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Improving the Odds in Metastatic Castrate-Sensitive Prostate Cancer

Announcer Introduction:
Welcome to CME on ReachMD. This activity, titled "***Improving the Odds in Metastatic Castrate-Sensitive Prostate Cancer***" is Provided by Partners for Advancing Clinical Education (PACE) in partnership with Smart Patients and is supported by an educational grant from Bayer HealthCare Pharmaceuticals Inc.

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Dr. Sims:
Welcome to our session in the Winter Oncology Conference. This session focuses on Imporving the Odds in Metastatic Castrate-Sensitive Prostate Cancer and we have a great faculty today, Sarah Traverso. She is a PA and a Physicians Assistant at the Division of Genitourinary Oncology at Northwestern Medicine in Chicago Illinois. And here are her disclosures.

Here are our learning objectives today: summarize current guidelines and evidence for treatment of metastatic castrate-sensitive prostate cancer, apply strategies to identify and manage treatment-related toxicities in metastatic CSPC, and integrate patient education and feedback to optimize patient experiences during treatment and survivorship.

Dr. Traverso:
Thank you. Thanks for having me today. Jumping right in with prostate cancer – it's our most common new cancer diagnosis in American men in 2021 with an almost 270,000 new cases in 2022. Now, almost 75% of these patients will have localized disease at diagnosis, but up to 30% of them will develop recurrent disease, and this is the second leading cause of cancer death in American men. Now, the 5-year relative survival rate does approach about 100% for most men diagnosed with local or regional prostate cancer. However, this drops to about 31% with distant disease, and the impact of COVID is not yet known on these rates.

So, let's just review some key terms that we utilize in prostate cancer. Biochemical recurrence is the symptomatic or asymptomatic rise in PSA following curative treatment with surgery or radiation. Castrate-sensitive prostate cancer, or CSPC, is disease that has either not been treated with or is still responsive to androgen deprivation therapy, or ADT. Castrate-resistant prostate cancer is disease progression on ADT and with castrate levels of testosterone, which is considered less than 50, and this could be in the form of progression of preexisting disease, new radiographic disease, or symptomatic clinical progression. High volume metastatic prostate cancer is when we have visceral metastases and at least 4 or more bone metastases with one or more being outside the spine or pelvis. High-risk metastatic prostate cancer is a poor prognosis with 2 or more of these high-risk features, which includes a Gleason score greater than or equal to 8, 3 or more bone metastases, or measurable visceral metastases. And then de novo metastatic prostate cancer is metastatic disease at the time of initial diagnosis.

Just like we mentioned, majority of patients are diagnosed with localized or locally advanced prostate cancer, and then they're treated with curative intent, and at some point after that, they might be noted to have a rising PSA, which would signify biochemical recurrence, and they should be started on ADT. Now, at the time of that biochemical recurrence, if they're found to have metastatic disease and we confirm they do not have castrate levels of testosterone, they would be considered metastatic CSPC, and for our patients that have biochemical recurrence without metastases and are started on ADT, if they're then found to have a rising PSA even though they have

castrate levels of testosterone, they're considered non-metastatic CRPC. Now, ultimately, most of these metastatic CSPC and non-metastatic CRPC patients will progress to metastatic CRPC when they have both that rising PSA with castrate levels of testosterone and metastatic disease, and about 10 to 20% of all patients will progress to this stage. Today, we're primarily going to be talking about metastatic CSPC patients.

Dr. Sims:
Here's our first case study: Tom, 63 years old. He presented to his PCP with new onset of fevers and underwent a workup, which included a PSA. His PSA was 664. His past medical history is significant for hypertension well-controlled on amlodipine 5 daily. He underwent a prostate biopsy that showed prostate adenocarcinoma, Gleason 4 plus 3 equals 7. His staging imaging showed enlarged pelvic lymph nodes and high volume of bone metastasis. Tom was started on degarelix by urology. He's presenting to you to discuss additional treatment recommendations. His PSA is now 98 with testosterone adequately suppressed at less than or equal to 10.

