management tools that we already have since nivolumab is approved in combination with chemotherapy already for the management of HER2-negative disease? And we will have to tease out how best to select patients that are the candidates for one or the other therapy.

Tonke de Jong

Yeah. Do you have any ideas on that Dr Dotan?

Dr Efrat Dotan
Yeah, I think this data is very exciting. Number one, what's exciting in my opinion, is the fact that we have a new biomarker in this disease. And, you know, gastric cancer is turning into a disease where now we can check for HER2 we can look at PD-L1 and MSI expression and now claudin 18.2 and this really helps us personalize therapy much better.

I think everybody's excited to use this drug once it's approved, but another hurdle is the testing. I think we have to understand how this can be done. It's IHC, so it shouldn't be very complicated. But labs will have to figure out how to assess the clinical biopsies and really provide the results and further research is needed to help us understand who starts their treatment with targeting claudin versus an immunotherapy. Is it based on expression of PD-L1? Is it based on claudin expression? I'm not sure how we would sequence this in this patient population.

I believe in this trial the expression of claudin was about 30% of patients that were screened, if I remember correctly. So it's not the majority of patients, but it's definitely a significant number of patients that could benefit from this treatment.

Tonke de Jong
Yeah, thanks. Do you have anything to add on this abstract Dr Uboha?

Dr Nataliya Uboha
You know, I think what Dr. Dotan is pointing out about biomarkers is a question on everybody's mind. Whom do we test? How quickly can we get test results and how do we pick treatment? What this study also showed is that the overlap between high claudin positivity and high PD-L1 positivity was seen in only 13% of patients. And so hopefully we won't have to struggle with this question in too many patients. But of course, we will need to see real-world data regarding the biomarker positivity once we actually start using these drugs.

Tonke de Jong
Yeah, yeah. Okay. I can imagine that the SPOTLIGHT study was not the only promising study at ASCO GI. So are there any more abstracts that we can talk about?

Dr Nataliya Uboha
Well, I think speaking of first-line management of advanced gastroesophageal adenocarcinoma, we should mention Rationale 305, which is a Phase 3 study that looks at the activity of tislelizumab anti-PD-1 antibody in combination with chemotherapy versus chemotherapy alone in patients with PD-L1 positive tumours. It was a positive study in favour of tislelizumab. The study design was similar to the study design of CheckMate 649. CheckMate 649 was a similar study with nivolumab and nivolumab is already approved for this indication in the United States, while tislelizumab is not. So in my opinion Rationale 305 just adds to the body of knowledge that we have about the use of anti PD-1 inhibitors in first-line setting. But is not really a surprising finding per se.

But it was also encouraging to see C CheckMate 649 updated results with longer follow-up. And we are seeing that about 20% of patients are alive at 36 months time point, which is amazing for this disease. And again, just great to see that our tools and management of these patients are growing.

Tonke de Jong
Yeah, great. Great results as well. So would there be any clinical impacts from this abstract?

Dr Nataliya Uboha
I believe we are getting more and more comfortable in using nivolumab in first-line setting and selecting patients for treatment. With nivolumab we know that the activity of this drug is limited primarily to those whose tumours have PD-L1 CPS five or greater. CPS stands for combined positive score. So I don't think it really impacts how we use the drug, but just supports the fact that PD-L1 testing, HER2 testing and hopefully soon claudin testing will be part of our standards.

Another study to mention in advanced setting is INTEGRATE IIa study, and this is the study that looked at the activity of regorafenib in advanced disease. Regorafenib is a multi-tyrosine kinase inhibitor, which is approved for the treatment of colon cancer and also GIST and HCC.

And so this drug, which is antiangiogenic activity, was studied in gastric cancer patients as well. Patients were randomized to either regorafenib or placebo in advanced setting. And the primary endpoint of overall survival was met, it was statistically significant. But the absolute numbers were disappointing, 4.5 months versus four months, questions whether this is a clinically relevant study. But admittedly, it's really hard to perform studies in this patient population because of the aggressive nature of this disease.

The subsequent study to INTEGRATE IIa, INTEGRATE IIb is already enrolling patients and it looks at the combination of regorafenib plus nivolumab versus chemo in similar patient population and my hope is that we will see a stronger signal when this drug is combined with immunotherapy.

Tonke de Jong
Yeah. Yeah. What do you think about this, Dr Dotan?

