Interview

In this expert interview, John Strickler, Professor of Medicine at Duke University, discusses pivotal advances in colorectal cancer treatment, including findings from the landmark MOUNTAINEER and NICHE-2 trials. He reflects on the growing role of molecular profiling, the promise of non-invasive testing, and the future of immunotherapy in gastrointestinal oncology.

Featuring: John Strickler

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Q1 As the lead investigator of the MOUNTAINEER trial, what were the key findings, and how have they impacted the treatment of *HER2*-positive metastatic colorectal cancer?

It has been known for years that there is a small subgroup of patients with colorectal cancer who have *HER2*-positive disease, which can be detected by various assays, including immunohistochemistry (IHC), fluorescence *in situ* hybridization (FISH), and next-generation sequencing (NGS) panels.

The goal of the MOUNTAINEER trial was to assess the activity, safety, and tolerability of a chemotherapy-free regimen for patients with *HER2*-positive, *RAS* wild-type metastatic colorectal cancer. The primary endpoint was objective response rate by blinded independent central review. The trial demonstrated a response rate in excess of 39%, which substantially exceeds the alternative standard of care options. Additionally, progression free survival exceeded 8 months, and overall survival approached 2 years. Overall, the study was successful; it demonstrated the safety, tolerability, and substantial clinical activity for a chemotherapy-free regimen. As such, it has been approved by the FDA for patients with *HER2*-positive *RAS* wild-type metastatic colorectal cancer, and represents a highly effective option for these patients.

> **We can use molecular profiles to find personalized treatment pathways**

Q2 You led the clinical trial that resulted in the first FDA-approved therapy for *HER2*-positive metastatic colorectal cancer. How have these findings reshaped treatment approaches in this area?

What this shows is that, instead of a one-size-fits-all approach for treatment of metastatic colorectal cancer, we can use molecular profiles to find personalized treatment pathways. This is part of a larger trend for cancer treatment:

oncologists are checking a tumor's molecular profile and then tailoring a treatment regimen to attack molecular vulnerabilities. This paves the way, not just for *HER2*-positive colorectal cancer, but also for other molecular alterations, whether it be *BRAF V600E*, microsatellite instability (MSI)-high, *KRAS G12C*, or other actionable variants.

Q3 Your work emphasizes non-invasive testing, such as liquid biopsies, to identify genetic drivers of treatment resistance. How do you envision these technologies transforming clinical practice in gastrointestinal oncology?

Molecular testing has been critical to the advancement of personalized treatment algorithms. However, there are a couple of challenges that we face in the clinic. The first is that, occasionally, tumor tissue is not available for testing, in which case we need an alternate way to assess these actionable molecular targets. Second, especially in colorectal cancer, needle biopsies may not provide a complete picture of the tumor's genomic diversity.

The use of non-invasive testing addresses these challenges: it allows a safe and convenient way to access tumor DNA, it assesses all the disease in the body simultaneously, and it allows us to assess tumor evolution over time. It is a highly effective complement to tissue testing.

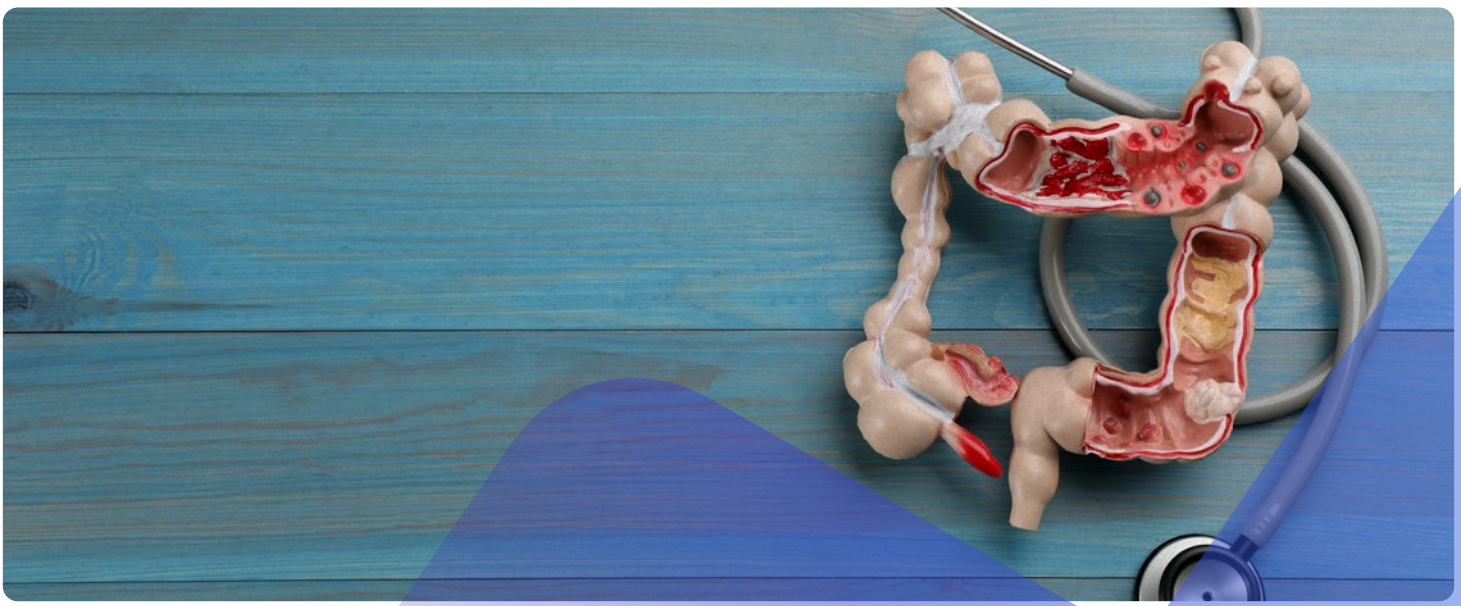
Every test has its strengths and limitations, but many of us have found that, when you add non-invasive, blood-based testing together with tissue testing, you get a more complete understanding of the molecular drivers of a tumor, and you're better able to create a personalized treatment algorithm for a patient.