Dr. Traverso:
There's really been a lot of advancements over the last 10 to 12 years in the prostate cancer realm. We initially started with chemotherapy back in 2004, and really up until 2011 where we saw the introduction of our second-generation hormone therapies, first in the post-chemotherapy setting and then in the pre-chemotherapy setting. We had the introduction of radiopharmaceuticals like radium, immunotherapy for appropriate patients, and then we saw the broadened use of our second-generation hormone therapies for metastatic CSPC patients and non-metastatic CRPC patients, some new agents there, and then we saw the introduction of PARP inhibitors to be used in appropriate patients, and then, of course, we have those PSMA radiotracers for imaging as well as lutetium PSMA for treatment in metastatic CRPC, the addition of oral ADT agents, and then most recently looking at triple combination therapies, those second-gen hormone therapies in conjunction with chemotherapy, so really a lot of options over the last decade or so coming up.

For our metastatic CSPC patients, the first thing we want to be doing is putting them on androgen deprivation therapy, or ADT. It's really the mainstay of management, and as the name obviously suggests, the goal of this is to reduce levels of circulating androgens in the body because we know that prostate cancer fuels its cells from testosterone, and that's the catalyst – the fuel supply – for it to grow and progress, and so ADT promotes prostate cancer cell growth arrest and apoptosis.

Originally, a bilateral orchiectomy was the primary form of ADT, but this has largely been replaced by medical castration, and I really like this diagram to show how all of our ADT options work to suppress our testosterone. Up at the top, we have our hypothalamus, which secretes our gonadotropin-releasing hormone which triggers the pituitary gland to release FSH and LH, and that triggers the testes to produce testosterone, and we can see at the bottom our prostate cell. That testosterone turns into dihydrotestosterone, or DHT, once inside the cell, and we have that AR – that androgen receptor. That presence of testosterone triggers target genes kind of leading to prostate cancer cell growth and progression.

And so where do our forms of ADT act to block this cascade? Well, our GnRH agonists like leuprolide or goserelin – those basically act like GnRH at those GnRH receptors at the pituitary. They're GnRH analogues. Actually, when we first start our GnRH agonists, we see an increase in the testosterone levels – we call it a testosterone flare – but eventually that prolonged activation of those GnRH receptors causes desensitization and a decreased production of testosterone, and then our GnRH antagonists like degarelix and relugolix lock the pituitary from responding to GnRH, which then decreases that production of androgens.

This is a brief summary table of some of those primary forms of ADT. So, for our GnRH agonists, two of the most common are goserelin and leuprolide. Goserelin is actually a subcutaneous implant, can be given every 28 days or every 12 weeks, which is probably more popular for patients, and then leuprolide can be a subcutaneous or IM injection, and then we have a few different dosing options for patients, kind of different frequencies they can get that. Our GnRH antagonists – degarelix is a subcutaneous injection, and this is given every 28 days, and it does have a first-time loading dose of 240 mg. And then relugolix is our only oral ADT option for patients. It's given 120 mg daily with or without food, and similarly, it does have that loading dose just on day one, so nice for patients to have an oral ADT option for your patients like our guy Tom who really doesn't want injections, but oral agent might not be the best choice for everyone. If you have a patient that's already struggling with their medication adherence, the last thing they want is another pill in the mix.

And then one note with the GnRH antagonists is we do see a more rapid testosterone suppression. Remember for those GnRH agonists, we have that increased level of testosterone first and then eventually the testosterone starts to wear off, where the antagonists just kind of block the pituitary from using GnRH so we have a much faster testosterone suppression. So, this might be a good option for your patients that have a lot of high volume disease, or we like to use this if we have patients that are diagnosed in the hospital. Maybe they presented really symptomatic from their disease; we really want to get this under control quickly. This could be a good option. And then with degarelix, if you start your patient on that and they get stabilized, their testosterone-suppressed PSA is coming down after several months, you could consider switching to one of the less frequent leuprolide injections. And then one other note for the relugolix is it does have a slightly better safety profile in patients with underlying cardiac disease, so this might be something to consider. If you

have a patient with a lot of cardiac comorbidities, that might be a good option to discuss with them.

