Gastrointestinal Cancer: Exploring the Latest Studies

Introduction:

Gastrointestinal (GI) cancers encompass a significant number of malignancies that can occur at several sites within the human body, including the alimentary canal (gastroesophageal, colorectal, and anal cancers), the hepatobiliary system (hepatocellular carcinoma and cholangiocarcinoma), and the pancreas (pancreatic cancer, and pancreatic adenocarcinoma). In a recent conversation, two GI cancer experts, Paul Oberstein, MD, Assistant Professor of Medicine and Director of GI Oncology at NYU Langone Perlmutter Comprehensive Cancer Center, and Eileen O'Reilly, MD, Professor of Medicine and Director of Clinical Research at the Rubenstein Pancreas Center at Memorial Sloan Kettering Cancer Center, highlighted some clinical results for GI malignancy-based studies presented primarily at the American Society of Clinical Oncology (ASCO) meeting in June 2019.

Pancreatic Cancer:

In the initial part of their conversation, Drs. O'Reilly and Oberstein discussed recent clinical studies focusing on patients with pancreatic cancer. The first clinical trial mentioned was the Phase 3 APACT study (NCT01964430) which compared the use of nab-paclitaxel plus gemcitabine vs. gemcitabine in the adjuvant setting for patients with surgically resected metastatic pancreatic adenocarcinoma.[1]

Study Endpoint	nab-Paclitaxel/Gemcitabin Arm	Gemcitabine arm	Hazard Ratio
Independent Reviewer-Assessed DFS, Median	19.4 months	18.8 months	0.88 (95% CI: 0.729-1.063; stratified log-rank P = 0.1824)
Investigator-Assessed DFS, Median	16.6 months	13.7 months	0.82 (95% CI: 0.694-0.965; Nominal P = 0.0168
Interim OS	40.5 months	36.2 months	0.82 (95% CI: 0.68-0.996; Nominal P = 0.045

Figure 1 APACT Trial Endpoints: DFS-Disease-Free Survival; OS-Overall Survival.

Regarding these results, Dr. O'Reilly noted, "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." O'Reilly continued, "Nonetheless, overall survival (OS) looks to be trending positive with a hazard ratio (HR) of 0.82; we'll have to see, but I would say right now, this does not impact routine adjuvant practice in pancreatic cancer, with Folfirinox for a fitter individual being the reference standard, and for those that are less robust, gemcitabine and capecitabine."

"I think it was a little surprising," Dr. Oberstein observed, then stating, "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."

In the next part of their discussion, results from the phase 3 POLO clinical study (NCT02184195) were highlighted.[2]

Study Endpoint	Olaparib Arm	Placebo Arm	Hazard Ratio
PFS, Median	7.4 months	3.8 months	0.53 (95% CI: 0.35-0.82; P = 0.004)
Interim OS, Median (46% Data Maturity)	18.9 months	18.1 months	0.91 (95% CI: 0.56-1.46; P = 0.68)

Figure 2 POLO Trial Endpoints: PFS-Progression-Free Survival.

"The POLO study," Dr. O'Reilly explained, "evaluated the use of the PARP inhibitor olaparib as maintenance therapy vs. placebo in patients with a germline BRCA1 or BRCA2 mutated metastatic pancreatic cancer; there were two key inclusion criteria: patients had to have disease that was responding to platinum-based therapy and have a confirmed mutation. Olaparib increased the time to progression of the cancer, yet, there wasn't an obvious impact on overall survival," she noted. "There has been much speculation as to why that might be, 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," O'Reilly stated.

"I agree, I think that was a really surprisingly well-done study." Dr. Oberstein concurred. He then asked Dr. O'Reilly if she thought these results warranted a change in the screening of patients for germline mutations. To this she replied, "So, perhaps the most 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, I would say yes."

