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Patient-Centric ADT Intensification in Hormone-Sensitive Prostate Cancer: Balancing Efficacy, Safety, Quality of Life, and Survival

Dr. Taplin:
Hello everyone. My name is Mary-Ellen Taplin. I'm a Genitourinary Medical Oncologist at the Dana-Farber Cancer Institute, which is located in Boston, Massachusetts. Today, I'm going to be presenting to you a lecture on patient centric androgen deprivation therapy intensification, primarily in hormone sensitive prostate cancer, both nonmetastatic and metastatic.

So, our plan of attack today will include an introduction and then we'll talk about which patients are best suited for intensified androgen deprivation therapy. We'll review the latest evidence with an eye towards individual patient-centered planning, optimizing our team for treatments, and then at the end, a couple cases.

Our learning objectives are: To perform risk assessment for patients with hormone sensitive prostate cancer to inform potential treatment planning. Number two: To analyze and contextualize recent clinical trial evidence for androgen deprivation therapy intensification, particularly in the high-risk patient setting. Number three: To develop collaborative treatment plans for patients. And number four: To incorporate interprofessional team-based approach to the treatment of our prostate cancer patients.

I'll just add, things have gotten more complicated in prostate cancer over the last few years. We've had a lot of new approvals, which is very exciting, a lot of new data to digest, and we'll go through this today and make it relevant for you.

So, this is just a little schematic that I like, to set the stage in different topics. So, you know the prostate cancer patient, many of them start with localized prostate cancer. If they're not cured, they develop a rising PSA and then transition into metastatic hormone-sensitive prostate cancer, or nonmetastatic hormone-sensitive prostate cancer. And eventually, under the selective pressure of androgen deprivation, developed castration-resistant prostate cancer and we will not be talking about castration-resistant prostate cancer today.

So, because we're going to be talking about clinical trial data, and in order to understand the data and then translate that into talking to our patients, we need to understand endpoints. So, I just wanted to take a moment to say, how does a treatment go from an idea to a standard of care? So, we have an unmet clinical need, which we have in spades in cancer therapy, a hypothesis developed around you know why a certain drug or compound should work in a certain type of cancer, and then an available compound is taken through Phase 1 dose and toxicity analysis, Phase 2, and ultimately Phase 3, which would be a prospective randomized well-powered trial with primary endpoints being validated. Eventually, you know the trial will be run, events will be reached, data will be analyzed. If it's a positive trial, the data will be submitted to the FDA for eventual approval and then, therapy standard use in the practice.

And here are some of the endpoints that are used in prostate cancer commonly. So, for many years, overall survival was the gold standard, historic gold standard, and occasionally prostate cancer specific mortality. In the more recent years, metastasis-free survival, MFS, or radiographic-free survival is a surrogate. It has been shown to be a surrogate for overall survival, and that was very important in drug development in prostate cancer because it takes much longer to wait for an overall survival end point, whereas MFS or RPFS are achieved earlier and we can get therapies to the clinic sooner.

Endpoints that are not validated to reflect overall survival or MFS, are PSA-based endpoints. So, PSA, progression-free survival, or biochemical recurrence-free survival. And those endpoints were used or are often used in earlier stages of trial, such as Phase 2, but are not used to change the standard of care in prostate cancer.

So, we're going to talk about some treatments in earlier stage prostate cancer, so I wanted to remind us what the definitions of failure are after local therapy. So, with prostatectomy, the definition of recurrence is a PSA of 0.2. However, now that we have more accurate PSA assays, and patients have followed very closely, the PSA recurrence will often be looked at 0.1, or between 0.1 and 0.2. And subsequent to that, patients are assessed with a PSMA PET scan and then, if it's a prostatectomy patient, salvage therapies are considered. Primarily salvage radiation with or without androgen depravation therapy.

In the context of patients who've received primary radiation as their treatment, the definition of recurrence is a PSA of 2.0 as opposed to 0.2. Similar staging is obtained, generally with a PSMA PET scan. There is some consideration for salvage therapy, but salvage therapy after radiation is used less commonly than after prostatectomy.