Our first action item is when choosing between ADT agents, consider the administration safety, need for testosterone suppression, and adherence when making that choice.

This is just showing those couple trials of GnRH antagonists compared to leuprolide – just a little bit more about those medications. We did see that the antagonists were non-inferior to leuprolide in sustained castration rate, and then relugolix is actually a little superior to leuprolide, and we do see that since there is that rapidly suppressed testosterone, we do often see actually a quicker recovery of the testosterone when this is discontinued as well.

With ADT comes a lot of major side effects and symptoms associated with that suppressed testosterone, and these are really important to know and discuss with your patients upfront to really manage expectations. So, this is a little summary table of some of the more common ones, but we're going to talk more about them. The hot flashes are very common, risk of osteoporosis. Fatigue's very common, issues with metabolic syndrome, weight gain, dyslipidemia, insulin resistance, that sarcopenic obesity, sexual dysfunction, as well as risk of cardiovascular disease and thromboembolic disease.

We have a figure that we can see here on the left-hand side – that muscle mass strength loss. Your patients might have gynecomastia, depression, mood swings. When monitoring these patients, it's important to talk about a lot of these potential side effects, but know that the intensity and the actual side effect profile can vary pretty greatly amongst patients. I have some patients that have very frequent hot flashes, and then I have some that never have any at all. So, it can really vary, but again, talking about this, educating your patients upfront.

I'm always recommending physical activity to patients to mitigate some of these, especially the fatigue, the obesity, muscle mass and strength loss. It might not completely stop them, but it might help to minimize those side effects, and then with that risk of osteoporosis, make sure they're taking calcium and vitamin D, they're getting DEXA scans, and you might want to consider bone-strengthening agents depending on those DEXA results. I usually encourage patients to continue following regularly with their primary care. Make sure they're having their cholesterol checked, A1C, having that cardiovascular workup and management, really optimizing that cardiovascular wellness.

Some of the more bothersome side effects for patients can be the sexual dysfunction as well as those body habitus changes. Sexual dysfunction's important to educate them about upfront. I'm always surprised how many patients I get several months or even years into their ADT treatment, and they're asking me why is this happening? Is this always going to be like this? So, I think it's really important to just set expectations for this upfront. Provide reassurance that it's normal and expected on these treatments. We do have ways to try and help erectile dysfunction, but there's not a whole lot we can do for the actual loss of libido, that loss of sex drive. So, again, education and reassurance can go a long way for these patients. And then for those body habitus changes, again, really encourage them to continue to be active. Exercising, resistance training can really help those things. And then for some of your older, more frailer patients that don't have a lot of muscle mass to begin with, you could consider physical therapy if you feel like that would be helpful.

We know now that for metastatic CSPC, ADT alone is really not enough for most patients, and we really should be recommending some sort of combination therapy to target their cancer, whether that be in the form of doublet therapy typically with an oral androgen pathway-directed therapy or even recently triplet therapy, which is ADT with an AR-directed therapy as well as chemotherapy, and then there is a role for radiation with ADT alone, but this would be more on a case by case basis, probably more of your low volume disease patients.

We have a few different AR-directed therapy options that we can use in metastatic CSPC, although the settings for some of them are a little bit different. For abiraterone, we can use this in metastatic high-risk CSPC as well as in combination with docetaxel for metastatic CSPC, and we can also use this in metastatic CRPC. Apalutamide is approved for use in metastatic CSPC as well as non-metastatic CRPC. Enzalutamide we can use in metastatic CSPC or CRPC, and then darolutamide is one of our more recent approvals in this space. It's approved for use only with chemotherapy in metastatic CSPC, not by itself, but we can also use it in non-metastatic CRPC. If we're considering that triplet therapy doing combination with chemo, remember we can only currently use abiraterone or darolutamide in combination with chemo for these patients.

