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Advancing Care in Gastrointestinal Cancers

Announcer
Welcome to CME on ReachMD. This activity, titled *Advancing Care in Gastrointestinal Cancers: A Refreshed View of ASCO 2019,* is provided in partnership with Prova Education and is supported by an educational grant from Merck & Co. and Celgene.

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Here's your host, Dr. Paul Oberstein.

Dr. Oberstein:
An improved understanding of the pathobiology of gastrointestinal cancers and substantial research efforts have led to rapid advances in the treatment and management of these malignancies in recent years. But as new evidence continues to be published and presented at scientific conferences, oncologists are finding it more difficult to stay on top of new information and, more importantly, how best to translate new science into patient care. That's why today we'll be breaking down some of the practice changing data that emerged at the American Society of Clinical Oncology, or ASCO, Annual Meeting. This is CME on Reach MD, and I'm Dr. Paul Oberstein, an Assistant Professor of Medicine and Director of GI Oncology at NYU Langone Perlmutter Comprehensive Cancer Center. Here with me today is Dr. Eileen O'Reilly, an Attending Physician, Professor of Medicine, and Director of Clinical Research at the Rubenstein Pancreas Center at Memorial Sloan Kettering Cancer Center in New York. Dr. O'Reilly, welcome to the program.

Dr. O'Reilly:
Oh, hi. Thank you very much, Dr. Oberstein. It's a pleasure to be here today.

Dr. Oberstein:
So, let's jump right into this. So, what were some of the recent and practice changing abstracts in pancreatic cancer.

Dr. O'Reilly:
So, we had a couple of key abstracts this year. The first one was the APACT study. This was in the adjuvant setting. This was for patients who had resection of their pancreas cancer where they were randomized to either gemcitabine and paclitaxel or gemcitabine alone. So, extrapolated directly from metastatic disease, and I think everybody's expectation was that this was going to be a positive study but to their surprise, there wasn't a clear difference in outcome as adjudicated by the primary endpoints, which was looking at disease recurrence by blinded independent central review, and that's distinct and separate from the patient and separate from the imaging and C – sorry, separate from CA 19-9 and the patient, and that clearly wasn't a good surrogate for outcome. Nonetheless, overall survival looks to be trending positive with a hazard ratio of 0.82. So, we'll have to see where this lands, but I would say right now, this does not impact routine adjuvant practice in pancreas cancer, with Folfirinox for a fitter individual being the reference standard, and for those that are less robust, gemcitabine and capecitabine. What was your take on these data?

Dr. Oberstein:
So, I agree. I think it was a little surprising. We all expected that it would be a very robust signal, but it was somewhere in the middle and it wasn't enough, I think, to change practice, especially given the background of the Folfirinox data from a year ago, which was so positive.

Dr. O'Reilly:
Yeah, so the other important one – and this was a highlight for pancreas cancer. It was on the plenary session this year. So, it was called the POLO study and it was looking at the use of maintenance olaparib in patients with a germline mutation in BRCA1 or BRCA2 and metastatic pancreas cancer, and there were two key points – patients had to be – have disease that was responding to platinum-based therapy and have a confirmed mutation. This was a positive study compared to placebo. Olaparib increased the time to progression of the cancer. There wasn't an obvious impact on overall survival and lots of speculation as to why that might be so, but right now, we would say that this supports the use of maintenance olaparib and this population has an alternative to chemotherapy, which I think for a lot of patients is an attractive consideration.

Dr. Oberstein:
I agree. I think that was a really surprisingly well-done study. I think it required them to screen over 20 – 2,000 patients. I think that was really impressive. Do you think that changes the way we should be screening patients for these germline mutations?

Dr. O'Reilly:
So, the most, perhaps, key point of this is that we should be testing patients for germline mutations. That's now in the NCCN Guidelines as standard of care, and other major guidelines also. So, yes.

Dr. Oberstein:
And as you mentioned, it was single-agent. I'm really curious to know what will happen when we start combining this, but I guess the future studies will answer that.

Dr. O'Reilly:
Yeah, so nice to have new drugs in this disease.

Dr. Oberstein:
So, let's continue with colorectal cancer. What were some of the highlights from recent conferences?