And the standard of care is generally androgen deprivation therapy, which we're going to talk about in detail because there's some new data to digest from the EMBARK and PRESTO trials. But starting hormone therapy for PSA recurrence after radiation really should be individualized in terms of the patient's risk factors. And here's some old data but data that I believe remains very relevant to our practice and to choosing the best treatments for our patients which shows that this is some data in about 300 men, after prostatectomy, came to Johns Hopkins, where hormone therapy was not started for PSA recurrence only, but hormone therapy was started at the time of metastasis.

And you can see what predicts for patients who will do well, as opposed to patients who will develop metastases sooner, are the Gleason Score, the time that the PSA rose after local therapy, and the PSA doubling time. So, patients with Gleason scores of 8 to 10, that curve there on the left, do poorly in terms of recurrence. If the PSA goes up within 2 years of prostatectomy, similarly, poor outcomes, and if the PSA doubling time was less than 10 months. And that PSA doubling time of less than 10 months from this older natural history study is why the PSA doubling time of 10 months or less was used in the more contemporary trials of the androgen receptor pathway inhibitors, such as the EMBARK trial.

So, let's now review some of the latest data, and let's start with metastatic hormone-sensitive prostate cancer. So, here is the stage if you will, for androgen deprivation therapy. So, testicular androgen suppression has been used since the 1970s with medications like leuprolide and goserelin. These are LHRH agonists, and now there are LHRH antagonists in use in our practice as well.

The sort of old school androgen receptor antagonists were flutamide, bicalutamide, nilutamide. They're rarely used anymore. And the first, if you will, CYP17 inhibitor was actually ketoconazole because it had nonspecific inhibition of CYP17, but again, is no longer used in prostate cancer.

Now, we have variably termed novel hormonal therapy. I like to refer to them as androgen receptor pathway inhibitors, and these include the 3 androgen receptor antagonists. So, a next-generation of bicalutamide, either enzalutamide, apalutamide and darolutamide, and then, the CYP17 inhibitor, abiraterone. There are other drugs that are in development and you may see clinical trials with them, including the AR degraders and next-generations of CYP17 inhibitors.

These are the trials, and I'm not going to go through them all in detail, but there are two trials looking at abiraterone in metastatic hormone sensitive prostate cancer, the STAMPEDE trial done in the UK, and the LATITUDE trial. Overall survival was the primary or coprimary endpoints in these trials. Two trials with enzalutamide, ENZAMET and ARCHES, one trial with apalutamide, the TITAN trial. Overall survival and RPFS were coprimary endpoints. And the ARASENS trial, which looked at the combination of darolutamide with docetaxel. And all of these trials, these Phase 3 trials in metastatic hormone sensitive prostate cancer, the control arm was androgen deprivation therapy and placebo.

So, let's just digest one of these trials, the TITAN trial, as an example of all of them. So, this is about 1,000 patients. It was accrued between 2015 and 2017. It was a one-to-one randomization with a backbone of ADT. They were randomized to apalutamide or placebo. And the primary endpoint initially was RPFS. There could be a second treatment at the clinician's discretion, and then we can look at in this trial PFS2, that's a second PFS, and then, overall survival. So, a very well done, well-designed trial with a standard population of castration-sensitive metastatic prostate cancer.

And here are the overall survival outcomes, the gold standard outcome if you will. Significantly in favor of apalutamide over placebo, and the IPCW is a way to control the data for the subsequent use of apalutamide. And you can see that even with this statistical analysis, the possible difference could be even greater with apalutamide compared to placebo. And this data, together with the other trials that I've mentioned, led to the approval and now the standard of care of these AR pathway inhibitors, including apalutamide, in this state of prostate cancer.

Here are some key secondary endpoints which, when you're talking to your patients, are very relevant and maybe sometimes even as relevant as overall survival. Patients are very focused on PSA progression, and you can see much in favor of apalutamide. The time to initiation of cytotoxic chemotherapy again, much in favor of apalutamide, as is the time to castration-resistant. So, these medications in the setting were ground-breaking, and really have led to a lot of benefit. And I will go out on a limb to say that there should be, unless

there's clear evidence that a patient has a very poor baseline status or intolerance to one of these medications for some reason, all patients with metastatic hormone-sensitive prostate cancer should be offered an androgen receptor pathway inhibitor based on these data.

