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Tracking Treatment Response: ctDNA Insights in MMR-p Colon Cancer

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Natera. Here's your host, Dr. Brian McDonough.

Dr. McDonough:
This is *Project Oncology* on ReachMD, and I'm Dr. Brian McDonough. Today, we'll be taking a look at a study that was presented at the 2025 ESMO Congress, which investigated whether neoadjuvant immunotherapy can induce immune activation and responses in mismatch-repair-proficient colon cancer. And joining me in this discussion is Dr. Christopher Chen, who's an Assistant Professor in the Division of Oncology in the Department of Medicine at Stanford University School of Medicine. Dr. Chen, welcome to the program.

Dr. Chen:
Delighted to be here.

Dr. McDonough:
So if we start with the big picture, Dr. Chen, could you walk us through the rationale for using neoadjuvant immune checkpoint blockade in mismatch-repair-proficient colon cancer?

Dr. Chen:
Mismatch proficient colon cancer accounts for about 85 percent of colon cancers, and unfortunately, they have not shown to be responsive to immunotherapy. But additional investigation in recent years has suggested that while metastatic mismatch-repair-proficient colon cancers may not be responsive, earlier stage mismatch-repair colon cancers may be.

And so studying the use of immunotherapy in the presurgical setting, as in the neoadjuvant space, is important to better understand its potential in this disease.

Dr. McDonough:
Now if we turn to this neoadjuvant study, patients received combination immune checkpoint blockade followed by surgery within six weeks, and the study confirmed this approach was both safe and feasible. From your perspective, does this strengthen the case for earlier use of immune checkpoint blockade?

Dr. Chen:
I think it does. I think the study was quite provocative. In this clinical trial, they showed that giving two immunotherapy drugs prior to surgery led to clinical responses in about a quarter of the patients involved, including one patient who had a complete response to the immunotherapy and never ended up going to surgery at all.

So the study, I think, does very much suggest that this strategy is something that can be done safely in the clinic as it provides some provocative early data about its possible efficacy. It's a small study, and so much more work needs to be done, but I think the promising results here will invite further investigation into this overall clinical strategy.

Dr. McDonough:
With all that in mind, let's shift our focus to circulating tumor DNA, which emerged as a standout translational endpoint. At baseline, over

half of patients were ctDNA positive, especially in clinical stage 3. What does this tell us about tumor burden and ctDNA's utility before treatment even begins?

Dr. Chen:
So circulating tumor DNA is DNA from cancer cells that is in the blood of a cancer patient, and we can actually track and detect those levels, whether or not it's positive or negative and detectable or not, and actually quantify the level of circulating tumor DNA in a patient's blood.

And so in this clinical trial, the results were consistent with previous work in showing that patients with higher stage disease—stage 3 for example—tended to have a higher burden of circulating tumor DNA among the median patient than those with earlier stage—stage 1 or 2 disease. So the data here did suggest that circulating tumor DNA could correlate with the amount of tumor burden in a patient's body.

Dr. McDonough:
If we look at ctDNA dynamics, most responders had ctDNA clearance before surgery while nearly all non-responders remain ctDNA positive. Can you tell us how this marker may reflect treatment response in real time?

Dr. Chen:
So in addition to using circulating tumor DNA potentially as a proxy or as a supplement to understanding the tumor burden in a patient's body, one key research question that has emerged is how serial monitoring or circulating tumor DNA might be able to track either cancer response or progression.

So in this study, as you alluded to, in most patients who responded to the neoadjuvant immunotherapy, their circulating tumor DNA become undetectable for surgery while those who did not respond continue to have circulating tumor DNA. So this suggests that circulating tumor DNA status could potentially be a proxy or a surrogate for a response to anti-cancer therapeutics.

Because circulating tumor DNA is relatively easy to obtain—you obtain it through a blood draw—you can potentially have more surrogate endpoints than you can with radiographic imaging, which requires more from patients to undergo.

Dr. McDonough:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Brian McDonough, and I'm speaking with Dr. Christopher Chen about a study that explores how neoadjuvant immunotherapy triggers immune activation and responses in mismatch-repair-proficient colon cancer.

So let's continue diving into the findings, Dr. Chen, and focus on the use of single-cell RNA sequencing in imaging mass cytometry. These methods uncovered distinct immune profiles, including enrichment of tumor-reactive CD8+ T cells in responders and fibrotic, TGF beta-driven microenvironments in non-responders. What do findings like these tell us about the tumor microenvironment's role in shaping responses to immunotherapy?

Dr. Chen:
To me, this was one of the most important aspects of the clinical trial. As I alluded to earlier, there's this broader question in the field of how we bring the benefit of immunotherapy to patients with colorectal cancer, and why colorectal cancer patients don't respond to immunotherapy while many other types of cancers—for example, melanoma and lung—do is an enormous question that has hung over the field.

Growing evidence has suggested that the reason for this is the microenvironment around the tumor, which consists of the immune cells adjacent to the tumor as well as the body's own stromal and fibrotic cells. And the evidence collected here in which they're able to obtain surgical tissue at the time of surgery to understand the changes in the tumor microenviroment was a really important advance in the field.

So the authors generated some provocative data suggesting that certain tumor microenvironment markers, including cellular proliferation of both tumor cells and T cells as well as chromosomal instability, could be associated with better response to immunotherapy.

Dr. McDonough:
Now if we look at all of these findings from a practical standpoint, how feasible is it to integrate ctDNA monitoring into clinical workflows for early-stage colon cancer, especially during short neoadjuvant windows?

Dr. Chen:
One of the advantages of circulating tumor DNA assays is that they're simple to collect because they're a blood draw. Patients receiving cancer therapeutics will receive standard-of-care blood draws typically at every cycle for safety monitoring, so potentially, circulating tumor DNA blood draws could be added on to blood draws that are already existing at certain time points.

Dr. McDonough:
Before we close, I'd like to look ahead, Dr. Chen. Do you think ctDNA will evolve from a response monitoring tool to a decision-making one that will help us tailor treatments in early-stage colon cancer?

Dr. Chen:
I am very optimistic that as continued research in the field develops and matures, we will be able to have increasing confidence and understand how to use circulating tumor DNA exactly, to not just monitor tumor burden, but to actually use it to guide therapeutic decision-making. And this could potentially come to relevance both in the neoadjuvant setting while we're getting drugs prior to surgery as well as in the adjuvant setting where we're giving cancer patients whose cancers have already been resected and trying to understand if they would benefit from additional therapy to help further reduce the risk of recurrence.

Dr. McDonough:
With those forward-looking comments in mind, I want to thank my guest, Dr. Christopher Chen, for joining me to share his perspective on this research and its potential implications for treating mismatch-repair-proficient colon cancer. Dr. Chen, it was great having you on the program.

Dr. Chen:
I enjoyed the conversation. Thanks for having me.

Announcer:
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