Precision Medicine in Advanced Prostate Cancer:
A Focus on PARP Inhibitors

Celestia Higano, MD, FACP: My name is Tia Higano, from the University of Washington. I'm very pleased to be with Dr. Joaquin Mateo, who is medical oncologist from Barcelona, and Dr. Daniel Petrylak, who is another medical oncologist from Yale.

I do want to mention that we'll likely be talking about some off-label use of drugs.

Let's just talk a little bit about *BRCA* mutations in prostate cancer.

If you think of genetic alterations, really the treatment algorithm has to do with those who do and those who don't have genetic alterations. And this could be either in the germline and/or the tumor testing, and so in either case right now the paradigm is to go through the regular options. Some of these are not available all over the world, but you would use any one of a number of treatment options for patients with metastatic castration-resistant prostate cancer (CRPC).

However, in those with these specialized mutations, the DDR mutations or microsatellite instability, etc, we have the options of using either poly (ADP-ribose) polymerase (PARP) inhibitors or platinum-based chemotherapy for the DNA damage response (DDR) mutations, or pembrolizumab in those patients who have failed the other usual treatments who have microsatellite insufficiency. In the latter category, that's a very small percentage of patients; however, there are some very good success stories with this approach under those circumstances.

So what are the DDR pathways all about? Well, we know that our cellular DNA is subject to continuous damage from various environmental factors or endogenous sources, and so our bodies are continually dealing with these thousands of breaks every day. There's single- or double-stranded DNA breaks, and the DDR pathway has evolved to maintain the DNA sequence the way it's supposed to run so that the engine runs smoothly, but several types of repair pathways exist depending on whether you have single- or double-stranded DNA breaks.

So where do these mutations occur? They can occur in the person who inherited this from one of their parents, so in the germline, and they can also come from the tumor. So the germline DNA mutations, as shown here, are inherited by regular Mendelian genetics.

Once a person has the tumor that is represented in the yellow circle, there's probably mutations there but not from the germline. But we know that tumor tends to mutate over time, and you could end up with a single tumor mutation, that now is a potentially targetable abnormality. If that tumor has another DNA hit, you could end up with a double tumor mutation. This is one of the things we have to remember when we test patients—things can change in the tumor over time, whereas they don't change in the germline.

Here's an instance where the carrier has a germline mutation and that tumor has a DNA hit, and now has a germline mutation as well as a tumor mutation. So these are the two sort of circumstances you can end up with.

You first have to understand the germline versus somatic issues before you can order testing, because you have to decide what you want to test for.

So in germline mutations we can test using saliva, blood, buffy coat, buccal smear, and they can be done either as a single test or in a panel that includes some of the DDR genes listed here.

I prefer a panel rather than a 1- or a 2-gene test, because in prostate cancer, results are more informative. So the results you get are positive for a pathogenic mutation, in which case that patient should be definitely referred for genetic counseling as well as cascade testing, which means other family members might be advised to undergo testing for this pathogenic mutation so that they could understand their risk for downstream cancer. A negative result means there's no known pathogenic mutation on this particular panel. And you might see a variant of unknown clinical significance (VUS)—this result should be treated as negative until further information is available.

So which patients should be tested for germline mutations? Certainly those with a positive family history for cancer should be considered for germline testing regardless of the stage of disease.

You should test those with DDR mutations in the family. So *BRCA2*, *BRCA1*, and *ATM* are some of the main germline mutations that we see in prostate cancer.

In the case of prostate cancer patients with a negative family history, the National Comprehensive Cancer Network (NCCN®) is now recommending that those with

intermediate- or high-risk localized prostate cancer, biochemical relapse, or metastatic prostate cancer of any kind have germline testing because it has clinical therapeutic implications.

And again, 1 in 10 men with metastatic prostate cancer have germline DNA repair mutations, which explains the recommendation by the NCCN.

Those with ductal or intraductal histology is a bit more controversial and was not adopted by the NCCN, but it's worth thinking about its potential significance.

Who should have genetic counseling? Any patient with a pathogenic or likely pathogenic germline mutation, and all patients with a strong family history of cancer even without a germline mutation. So that should be a takeaway message.

What about testing for somatic mutations of the tumors—who would you want to test for this?