And here are the toxicities, and the more common ones in terms of the apalutamide are shown at the top of the table here: all-grade fatigue about 20%, but Grade 3 or greater only 1%. Similar to control. Increase in hypertension, which are known side effects of these medications. And arthralgias, which are general side effects of androgen deprivation therapy. In terms of apalutamide, there was a 25% increase in rash, which has been a known side effect, and a 6% increase in hypothyroidism, which is a class effect in general of these AR drugs and patients should be followed for that.

And here, combining this data on the right with the apalutamide with the data from some of the other trials, same with enzalutamide in ENZAMET, and abiraterone in the LATITUDE trial. And this is where you need to apply the data to your specific patient and knowing your patient's baseline comorbidities. And you can see, for instance, while abiraterone is just as efficacious as the others, and I have a slide coming up to show that for all these drugs, there's a bit more increase in cardiac issues and fluid retention with abiraterone with the other drugs. And if you have a patient who has active cardiovascular issues, abiraterone wouldn't be the choice over apalutamide or enzalutamide for that patient. Similarly, abiraterone can cause an elevation in liver enzymes about 15 to 20% of the time, or low potassium. So, if you have a patient who has any hepatic or baseline renal issues, abiraterone might not be the drug for them.

A class effect across all of these drugs is hypertension and you need to give your patients special attention to their blood pressures. As medical oncologists treating prostate cancer, there's a lot of cardiovascular issues that we need to be aware of for our patients to optimize their therapy.

And a word about radiation to the prostate. So, say you have a patient newly diagnosed in your clinic who has low volume, which is defined as 4 or fewer metastases in the STAMPEDE and the ENZAMET trials and others. You see the data on the right here that shows that the addition of prostate radiation to the ADT and the abiraterone contributed to increased overall survival. Whereas the curve on the left is all the patients, and there was not an increase in survival and that's because radiation to the prostate did not provide benefit to the high-volume patients.

So, based on this data, again, standard of care for a patient with newly diagnosed metastatic hormone sensitive prostate cancer should be an AR pathway inhibitor and ADT and radiation to the prostate. Very good prospective randomized phase 3 data to support that conclusion.

And here is the promised table. The patients always ask us, well, "Which one of these drugs is better, doc? Which one you know should I have?" And in terms of efficacy, and you can see the columns for, separately, for high volume and for low volume. These are *P* values for overall survival, and they're all very consistent across these groups; abiraterone, enzalutamide, apalutamide and darolutamide. There will never be a trial comparing these drugs one-to-one, and so this is the best data that we have, at least in terms of efficacy. I'm not mentioning here toxicity, which we just talked about. There may be a reason to choose one of these drugs over the other for individual patients, but when you compare low-volume to low-volume and high-volume to high-volume, the improvement in overall survival and the other secondary endpoints are very similar.

Okay. So, that was metastatic hormone sensitive prostate cancer and now we'll change gears a little bit to the patient who doesn't have metastases, but they've been treated with local therapy, surgery or radiation and now they have a rising PSA.

So, this group of patients, as I showed you in the earlier slides, is a very heterogeneous group of patients where some patients with a very long PSA doubling time and a low Gleason score, initially may not need therapy. They may be at very low risk for metastasis, and they can just be followed over time. Whereas other patients who have a shorter PSA doubling time, higher Gleason score, at risk for metastasis, and it's in those patients who this contemporary clinical trial data that I'm going to share for you now, are relevant.

And this is again, older data, but showing prostate cancer specific survival based on the PSA doubling time. And people with PSA doubling times that are long, you can see here, greater than 15 months in this case, do not have a threat from their prostate cancer coming back, and I would argue, should be followed and not treated with androgen deprivation therapy which can have significant morbidity itself. But the patients with the PSA doubling times in this analysis of 9 months or less are the patients who have reduced prostate cancer specific survival and should be considered for therapy.

And just a word before we look at the EMBARK trial and the PRESTO trial. What about intermittent androgen deprivation therapy in general? So, just you know our older hormone therapy, leuprolide say. And what this trial showed, randomized prospective phase 3 trial, was that continuous androgen deprivation therapy and intermittent androgen deprivation therapy were no difference in overall survival. This was an older group of patients and in fact, almost 60% of them who passed away passed away from a non-prostate cancer diagnosis.

