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Urinary and Circulating Tumor DNA in Muscle-Invasive Bladder Cancer: NIAGARA Data

**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 we'll be discussing recent findings presented at the 2026 ASCO Genitourinary Cancers Symposium focusing on the role of urinary and circulating tumor DNA in patients with muscle-invasive bladder cancer treated with perioperative durvalumab in the NIAGARA trial. And joining me in that discussion is Dr. Petros Grivas, who's a Professor in the Division of Hematology and Oncology at the University of Washington School of Medicine, as well as the Clinical Research Division at the Fred Hutchinson Cancer Center, where he's also the Medical Director of the International Program and of local and regional outreach. Dr. Grivas, welcome to the program.

**Dr. Grivas:**
Charles, thank you so much for having me. It's such an exciting time to be in the field of medical oncology and specifically doing research in bladder cancer and helping patients do better and live longer.

**Dr. Turck:**
Well, I'd love to start with some context here, Dr. Grivas. In the phase 3 NIAGARA trial, we saw that adding perioperative durvalumab to neoadjuvant chemotherapy and radical cystectomy improved event-free and overall survival rates, with a numerical increase in pathologic complete response. And now, this exploratory analysis looks at urinary and circulating tumor DNA in that same setting. So would you walk us through the rationale for incorporating these biomarkers in the perioperative setting like in that of the NIAGARA trial?

**Dr. Grivas:**
Thank you, Charles. It's a very important question. We have been trying for many years to develop tools and biomarkers that can help us better understand the tumor biology—genomic profiling, for example—and, more recently, quantify the risk of recurrence or risk assessment, evaluate response to treatments, and also try to predict risk of recurrence in the future and prognosticate.

So in the context of developing prognostic biomarkers and also predictive biomarkers that can help us predict benefit from individual treatments, we have been pleased to see the emergence and the expanding role of plasma circulating tumor DNA using a tumor-informed assay that has shown across different trials that it can be very useful for those goals—risk assessment, prognostication, and potentially informing the dialogue with the patient about the decision-making indirectly or directly depending on the setting.

In the context of the NIAGARA trial, we have seen data with plasma ctDNA, and urinary tumor DNA. We have, of course, more experience so far with plasma ctDNA in practice. And in the context of the NIAGARA trial, we saw three different time points: we saw the collection of baseline before cycling on day 1, so this was pre- neoadjuvant therapy; we saw post-neoadjuvant therapy, so pre-radical cystectomy; and we also saw post-radical cystectomy. So through different time points, we have seen data for plasma ctDNA in the context of NIAGARA trial. And now more recently at ASCO GU 2026, we saw data with urine DNA serially collected. That can also be very interesting, and I think it can have some interesting correlations with some of the endpoints.

**Dr. Turck:**
Well, I'd like to take a closer look at how this analysis was conducted. And so you mentioned the biomarker-evaluable sample included 265 patients, with urinary and circulating tumor DNA assessed at baseline and again prior to cystectomy. From your perspective, what stands out to you most about this trial design?

**Dr. Grivas:**
I think it's very useful to see. So if we look at the NIAGARA trial design, we know that patients received a neoadjuvant therapy phase with gemcitabine cisplatin—standard of care—alone or with additional of durvalumab, an anti-PD-L1, in the neoadjuvant therapy phase. And then patients underwent radical cystectomy and lymph node dissection and then adjuvant therapy with durvalumab in the experimental arm.

If we look at the plasma ctDNA and the urine DNA collection, specifically if we focus our discussion in the neoadjuvant therapy phase—again, we saw the baseline timepoint collection pre-neoadjuvant therapy and we saw the post-neoadjuvant therapy before radical cystectomy—and if we look at the data, we saw higher degree of ctDNA clearance—from positive becoming negative, that means clearance. And that rate was higher in the durvalumab arm; it was about 77 percent versus 57 percent with neoadjuvant alone, showing that durvalumab not only is increasing pathologic complete response rate and prolonging event-free and overall survival, but it also contributes to a higher ctDNA clearance rate based on this post- versus pre-neoadjuvant therapy phase.

Also, we saw some interesting data about ctDNA overall being very prognostic. We know that patients with undetectable negative ctDNA have much better prognosis. They have a lower chance of recurrence and much longer survival as opposed to those with detectable positive ctDNA that corresponds to higher cancer recurrence and shorter survival. So we definitely have prognostic information.

And, of course, we have also seen interesting data with urine DNA that we can discuss more. But I think it's very important also to think about how this data are evolving and how it may or not impact individual decision-making at the individual patient level. That's an open question, but there's no doubt in my mind that having information about ctDNA is very highly prognostic and may inform the dialogue on the individual patient level regarding prognostication and may potentially indirectly inform decision-making based on other nuanced approaches, like efficacy of treatment, toxicity, and other factors.

**Dr. Turck:**
Now, we know from prior analyses of this study that negative plasma circulating tumor DNA status before surgery was associated with improved event-free survival, but not with pathologic complete response. So how do you interpret those findings, and what limitations do they highlight in this setting?