I don't usually perform somatic testing unless I'm going to use that information to decide about a therapy, whether it's an investigational agent or hopefully the newer PARP inhibitors. But at least I will know from my germline testing that I've already gotten if there's a germline mutation, but if I want to push it further and see if I have a *BRCA2*, for example, that's happened during somatic mutations, that's when I will do this testing.

But, remember, the presence of a pathogenic mutation in the tumor testing may actually be from germline because it's all part of the same DNA. So if you haven't done germline testing but you get tumor testing that shows like a *BRCA2*, then you need to go back and figure out whether this is of germline origin or is this just from the tumor because of its importance in relation to other family members and the need for cascade testing and genetic counseling.

So the tests that are available to look at tumor DNA. Tissue is considered the gold standard, at least at this point, although liquid biopsy is coming a long way.

As far as tissue sources, you can go anywhere but it's really much more successful getting a soft tissue sample rather than performing a bone biopsy. The other thing is germline testing is more established and standardized in terms of their reporting compared to somatic testing.

So somatic testing could show you these DDR mutations; if you don't know whether it's germline, you need to go back and perform germline testing for the presence of DDR in the tumor.

The tumor specimen that you send off is only going to tell you the status of the tumor at the time that you perform the biopsy; it doesn't mean that 1 or 2 years from now there might not be new changes that are targetable with some other drugs.

Tumor testing with tissue can also be a problem if it's older than 3 to 5 years.

So I hope that this gave you a sense of how we use genetic testing, either germline or somatic testing, in the context of patient care, and when we would go on to act on that in this smaller percentage of patients who will have these various mutations.

Joaquin Mateo, MD, PhD: We're going to be talking a bit about this family of drugs we're introducing now in prostate cancer, PARP inhibitors, which we've been using for a number of years in ovarian and breast cancer.

PARP comprise a family of proteins, a family of enzymes that are in charge of transmitting signals by marking other proteins or DNA. They go next to a protein or a chain of DNA where something is happening, and they add poly(ADP-ribose) chains to tag them. And by tagging them, they mark them to start a signaling process.

There are many PARP proteins, but we are going to focus here on PARP1 and PARP2 because they have an important role in detecting the sites of DNA single-strand breaks.

And once PARP1 or PARP2 have detected the single-strand DNA breaks, they sit on these breaks, add the poly(ADP-ribose) chains around them, and then the proteins move out, and the DNA with the tags—with this poly(ADP-ribose) chain—is calling for other effector proteins to go there and repair the DNA damage. They go there, they attack, and then they have to move away to allow the repair to properly happen.

So PARP inhibitors are a family of drugs that inhibit the catalytic function of the PARP enzymes, they stop this process of tagging that we call parylation. On the top of that, we also now know that part of the anti-tumor activity of this drug is because when they are

paired with the protein and the protein tries to go to the DNA, first of all it's not only allowed to tag the DNA so it's not able to initiate the cascade of signaling for the repair, but also it doesn't allow the protein to move out again.

And by blocking it, it causes it what we call traps of the protein with the DNA. And this is important because the next time the cell is going to try to replicate the genome, the replication fork is not going to proceed through these traps, it's going to find an obstacle, and this is going to generate more DNA damage and the collapse of the process of replication.

So there are two main mechanisms of action but one is they stop the process of parylation, so they block the initiation of the repair signaling, and they cause cell damage.

So if they don't allow for the repair to start, what happens is that these single-strand breaks will progress to double-strand breaks, which are more toxic for the cell. In normal conditions, these double-strand breaks would be repaired by a homologous recombination. And to be honest, the effect of PARP inhibition would be neutral for the cell because it will be able to overcome the damage.

However, when we have a cell that is deficient for this homologous recombination processes, the accumulation of double-strand breaks will continue to proceed and will lead to a process of cell death.

This is the concept of synthetic lethality applied to PARP inhibitors. So synthetic lethality is a biological concept by which 2 events that, when they occur separately, are not lethal but when they occur at the same time on a cell become too toxic for the cell. So in this case, inhibiting PARP is not toxic for the cell if the cell is able to repair. But, when the cell is incapable of repairing the double-strand breaks, inhibiting PARP starts a process that will lead to cell death.