There were some quality-of-life benefits to intermittent therapy, but not as high as expected. And that may be because only 35% of

patients, even with intermittent therapy, returned their testosterone to the pretreatment levels. And I have some slides coming up later on that we can digest testosterone recovery after hormone therapy in a little more detail. But in my practice, I do use intermittent androgen deprivation therapy for the nonmetastatic patient.

So, this is a trial that was published a year ago, very well done trial called the EMBARK trial. This is for patients who have nonmetastatic prostate cancer by conventional imaging. We haven't talked about in this context staging with PSMA PET, but these patients had PSA recurrence of PSA doubling time of less than 10 months. They had a PSA over 2 if they were treated with radiation, and over 1 if they were treated with prostatectomy. And they were randomly assigned to leuprolide and enzalutamide, leuprolide alone, or non-castrating hormone therapy with enzalutamide alone. The treatment was for about 9 months, so a backbone of intermittent therapy. Treatment was stopped if the patient had had a good PSA response of less than 0.2 and per the protocol, the treatment arm that they were started on was restarted if their PSA rose to greater than 2 if prostatectomy or greater than 5 if radiation. The primary end point was MFS.

And here's how the curves look. For first, on the left, enzalutamide and leuprolide versus leuprolide alone. Significantly in favor of the combination therapy, with a hazard ratio for progression of 0.4. And on the right is enzalutamide monotherapy on the top curve, versus leuprolide. So, non-castrating therapy versus castrating therapy. And the enzalutamide did somewhat better here with a hazard ratio of 0.6.

And looking at the data in a little more detail, and I actually really started to pay attention to this when I was making this slide set, as well, enzalutamide monotherapy looked like it might be a little bit better than leuprolide. You can see that the amount of time that patients were off therapy was significantly different.
The enzalutamide monotherapy patients started therapy around 1-year, so that's about 3 months or so off treatment, whereas the patients who had leuprolide or leuprolide in combination were off therapy for much longer; 20 months. So, that has to be part of the conversation when you're talking to a patient about monotherapy, that they will be off, likely, for a shorter period of time, because when they stop therapy their PSA will rise quicker.

And here is the safety. And I just wanted to bring a couple things to your attention. Number one is that the proportion of patients coming off therapy because of an adverse event in either of the enzalutamide cohorts, so monotherapy or combined with leuprolide, was about 20%, and these are generally for side effects like fatigue, and issues related to fatigue like falls. And then secondly, further down on the curve, the enzalutamide monotherapy had a 45% rate of gynecomastia and gynecomastia with nipple pain.

So, I think this trial gives us the option of using enzalutamide monotherapy. There's been many trials over the decades looking at monotherapy with bicalutamide and other therapies. But to understand the data, you need to understand and discuss with your patient the potential toxicity, the potential for coming off treatment because of toxicity, and the potential for restarting hormone therapy sooner than if a patient had a castration-based therapy. All relevant to the conversation.

This is the second trial that was done by the Alliance Cooperative Group. It's called the PRESTO trial and it's a similar premise. Patients with a rising PSA after prostatectomy, 3-arm trial, ADT alone, ADT with apalutamide, or ADT with apalutamide and abiraterone. So, exploring the hypothesis that hitting the androgen receptor axis on the receptor level without apalutamide, and on the ligand level with abiraterone, potentially could be significantly more effective therapy. This trial, however, when it was designed, did not use RPFS or MFS, as a primary endpoint but used a PSA-based endpoint which, as I noted, is not validated for approval. It did show, on the left here is leuprolide and apalutamide versus an LHRH antagonist alone in favor of the apalutamide. And similarly on the right, the dark curve favors apalutamide and abiraterone.

So, as I mentioned, because of the endpoint of this trial, which is why I wanted to review how important it is to focus on endpoints, this trial will not go to the FDA to look at approval for apalutamide or apalutamide and abiraterone for rising PSA, but does provide some data for us that these drugs, like enzalutamide, are likely effective in this setting.