Let's touch briefly on our original doublet therapy option, which was ADT with docetaxel in metastatic CSPC. So, this was originally looked at in the CHAARTED trial, looked at men with metastatic CSPC, and they were treated with either ADT alone or ADT in combination with docetaxel, and the typical dose is 75 mg per meter squared every 3 weeks for 6 cycles, and this study showed that the median overall survival was 10.4 months longer with the addition of earlier docetaxel with ADT compared to ADT alone, and the trial also noted that adding docetaxel to ADT showed greater benefit in our high volume disease patients, and so we need to be mindful to avoid over treating our lower volume disease patients. Just because they have maybe one or two sites of metastatic disease does not mean that the benefits of adding chemo outweigh those risks of short and long-term side effects for those patients, so really keep that in

mind.

I would say the double therapy is pushed more towards ADT plus one of these second-generation AR inhibitors, less so ADT with docetaxel. We have two different places that these medications work at. Abiraterone blocks CYP17 at the adrenal gland from making other versions of testosterone, which we know that prostate cancer cells need to continue growing, and then apalutamide, darolutamide, and enzalutamide actually work at that androgen receptor to block androgens from attaching so that the prostate cancer cells cannot utilize that to continue growing. Basically, we're targeting the cancer from two different angles. ADT is working to minimize the actual levels of testosterone floating around, and then these AR inhibitors are actually keeping the prostate cancer cells from using any testosterone that might still be there.

First, we'll talk about abiraterone and prednisone in combination with ADT. So, this was looked at in a couple different trials. The LATITUDE trial looked at patients with high-risk metastatic CSPC, and the STAMPEDE trial, which was a bit of a more complex multi-arm trial, looked at patients with advanced or recurrent CSPC, and so for both trials, this looked at patients on ADT either with or without abiraterone and either prednisone or prednisolone. So, the LATITUDE trial showed that the doublet therapy arm had a reduced risk of death by 38% compared to ADT alone, and similarly, the STAMPEDE trial showed a reduced risk of death by 39% on the doublet arm compared to ADT alone in this subgroup.

More recently, we have the PEACE-1 trial, and this is actually looking at ADT plus abiraterone in combination with docetaxel with or without radiotherapy, so our triplet therapy option, and this looked at patients with de novo metastatic CSPC, so remember, those are patients initially diagnosed with metastatic prostate cancer, and this looked at patients on ADT with docetaxel either with or without abiraterone, with or without radiation. This study found that the triplet therapy arm of ADT plus docetaxel plus abiraterone either with or without radiation saw a significantly reduced risk of death by 27% compared to ADT and docetaxel. As you can imagine with adding in a third agent, we do see a slightly higher incidence of grade 3 or higher side effects, although the side effect profile is pretty similar between the doublet and triplet arms with hypertension and hepatotoxicity being two of the biggest side effects we saw.

Moving on to enzalutamide, this was looked at in the ARCHES trial, and this looked at metastatic CSPC patients. They were allowed to have prior ADT and docetaxel, and this looked at patients on ADT alone versus in combination with enzalutamide, and this study found that adding enzalutamide to ADT significantly reduced the risk of death by 34% compared to ADT alone. Then, we have the TITAN trial, and this looked at apalutamide in combination with ADT for metastatic CSPC patients, and this study found that the combination of apalutamide with ADT significantly reduced the risk of death by 35% compared to ADT alone.

Most recently, we have the ARASENS trial, and this looked at darolutamide in combination with ADT and docetaxel in newly diagnosed metastatic CSPC patients. So, up until this point, darolutamide was only approved for use in non-metastatic CRPC patients, and this study found that there was a significantly reduced risk of death by 32.5% for patients on that triplet therapy arm of darolutamide plus ADT plus docetaxel compared to ADT and docetaxel alone. Really, the combination of ADT with docetaxel doublet therapy is falling out of favor. If you're considering doing docetaxel in your patients, you should probably be considering doing that triplet therapy.

