Transcript Details

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ctDNA-Guided Immunotherapy Shows Survival Benefit in MIBC: IMvigor011 Results

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. Joining me to discuss the IMvigor011 phase 3 trial, which evaluated ctDNA-guided adjuvant atezolizumab in patients with muscle invasive bladder cancer, is Dr. Andrea Necchi. Not only is he an investigator on this research, which was presented at the 2025 ESMO Congress, but he is also an Associate Professor of Oncology at Vita-Salute San Raffaele University and the Director of Genitourinary Medical Oncology at IRCCS San Raffaele Hospital and Scientific Institute in Milan, Italy. Dr. Necchi, welcome to the program.

Dr. Necchi:
Thank you, Charles, for inviting me. It's a pleasure to be here.

Dr. Turck:
To begin, Dr. Necchi, let's focus on the study's design. How was the IMvigor011 trial structured?

Dr. Necchi:
Well, the IMvigor011 trial enrolled patients with muscle-invasive bladder cancer who had received radical cystectomy with or without previous neoadjuvant cisplatin-based chemotherapy and who showed a pathological feature portending a high risk of disease relapse, meaning pT2, pT3, or pT4, or pN+—so involvement of the lymph nodes. After screening, patients started surveillance with ctDNA monitoring until 1 year post-cystectomy. And the patients who had the occurrence of positivity of a ctDNA test were randomized to receive atezolizumab or placebo, while ctDNA-negative patients—so patients who remained negative with the test—started surveillance and follow-up protocol until the end of the study. So only patients who had the evidence of at least one ctDNA positivity during the surveillance phase received a randomization. They were randomized 2:1 to receive atezolizumab in the experimental arm or placebo as a control arm.

The primary endpoint of the study was the investigator-assessed disease-free survival; overall survival was the secondary endpoint. The statistical analysis implied a hierarchical control for OS secondary endpoint, based on the alpha.

This approach could potentially spare low-risk patients—so patients who remained ctDNA-negative post-cystectomy despite a high-risk feature disclosed by pathological stage—from unnecessary treatment, meaning unnecessary adjuvant treatment with either the use of adjuvant immunotherapy or adjuvant chemotherapy as a standard of care.

Dr. Turck:
And as a follow-up to that, one of the more unique aspects of this trial was its use of molecular testing to guide treatment decisions. Would you talk a bit more about how the ctDNA monitoring was implemented, and what makes that approach meaningful in this context?

Dr. Necchi:
The basis of the trial and the IMvigor011 trial design was generated through the IMvigor010 design that randomized patients regardless of the ctDNA assessment. Among patients with high-risk features—similar to patients in 011—the post-hoc analysis for this trial that randomized patients to receive atezolizumab or placebo showed that patients who had a ctDNA-positive test post-cystectomy were those who benefited the most from adjuvant atezolizumab.

And in that trial, as well as in IMvigor011 trial, a personalized tumor-informed ctDNA assay was used, meaning that it was a ctDNA test based on a signal of the next-generation sequencing of the tumor of the patient, so the radical cystectomy specimen. So based on the molecular features of a certain patient and of a certain tumor, the technology allows us to develop a probe that is able to determine the ctDNA status for a certain patient. So it's actually a very personalized approach according to the molecular features of each single patient.

The other point that's related—and it's a very frequently debated point in the GU oncology community—is that it's a serial assessment of the test in the follow-up period post-cystectomy. So it's not a one-time approach; it's a serial sequencing—not just at the time of screening surveillance before randomization, but also when patients started the surveillance phase and were negative and then when they had a follow-up test until the end of the study.

So it's a two-fold test that means a personalized approach based on the whole exome sequencing of the tumor first, and then using this test and applying this test sequentially in the treatment course or in the follow-up course of the patient post-cystectomy.

Dr. Turck:
Now, with that background in mind, let's turn to the results. The patients receiving atezolizumab had statistically significant improvements in both disease-free and overall survival. So what do these findings tell us about the role of immunotherapy when we use it in a targeted manner in patients with molecular evidence of residual disease?

Dr. Necchi:
Patients randomized to atezolizumab showed a hazard ratio for DFS, which is the primary endpoint of the study, of 0.64, whereas the hazard ratio for overall survival was 0.59. So this is one of the first phase 3 studies to show a benefit in solid tumor oncology with a personalized ctDNA-guided approach and, in particular, in urothelial cancer in which we have an unmet need with regards to the decision-making for a treatment post-radical cystectomy.

It's clearly an important step forward for an indication for patient selection and for exclusion of patients who have the highest chances of benefitting with the follow-up period only—they have a very low risk of developing disease relapse without any further treatment, sparing them of any further side effects from treatment.