Colorectal/Colon Cancer:

Next, Drs. O'Reilly and Oberstein discussed recent clinical studies performed in patients with colon or colorectal cancer (CRC). In a pre-randomization lead-in for the Phase 3 BeACON study (NCT02928224), the triplet combination of cetuximab (an anti-EGFR antibody), encorafnib (a BRAF inhibitor), and binimetinib (a MEK inhibitor) was evaluated in 29 patients with BRAF V600E-mutant metastatic CRC.[3]

Study Endpoint	Safety Lead-In Patient Data
OS, Median	15.3 months (95% CI: 9.6 months-not reached)
12 Month OS Rate	62% (95% CI: 42.1% -76.9%)
ORR	48% (95% CI: 29.4%-67.5%)
DOR, Median	5.5 months (95% CI: 4.1 months-not reached)

Figure 3: BeACON Trial Endpoints: ORR-Overall Response Rate; DOR-Duration of Response.

"BRAF-mutated colorectal cancer, a poor prognostic patient subpopulation, don't tend to do so well with chemotherapy; thus, it was really interesting to look at this combination to try and overcome the resistance mechanisms that hamper BRAF-inhibitors in CRC," Dr. O'Reilly stated. "This was a non-chemotherapy combination, and compared to chemotherapy plus cetuximab and doublet and triplet, this was positive data in the second- and third-line setting in CRC," O'Reilly added. "This is clearly going to be developed and will probably move into frontline setting, and maybe even in the adjuvant setting for this relatively poor-risk subgroup of CRC," she commented.

Agreeing, Dr. Oberstein said, "I thought the data were really, really exciting; it's a very hard-to-treat population, BRAF-mutated CRC, and there were definitely robust responses. As you said, hopefully earlier, it may actually have an even greater benefit."

In the Phase 1b REGONIVO clinical trial (NCT03406871), the use of the tyrosine kinase inhibitor (TKI) regorafenib plus the anti-PD-1 antibody nivolumab is being tested in patients with gastric or CRC.[4]

	All Patients	Gastric Cancer (MSS)	Colorectal Cancer (MSS)	Colorectal Cancer (MSI-H)
Responders	19	11	7	1

Figure 4: REGONIVO Trial Responders: MSS-MicroSatellite-Stable; MSI-H-MicroSatellite Instability-High.

Dr. O'Reilly noted, "These results caught a lot of people's attention; can you make microsatellites stable (MSS) GI malignancies responsive to immune therapy?" Regarding the results, Dr. O'Reilly stated, "There were some responses in this setting, in MSS 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." Seconding this notion, Dr. Oberstein stated, "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 patient groups, but this seems like a very promising avenue."

Gastroesophageal Cancer:

The phase 3 KEYNOTE-181 study (NCT02564263) is evaluating the checkpoint inhibitor pembrolizumab (pembro) vs. chemotherapy (chemo) as a second-line therapy for patients (pts) with advanced/metastatic esophageal squamous cell carcinoma (SCC) and adenocarcinoma (ACC).[5]

Study Endpoint	Pembro Arm	Chemo Arm	Hazard Ratio
OS, Median (CPS ≥10)	9.3 months	6.7 months	0.69 (95% CI: 0.52-0.93; P = 0.0074)
OS, Median, SCC histology (CPS ≥10)	10.3 months	6.7 months	-
OS, Median, ACC histology (CPS ≥10)	6.3 months	6.9 months	-

Figure 5: KEYNOTE-181 Trial Endpoints: CPS-Combined Positive Score; SCC-Squamous cell Carcinoma; ACC-Adenocarcinoma.

"This study," Dr. O'Reilly said, "was looking at pembrolizumab in esophageal SCC in the second-line setting compared to chemotherapy, and there was a nice positive signal, particularly in those patients with combined positive scores (CPSs) of 10 or greater."