Dr. O'Reilly:
So, I think the beacon data was a major study and just a little bit of background here – BRAF-mutated colorectal cancer, poor prognostic subset, don't tend to do so well with chemotherapy – so this was really interesting looking at a triplet combination of cetuximab encorafenib, and binimetinib in combination to try and overcome the resistance mechanisms as to why BRAF-inhibitors don't work so well in colorectal cancer. And this was a non-chemotherapy combination, and compared to chemotherapy plus cetuximab and doublet and triplet, this was positive – positive data in the second and third-line setting in colorectal cancer, so this is clearly going to be developed and probably will move into frontline setting, and maybe even in the adjuvant setting for this relatively poor-risk subgroup of colon cancer.

Dr. Oberstein:
Yeah, I thought the data were really, really exciting. It's a very hard to treat population, BRAF-mutated colon cancer, and there were definitely robust responses. As you said, hopefully earlier it may actually have even a greater benefit.

Dr. O'Reilly:
Yeah, so we'll probably see a number of trials stemming from this over the next year or two. Exciting.

Dr. Oberstein:
Carrying on – any other abstracts in colon?

Dr. O'Reilly:
Yea, so I think the other one that was of interest – and it was in a poster session, but it caught a lot of people's attention, can you make microsatellites stable GI malignancies responsive to immune therapy? So, this was a combination of regorafenib and a checkpoint inhibitor together in two subsets of diseases in colorectal cancer and in gastric cancer, and nice thing to say was that there were some responses in this setting in microsatellite stable colorectal cancer and gastric cancer, and even some activity in checkpoint refractory gastric cancer. So, if that holds up, that's really interesting, and that needs to be replicated – I think no question about that. We are going to see this combination, right? Being developed in a number of GI malignancies.

Dr. Oberstein:
So, I agree. I think that was very exciting. We're still waiting for the breakthrough in immunotherapy and GI cancers, in general, and especially in colon cancer, and this needs to be validated in larger patients, but it seems like a very promising avenue.

Dr. O'Reilly:

Exactly. And toxicity required some dose adjustment but – for the TKI – but, overall, reasonably tolerated.

Dr. Oberstein:
So, we look forward to those follow-up studies for sure.

Dr. O'Reilly:
Definitely.

Dr. Oberstein:
Great. So, let's continue right on in. How about gastroesophageal cancers. What recent abstracts were interesting to you?

Dr. O'Reilly:
Yeah, so we had a number of key studies presented over the last few months at major meetings. One of them was KEYNOTE-181. This was looking at pembrolizumab in squamous esophageal cancer in the second-line setting compared to chemotherapy, and there was a nice positive signal, particularly in the CPS ≥ 10, and I think that really supports the use of a checkpoint inhibitory now as a second-line study and builds on the nivolumab data in the TRACTION as well in the setting of squamous cell cancer, too, but there was non-selected, so not limited by PD-L1 status. The other, sort of complicated abstract was KEYNOTE-062 – that's a little tricky to get one's head around it, but it had a design looking at immunotherapy plus chemo plus immunotherapy with pembrolizumab as a noninferiority design, and it actually did meet noninferiority with pembrolizumab, and then it looked at the combination in different subsets. So, I think if you have a fit patient with low volume disease and elevated CPS score based on the KEYNOTE-062 data, then you feel comfortable using single-agent immunotherapy. What would be your take on this? It's a little controversial, right?

Dr. Oberstein:
This was a lot of data and it was a lot of work, and it's really complicated, as you said. I think that the most positive thing is the single-agent therapy, which is now FDA approved, for esophageal squamous cancer and second line for CPS ≥ 10, and I think that's, you know, similar to the nivolumab data, which has looked mostly at an Asian population, and even that single-arm – single-line data in first-line gastric cancer where the CPS ≥ 10 group did very well. The flip side, I think, is that the combination with chemotherapy really didn't seem to provide benefit, and that was surprising to a lot of us, and I'm not sure how that's going to impact further trials in that setting.

Dr. O'Reilly:
Exactly. It's – I mean it was expected with the lung cancer data that that might hold true, but it clearly isn't going to be practice changing, but nice to know we have some new options for squamous cell cancer, and just thinking on a global basis, that's actually the most common form of esophageal cancer.