Dr. Turck:
In terms of safety, 28.5 percent of patients who received atezolizumab experienced grades 3 or 4 adverse events versus 21.7 percent who received placebo. Now, the events that were determined to be related to treatment were relatively low at 7.3 percent versus 3.6 percent, respectively, but at the same time, 1.8 percent of patients on atezolizumab did experience treatment-related fatal events. So putting all of this together, what are we to make of these findings? How do you view the tolerability profile of atezolizumab?

Dr. Necchi:
Yes, so from the safety standpoint, we did not see any particular signal that stands out of the knowledge that is already acquired for atezolizumab as well as for any other immune checkpoint inhibitor, particularly when used as single-agent therapy in patients with organ-confined non-metastatic disease or in patients with a bladder cancer in general.

So as you mentioned, the rate of treatment-related grade 3/4 severe side effects is below 10 percent, which is the cut point for all the checkpoint inhibitors tested so far in bladder cancer. The overall safety and tolerability did not provide any new safety signals.

So the most important message here is that rather than focusing on the side effects related to treatment, we should focus on the side effects that are spared to the rest of the patients who did not receive atezolizumab—so patients who were not randomized because of the persistent negativity of the ctDNA test.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Andrea Necchi about the IMvigor011 phase 3 trial of ctDNA-guided adjuvant atezolizumab in patients with muscle-invasive bladder cancer.

So, Dr. Necchi, another interesting finding was that the 357 patients who persistently tested ctDNA-negative didn't receive treatment yet still had a very low recurrence rate. Would you tell us how this finding might influence future surveillance strategies?

Dr. Necchi:
The general feeling of the GU oncology community is that this is a practice-changing study. As you have mentioned, the study results are related to the ctDNA-negative patients who started the surveillance period that are pretty much outstanding. So out of the 357 patients who started the surveillance phase, only 15 patients who experienced disease recurrence during the ctDNA monitoring period were discontinued from the study and censored for OS.

Overall, the two-year estimate of disease-free survival and overall survival were around 88 percent and 97.1 percent OS, which is pretty much upstanding for either disease-free survival or overall survival. This is something that is really important to consider whenever we counsel the patient after radical cystectomy for any kind of adjuvant or additional therapy after that surgery.

Dr. Turck:
And based on these data, what does the IMvigor011 trial tell us about the potential of ctDNA as a biomarker in bladder cancer?

Dr. Necchi:
Well, there is an explosion of the use of ctDNA as a biomarker for patients with bladder cancer, as well for many other indications in solid tumors. But based on this study, which is the first one of its kind, I presume that we will accumulate a lot of data from other practice-changing studies focusing on ctDNA as a way of selecting patients who are most likely to benefit from a certain systemic therapy. In particular, the serial use and the personalized feature of the test, which is based on the molecular features of each single tumor of each single patient, is outstanding, and the technology provides a way of adapting the therapy based on this test.

So further developments are awaited. We are just moving around the pillar of radical cystectomy. So many other perioperative trials, including a preop period of treatment and postop period of treatment, are already implementing ctDNA as a biomarker for MRD—minimal residual disease—assessment. So it's really a way of rethinking the way we monitor the response to treatment and the overall outcome of the patient as compared to the standard imaging tools.

Dr. Turck:
Now, looking ahead before we close, Dr. Necchi, do you see these results influencing future guidelines to include molecular tools like ctDNA as part of routine post-surgical assessment and adjuvant therapy planning?

Dr. Necchi:
Well, my personal answer is yes. Based on the trial data, we have an opportunity for incorporating ctDNA monitoring post-surgery to guide treatment decisions outside of any further clinical trial. So more personalized, risk-adapted approaches may replace the one-size-fits-all approach that is currently pursued by international guidelines on the both sides of the Atlantic—in the U.S. as well as in Europe for nivolumab, for example, and for other checkpoint inhibitors. And this trial, IMvigor011, is already serving as a model for informing the next generation of clinical trials that base patient stratification and selection in the perioperative setting—so neoadjuvant and adjuvant therapy added to radical surgery.

So the findings from 011, in particular, related to ctDNA and indicate that the serial monitoring of the test can identify patients with MIBC who benefit from adjuvant atezolizumab while sparing those who have persistently negative ctDNA tests from unnecessary treatments. So it's a big step forward—the first of its kind, at least in urothelial cancer. So it’s definitely a thing that all physicians who are treating bladder cancer patients will consider tomorrow in their practice.

Dr. Turck:
Well, with those closing comments in mind, I want to thank my guest, Dr. Andrea Necchi, for joining me to share his perspective on the IMvigor011 trial and its findings. Dr. Necchi, it was great having you on the program.

Dr. Necchi:
It has been a real pleasure. Thank you, Charles, for inviting me.

Announcer:
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