The Phase 3 KEYNOTE-062 study (NCT02494583) is evaluating the use of the anti-PD-1 antibody pembrolizumab alone or in combination with chemotherapy vs. chemotherapy in patients with advanced gastric or gastroesophageal junction adenocarcinoma.[6]

Study Endpoint	Pembro Arm	Chemo Arm	Hazard Ratio
OS, Median (CPS ≥10)	17.4 months	10.8 months	0.69 (95%CI: 0.49-0.97)

Figure 6: Keynote-062 Trial Endpoint: CPS- Combined Positive Score.

Regarding this trial, Dr. O'Reilly observed, "This trial is 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; this study actually did meet noninferiority with pembrolizumab, and then it looked at the combination in different subsets." Summarizing, Dr. O'Reilly commented, "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."

When asked what his view on these results were, Dr. Oberstein 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 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," Dr. Oberstein stated, "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."

Hepatobiliary Cancers:

"There are a lot of data emerging about how to treat hepatocellular carcinoma (HCC), specifically around immune checkpoint inhibitor therapies," Dr. O'Reilly observed. The first trial discussed was the phase 3 CheckMate-459 study (NCT02576509), which assessed the use of the checkpoint inhibitor nivolumab vs. the TKI sorafenib as a first-line therapy in patients with advanced HCC.[7]

Study Endpoint	Nivolumab Arm	Sorafenib Arm	Hazard Ratio
OS, Median	16.4 months	14.7 months	0.85 (95% CI: 0.72–1.02; P = 0.0752)
12 Months OS	59.7%	55.1%	-
24 Months OS	36.8%	33.1%	-
PFS, Median	3.7 months	3.8 months	-
ORR	15%	7%	-

Figure 7: CheckMate-459 Trial Endpoints.

Dr. O'Reilly stated, "This was a long-awaited trial looking at nivolumab vs. sorafenib in frontline; the data have taken several years to mature, but not clearly a positive study, although a signal, not statistically significant, in favor of nivolumab. Based on how the study was designed, we would have to say these results don't warrant moving the checkpoint inhibitor into frontline," she noted.

The phase 3 KEYNOTE-240 clinical trial (NCT02702401) compared pembrolizumab to best supportive care as a second-line therapy for patients with advanced HCC.[8]

Study Endpoint	Hazard Ratio	Result
OS	0.78 (one sided p = 0.0238)	Significance not met
PFS	0.78 (one sided p = 0.0209)	Significance not met

Figure 8: Keynote-240 Trial Endpoints.

Dr. O'Reilly noted of the trial that "the results were not definitively positive by statistical design, but there was a three-month difference in median survival, and, as you know, the tail on the curve in these diseases with this class of drugs that was of interest."

Another important study is the phase 3 ClarIDHy trial (NCT02989857) evaluating ivosidenib vs. placebo in patients with advanced cholangiocarcinoma bearing an isocitrate dehydrogenase 1 (IDH1) mutation.[9]

Study Endpoint	Ivosidenib Arm	Placebo Arm	Hazard Ratio
PFS, Median (Centrally-Assessed)	2.7 months	1.4 months	0.37 (95% CI: 0.25- 0.54; p < 0.001)
6 Month PFS Rate	32.0%	0.0%	
12 Month PFS Rate	21.9%	0.0%	
OS, Median (ITT Analysis)	10.8 months	9.7 months	0.69 (one-sided p = 0.06)

Figure 9: ClarIDHy Trial Endpoints.

"These results were positive, providing proof of principle and underscoring the need to look at genetic testing and somatic mutation profiling in patients with cholangiocarcinoma," Dr. O'Reilly explained.

Regarding the current state of hepatobiliary malignancies, Dr. Oberstein observed, "I think it is gratifying to see one cancer – HCC, 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 added, "It's getting complex to treat HCC now, as we have to think front-line, TKI versus whether or not we'll see some data with TKI and checkpoint inhibitors soon."

Conclusion:

When offering her assessment of the current state of treatment for GI cancer, Dr. O'Reilly stated, "I think there are 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 CRC, 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, in the front-, second-, and third-line settings." To this, Dr. Oberstein added, "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."

References:

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