All right. Now, we're going to talk about clinically localized prostate cancer. So, we talked about metastatic hormone sensitive, rising PSA hormone sensitive, no mets, and now localized high risk prostate cancer. So, localized high risk prostate cancer occurs in about 15 to 20% of newly diagnosed localized prostate cancer patients based on a Gleason score of 8 or higher, PSA of 20 or higher, or T3 disease. These patients have a very high risk of relapse after prostatectomy or radiation that can be 50% or higher.

So, my group over the last 10 years has done a series of Phase 2 trials looking at the use of an androgen receptor pathway inhibitor combined with prostatectomy. So, I'm not going to go into the details of these four phase 2 trials. We looked at various combinations of abiraterone, enzalutamide and abiraterone and apalutamide. Our primary endpoint was generally pathologic response in the prostate with secondary endpoints of PSA remission and radiographic response.

And what we showed is that these AR pathway inhibitors, again, in the phase 2 setting, led to either a pathologic complete response or what we termed minimal residual disease, a few millimeters of cancer left in the prostate. About 25% of the time, it was between 22% and 40% of the time we had these exceptional pathology responses. And we decided to look over time of what this meant for PSA failure. And you can see that that top line there in the red, on the right-hand curve, very few patients had any relapse if they had an

exceptional response in their prostate to neoadjuvant therapy with an androgen pathway inhibitor. And we decided to look, then, at a metric in the prostate called residual cancer burden which looks at tumor volume and the cellularity of tumor, and to look and see how this correlated with outcomes. And again, like PCR and minimal residual disease, residual cancer burden was very prognostic on the risk of relapsing.

So, these readouts in the prostate can be very powerful for testing new combinations of treatment with local therapy to affect better outcomes, similar to cancers that you all treat all the time, like breast cancer and colon cancer, where combination systemic therapy and local surgery has become standard of care. To this point in prostate, it hasn't become standard of care.

The ARNEO trial is a similar trial done in Europe, looking at apalutamide and ADT combined with prostatectomy. And this trial also showed that the combination with apalutamide had a much higher rate of residual cancer burden.

So, what about other states of localized high risk prostate cancer? So, the Apa-RP trial is a single-arm phase 2 trial looking at adjuvant therapy as opposed to neoadjuvant therapy after prostatectomy for localized high risk patients. These are very high-risk patients. Sixty-percent of them had recent scores of 8 to 10, and they received apalutamide and ADT post-prostatectomy. The primary endpoint of this phase 2 trial was freedom from biochemical failure at 2-years, which was very high with this treatment. And you can see that testosterone recoveries, here, that 77% of patients had recovered testosterone to greater than 150 at 1-year post treatment. So, a quarter of the patients still were not recovered, which is relevant to this data. And the safety was similar.

The ATLAS trial has not read out. The ATLAS trial is a primary radiation trial for localized high-risk patients, evaluating apalutamide versus bicalutamide together with ADT and standard radiation, and this trial will read out in December of this year [2025]. And if it's a positive trial, would be the first AR pathway inhibitor likely to get approved in the context of radiation for localized high risk prostate cancer.

Keep that one on your radar, together with this trial. The PROTEUS trial. Which was born out of that Phase 2 data that I just shared with you. Localized high-risk prostate cancer, candidates for prostatectomy. These patients received 6 months of apalutamide and ADT, or placebo and ADT, prior to prostatectomy and 6 months post prostatectomy, and there's coprimary endpoints of the tumor response in the prostate together with MFS. This trial will also read out in December of this year [2025] and likely be presented at ASCO of next year [2026].

And this is the largest Phase 3 trial in localized prostate cancer in the context of prostatectomy to ever done. Twenty-one-hundred patients were randomized to this trial. And was the first Phase 3 trial to be done in 12 years. So, the PROTEUS trial is a very important trial. PROTEUS and ATLAS as I said, the data will be finalized in December of this year [2025] and both trials will likely be presented a year from June at ASCO [2026].

How about some real-world evidence? And this was an analysis. It's called the OASIS Project, looking at about 116 patients that shows – and this is important metric or pearl for your clinical practice – that the PSA nadir that patients reach on, in this case it was apalutamide, is predictive for survival, whereas PSA is becoming undetectable, or PSA90, the survival rate was very high. But when patients did not reach these favorable PSA responses, the progression was quicker and doing poorly from prostate cancer.