This is just a table summarizing some of the common side effects and safety considerations with these other three AR inhibitors. You'll see that a lot of the side effects are pretty similar across the board – fatigue, hot flushes, arthralgia, decreased appetite, hypertension – but some of them do have a little bit more unique side effects to watch out for, which we'll talk about on the next slide, and this is breaking down the major side effects that we see and to monitor for each of these different AR inhibitors.

First, on the left, we have abiraterone and prednisone with ADT either with or without docetaxel, and you'll see that we have a fairly high incident of hypertension, and this can be due to that mineralocorticoid excess. We also see adrenocortical insufficiency, hypoglycemia, fluid retention, and hypokalemia also due to that mineralocorticoid excess. Remember that abiraterone acts on that CYP17 at the adrenal gland, which is why we can see that. So, with abiraterone and prednisone, we do need to monitor a little bit more closely, a little bit more things to be watching out for with that blood pressure as well as checking those electrolytes, and we also see hepatotoxicity, so really need to be checking the LFTs as well.

And then for enzalutamide and apalutamide, those actually do cross the blood-brain barrier. With those, we need to be thinking of some of the neurocognitive side effects we can see. So, for enzalutamide especially, I'm always asking about dizziness, lightheadedness, falls, headaches, certainly if they've had any seizures, and then apalutamide, similar there with the neurological side effects, also watching a little bit more for cognitive and memory impairment, and then some unique ones with apalutamide are hypothyroidism. We can see that, so you should be watching a TSH in those patients, and then there is an incident of rash, more so with enzalutamide, apalutamide, and darolutamide. However, with apalutamide, there was a bit more incidence of severe cutaneous adverse reaction, so really be watching for that closely.

And then darolutamide on the right, we don't see many unique side effects to watch out for with that, but you'll notice across the board

for all of these medications in this class, we do see risk of hypertension and ischemic heart disease as well as fatigue. So, no matter what medication you put your patient on, those are some things you should always be watching for in your patients. And then we also see embryo-fetal toxicity, so people of childbearing age should not be handling these capsules or tablets.

The big takeaway is with this class of medication, remember that hypertension and cardiovascular issues as well as fatigue are really key side effects that we can see here.

Just to quickly go over the dosing differences for these medications, for abiraterone, the dosing is 1,000 mg per day. It usually comes in 250 or 500 mg tablets. You do need to take prednisone with abiraterone, and the reason is because, remember, abiraterone works at that adrenal gland blocking that CYP17, so we actually can block some production of cortisol. So, giving the prednisone helps to replace some of that lost cortisol and mitigate some of those related side effects like the hypokalemia, swelling, and high blood pressure, so really important to take that. If you're giving it alone without docetaxel, the dosing is 5 mg per day for the prednisone, and then with docetaxel it's 5 mg twice per day. The docetaxel dose, as I mentioned, is 75 mg per metered square every 3 weeks for 6 cycles, and abiraterone does need to be taken on an empty stomach. Actually, taking it with food increases the absorption, so taking it on an empty stomach just allows us to have a more predictable dose. You know your patient's getting the appropriate dose and not getting a much higher dose, which could increase the risk of side effect. With abiraterone, if you do have a patient presenting to you with a lot of side effects, I always make sure I'm asking them are you taking your prednisone and are there any missed doses, and then also are you taking it on an empty stomach, which we consider not eating for two hours prior and one hour after, so really remember that with those patients.

Enzalutamide is taken 160 mg a day, no prednisone needed, and you can take it with or without food; apalutamide is 240 mg per day, no prednisone, taken with or without food; and then darolutamide is a little bit different. It's given twice per day 600 mg. You don't need prednisone, but you can give it with docetaxel like we talked about, and you should take this one with food.

