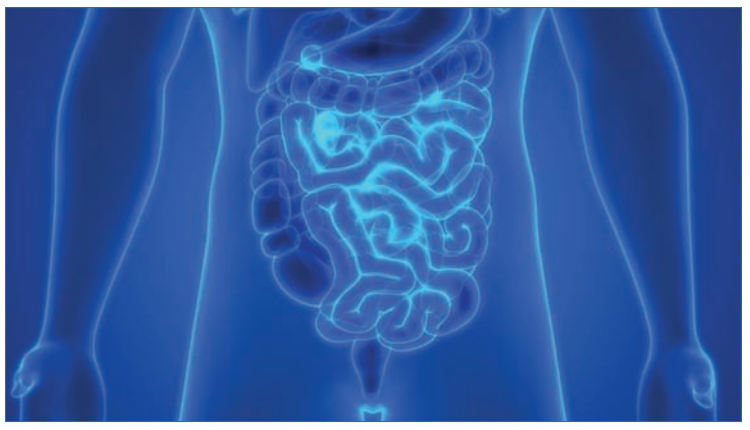
Driving Change in Small Bowel Adenocarcinoma

BY CHUCK HOLT

Katrina Pedersen, MD, MS, was investigating the molecular biology informing the development of pancreas cancer at the Mayo Clinic in Rochester, Minn., under the leading small bowel adenocarcinoma (SBA) researcher, Robert McWilliams, MD, when promising results from trials of immunotherapies for cancer began to be reported.

"This was during the very early, heady days of immunotherapy, when everyone was wondering, 'OK, it works for melanoma. But will it work for these other cancers?'" said Pedersen, Assistant Professor of Medicine, Division of Medical Oncology at Washington University School of Medicine in St. Louis.

To find out if immunotherapy is active in SBA, the researchers began looking at PD-L1 expression using a bank of tumors. Their work would eventually lead to the ZEBRA study, which is the first and largest-ever clinical trial of immunotherapy for SBA led by Pedersen, who also was lead author of the first set of SBA-specific guidelines from the National Comprehensive Cancer Network (NCCN) released in August.



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Prior to the Pedersen-led clinical trial, prospective studies had confirmed the activity of 5-FU and oxaliplatin (FOLFOX), as well as a combination of bevacizumab and CAPOX. However, there remains no standard of care for metastatic disease beyond the first line, while second-line treatments emulate colorectal cancer.

Recent studies suggest SBA tumors have a distinct genomic profile with higher incidence of microsatellite instability compared to gastric and colon cancers, and a tumor microenvironment reflecting a higher degree of PD-L1 expression and tumor infiltration by lymphocytes. Immune checkpoint inhibitors, however, had not previously been tested in SBA unselected for MSI status.

The Pedersen-led study would change that. The ZEBRA trial, a phase II, multicenter, single-arm clinical trial of pembrolizumab (200 mg IV every 3 weeks) was designed for patients with unresectable or metastatic SBA refractory to first-line chemotherapy.

The primary objective of the study was assessing confirmed response rate (H0 p < 10%, HA: p >30%) to pembrolizumab. Secondary endpoints were PFS, OS, and adverse events. Correlative aims included assessing blood and tissue biomarkers (i.e., PDL1, MSI-H/MSS status, cfDNA biomarkers, mutation burden, etc.,) for association with clinical benefit. Tumor responses were analyzed every 12 weeks for overall response rate (ORR) per RECIST v1.1 criteria (NCT02949219).

"What we found was that the rates of expression actually were much higher for [SBAs] than for colorectal cancer (CRC). And that was very interesting because [SBA] traditionally has been treated like [CRC] as though the tumors were the same thing," Pedersen said. "So, because the rate of expression was so much higher than with CRC, we thought, 'Can people with [SBA] actually respond to this?'"

MSI-high had been identified as a predictive biomarker of CRC, indicating an immune checkpoint inhibitor like pembrolizumab or nivolumab, she said. "But that's only 4 percent of the metastatic colon population, so a very small group gets benefit out of it. It is a very real benefit, however. It is very durable and patients can live for months or years."

The question was whether MSI-high SBA would respond. "We were seeing this much higher portion of patients with PD-L1 expression in upper GI cancer, like esophageal or gastric cancer. For them, PD-L1 positivity suggests that they might get some benefit from immunotherapy as well," Pedersen said. "And that's where that trial came from. I drafted the study under Dr. McWilliams' tutelage and it opened at six centers nationwide."

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The clinical trial recruited 40 patients in just 15 months, which was much faster than expected for such a rare cancer. The primary endpoint was not met, however, Pedersen said. "We were hoping to see a 20 percent response rate to immunotherapy and a mixed population of MSI-high and MSS patients," she noted. "That was not the case."

