Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/project-oncology/adjuvant-nivolumab-in-high-risk-muscle-invasive-urothelial-carcinoma/36306/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Adjuvant Nivolumab in High-Risk Muscle Invasive Urothelial Carcinoma: 5-Year Data

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:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Brian McDonough, and joining me to discuss the 5-year data from the CheckMate 274 trial on adjuvant nivolumab, which he presented at the 2025 European Society for Medical Oncology Congress, is lead investigator Dr. Matthew Galsky. He's a Professor of Medicine and the Director of Genitourinary Medical Oncology at the Icahn School of Medicine at Mount Sinai in New York. Dr. Galsky, thanks for being here today.

Dr. Galsky:
Thank you for having me.

Dr. McDonough:
To help set the stage for us, Dr. Galsky, could you explain the original CheckMate 274 findings and why they were so pivotal for the adjuvant treatment of high-risk muscle invasive urothelial carcinoma, or MIUC for short?

Dr. Galsky:
After radical surgery for muscle invasive urothelial cancer—and those are cancers that start in the bladder or the upper part of the urinary tract—historically, approximately 50 percent of individuals after surgery would have metastatic recurrence. And even though we've had treatments that we give prior to surgery to help reduce that recurrence, patients are still at risk. And so there was an unmet need for an adjuvant treatment—a treatment that could be given systemically after surgery to help decrease that risk of recurrence.

One of the reasons why there was that knowledge gap is that we just didn't have so many different types of treatments for urothelial cancer that worked well. And then along came immune checkpoint blockade, commonly referred to as immunotherapy—medicines to try and get the body's immune system to attack cancer. Those were demonstrated to be safe and effective for patients with metastatic urothelial cancer—urothelial cancer that had spread—so it was logical to move those treatments into the immediate post-surgery setting to see if they could be used to decrease the risk of recurrence.

So CheckMate 274 was designed to address that very question. The study enrolled patients after they had radical surgery for cancer of the bladder or cancer of the upper urinary tract. Patients could have received chemotherapy prior to surgery—what we call neoadjuvant therapy—and there were high-risk pathological features for recurrence. Patients were randomized in a 1:1 fashion to receive nivolumab, an immune checkpoint inhibitor administered intravenously every other week for a year, or placebo for a year.

The primary endpoints of this study were disease-free survival in the overall patient population and then in the subset of patients with tumors showing high levels of the expression of a protein called PD-L1, which is the target for this immunotherapy. And the trial met its primary endpoints, showing a significant reduction in the risk of disease recurrence or an improvement in disease-free survival in the all-comer population and in the subset of patients with tumors with high PD-L1 expression, ultimately leading to FDA approval of adjuvant immunotherapy for this indication.

Dr. McDonough:
And from a design standpoint, what were some of the key elements of this study, especially when it comes to patient eligibility or endpoint selection?

Dr. Galsky:
Patients eligible for CheckMate 274 had undergone radical surgery, either removal of the bladder—radical cystectomy—or nephroureterectomy—removal of the kidney and the ureter—if they had an upper tract urothelial cancer. The cancer had to have high-risk features for recurrence under the microscope, meaning pathological stage T2 or higher disease if they had received neoadjuvant chemotherapy or pathological stage T3 or higher disease if they had not received neoadjuvant chemotherapy.

The primary endpoints were disease-free survival in the all-comer population and in the subset of patients with tumors with high levels of PD-L1 expression. In addition, there were a number of secondary and exploratory endpoints.

Dr. McDonough:
With that background in mind, let's zero in on the 5-year follow-up results. Adjuvant nivolumab continued to show disease-free survival benefits versus placebo. Additionally, both overall survival and disease-specific survival were longer with nivolumab in the intent-to-treat population and in patients with PD-L1 expression greater than or equal to 1 percent. So how do these long-term results reinforce or even expand nivolumab's role in high-risk MIUC care?

Dr. Galsky:
So the 5-year follow-up results are important because we have to think about the context for adjuvant treatments for solid tumors after radical surgery. And the context is that we give treatment for a fixed period of time in hopes of eradicating microscopic spread of cancer such that it never recurs. So this treatment ultimately is given with curative intent. That's what we're trying to achieve in the perioperative space.

Remember, this is one year of treatment. It's fixed duration. So if the treatment is truly beneficial, one would expect to see a sustained benefit even after the treatment is stopped—that is, the cancer is ultimately eradicated and no further treatment is needed. And so one would want to see a similar effect size of the treatment on outcomes later on that you see early on while many patients are still getting the treatment. And that's exactly what the 5-year data show: the effect size for the primary endpoints, for secondary endpoints, and for exploratory endpoints are almost identical to what we've seen in earlier looks at the data, such as after 3 years.