This was first demonstrated around 15 years ago now by several groups, that in tumor models that were lacking *BRCA1* or *BRCA2* (BRCA1 or BRCA2 are key proteins for the process of repairing double-strand breaks) these tumors would become very sensitive to PARP inhibitors.

So this concept was rapidly moved into the clinic using a compound called olaparib. And in a phase 1 trial, a proof of concept was generated that patients primarily with ovarian cancer patients who had these mutations responded very well to PARP inhibition with olaparib.

And there was actually 1 patient with prostate cancer who achieved a prostate-specific antigen response and an improvement in bone metastases on scans.

There are 4 PARP inhibitors in the latest stage of clinical development in prostate cancer: olaparib, rucaparib, talazoparib, and niraparib. There is another PARP inhibitor called veliparib that has less of a potency, particularly when it comes to trapping the PARP enzyme in the DNA. It's still in development but primarily included in combination trials.

The first test of a PARP inhibitor in, let's call it a sporadic ovarian cancer, was an expansion cohort in prostate cancer in the first human trial of niraparib a few years back. We started to see some circulating tumor cell (CTC) responses in some patients who achieved prolonged stabilization, but that was a very small cohort of 12 patients.

With these data in the early 2010s, some data started to emerge about the potential for these drugs in prostate cancer. It was known that prostate cancer is a disease characterized by high genomic instability. And most of the preclinical data supported the development in patients who have this high burden of translocations, particularly patients with homologous recombination rearrangements.

So the proof of concept study for developing PARP inhibitors in prostate cancer was the TOPARP trial. It was an investigator-initiated study that tested olaparib in a population of patients with metastatic prostate cancer without prior knowledge of their molecular background. So we treated 50 patients and went back to their biopsy results to check if they responded to olaparib correlated with a particular genomic background.

Our primary endpoint was response rate, and we used a wide definition of response including PSA decline or CTC because what we were looking for was a signal to support further development of the drug, and then we look at other things like progression-free survival (PFS) or overall survival.

What we learned from those initial 50 patients was that around one-third of them presented some benefit either in the scans, or in PSA decreases, or by conversions of the CTC count going low with the patient becoming stable for a time. Out of these 33%, not all of them, but the vast majority of them, were those with mutations in these DNA repair genes.

Again, the most common mutation was *BRCA2*, and all the patients who had *BRCA2* mutations in that initial study, responded.

After that, we moved to the second stage in the trials—it was a multi-stage trial—to prospectively validate this concept by looking for patients that had these alterations and then treating them with olaparib. So the hypothesis was if we're going to reach our population for patients with these mutations, we will see a higher response rate than when we treat an unselected population.

So we tested over 700 patients until we managed to treat around 100 patients who had somatic or germline alterations in these genes.

So this is the population we tested. So we were testing 2 different dose levels of the drug because of data that we had generated over the years in testing different formulations of the drug; however, that's not important for what we are discussing today—just consider the total.

These were patients who had received docetaxel, and almost all of them had also received either abiraterone and/or enzalutamide and disease was progressing actively at the time of starting the treatment. You can see that there is a high proportion of patients with visceral disease and a high proportion of patients with measurable disease.

So our primary endpoint, again, was response. As we hypothesized, we saw that by enriching the population for patients with DNA repair mutations, we saw a higher response rate than when treating an unselected population.

So around half of the patients derived some benefit. However, if you look at the patient-by-patient scenario, it was very clear that patients with alterations in *BRCA1* or *BRCA2*—represented in blue in this waterfall plot—were the ones more commonly responding but also achieving the more profound and long-lasting responses.

Other phase 2 trials have now tested different PARP inhibitors. The TRITON trial is testing rucaparib in patients with metastatic prostate cancer. This is the panel of genes they are testing for, which is pretty much similar to what we were testing in TOPARP.

At last year's ESMO meeting, they reported a preliminary analysis of the first 57 patients with *BRCA1* or *BRCA2* alterations. Similar response rates were seen, and also a similar proportion of patients achieving long-lasting responses.

Niraparib is also being tested in prostate cancer; the phase 2 trial is GALAHAD. Again, the eligibility criteria are very similar, they are using another strategy that is testing cell-free DNA rather than testing the tumor. They are recruiting patients who are known to have these DNA repair alterations.