So, with these medications, we do have the option for dose holds and dose modifications for side effects or comorbidities. For abiraterone, since those tablets are 250 or 500 mg, we do have a couple dose reduction options. For hepatotoxicity or really any grade 3 or intolerable side effect, you can consider a dose reduction, but then of note, if your patient does have moderate hepatic impairment at baseline and you want to start them on abiraterone, you should start them at 250 mg per day, and I would in general just avoid using abiraterone if your patient has severe hepatic impairment. Enzalutamide, we have a couple dose reduction options, same with apalutamide, and then darolutamide is given twice a day. I would typically reduce to 300 mg twice per day, not necessarily 600 once per day, and then for all these medications, if your patient does have a side effect, typically in our practice we like to hold the AR inhibitor for a couple weeks just to make sure that whatever side effect they're experiencing is actually from this medication, and then depending on the severity or what the side effect is, you could do a trial of resuming at the original dose after a hold or resume at a slightly lower dose, and then for all these medications, we do have interactions with CYP inducers and inhibitors, so just make sure you're being mindful of that. Just a take-home point – make sure you know how to implement dose modifications and dose holds as needed to manage some of those high-grade or intolerable side effects for your patients.

So, let's talk a little bit more about a lot of these common side effects and how we can manage these. Fatigue we've already talked about – make sure you're encouraging physical activity, and then you could consider having them take it at nighttime before bed just to see if they – the fatigue is not as bothersome at nighttime, and then just remember, though, for abiraterone, it does need to be taken fasting, so just keep that in mind for those patients. GI toxicities I see a little bit less frequently, but you can try antiemetics, antidiarrhea, laxatives, stool softeners as needed. For a rash, I would say it's typically pretty mild to moderate, could be with or without itching, but just remember, again, that apalutamide does have that potential for more serious skin and side effects, so just be mindful of that if those patients do develop a rash. Typically, we can manage conservatively with emollients, topical corticosteroids, but remember, you do have that option for dose holds or modifications if needed.

And some other ones – so, for seizures, I would say if your patient develops seizures on any of these medications, you should probably be discontinuing, but make sure you educate your patients that there is a possibility of this. Counsel them on that risk of sudden loss of consciousness. We really don't know the benefit of antiepileptic medications as seizure prophylaxis, so I wouldn't recommend it. If you patient does have like a history of seizures or seizure disorders, you should probably be avoiding those AR inhibitors that have a higher incidence of that like the enzalutamide and apalutamide.

With falls and fractures, make sure you assess for fall risk at each visit. You can maybe have them do a get up and go test in your office and be talking to them about their home surroundings. They might need nightlights if they're getting up a lot at night to urinate, which a lot of our prostate cancer patients are. Talk about removing rugs or other fall hazards, and then you could consider for in improving their strength and balance maybe a PT or OT consult for some patients.

And then headache and dizziness, especially for our patients on enzalutamide, you can manage those headaches with over-the-counter

medications. Make sure you're looking at their medication list, seeing if anything else could be causing or contributing to dizziness. A lot of our prostate cancer patients are on tamsulosin. I have patients that have dizziness from that, so just keep that in mind, and then make sure you educate your patients. If they do have a really bad headache, they should immediately be contacting you or going to the ER because there is that rare but possible side effect of like encephalopathy issues, and then if the headache and dizziness is not manageable with over-the-counter meds, consider doing that dose hold and then dose reduction if needed, and again, if your patient does have some issues with headache or migraines or things at baseline, might be best to avoid enzalutamide. That might not be a good fit for them as your AR inhibitor choice.

And then cognitive impairment, more so with apalutamide. Be asking about their cognition. You could consider doing some cognition tests there.

And then hypertension and cardiovascular toxicity, we said across the board this is something we need to watch for for all of our AR inhibitors and especially abiraterone. Make sure you're getting a good blood pressure read at baseline, monitoring that really closely, maybe having them check it at home, especially if they're someone that deals with some white coat hypertension. If they do develop high blood pressure, you can start them on antihypertensive medications. Sometime depending on how severe the hypertension is, you might want to hold the AR inhibitor while you get that blood pressure under control and then retry getting them back on the medication. If they're already on meds when you start, you need to maximize the dose of those to get that under control. Make sure they're really optimizing their treatment of cardiovascular risk factors, and you probably want to be communicating good with their other providers like cardiology or primary care, especially if you need assistance getting the high blood pressure under control. And again, that special note with abiraterone – if they do have really severe hypertension, make sure you're asking if they're taking that prednisone and they haven't missed any doses. And then we mentioned with apalutamide, we have that unique possibility of hypothyroidism, so make sure you're getting a TSH at baseline and then checking that regularly.