Dr Efrat Dotan
You know, the INTEGRATE study adds important data that this drug does have activity. There is a role to targeting VEGF and using a tyrosine kinase inhibitor in this disease. I guess one of my concerns with this trial was the dose that was used. The dose of regorafenib was 160 milligrams used daily for three weeks on one week off out of a four-week cycle. And we know from colon cancer and also from HCC that this is not an easy drug. It carries some toxicities and there is some data out there using this in a more gentle dosing schedule. So I was very happy to hear that the INTEGRATE IIb is actually using a lower dose of, I believe, 90 milligrams. And I hope that it could actually be that with the lower dose, patients can tolerate the drug longer and maybe benefit from it more. I think we saw that in the ReDOS trial with metastatic colon cancer, that actually using a lower dose was beneficial because patients were able to be on the drug for longer. So I'm hoping that's going to, again, give us another treatment option for this very aggressive and challenging type of tumour.

Tonke de Jong
Thanks. So I think we now touched upon the metastatic studies. Are there any other studies that were of interest during ASCO GI?

Dr Efrat Dotan
Yeah. I'm going to talk a little bit about the studies that were done in the early stage. The first study I want to talk about is the Neo-AEGIS trial, and this is actually a trial that’s older and it started quite a few years ago, but in fact, it still answers a very important question. The study basically evaluated the use of preoperative chemotherapy versus chemoradiation in patients with oesophageal adenocarcinoma and GI junction adenocarcinoma.

The study enrolled patients with T2-3, M0-3 M0 disease and randomized patients to one of two arms. The preoperative chemotherapy arm started off with the use of ECF for three cycles, followed by surgery, followed by another three cycles of ECF. And later on in the trial, when the FLOT regimen became more standard of care, the study was amended to allow for the use of FLOT regimen, giving four cycles pre-op and four cycles post-op. The other arm was neoadjuvant chemoradiation using the CROSS regimen as was published followed by surgery. And the primary endpoint of the study was overall survival with multiple secondary endpoints looking at disease-free survival, time to treatment failure, toxicity as well as pathologic and surgical outcomes like R0 resection, rate of past CR, post-op complications and quality of life.

So it is very interesting to see the results of this trial. The bottom line was that when they looked at outcomes in terms of path CR, there was a significant difference between the two groups. The path CR rates were definitely higher with the chemoradiation it was 17% versus 5%. In addition, major path CR was also higher. That was almost up to 47% for the chemoradiation group. R0 resection was a little bit higher and then nodal staging was better with the CROSS arm and these were all statistically significant endpoints. However, when they looked at three years overall survival, there was actually no difference between the two arms. So it was 55 versus 57%. They did exactly the same at three years overall survival. I find this data very interesting because despite getting better pathological responses, better surgical outcomes, still the survival was the same.

Tonke de Jong
Yeah, that's interesting. So what would that mean for you and for clinical practice?

Dr Efrat Dotan
Exactly. Well, I think we have been choosing between these two regimens. I'm not sure we had the perfect way to make the choice. It was a lot about surgery and disease team preferences, and now we have data that shows that the survival is not different. I want to point out two caveats that we have to think about in this trial.

Number one, when we look at the pre-op chemotherapy arm, only about 15% of patients actually received FLOT, which is now considered the standard of care and we know that that's a better regimen than ECF. So did that affect how that arm did in terms of the path responses? And the second thing I want to point out is that now for these patients, we know that there is evidence to use nivolumab in the adjuvant setting. So does that affect how the results should be used? Over the time, of course, that this trial was conducted, we added multiple drugs in the metastatic setting. Does that affect the survival? Because we know even though patients can have path CR many of them will be recurrent evolved metastatic disease.

So I don't know if this absolutely changes practice, but I can say I feel very good about using CROSS now. I think it's a better-tolerated regimen and I was very happy to see the response rates that we're seeing. I don't know if Dr Uboha has other insights into this.

Dr Nataliya Uboha
I agree. I really like this study. In the medical oncology community, we have debated for years what's better, CROSS of FLOT or it used to be CROSS or MAGIC. And what this trial showed us that you can use either one and you will get similar results. And of course, the practice has changed both for patients who received CROSS because they get adjuvant nivolumab now, as Dr Dotan pointed out, and for the chemo arm because of using more FLOT. But these regimens demonstrated similar activity. And so either one of those regimens, I think, are appropriate for the management of these patients. I tend to use neoadjuvant chemoradiation for distal oesophageal and proximal GE junction tumours, 0s, 1s and 2s, whenever the tumours are in their stomach or involved GE junction with it,

you know, type 3 fashion I use preoperative chemotherapy. But what this regimen, what this study also showed us is that maybe we don't need as much chemotherapy as four months of FLOT, which is quite toxic if we can achieve similar results with just weekly paclitaxel and carboplatin in the neoadjuvant setting. Maybe more is not better. This was a theme from some of the other sections during GI ASCO.