The response rates they are seeing in the *BRCA*-mutant population again are very similar to what we saw in TOPARP and what the TRITON trial is observing with rucaparib. In the non-*BRCA* population, it's more difficult to understand because in the preliminary report, they only reported those with biallelic loss of the protein, but they treated other patients too. I think we just need to wait until the trial is published, and we can assess all the data properly.

Talazoparib is the fourth PARP inhibitor that is being developed in prostate cancer. Researchers just presented preliminary data about the first 53 patients with DNA repair mutations that have been tested in this trial. The response rate in *BRCA1* or *BRCA2*-mutation–positive prostate cancer is 68% when combining radiology findings and decreases in PSA. So again, similar to what we saw in TOPARP-B, which was over 75%.

Interestingly, the radiographic PFS (rPFS) for the *BRCA1*/*BRCA2* mutant population was 8.2 months; the same as we observed in TOPARP. These are patients in very latest stage setting post-taxanes with abiraterone/enzalutamide, so actually achieving an rPFS of over 8 months I think it's quite remarkable.

Based, in part, on the TOPARP data, PROfound was designed as the randomized phase 3 trial of olaparib versus physician choice of abiraterone or enzalutamide for patients who had already experienced disease progression on enzalutamide or abiraterone first.

The trial was stratified into 2 cohorts. Cohort A included patients with alterations in *BRCA1*, *BRCA2*, or *ATM* because these are the most common mutations. Cohort B included patients who had alterations in any of a list of 15 genes.

Patients were randomized 2:1 to the experimental arm, olaparib, compared to the control arm, and we offered the patients the possibility to be crossed over to olaparib upon progression to a standard of care. This was a nonblinded trial. And the primary endpoint was rPFS and not overall survival precisely because we were offering the option of crossover.

A higher proportion of patients with measurable disease, a higher proportion of patients with visceral disease—maybe because this is more representative of the *BRCA* population, this is something we are learning now.

All patients had been treated with abiraterone or enzalutamide. Most of them—65%—had been treated with docetaxel or cabazitaxel.

The primary endpoint was rPFS in the cohort A population, so in those patients with alterations in *BRCA1*, *BRCA2*, or *ATM*. You can see by the Kaplan-Meier curves that clearly olaparib improved rPFS in this population compared to abiraterone or enzalutamide once patients had disease progression first on enzalutamide or abiraterone. The rPFS was over 7 months. Again, it seems quite consistent with the prior data; around 7 to 8 months. The median rPFS was clearly superior to that in patients in the control arm.

Overall survival was a secondary endpoint, and results are not mature yet. However, when we took the first planned look with only 38% maturity and despite actual 80% of the patients with disease progression on abiraterone or enzalutamide crossed over to the olaparib arm, we were able to see the survival curves splitting. We need to wait until we have mature data; however, this is very encouraging. This also reflects that probably the earlier we use these drugs, the better. Because the later we go the patient probably will have more toxicities and probably end up dropping out of the study for several reasons.

So initial subgroup analysis of the trial is to try to understand which population benefits the most. We start to see that, as we have shown in TOPARP-B and in other trials,

there are differences depending on the gene that has been lost, and that confers more or less magnitude of sensitivity. If you look at this plot and you see the bars, the degree of sensitivity is pretty much the same as the bars that I was showing you from the preclinical experiments in the laboratory.

What have we learned with the development of PARP inhibitors in prostate cancer over the past 5 years? So one is that PARP inhibitors are active in metastatic prostate cancer, particularly in those cases with DDR gene alterations. Clearly, *BRCA2* mutations are the low-hanging fruit, but there is benefit in other populations that we probably need to refine a bit more for the optimal of PARP inhibitors for these patients.

It is reassuring to see data consistently reported from different PARP inhibitors in different clinical trials with slightly different strategies of selection. But in the end, you see some numbers that keep repeating, suggesting that the effect is really consistent.

I think that it's very important that PROfound has set a mark as the first ever precision medicine randomized trial in prostate cancer that was conducted and that is positive, and I think that is going to be a game-changer for the practice in prostate cancer. Because it's not only opening the opportunity for new treatment, but it's also opening the opportunity of a new concept, which is to molecularly stratify patients. I'm sure this is going to lead to a cascade of opportunities to identify other alterations that are targetable. And that it's actually not only going to bring us a new drug to the clinic, but it's also going to accelerate the development of other compounds in the face of prostate cancer.