We've talked a lot about all the different treatment options and combinations for these patients, so how do we decide what regimen is best for our patients? Like I mentioned earlier, it's really recommended for almost all of our metastatic CSPC patients to be on at least a doublet therapy regimen, and you might prefer a doublet over a triplet therapy for your older patients, if they have lower volume disease, maybe depending on their comorbidities, and then choosing your agent for doublet therapy will depend on a lot of different things – cost, side effects, comorbidities. We have docetaxel listed, but as I mentioned, if you're considering chemo, you should probably be considering triplet therapy rather than just ADT with docetaxel. So then for our different AR inhibitors, abiraterone is available as a generic, but it does require a little bit more intensive monitoring, need to be checking those electrolytes, the liver function, the blood pressure monitoring, and then there is concern for long-term high blood pressure. This seems to be a little bit less favorable in your patients with a lot of underlying cardiac comorbidities, cardiac toxicities, and then consider that they have to take daily prednisone. If you have a patient with really uncontrolled diabetes, adding in daily prednisone is probably not going to be the best option for them, so be thinking about that as well. Enzalutamide has a little bit less monitoring required, but remember we have a little bit more risk of neurocognitive issues, so your patients with underlying neuro issues, this might not be the best choice, and same with apalutamide as well as that risk of rash – if your patient has a lot of skin issues, might not be the best choice. And then there was a subgroup analysis from that STAMPEDE trial that supports radiation to the prostate in conjunction with ADT for low volume disease. There was unknown benefit with the best systemic therapies, so I would say the discussion of ADT plus radiation would be more on a case-by-case basis.

For our triplet therapy, you might be thinking about this for your younger, more chemo-fit patients if they have higher volume disease, but again, it might be overtreatment for your lower volume patients, so just remember that, and adding in docetaxel does have risk-benefit tradeoffs. Docetaxel has that risk of neuropathy. If your patient has a lot of issues with neuropathy at baseline, be mindful of that. One other thing that I see a lot is lower extremity edema, especially with docetaxel and abiraterone. So, if your patients have lymphedema or something like that, just be mindful there, and then if you are going to do chemotherapy, typically you would like to try to get through the full recommended 6 cycles. In our practice, a lot of times we'll make a dose adjustment if needed or we'll get them even like a month or two break to kind of let side effects calm down and then jump back in to get through the full 6 cycles.

And then now that we have two choices of AR inhibitors that we can use as triplet therapy, how do we pick between the two? Again, it's not really a black and white answer. We really need to be thinking about all those different things – comorbidities, cost, and patient goals. Again, abiraterone has a lot more monitoring, and again, maybe not as favorable to use in your patients with underlying cardiovascular disease or underlying CVD risk factors. You might lean more towards darolutamide, but darolutamide's new in this metastatic CSPC setting, so as a provider, if you're just not comfortable using and monitoring darolutamide, you might favor more abiraterone, something you're more used to. So, really no black and white answer – a lot of things to take into consideration.

And so this is just a nice summary table, and, of course, this is not the only things you should be thinking about but just a good summary of those things to take into consideration. So, again, thinking about the level of their cancer – what's their disease volume? What's their

risk? And then thinking about their treatment goals – do they have other comorbidities? Are they old? I have quite a few patients with bad CHF or really progressive Parkinson's, things that are a little bit more life-limiting, and so for those patients, you have to think about what are the negative impacts of really highly intensifying their prostate cancer treatment. That might not be the best choice for everybody. And then other patient factors – what's their performance status? How symptomatic are they from their cancer? And social characteristics – do they have good insurance? What are these medications going to cost? Unfortunately, a lot of these meds are still very expensive for patients, and most people are not going to want to be compliant with the medication that costs them 3,000 dollars a month. So, you need to be keeping that in mind, as well as caregiver support. Do they prefer an oral or IV regimen? And if you are thinking about chemo, do they have transportation to come every three weeks? Do they have the time commitment to stay for an infusion? Those sorts of things, so I think the big takeaway is really with so many different options and things to consider, you should really have a thoughtful discussion and shared decision-making with your patient about what is going to be the best option for them.