And this is similar data, again with apalutamide with the TITAN trial showing patient deterioration by FACT-P. The importance of patient-reported outcomes you know was less good in patients who did not receive an early and deep PSA decline.

So, you know I showed you some very old data from PSA, PSA doubling times, and it turns out that the metric of PSA and PSA changes in the context of treatment remains important with our newer therapies, our AR pathway inhibitors.

These are some quality-of-life data reported from the STAMPEDE trial that shows that the AR pathway inhibitors. In general, patients feel better than on docetaxel. I think any of us who are clinicians would have predicted that. Except for, look at that one graph on the right lower. Cognitive function was equivalent with AR pathway inhibitor, in this case abiraterone or docetaxel. Again, data to use when thinking of your individual patient and which one of these compounds would be best for them.

This slide is a little hard to see, but the basic take home message is that enzalutamide, in terms of FACT-P, which are quality of life outcomes, did not perform as well as basically, leuprolide alone. So, at least for enzalutamide, either monotherapy or in combination, quality of life issues need to be considered with enzalutamide contributing to some possible detriment in quality-of-life function as reported by the patients. This is the same.

So, whenever you're treating a patient with androgen deprivation therapy – and we just reviewed data for treating intermittently with metastatic hormone sensitive if low volume, rising PSA, and in the context of local therapy – it's important to talk about the patient about testosterone recovery.

So, what do we know about testosterone recovery when we stop hormone therapy? Well, we do know that it's very important to get a

baseline testosterone before any patient is started on hormone therapy because a lot of patients in our practice have baseline low testosterone that nobody knows about. So, if you have a patient with a low testosterone and you start them on hormone therapy, they will not recover their testosterone. It will probably be even lower than it was, and so that's an important factor to know and discuss with the patient. Patient age is also involved in testosterone recovery. As you can imagine, older patients recover their testosterone less well. And also, the duration of androgen deprivation therapy. Longer hormone therapy, more at risk for not recovering their testosterone. And I'll show you a nice curve with that. Similarly, we don't always think about this, but patients with other medical comorbidities, such as diabetes, have a poorer testosterone recovery.

Some of the more recent data we have about testosterone recovery are from a trial called the HERO trial, which I did not review with you today. But that's a trial in which the drug relugolix, it's an oral AR antagonist that was approved. In this trial, relugolix was compared to Leuprolide. Median age was 72. And it was 9 months of hormone therapy. And the PRESTO trial was 4 months of hormone therapy. And you can see the way the trials report out testosterone recovery is very variable.

So, in the HERO trial, the testosterone basically normal range, greater than 280 at 90-days off therapy, was 54% with relugolix and 3% with leuprolide. So, that's telling you that at 3 months off leuprolide, almost nobody has recovered yet. And this shows testosterone recovery, and the take-home message is this: When someone is on a drug like leuprolide and you add an AR pathway inhibitor to it, that does not affect the testosterone recovery. The addition of the AR pathway inhibitor, in this case the apalutamide, did not lead to lower or longer time to testosterone recovery. And this is a trial that I think will be very important for you to digest and have in your mind in your practice.

So, this is looking at two Phase 3 trials in the radiation therapy context, 0 versus 6 months of hormone therapy and 18 versus 36 months of hormone therapy. So, 6, 18 and 36 months of ADT.

The ADT was an LHRH antagonist. Median age 71, so pretty consistent with what we're treating in the practice. And T recovery was defined as a testosterone within the normal range of the assay that was used. And what they showed in this paper was, in the graph on the right, hormonal duration very important, baseline testosterone very important. Age was an influence, and medical comorbidities, as I mentioned, cardiovascular, COPD, hypertension and diabetes.

And it's really remarkable when you see that patients who received 3 years of hormone therapy, you know the testosterone recovery rates at 10 years are only 44% compared to 6 months, it was 77%. So, when we start getting into the longer durations of hormone therapy, it's important to have this in mind and be counseling patients. And if their testosterones are not recovered from treatment we give, then there's other things that come into play, right? Like, following their bone density and their cardiovascular risks.

