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mCRPC Care: Reducing Progression Risk by Combining Enzalutamide and Talazoparib

Dr. Turck:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss the research he did in the TALAPRO-2 study is Dr. Neeraj Agarwal. Dr. Agarwal is a Professor of Medicine and a Presidential Endowed Chair of Cancer Research at the Huntsman Cancer Institute at the University of Utah.

Dr. Agarwal, thanks for being here today.

Dr. Agarwal:
Thanks for having me.

Dr. Turck:
Well, to start us off, Dr. Agarwal, would you tell us about the TALAPRO-2 study and its significance in the context of treating metastatic castration-resistant prostate cancer?

Dr. Agarwal:
So TALAPRO-2 is a randomized phase 3 trial, which was conducted in first-line mCRPC setting in patients with newly diagnosed mCRPC who could have received chemotherapy or androgen receptor pathway inhibitors in the metastatic hormone-sensitive setting, but they could not have had any therapies in the metastatic CRPC setting. So these patients were randomized to enzalutamide, which is a standard-of-care drug in these patients, versus enzalutamide plus talazoparib 0.5 milligrams daily; and, of course, the control arm had placebo for talazoparib, so enzalutamide plus placebo versus enzalutamide plus talazoparib 0.5 milligrams daily. Primary endpoint was radiographic progression-free survival, and key secondary endpoint was overall survival. And, as we know, there are other clinically meaningful endpoints for our patients, which included time to chemotherapy, time to progression on subsequent therapy, objective responses, and patient-reported quality of life.

So in this trial, patients were recruited regardless of homologous recombination repair mutations. So just to make sure that we have a proper understanding of the trial design, there were two cohorts in the trial. Cohort 1 had about 800 patients, and these patients were recruited regardless of HRR mutations, so these were all-comer patient population. And then we added 230 patients who had homologous recombination repair mutations. And if you combine the 169 patients who had HRR mutations in cohort 1, we had 400 patients who had HRR mutations in cohort 2.

Dr. Turck:
So, Dr. Agarwal, if we zero in on the results, what were the key findings with respect to the efficacy of combining talazoparib and enzalutamide?

Dr. Agarwal:
There was a 37 percent reduction in risk of progression or death in this all-comer patient population on treatment with enzalutamide plus talazoparib versus enzalutamide plus placebo. If you look at the median radiographic progression-free survival established by blinded independent radiology assessment, it was 22 months on the enzalutamide arm, and it was not reached in the talazoparib plus enzalutamide arm. If you look at the subgroup analysis of RPFS, all subgroups seem to be benefiting regardless of age, performance status, Gleason score, whether they had de novo metastasis in the past or what kind of site were involved as far as metastatic disease is concerned, or whether they had received abiraterone or docetaxel therapy in the past, with the caveat that a small number of patients received an ADT intensification therapy in the metastatic castration-sensitive prostate cancer setting. Regardless, all patients seem to

be benefiting. In fact, the hazard ratio was lower, meaning they seem to have more benefit by adding talazoparib if they had abiraterone or docetaxel treatment during the hormone-sensitive prostate cancer setting.

Now I would like to highlight the benefit with talazoparib in patients based on homologous recombination repair deficiency status. So if you look at those patients who had HRR-deficient or who had HRR mutations, the hazard ratio for benefit was 0.45 favoring the combination arm. It means there was a 55 percent reduction in risk of progression or death if these patients had homologous recombination repair deficiency. In patients who did not have homologous recombination repair deficiency by prospective tumor tissue testing, which is a gold standard to rule out HRR deficiency, there was a 34 percent reduction in risk of progression or death with talazoparib, so this is very interesting that we are seeing benefit in both groups of patients regardless of HRR deficiency. Although the magnitude of benefit is much higher in patients who have HRR deficiency, it was still present with a 34 percent reduction in risk of progression or death in patients who were HRR nondeficient by prospective tumor tissue testing.

Dr. Turck:
And what were some of the other clinically meaningful endpoint results you saw in the trial?

Dr. Agarwal:
If you look at other meaningful endpoints, there was a 11-month delay in all-comer population in time to PSA progression. There were a 17-month delay in time to PSA progression in patients who have HRR mutations with talazoparib. If you look at overall survival, obviously overall survival data are immature at 31 percent maturity when I presented the data in 2023 in the ASCO GU, but still there is no reverse trend, and there is a trend favoring the talazoparib arm. If you look at time to chemotherapy and time to progression on subsequent therapy, all these secondary endpoints seem to be favoring talazoparib. If you look at objective responses, they were much higher with talazoparib. If you look at complete responses, it was 18 percent in the enzalutamide-only arm, and it was 37.5 percent in the enza plus talazoparib arm.

Now if you look at the presence of BRCA1 and BRCA2 mutations, only 7 percent of patients in all-comer patient population had BRCA1 and BRCA2 mutations. If you look at excessive or higher complete responses, there were 18 percent higher complete responses, so there is no way these complete responses are being driven only by BRCA 1 and BRCA2 mutations.

Dr. Turck:
And what were the results in patients with some of the other mutations?

Dr. Agarwal:
So initial data were published in *Lancet,* and then we published the data focusing on HRR mutation patients in *Nature Medicine* where we show very clearly that patients beyond BRCA1 and BRCA2 mutations seem to be benefiting, such as CDK12 mutation, which is one of the most common HRR mutations in these patients, and there was a 50 percent reduction in risk of progression on that. We also found encouraging signals in patients with PALB2 mutations, RAD51 mutations, and many other mutations, with the big caveat that once we start getting into these small subsets of mutations, the trial was not powered to look at individual mutation subsets, but there is no question that enza plus tala combination seem to have benefit beyond patients with BRCA1 and BRCA2 mutations. And we will continue to present data in upcoming meetings to further highlight those aspects of the trial.

