Transcript Details

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ctDNA-Guided Adjuvant Atezolizumab in MIBC: IMvigor011 Insights

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

Dr. Turck:
This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Today, I am joined by Dr. Guru Sonpavde to discuss new data on ctDNA-guided adjuvant atezolizumab in muscle-invasive bladder cancer from the IMvigor011 trial. These findings were presented at the 2026 ASCO Genitourinary Cancers Symposium, and Dr. Sonpavde is the Medical Director of Genitourinary Oncology and the Phase I Clinical Research Unit, and the Christopher K. Glanz Chair for Bladder Cancer Research at the AdventHealth Cancer Institute in Orlando. Dr. Sonpavde, welcome to the program.

Dr. Sonpavde:
Thank you.

Dr. Turck:
For some context, would you walk us through the clinical need for better risk stratification after cystectomy in patients with muscle-invasive bladder cancer and where ctDNA monitoring fits into that landscape?

Dr. Sonpavde:
So muscle-invasive bladder cancer is an aggressive disease, and historically, we've given these patients cisplatin-based neoadjuvant chemotherapy when they were cisplatin eligible. But we know that patients who have muscle-invasive disease—despite neoadjuvant chemotherapy and those who have extravesical disease without any new adjuvant therapy—have a high risk of recurrence, but we don't know how to predict and how to detect molecular residual disease. And this is where something like circulating tumor DNA, or ctDNA, could help in detecting patients who may have this residual disease or the patients who will benefit from some form of adjuvant therapy.

Dr. Turck:
So taking a closer look at the IMvigor011 trial, ctDNA was used to guide treatment decisions after cystectomy, with ctDNA-positive patients randomized to atezolizumab or placebo. How does this biomarker-driven approach differ from traditional adjuvant strategies?

Dr. Sonpavde:
Right, so the traditional strategy was high-risk patients warrant adjuvant therapy. So all of these patients are offered adjuvant immune checkpoint inhibition. Now we have the advent of newer regimens, but we used to give nivolumab alone after neoadjuvant cisplatin with chemo potentially in those patients.

Now, this was an all-comer strategy, and in Europe, nivolumab was approved for PD-L1 high patients only based on more robust benefit in patients who had PD-L1 high tumors. While in the US, it was approved for all comers regardless of PD-L1. But this overtreats many patients because we want to give these agents to patients who really have molecular residual disease and microscopic disease, and that is something that we don't have a good handle on with current clinical staging. Even PET scanning does not detect patients who have microscopic disease. So this is where using something like ctDNA to detect molecular residual disease will help us select the right patients likely to benefit from adjuvant therapy.

Dr. Turck:
For those just joining us, this is *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Guru Sonpavde about new findings from the IMvigor011 study on ctDNA-guided adjuvant atezolizumab in muscle-invasive bladder cancer.

Turning to the findings, Dr. Sonpavde, we saw that about 74 percent of patients who became ctDNA-positive did so within 24 weeks after surgery. How does that early window of molecular relapse influence how you think about surveillance in clinical practice?

Dr. Sonpavde:
As you said in the IMvigor011 trial, the vast majority of patients were positive for the ctDNA tumor-informed platform, and basically, this is an early relapsing aggressive disease. And this is actually what this trial shows even now: a quarter of patients did convert from negative to positive ctDNA during tracking of the ctDNA.

So really at the end of the day, the early recurrent patients had higher levels of ctDNA and also had worse outcomes. And so this is a very important fact to consider when monitoring these patients, and early therapy is very important because you might miss the window of opportunity to treat these patients before they have clinical decline, potentially upon clinical recurrence.

Dr. Turck:
And we also saw during treatment that ctDNA levels decreased with atezolizumab between cycles one and three while they increased with placebo. What does that early divergence tell us about the biologic activity of immunotherapy in this setting?

Dr. Sonpavde:
Yes, so the ctDNA was tracked in the patients who received the therapy atezolizumab or placebo, and as you mentioned, there was a clearance of ctDNA, which was higher in the atezolizumab arm as opposed to the placebo arm, which suggests and is consistent with the activity of PD-L1 inhibition—in this case, atezolizumab compared with placebo—and it was also noted that patients who had clearance of ctDNA had better outcomes. So really, all of this is consistent biologically with the level of efficacy of this drug.

Dr. Turck:
So a bit more about ctDNA clearance: clearance in cycles three or five was associated with 12-month disease free survival at 84.4 percent versus 31.2 percent and 24-month overall survival at 86.2 percent versus 54.9 percent depending on clearance status. With that being said, how do you interpret ctDNA clearances, both as an early response marker and a predictor of long-term benefit?

Dr. Sonpavde:
So this data again suggests that ctDNA clearance is a good prognostic marker as you just described the data here. If the ctDNA was continuously negative in this trial, it was done again every six weeks in patients who were negative at the outset. So the ctDNA dynamics really is a great indicator of prognosis: clearance is good, and going from negative to positive is a bad prognostic factor. So I think that these data hold up even in this trial.

Dr. Turck:
Finally, Dr. Sonpavde, if we look ahead, how do you see ctDNA-guided strategies shaping the future of adjuvant therapy in bladder cancer?

Dr. Sonpavde:
Yeah, so now we have the advent of perioperative EV—enfortumab-vedotin—plus pembrolizumab. Just before that, we also had gemcitabine-cisplatin plus durvalumab. But it's likely that given the recent data in cisplatin-eligible and cisplatin-ineligible patients, perioperative EV plus pembrolizumab is going to dominate in that setting because of the robust efficacy seen with EV plus pembrolizumab compared to even cisplatin plus gemcitabine in the neoadjuvant setting.

So now the question for the field becomes, since this is a different setting now with neoadjuvant EV plus pembrolizumab in most patients, how are we going to apply the IMvigor011 data? Can we use ctDNA to measure MRD to tailor our adjuvant approach, i.e., if patients are negative post EV- pembrolizumab and are radical cystectomy negative for the ctDNA post-op, can we monitor those patients and treat only if they turn positive? And in patients who are positive post EV-pembrolizumab and surgery, what do we do now? Do we apply the regimen as was done in the trials, which is continuation of more EV-pembrolizumab? Or do these patients really need a new strategy if they're still positive post-op?

And one of the important trials going on now trying to answer this question is the MODERN clinical trial. This is an intergroup trial, and this is open at our site and basically what this trial does is it allows neoadjuvant EV-pembrolizumab, gemcitabine-cisplatin plus durvalumab, the previous standard of cisplatin-based chemotherapy, or even untreated patients to be randomized if they're post-op ctDNA-positive using the Signatera platform to nivolumab or nivolumab plus the LAG-3 inhibitor relatimab. And if they're ctDNA-negative, there's randomization to nivolumab versus surveillance. But the surveillance group then can then go on to get nivolumab if they become ctDNA-positive during monitoring. So this is a trial that we are accruing patients to to answer some of these questions.

Dr. Turck:
Great comment for us to think on as we come to the end of today's program. And I want to thank my guest, Dr. Guru Sonpavde, for

joining me to explore findings from the IMvigor011 trial. Dr. Sonpavde, it was great having you on the program.

Dr. Sonpavde:
Thank you.

Announcer:
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