"But what's interesting is when you look at those patients whose tumors maybe did not shrink by 30 percent, they also did not grow during treatment," she noted. "Preliminarily, through 65 percent of our patients, we have a 50 percent response rate in the MSI-high patients and a 50 percent disease control rate in MSS."

The results were in line with what they were seeing in CRC with nivolumab and pembrolizumab, so it was reasonable that pembrolizumab for SBA would be about the same rate as CRC, Pedersen said. Two patients with MSS also responded, although one is unconfirmed. "And that is interesting as well, because it is higher than you would expect to see with colorectal cancer."

The final results of the study should be ready for publication early in 2020. "We're finalizing this now," Pedersen said. "And then we are doing some other biomarker analyses to see if we can figure out how to select these MSS patients who might derive some clinical benefit from immunotherapy treatments."

A Big Shift

SBA and CRC share some characteristics, such as developing in the adenoma-carcinoma sequence; occurring more often in patients with familial adenomatous and hereditary nonpolyposis colon cancer; and developing, or co-occurring, in the same patient.

There are many differences, however. For example, despite the small intestine having a much larger surface area than the large intestine, SBA is very rare. It is diagnosed in an estimated 3,600 to 4,200 people the U.S. annually.

By comparison, there were 101,420 new cases of colon cancer and 44,180 new cases of rectal cancer diagnosed in 2018 alone, excluding metastatic melanoma, and more than 51,000 CRC-related deaths are expected in 2019.

Five-year survival rates are also significantly worse for patients with stage I and stage II SBA (<30%) than with localized CRC (90%) and all stages of CRC combined (65%). Possible explanations for the disparity may include delayed diagnosis due to difficulty imaging small bowel tumors, a lack of prospective data on SBC, and a high rate of immunosurveillance in baseline small bowel function.

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Citing these differences, as well as the increasingly rapid pace of SBA research and discovery due to strong multi-institutional collaborations, Pedersen recommended NCCN develop SBA-specific guidelines for patients. The NCCN Steering Committee welcomed the idea, and the new guidelines were published in August 2019.

The new guidelines provide recommendations on the workup of SBA, primary treatment options, adjuvant treatment, surveillance, and systemic therapy for metastatic disease. Additionally, principles of imaging and endoscopy, pathologic review, surgery, radiation therapy, and survivorship are described (*J Natl Compr Canc Netw* 2019; doi:10.6004/jnccn.2019.0043).

"Currently, in early disease management there is a high degree of extrapolation from what we know about [CRC], particularly with adjuvant chemotherapy and employing it for stage III [SBA], and for patients with a high-risk profile for stage II," Pedersen said.

"But in the metastatic setting, there are more differences between SBA and CRC in how we use chemotherapy. Unlike colon cancer, for which FOLFOX/FOLFIRI have been found to be essentially equivalent to each other in the first line and the second line, only prospective data exists for oxaliplatin-based chemotherapy in frontline SBA treatment. For that reason, we do not recommend FOLFIRI upfront. It's probably active, but since we don't have the same level of evidence, we recommend reserving it for a second- or later line of treatment."

Another significant difference from CRC is that taxanes are active in SBA, Pedersen added. "The only prospective data available is on nab-paclitaxel, but retrospective studies appear to show benefit with other taxane regimens as well. So that opens up a whole new option for patients with stage IV incurable SBA that they might not have otherwise had per the prior guideline structure.

"One might think that taxane activity makes sense, because about 70 percent of SBAs occur in the duodenum, which is proximate to the pancreas and biliary tract," she said. "But the study shows that people with tumors in the jejunum and ileum actually respond to it as well. And that is a big shift."

Meanwhile, a global adjuvant therapy trial led by Mayo's McWilliams and the International Rare Cancer Initiative (IRCI) SBA group is helping answer a basic but very important question while also helping to expand the knowledge base of SBA, according to Pedersen.

"We have never had a clinical trial taking a look at whether chemotherapy actually help patients following surgery, which is incredible really," she said. "But with our study, the IRCI study, and an upcoming SWOG trial helmed by Michael Overman [MD] from MD Anderson prospectively assessing FOLFIRI versus ramucirumab and paclitaxel, we are building a foundation from which we can learn so much more about the biology of this cancer. And that is really exciting." OT

Chuck Holt is a contributing writer.

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Learning Objectives for This Month's Activity:

After participating in this activity, readers should be better able to:

1. Analyze recent developments in understanding and treating small bowel cancer adenocarcinoma (SBA).
2. Compare and contrast characteristics of SBA and colorectal cancer (CRC).

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