This is a little bit of change of gear, but we touched on this before. If a patient does not obtain an optimal PSA nadir on ADT with an AR pathway inhibitor – this is just ADT – but the overall survival correlates with that. So, PSA generally, metric is less than 0.2. If you have a PSA of less than 0.2, you're going to do better. And if it's between 0.2 and 4, not as good. And if your PSA – you might have a patient who comes in and their PSA is 200 and it drops to 10 and they're really happy and you're looking at that 10 and based on this data, you're like, oh, trouble ahead. That's not a good PSA nadir, even though you started high.

And I'm not going to go through all this data, but all of these AR pathway inhibitor trials have publications that show PSA nadir is very prognostic in the use of drugs like apalutamide and enzalutamide and abiraterone.

So, I'm going to skip through a little bit of this to this slide. This was a slide that I put together for an investigator meeting and this is what I want you to think about. When you're in the clinic with a patient on ADT, with an AR pathway inhibitor, who has a suboptimal PSA nadir, so a PSA above 0.2, you want to check, is your ADT optimal? Check a testosterone level on therapy. Are they castrate? If the testosterone is measurable, which happens sometimes, you can consider changing the ADT agent or making sure that your nurses are giving the injection correctly. There's actually a whole literature out there on incorrect administration of that pellet in the depot injection.

If they're on an oral such as relugolix, assess if the patient is taking it as prescribed. I would posit that they're not if the testosterone is measurable. They may tell you that they are, but they're probably not. If they're on an oral access inhibitor and they're dose-reduced, because oftentimes our patients on drugs like enzalutamide and abiraterone, we dose reduce them, consider the risk, benefit, or the possibility of increasing that drug up to full dose because the patient is getting a suboptimal PSA nadir.

If for some reason radiation to the prostate was skipped, something that was going on at the time, reconsider giving radiation to the prostate, if applicable. So, you know a patient with metastatic hormone sensitive disease, if the patient was a candidate for SBRT to metastasis and for some reason didn't get it at that time, again, consider giving SBRT to the metastasis. If the patient was a candidate for triplet therapy, this is metastatic high-volume hormone sensitive disease, but for some reason didn't get it, consider adding the chemotherapy in at that point because they're having a suboptimal response to the AR pathway inhibitor. And if not performed today, recommend germline testing to prepare for subsequent therapy, if you have a BRCA therapy. And if not performed, consider somatic sequencing similarly, for future assessment of therapies.

All right. I am going to skip these, except to say that, look at the numbers of prostate cancer in the world that is predicted. Prostate cancer is going to become an increasing diagnosis in your clinic, I believe, and it's important to have a multidisciplinary team that includes not only the big three; the urologist, radiology oncologist, and medical oncologist, but our practitioners such as specialist, cardiologists, radiologists, our clinical trial staff, nurses, pharmacists, nutritionists, psychologists and social workers. And how you communicate with your team needs to be established.

So, I am going to move on to the cases. A sixty-five-year-old man. He's healthy. He has a history of hypertension. Has a prostatectomy two years ago for Gleason 8, so high risk cancer. Had a good PSA nadir post prostatectomy. However, at one year post prostatectomy, the PSA is rising: 0.05, 0.08, 0.1, 0.13.

He is treated per standard with salvage radiation and he got 6 months of hormone therapy. Again, he had a good PSA nadir, undetectable. Off therapy, his testosterone is recovered, but then his PSA starts to rise again. Short PSA doubling time of 5 months. Conventional imaging was done and there were no metastases.

Androgen deprivation therapy with LHRH and enzalutamide. And from what we told you in this question, if the patient was healthy, that would be the correct answer based on the data that we just reviewed today from the EMBARK trial.
The key here being the patient's PSA doubling time was short, 5 months. Short PSA doubling time predicts to short time to metastasis and this therapy can reduce that risk.

I think we covered this, except has the patient had any additional local therapy options. No, because he's had prostatectomy and salvage radiation.

Should any additional radiographic staging be done? The field is moving and PSMA PET scans are usually done in the context with PSA failure.