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. Matthew Galsky about the long-term results from the CheckMate 274 trial, which examined adjuvant nivolumab versus placebo for high-risk muscle invasive urothelial carcinoma.

Now, Dr. Galsky, the exploratory ctDNA analysis showed that adjuvant nivolumab improved disease-free survival in ctDNA-positive patients but *not* in ctDNA-negative patients when compared to placebo. So how should we interpret these results?

Dr. Galsky:
So remember, the reason that we give adjuvant treatment for patients with pathological features that suggest a high risk of recurrence is that we think these patients harbor microscopic evidence of cancer that we can't see on imaging, and so the intent is to treat that before it becomes clinically apparent.

If we had a test to determine which patients actually do harbor residual microscopic cancer, then we could apply these treatments in a much more rational way, and that's the promise of ctDNA, or circulating tumor DNA. So this approach uses a tumor-informed ctDNA assay, which means that each patient's tumor undergoes DNA sequencing. The alterations in that patient-specific tumor are identified and made into an assay that can check for those mutations in the blood. So this is a bespoke test designed for each individual patient based on their tumor.

One then seeks to determine whether or not those mutations can be detected in the blood as a surrogate for the presence of residual cancer in the body. And what we showed in this study is that in a retrospective look—and remember, when we designed this study, it was many years ago; ctDNA was not quite on the radar like it is today, so we had to rely on banked specimens—we were able to do this assay in 19 percent of the total study population. And when we looked at the 19 percent of patients who could do the assay, 40 percent had detectable ctDNA in the blood while the rest had undetectable ctDNA.

In those with detectable ctDNA in the blood, as you might expect, there was a markedly higher risk of cancer recurrence. And if you looked at the outcomes based on treatment arm, there was a substantial reduction in the risk of recurrence in patients who had detectable ctDNA who received nivolumab versus placebo, but it was harder to show that, as you would expect, in patients with undetectable ctDNA after surgery.

And so again, these are exploratory findings, but they showed exactly what one would want to see if this assay is really detecting microscopic residual cancer in the body.

Dr. McDonough:
Moving on to safety, no new safety signals were observed over 5 years. But can you remind us of the adverse events we should look out for in patients being treated with nivolumab?

Dr. Galsky:
So nivolumab is a PD-1 inhibitor. Immune checkpoint inhibitors have a range of what we refer to as immune-related adverse events, and these are all side effects that end in the suffix "-itis" for inflammation. So there can really be inflammation of any organ system with immune checkpoint blockade—side effects that mimic all the known autoimmune diseases that we learned about in medical school.

However, there are a few unique aspects to immune checkpoint blockade when used for cancer. One is that the risk for those side effects overall is moderate, meaning that many patients receive these treatments and have no side effects at all. The second is that when the side effects occur, it could be a little bit unpredictable in terms of which organ system is affected in a given individual, unlike something like chemotherapy where there's a constellation of side effects that we expect to occur, but they might differ in severity from one person to another.

The most common side effects related to inflammation of the body with immune checkpoint blockade include things like dermatitis—a rash or itching. There can be colitis—inflammation of the bowel or diarrhea. There can be pneumonitis—inflammation of the lungs manifesting as cough or shortness of breath. When those side effects occur and they're mild, we simply hold the treatment. When they occur and they're more severe, typically these side effects are treated with corticosteroids.

Dr. McDonough:
Lastly, Dr. Galsky, what are your biggest takeaways from this 5-year update, and how do you see it impacting clinical decision-making moving forward?

Dr. Galsky:
So nivolumab is approved by the FDA for the adjuvant treatment of patients with muscle invasive urothelial cancer at high risk for recurrence, and I think these 5-year follow-up data solidify that indication. And certainly, the data are robust—standing up at 5 years—even though treatment was only administered for one year.

I think this also offers a glimpse into the future, and that is that even though the use of perioperative systemic therapy has been one of the major advances in solid tumor oncology, we still apply this treatment in a relatively crude way—in a one-size-fits-all approach—and we need to be able to identify who actually needs this treatment after surgery versus who's already cured with surgery alone or surgery and neoadjuvant treatment. And that's where ctDNA might play a role. We need additional studies to establish clinical utility now that we've established clinical validity, and those studies are coming quickly.

Dr. McDonough:
With those key takeaways in mind, I want to thank my guest, Dr. Matthew Galsky, for joining me to discuss the 5-year results from the CheckMate 274 trial and their implications for high-risk muscle invasive urothelial carcinoma treatment. Dr. Galsky, it was great having you on the program.

Dr. Galsky:
Thank you.

Announcer:
This episode of *Project Oncology* was sponsored by Natera. To access this and other episodes in our series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!