This is a bit of a summary of the status of the different PARP inhibitors that have been evaluated already by regulatory agencies. All 3—olaparib, rucaparib, and niraparib—were granted Breakthrough Therapy designation by the FDA.

Daniel Petrylak, MD: So I'm going to be talking about 2 different things. First, what are some of the most common side effects that we see, and then second, what are the clinical trials and how can we also extend BRCAness to other patients that may not have the *BRCA* or DDR gene mutations.

These are some of the common toxicities with PARP inhibitors. Most common, of course, is hematologic—anemia, thrombocytopenia, and neutropenia. Nausea can

occur; it's an oral drug so nausea can be involved with its administration. Fatigue and asthenia, again a common side effect with chemotherapy, and liver function enzyme elevations.

For most of these adverse events (AEs), they're low-grade except for anemia. Grade 3 to 4 AEs leading to treatment interruption, dose reduction, or discontinuation are more common in PARP inhibitors than in the controls, and then often these toxicities are tolerated after tailoring the dose or adjusting it for a given patient.

So let's look at some of the individual trials and see what the rates of Grade 3 to 4 anemia are. This is the TOPARP-A trial with olaparib. The most common side effect is anemia, with 20% of patients affected.

TOPARP-B has a very similar pattern, maybe a little bit more anemia.

In TRITON2, there was a similar pattern, asthenia, nausea. Anemia occurred in about 17%, so we're looking at about the 20% range for a significant anemia.

GALAHAD showed the same pattern anemia in 29%, thrombocytopenia in 15%, and neutropenia at 7%.

In the PROfound trial, I don't think the pattern is much different. About a 20% rate of anemia and about 1.2% rate of nausea.

How do we manage this nausea, vomiting, and hematologic toxicities? We don't want to, of course, lead to dose delays and interruptions, but if you need to you have to do it. With neutropenia, thrombocytopenia, and anemia, you have to monitor blood cell counts, reduce the dose as appropriate, and to think about how there may be other drug interactions that may occur with the patients who are being treated with polypharmacy for pain medications and other issues as well.

There are some trials that are now accruing patients.

This is the PROpel trial looking at olaparib plus abiraterone, and the primary endpoint is PFS. This is being compared to placebo plus abiraterone randomized in the 1:1 basis. Again there seems to be some synergy between the PARP inhibitors as well as some of the next-generation antiandrogens.

TRITON3 is a phase 3 trial, and this is taking patients who have received prior next-generation hormonal therapy and they're being randomized to rucaparib or the physician's choice of either docetaxel, enzalutamide, or abiraterone. And again the primary endpoint is rPFS.

The MAGNITUDE trial is a phase 3 study, first-line CRPC in 2 different cohorts, those who have DNA repair mutations and those who are not positive for DNA repair mutations. Patients are randomized to the combination of niraparib plus abiraterone or abiraterone alone, and again the primary endpoint is PFS.

The QUEST trial was a phase 1/2 nonrandomized study, it's multi-centered. It's also looking at niraparib in combination with anti–programmed cell death protein ligand 1 (PD-L1) and abiraterone. This is primarily looking to define toxicities, objective response rate.

The TALAPRO trial is a phase 3 study of talazoparib. Part 1 is to confirm the dose and it's talazoparib to be combined with enzalutamide, and then part 2 will take that and look at this in terms of rPFS. It's designed to take unselected patients for DDR, and they'll be randomized to receive talazoparib once a day, and then this will be in combination with enzalutamide.

A phase 2 trial is being performed with veliparib, and it's being combined with abiraterone and prednisone. The primary endpoints are PSA response rate and whether *ETS* fusions will predict response.

In some of the preliminary reports there didn't seem to be a difference between abiraterone plus prednisone plus veliparib versus abiraterone plus prednisone alone. *ETS* fusions did not predict response, and an exploratory analysis identified a novel DNA repair mutation with outcomes. So again with this DRD mutation, 90% had a PSA response rate versus the wild-type.