We talked about the doubling time, treatment options, and is this a good time to consider germline or somatic sequencing.

It's definitely a good time to consider germline sequencing. I think any prostate cancer patient, germline sequencing is reasonable for a variety of reasons; if they have a mutation in a DNA repair gene that puts them at risk for other cancers that you need to think about screening for, and you need to consider cascade testing for first degree relatives. So, I think you know the sooner the better and the more the merrier for germline testing.

Somatic sequencing is a little bit debatable. If you're going to do somatic sequencing in this patient, it's probably going to be on their original prostatectomy specimen, whereas they might not need consideration for say, a PARP inhibitor for many years and it might be more prudent to do that testing on a more contemporary blood biopsy or metastasis biopsy at the time they needed consideration of that treatment. But it could be done.

So, this patient was treated per EMBARK, ADT and enzalutamide. He had a great PSA nadir and the treatment was stopped at 9 months, like it was done in the trial. This patient was on the young side and his testosterone recovered to the normal range at 5 months. However, the PSA started rising again at 9 months and PSA was followed to establish double time. This time, a PET scan was obtained which did show two metastases, one in the bone, one in the lymph node, and the patient was treated with SBRT to these two metastases, ADT, and an ARPI. And I left it general ARPI because now this patient has metastatic hormone sensitive prostate cancer and there are four ARPIs to choose, that you should choose based on what you learned today and based on your patient's baseline status.

OK. So, we have a second case. This is the case of a patient with synchronous metastatic hormone sensitive prostate cancer and this is his history. Sixty-five years old. He is also healthy. He has treated hypertension. Both of these cases treated hypertension and the reason they're in here is because hypertension is common and all the drugs that we use can make the hypertension worse, so you need to be aware of that and be engaged in watching. In the GU clinic, we need to be engaged in watching, or a medical oncology clinic, a patient's blood pressures.

This patient had urinary urgency and frequency. He went to his PCP. This is at the time of diagnosis. A rectal exam was done, which is heroic because not many people are doing rectal exams anymore. It was abnormal. The patient got a PSA, it was 35. Repeated, was real. He had conventional imaging, large prostate, three bone mets in the pelvis. Prostate biopsy was done and he had recent cancer and a large number of cores. So, this is a patient with high Gleason, low volume because it's three bone mets, metastatic hormone sensitive prostate cancer.

So, there's data which we reviewed, that shows that survival is improved when you add radiation to the prostate to low volume patients. So, this was high Gleason, but low volume. Three mets, not more than 4, which is high volume. It's a little bit semantic, but that's what the data is.

So, standard of care for this patient should be you know standard hormone therapy, an AR pathway inhibitor – again, you choose among the four based on you know your patient's individual characteristics – and prostate radiation.

The data does not support docetaxel necessarily, but the data is a little bit gray. Like answer D, I think would be fine as well because the ARASENS trial showed that darolutamide and docetaxel had benefit for both high and low risk patients.

So, if you have a young patient, a bad Gleason score, and they have you know low volume but 3 or 4 mets, bone mets not just lymph node disease, you could even consider triplet therapy and prostate radiation because you know this patient is young and you know not going to do well in the end.

What is the role of prostate radiation? We definitely covered that.
What type of imaging? This is a metastatic patient, so if you know they have metastatic disease on conventional imaging, you don't necessarily need to get a PET scan. I think a lot of people are getting PET scans this year. Should the patient have germline and somatic testing? Definitely germline. It's metastatic, so he's going to probably have consideration of a PARP inhibitor sooner than our past case, so somatic sequencing on the biopsy or metastatic biopsy is definitely reasonable. Or a blood biopsy.

And how should this patient be followed in clinic? We all have our different styles with that, and sometimes it depends on what they're on for a backbone of AR LHRH therapy, like if they're on an oral versus an injection which they're getting every 3 or 4 months. So, my patients on AR pathway inhibitors, I see them in clinic every 2 to 3 months to assess PSA response, testosterone. Every PSA, I get a testosterone. I need to know where that testosterone is. Blood pressure and toxicity assessment with a comp panel. If they're on an AR antagonist, I get a TSH and that's how they're followed.

Well, it's been a pleasure to spend this hour with you.