**Dr. Grivas:**
Great question. We try to evaluate the plasma ctDNA in the context of different endpoints. And as you pointed out, interestingly, there was some degree of discordance between the degree of ctDNA negativity. Let's say the negative ctDNA before radical cystectomy; in those patients, about half of them had pathologic complete response, and half of them did not. So in negative plasma ctDNA before radical cystectomy, it's about 50/50 or so whether this will correspond with pathologic complete response. It's interesting because there's this notion that plasma ctDNA may correlate with the chance of systemic metastasis but may not be that great in terms of evaluating minimal residual disease inside the bladder.

So we need, of course, more data from different trials. But I think it just speaks to the point that we need complimentary information that we may get from the pathologic assessment of the radical cystectomy specimen when the bladder is removed, and for radical cystectomy and lymph node dissection, the pathologist's review of that specimen is critical and the plasma ctDNA may provide complementary information. But as you said, plasma ctDNA before radical cystectomy does not correlate very well with a chance of pathologic complete response based on what we discussed.

**Dr. Turck:**
For those just joining us, this is *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Petros Grivas about recent research focusing on the use of urinary and circulating tumor DNA in patients with muscle invasive bladder cancer who receive perioperative durvalumab as part of the NIAGARA trial.

So let's dig further into the urinary tumor DNA findings, Dr. Grivas. Lower baseline levels were associated with longer event-free survival, and clearance from baseline to pre-surgery was associated with significantly improved outcomes, with higher clearance rates seen in the durvalumab arm. In addition, pre-surgery urinary tumor DNA negativity was strongly associated with pathologic complete response at 72 percent versus 18 percent in patients who were urinary tumor DNA positive. What do you make of all these findings?

**Dr. Grivas:**
It's another great question. I think urinary tumor DNA is another emerging, very interesting, and promising tool and biomarker that can help provide complimentary information to what we discussed before—status and plasma ctDNA. And we saw from the NIAGARA trial along with other trials at ASCO GU 2026 that urinary tumor DNA might provide additional useful information, and the urinary tumor DNA may correlate even more with the chance of pathologic complete response based on the data of the NIAGARA trial.

Of course, the utility in clinical practice of urinary tumor DNA still remains to be confirmed. We need more data to validate findings from the NIAGARA trial, and as I mentioned, there are a few other studies looking at urinary tumor DNA, but it seems that it actually has a higher degree of correlation with the pathologic complete response at the time of radical cystectomy as opposed to plasma ctDNA.

So I see in the future, complementary roles between plasma ctDNA and urinary tumor DNA. The plasma may give us a better sense of what is happening systemically and the chance of systemic recurrence. Of course, it can be impacted by what is happening in the bladder to a degree, and urinary tumor DNA may capture to a higher degree what's happening in the bladder, especially with non-invasive disease because if you have non-invasive disease in the bladder, there's a question about plasma setting in the blood. So I think in the future, we need further validation about urinary tumor DNA, but I see a future state of using both complementary plasma and urine.

**Dr. Turck:**
Well, in our final few moments here, Dr. Grivas, let's bring this all together. Given that this combined urinary and circulating tumor DNA analysis was associated with outcomes like event-free survival and pathologic response and may even offer complementary insights into disease stage, how do you see these biomarkers potentially informing future management strategies, and what additional validation is still needed?

**Dr. Grivas:**
Excellent question. I'm very excited about the increasing promise of these circulating biomarkers. In the plasma, we have more data with the plasma ctDNA using a tumor-informed assay across different trials, including the NIAGARA Phase 3 trial. And now, we're starting to see data sets, including NIAGARA, for urinary tumor DNA. And as we discussed a few minutes ago, I think these assays may provide complementary information about the risk of systemic recurrence and also residual disease in the bladder. As we discussed, if you have non-invasive disease in the bladder, that potentially may be captured more with urinary tumor DNA.

There are a lot of questions regarding the optimal assay of the urinary tumor DNA methodology. As I mentioned, there's a need for longer follow up to see whether this correlation with event-free and overall survival may be shown. I think we also need urinary tumor DNA data with other trials, but I see a very promising future state where we have plasma and urinary tumor DNA that can longitudinally and serially be captured and measured, and they can provide complementary information regarding the risk assessment, risk of relapse, treatment response assessment, pathologic states, and cystectomy. And even in the future as we move towards an individualized approach, it can help us materialize that individualized approach in the future because one size does not fit all, and we need more biomarkers and customized treatment approaches for patient.

I think the other important point is access to those assays. Across the board, I think having equitable access is important. Reimbursement, of course, is important. And of course, as we get in the future to a state where we may do more bladder preservation, I see a huge promise with plasma ctDNA and urinary tumor DNA in helping us select which patients, may need radical surgery, bladder preservation with chemo radiation, or potentially active surveillance in some of the patients after systemic therapy. So I think the future is brighter, and the data we have seen from the NIAGARA trial on the use of ctDNA in plasma and urine along with other trial data sets are creating this infrastructure and framework for better individualized approaches and hopefully outcomes in the future.

**Dr. Turck:**
Well, with those forward looking comments in mind, I want to thank my guest, Dr. Petros Grivas, for joining me to explore how urinary and circulating tumor DNA are being evaluated in patients with muscle invasive bladder cancer who are receiving perioperative durvalumab. Dr. Grivas, it was great having you on the program.

**Dr. Grivas:**
Thank you so much for the invitation. Looking forward for more discussions as the field is changing rapidly and we have more data in the future regarding this very important topic.

**Announcer:**
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