Tonke de Jong
Yeah, yeah. We definitely need to know more, and discover more. Are there any more abstracts that you would like to discuss or talk about?

Dr Efrat Dotan
Yeah, I think another very interesting abstract in the early stage setting was the INFINITY trial. The INFINITY trial actually focuses on a very specific group of patients, and that is the MSI high resectable gastric cancers or GE junction tumours. This study looked at the use of tremelimumab and durvalumab in the perioperative settings, so in the neoadjuvant setting for a total of three months of therapy. The study included patients with MSI high resectable gastric cancer. The MSI high was centrally confirmed both by IHC and PCR. They included tumours that were T2 or higher with any nodal status and no metastatic disease, and patients received one dose of tremelimumab, 300 milligrams on day one, durvalumab 1500 milligrams was given on day one then once every four weeks, and following that they went on to surgery.

The primary endpoint of this trial was actually pathologic complete response and negative ctDNA status after they completed the neoadjuvant therapy. And of course, they looked at multiple other endpoints within this trial. They accrued a total of 18 patients. However, ultimately they completed the analysis only on 14 because three patients withdrew consent or didn't participate. One patient ultimately decided not to go to surgery. So there were 14 patients for the analysis. And what was really interesting is that the median age of these patients was 71 years old. So actually an older patient population that had MSI status, we have to keep that in mind.

The results were very, very encouraging. They had 60% rate of path CR and if you looked at major to complete path CRs, so like any major pathological response that you would expect and they defined it as less than 10% viable cells, that was up to 80% of the patients. There was one patient that actually was found to have sort of a mixed tumour. There were a few areas that were MSI high and a few areas that was MSI stable and that patients did not have a path CR. And that also adds to the importance of getting good biopsies and really understanding this disease.

In terms of outcome, they had a very good overall survival. There was one patient that progressed and then there were two patients that had perioperative complications and another patient that had secondary disease. But ultimately, they had really, really good responses in the patient that did get path CR. One other interesting analysis that they have done is that they showed that the response was very good in the groups of patients that had T2 to T3 tumours, but those with T4 had a little bit less chances for response. And also they showed that there was a very good correlation between response and TMB status, but not so much with the PD-L1 score.

So to conclude this study, basically we can see that the use of immunotherapy for three months before surgery is highly effective in this patient population. And in fact, the results are so encouraging that there is a second cohort to this trial that's currently ongoing evaluating the option for non-operative therapy for this disease. So patients will get this combination and then will just be followed with a very strict surveillance program with EGDs and scans and ctDNA to make sure they're not recurring and in the face of recurrence will be referred for surgery.

Tonke de Jong
That sounds super interesting. Thanks for giving this overview of the abstracts from ASCO GI. If you could please summarize what you feel have been the key developments of ASCO GI for upper GI.

Dr Efrat Dotan
So I guess I can start I mean, I think at the early stage setting, what we know is that using perioperative chemotherapy versus neoadjuvant chemoradiation ultimately will have the same outcomes. So choose based on clinical factors and more data awaits to try and help us figure out what's better. And if you have a tumour in the early stage setting, please test MSI because the management of these patients based on the INFINITY trial and the prior published NEONIPICA trial, both really, really support the use of immunotherapy in that patient population.

Tonke de Jong
Great. What would you like to add, Dr Uboha?

Dr Nataliya Uboha
I think the key takeaway is that we are starting to personalise care of these patients more and more, both in early stage and in advanced stage. In early stage certainly MSI testing is extremely important, as was just discussed and in advanced stages, we have a novel biomarker claudin 18.2 and there are a number of different agents in development. I believe there were four or five poster abstracts that were GI ASCO, looking at this. So there are going to be more and more agents going into clinical trials and into development. And so again, testing, testing and testing and really picking the right treatment for the right patient at the right time.

Tonke de Jong
Great. Thank you both for summarising this. I feel that you provided me and our listeners with a great overview of the key upper GI studies from ASCO GI 2023. I would like to thank you both for your contribution, Dr Dotan and Dr Uboha.

Dr Efrat Dotan
Thank you. This was a lot of fun and exciting to be part of this.

Dr Nataliya Uboha
Thank you so much for the invitation.

Tonke de Jong
Thank you so much again. If you liked this episode, then you should look out on the COR2ED channel for more. In particular, we will have another episode with an update for you from ASCO GI on lower GI from Dr Andrea Sartore-Bianchi from Italy and Dr Shubham Pant from the USA. So make sure to listen to that episode too. Also, don't forget to rate this episode and share our podcast on social media or with your colleagues. If you want to know more specifically about this episode that you're listening to, then please know that you can download the summary slides on the COR2ED website. Thank you for listening and see you next time.