Q4 From your experience, what has been the biggest breakthrough in gastrointestinal oncology in the past decade?

One of the most exciting developments that we've had in this space is the emergence of immunotherapy for patients with metastatic colorectal cancer, especially those with mismatch repair-deficient or MSI-high tumors. We learned approximately a decade ago that immune checkpoint inhibitors are highly effective for this subgroup of patients. Additionally, we've been able to extend that work into specific areas beyond metastatic disease, to patients with earlier-stage disease, which has been quite interesting and exciting. Now we're starting to look at ways to extend those groundbreaking results to patients who have immunotherapy-resistant disease, specifically those patients with microsatellite stable disease. It is work that's ongoing, but I think this represents a paradigm shift for treatment of patients with colorectal cancer.

Q5 You have previously spoken on the NICHE-2 trial, which assessed the use of immunotherapy for non-metastatic MSI-high colon cancer. Could you summarise the key findings and outline the next steps in this research?

The NICHE-2 trial exemplifies some of these groundbreaking developments for patients with MSI-high or mismatch repair–



deficient colon cancer. What's unique about NICHE-2 is that these patients had non-metastatic disease (earlier-stage colon cancer). The current standard of care is to send these patients directly to surgery, and give them adjuvant chemotherapy if they have high risk disease. However, chemotherapy is generally ineffective for these patients. Additionally, in the metastatic setting immunotherapy is superior to chemotherapy.

The NICHE-2 study included patients with previously untreated, non-metastatic, mismatch repair-deficient colon cancer (dMMR/MSI-H), all of whom had either clinical Stage T3, clinical Stage T4, or node-positive disease based on radiographic staging. Patients received one dose of ipilimumab and nivolumab, followed by a second dose of nivolumab, and then went on to surgery at 6 weeks.

The results of this study were truly extraordinary. In the 111 patients that were treated, there was a 98% pathologic response rate. There was a major pathologic response in 95% of patients, and a complete response in over two-thirds of patients. When you look at circulating tumor DNA (with non-invasive testing patterns), nearly all patients had cleared their tumor DNA before surgery, and after surgery, there was no circulating tumor DNA detected, which is an indicator of treatment response.

When you look at the 3-year disease-free survival, it is 100%, which is unprecedented. This study demonstrates that we can bring these immune therapies to patients with earlier stage disease and have exceptionally favorable results.

Q6 With the growing emphasis on personalized medicine, what strategies do you recommend for integrating molecular profiling into routine clinical practice for patients with gastrointestinal cancer?

Molecular profiling helps our patients, but there are difficulties operationalizing testing into routine practice: getting the right test at the right time for the right patient. In the metastatic setting, we need to order next-generation sequencing as soon as the diagnosis of metastatic disease is made. That requires obtaining tissue or blood and identifying the appropriate diagnostic test. Additionally, there can be financial constraints around testing, which need to be navigated by the clinician and the patient. In earlier-stage disease, we need to ensure that patients are receiving mismatch repair or MSI-high testing, and then incorporate those results into our clinical care.

These are the challenges we face today: operationalizing the test and finding a financially sustainable testing option for patients and healthcare systems.

Q7 What do you consider the most promising emerging biomarker or therapeutic approach that could significantly impact the treatment landscape for gastrointestinal cancers in the near future?

We know that mismatch repair-deficiency or MSI-high predicts immunotherapy benefit. However, there are many patients, particularly those patients with mismatch repair proficient or microsatellite stable (MSS) tumors, that still do not benefit from immunotherapy. One challenge in the years to come will be utilizing biomarkers to identify those patients with MSS tumors who may still benefit from immunotherapy. Another challenge is identifying strategies to convert an immunotherapy-resistant tumor into an immunotherapy sensitive tumor. I am optimistic we will address these challenges over the next 5–10 years.