We need rational combinations, and this is where we can expand our use of *BRCA* and BRCAness. And this is "BRCAness" because what we're trying to do is induce BRCAness by reducing the levels of DNA repair mutations. So I think we have to think of this in terms of the fact that when you're seeing response rates of 50% with these drugs, half of patients don't respond. Why? Well, we'd like to try to make these

unresponsive patients responsive. Eventually as we see with all these drugs, drug resistance does become inevitable, so we would like to deepen the response, increase the duration, and then widen the applicability of these PARP inhibitors. So can we increase the survival rates by doing this, can we make the tail of the curve longer in these patients? This is why we need these rational combinations.

There are other functions of PARP inhibitors aside from DNA repair. As we know, the repair is in the single-stranded end of DNA and also does regulate transcription. PARP inhibitors will affect inflammatory genes, and this is again one of the reasons or rationales why we're going to combine it with immunotherapy. And it will also promote oncogenic phenotypes and will also be involved in transcription of the androgen receptor as well as ERG, and that was the reason before why this was looked at in terms of a marker in this disease. So these castration-resistant tumor cells will also show increased levels of PARP1 activity.

A randomized phase 2 study from the NCI is assessing abiraterone and prednisone by itself, or abiraterone, prednisone, plus veliparib. The primary endpoints were confirmed PSA response rate, and this study is asking the question as to whether ETS fusion predicts response.

There was no difference in the PSA response rate. There's really no significant difference in measurable disease and no difference in PFS.

If you start looking at an exploratory analysis based upon the DNA repair mutations, the confirmed PSA response was 90% versus 56.7%, again positive in DNA repair. PSA declines, RECIST responses, PFS all seem to be better in those with DNA repair mutations versus the wild-type.

This trial is fairly interesting. As we saw from the phase 3 study that was the genesis of that particular trial looking at olaparib combined with abiraterone versus placebo plus abiraterone, it was a randomized phase 2 trial. The primary endpoint was rPFS.

The rPFS curve is fairly intriguing. You've got a higher rate of events in the monotherapy arm, and there's a difference of about 5 months in the overall rPFS.

However, when we look at the secondary endpoint, there's no difference in overall survival. There were small numbers in this randomized phase 2 trial.

The intriguing part of this trial is the third graph on the right where you look at the patients with wild-type mutations and you look at the difference between olaparib plus abiraterone versus abiraterone. This supports that concept of inducing BRCAness. The hazard ratio is 0.52 in favor of the combination, and you also see the same with the patients who've had a DNA repair. But this is basically saying that you may be able to induce BRCAness by giving this combination to patients, and of course that larger trial we talked about before is going to confirm these particular observations.

Now this is where we have a little bit of a problem in the AEs. What is particularly concerning are the cardiovascular events. This is something that's been identified with abiraterone.

As we see on the right concerning AEs with olaparib plus abiraterone, myocardial infarction in 4 patients and cardiac failure in 1 patient, compared to abiraterone alone only 1 with myocardial infarction. This is something you've got to be careful about when selecting your patients for therapy—preexisting cardiovascular disease is something I would not recommend.

This is an interesting concept, the concept of hypoxia. What does hypoxia have to do with prostate cancer? Well, hypoxia downregulates DNA double-stranded repair, *BRCA1*, *BRCA2*, and *RAD51*, and this has been seen in multiple cell lines including prostate cancer, and this concept has been looked at in ovarian cancer as well as in breast cancer.

So as we see here looking at these particular agents, there are 3 different human prostate cancer cell lines—DU145, PC3, and GM05757—and as we see there's downregulation of these particular markers.

Olaparib works in a significant subset of castrate-resistant prostate cancer patients, most of those with loss of function of DNA repair pathways. Olaparib and cediranib in combination may work synergistically even in the absence of mutation of DNA repair via this hypoxia pathway, and this may actually be the way of inducing BRCAness. We're actually moving forward with this combination in CRPC.

This is the design of the trial. As I mentioned previously, there was a 7-month improvement in rPFS.

These are the trials that have been looking at combining olaparib or other PARP inhibitors with PD-1 or PD-L1 agents—olaparib with durvalumab, pembrolizumab. Also there are trials comparing this to abiraterone and prednisone or enzalutamide.

Celestia Higano, MD, FACP: I want to thank the audience, and thank you to my colleagues.

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