Dr. Oberstein:
But I think that other intriguing aspect, which I don't think we have a final answer to, which is who's the patient with first-line gastric cancer with a CPS score high enough or sick enough that it makes sense to just give single-agent immunotherapy? I think there's someone, but we have to clearly define who that person is.

Dr. O'Reilly:
Yeah, maybe the MSI high subgroup. Maybe the EBV-positive subgroup. PD-L1 CPS ≥ 10, but still a discussion, right? Outside of MSI high and even there it's…

Dr. Oberstein:
Still unclear.

Dr. O'Reilly:
Clearly indicated frontline, yes.

Dr. Oberstein:
And now for our last topic – getting on to hepatobiliary cancers. Was there any really interesting abstracts that popped out to you from the recent meetings?

Dr. O'Reilly:
Yeah, so I think this is getting to be a really crowded space, right? How to treat HCC and a lot of data emerging immune checkpoint inhibitor therapies and where they fit in this disease, so we had the CHECKMATE 040 study , right, long-awaited trial looking at nivolumab versus sorafenib in frontline. And this has taken number of years to mature, but not clearly a positive study, although a signal, not statistically significant, in favor of nivolumab. I think more palliative from the toxicity perspective but based on how the study would – was designed, we would have to say it doesn't move the checkpoint inhibitor into frontline. The other big trial this year was looking at

pembrolizumab versus supportive care in the second-line setting, and both of these trials were following on the conditional approval of the checkpoint inhibitor studies in second line. So, this again was not definitively positive by statistical design, but was a three-month difference in median survival and, as you know, tail on the curve in these diseases with this class of drugs that was of interest. And then I think the third study was the CLARITY study looking at a targeted agent in cholangiocarcinoma in patients with an IDH mutation, so ivosidenib, and this was compared to placebo in second line and positive, providing proof of principle and underscoring the need to look at genetic testing and somatic mutation profiling in patients with cholangiocarcinoma. So those are the big three for me. What did you think?

Dr. Oberstein:
I agree. I think it is gratifying to see one cancer – hepatocellular cancer where immunotherapy does seem to make a difference and we have two approved agents second-line, but as we've seen in these studies, the exact way to use them and whether first-line, second-line, in certain combinations, other data coming out soon, I think still remains to be clarified. The other one, the cholangiocarcinoma, I think that's an area that needs a ray of hope, and I think to see at least a signal, even in a small patient population, is very exciting.

Dr. O'Reilly:
Yeah, so it's getting complex to treat HCC now, right? We have to think front-line, TKI versus whether or not we'll see some data with TKI and checkpoint inhibitors soon. That might suggest that that's going to become a new front-line standard. And then the question will be what to do second line because all of our studies are sort of designed in an older era. It's going to be interesting, but that's – these are good challenges.

Dr. Oberstein:
It's a good problem to have.

Dr. O'Reilly:
Yeah.

Dr. Oberstein:
The fact that there's so many drugs that have been approved in first and second-line in the last five years for HCC, it's going to come out where some of them are going to be combined, and I think we're going to need to do those studies to figure that out.

Dr. O'Reilly:
Exactly. Exciting.

Dr. Oberstein:
So, Eileen, just to conclude, any final thoughts about recent abstracts from these meetings?

Dr. O'Reilly:
Yeah, so in the GI cancer world, I think there's a few key take-home messages. For pancreas cancer, we want to think germline testing. For cholangiocarcinoma, we want to think somatic profiling for these patients, looking for IDH and FGS fusions and other alterations that are potentially targetable. For BRAF-mutated colorectal cancer, to watch the triplet combination, as that gets developed, and I think the continuing evolution of where immunotherapy fits in GI malignancies but it's clearly established now for squamous cell esophageal cancer, potentially for some adenocarcinoma patients, front, second, and third line. So, they would be the key points that I would think about. Yourself? Anything you would like to add?

Dr. Oberstein:
Yeah, I think it's true. I think it's great to see so many studies coming out in GI cancers. They're not all that clear, but I think the continued studies will definitely clarify how we continue to practice. Well, with that, I want to thank Dr. Eileen O'Reilly for sharing her valuable insights into our discussion of Key Data on Gastrointestinal Cancers Coming from the ASCO 2019 Meeting. It was great speaking with you today, Eileen.

Dr. O'Reilly:
Oh, thank you so much, Paul. I enjoyed our disucssion and look forward to the next session in 2020!

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