Dr. Turck:
And what about the safety findings?

Dr. Agarwal:
As we know, that PARP inhibitors are associated with three overall type of toxicities. Number 1 is fatigue, which is common with many other anticancer drugs. Number 2 is hematologic toxicities. All these drugs cause a degree of hematologic toxicities—anemia and thrombocytopenia mostly. And then, of course, nausea and vomiting, so gastrointestinal side effects. And these PARP inhibitors are not created equal. Although these are class effects, some PARP inhibitors are more associated with gastrointestinal side effects, like olaparib for example. Some PARP inhibitors are more associated with hematologic side effects, such as talazoparib. And some PARP inhibitors, like niraparib, may have unique side effects, such as hypertension or cardiovascular side effects.

So the bottom line is, regarding toxicities which is a theme with toxicities across the cancer drugs, we know that some patients are going to develop grade 3/4 toxicities. And as long as we diagnose those grade 3/4 toxicities in a timely fashion, whether it is nausea, vomiting, diarrhea, or hematologic side effects, as long as we diagnose them in a timely fashion and reduce the dose, most of these patients are able to continue the drugs—in this case talazoparib—for a long time, which is evident by the remarkable efficacy profile of talazoparib in this trial. And also, I'm not surprised that FDA approved the combination for patients with new mCRPC with HRR mutations, and I'm really hoping that we see significant overall survival in this patient population in the near future, which will further consolidate the efficacy of this combination or the utility of this combination for our patients.

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. Neeraj Agarwal about the TALAPRO-2 study.

How do you think the TALAPRO-2 study and other similar trials might influence first-line treatment decisions for patients with metastatic castration-resistant prostate cancer?

Dr. Agarwal:
So a question often comes up, why we should combine a PARP inhibitor with an androgen receptor pathway inhibitor in the first-line mCRPC setting, and why we should not sequence them. So if a patient with a new mCRPC has a homologous recombination repair mutation, why shouldn't we treat them with abiraterone or enzalutamide followed by an approved drug, which is olaparib? And this is a great question. I think that is partly answered by the results of the BRCAAWAY trial, which was presented by Dr. Maha Hussein in the ASCO-GU 2024 meeting. So this was an investigator-initiated, multicenter trial where we had the honor of participating as well. And this trial randomized patients to monotherapy with abiraterone to monotherapy with olaparib and then combination of abiraterone plus olaparib, and these patients had new metastatic castrate-resistant prostate cancer, and they could not have received an ARPI prior to enrolling on this trial.

The results of this trial basically reinforces the idea of combining an ARPI plus PARP inhibitor upfront in patients with newly diagnosed mCRPC who have the homologous recombination repair mutations or who have BRCA1 and BRCA2 mutations.

This trial also brought up one important point or one important issue which we know seems to be prevalent in the real world, which is that there is a high attrition rate among patients with metastatic CRPC, with up to 50 percent patients not receiving a subsequent line of therapy. So anytime our patients experience disease progression, we lose them to disease, so that is another reason why I feel more convinced to use combination therapy up front. And that may be one of the reasons why combination therapy or intensification therapy works in metastatic prostate cancer setting, whether it is metastatic hormone-sensitive setting or metastatic castrate-resistant prostate cancer setting, because by combining drugs up front, we allow every patient to get those drugs rather than losing half of them to disease when we treat them with monotherapy first or single agent first and when we wait for sequencing these drugs. So I just wanted to highlight the results of the BRCAAWAY trial, which we just presented, and I think these are practice-influencing results.

Dr. Turck:
And before we close, Dr. Agarwal, do you have any final takeaways you'd like to leave with our audience today?

Dr. Agarwal:
Another issue I would like to highlight is that patients are not getting tested for these mutations, and that brings me to the genomic testing or germline testing in patients with metastatic prostate cancer. So right now, almost all guidelines across the world recommend genetic testing or genomic testing of our patients who come to us with metastatic prostate cancer, so in my clinic, I offer these patients germline testing to look for inheritable germline mutations because it doesn't only have implications on our patients' treatment, but these also have implications on my patients' families, their siblings, their children, and then, of course, the comprehensive genomic profiling of the tumor tissue. And if the tumor tissue is not available or is not of good sufficient quantity or good quality, I offer them ctDNA testing, or circulating tumor DNA testing.

The good news is all these tests are widely available now, and there are many companies, CLIA-certified labs, which are offering them, so there is no reason for us anymore to not test these patients because if we do not test these patients, we will not know whether these patients have HRR mutations or not. And this doesn't only pertain to these homologous recombination repair gene mutations, but this also pertains to many other mutations against which clinical trials are going on or drug development is ongoing, so not only to select for approved drugs, but also to select these patients or multiple ongoing clinical trials.

Dr. Turck:
Well, those are some great insights as we close our discussion today, and I want to thank my guest, Dr. Neeraj Agarwal, for joining me to share his findings from the TALAPRO-2 study. Dr. Agarwal, it was great having you on the program.

Dr. Agarwal:
Thank you for having me. It was a pleasure.

Dr. Turck:
For ReachMD, I'm Dr. Charles Turck. 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.