And then just to summarize – this is the recent NCCN guidelines for first-line treatment for metastatic CSPC – again, just really hammering home that the preferred is some sort of combination therapy, either ADT with an AR inhibitor or even triplet therapy by adding in that chemotherapy, and again, ADT alone or ADT with just radiation could be considered in certain patient cases, and that action item should be offering at least doublet therapy if not triplet therapy for most of these patients.

And so just to briefly go over some other ways to optimize patient and caregiver experience during treatment, again, we've really hammered home talking about these potential side effects. Educating about it upfront can really help set expectations, provide reassurance. Remember, you can advise them we have ways of managing side effects with dose modifications and supportive care. Really need to be mindful about a patient's ability to adhere to their treatment regimen, which we'll talk about more on the next slide, thinking about clinical trials and referring to those when appropriate. You could consider using symptom questionnaires to better direct your clinic visits. In my practice, we do send symptom questionnaires out the day before via the portal system, asking about things like fatigue, pain, mood. If they need some extra supportive care, it can be helpful to direct your visits and then referring patients and caregivers to additional support systems as appropriate, and I always like to make a special mention of our LGBTQ patients. Sometimes they have very unique concerns and means in relation to their prostate cancer treatment and side effects, so just be mindful of that, and if you do have more demographic-specific resources for them, that could be helpful for some patients.

We've talked a lot about all these oral medications. All of our AR inhibitors are oral, that relugolix is oral, so make sure you're talking with your patients and really promoting adherence to their drug regimen. You really want to simplify their regimen as much as possible, maybe writing things down on when they should be taking it, if it's with or without food. You know, some patients, they're multiple pills. Sometimes they're taking one tablet twice a day when it should all be taken just at once. Really talking through those things, assessing which patients might need some extra help there. In general, in our practice, we like to have a short interval follow-up for our patients 2 to 3 weeks after starting their ADT as well as 2 to 3 weeks after starting their AR inhibitors just to check in, check their blood pressure, check their labs, talk through if they're having any side effects to watch them a little bit more closely in the beginning.

And then just a quick note on genetic testing in prostate cancer. So, all men with metastatic prostate cancer should receive genetic testing and counseling regardless of their family history, and there's a list of certain mutations that if you do identify them, you absolutely should be referring them and their family to genetic counseling, and while genetic testing results probably won't change your decision on front-line CSPC treatment as of right now, it can be helpful to know if you have additional treatment options down the road for when they progress to CRPC, and then there's quite a few trials going on looking at other combinations in first-line treatment for metastatic CSPC looking at darolutamide with just ADT, so kind of as a doublet therapy option, combining AR inhibitors with immunotherapy, targeted agents, as well as PARP inhibitors, and then looking at lutetium PSMA treatment in the earlier setting as well, so a lot of things to keep your eyes out for.

And so we'll just go over our action plan one last time. Remember that when choosing between ADT agents, consider administration, safety, need for testosterone suppression, and adherence. Recognize that hypertension and cardiovascular issues as well as fatigue are key adverse events associated with second-generation AR inhibitors, know that you can implement dose modifications and dose holds as needed to manage high-grade or intolerable side effects, and for most patients with metastatic CSPC, it's standard of care to use either doublet therapy with an AR inhibitor plus ADT or a triplet therapy with adding in docetaxel for these patients.

Dr. Sims:
We have a few minutes for questions. Could you switch from relugolix to leuprolide just as you can with degarelix?

Dr. Traverso:
Yeah, you definitely can. We've had some patients where we switched to that, whether it be for patient preference or even financial issues, but you can switch them over to an injectable after the relugolix. You might want to chat with a pharmacist just to make sure you kind of have the best way of transitioning that over, but you can switch over to an injection.

Dr. Sims:
And another question was would you put one of your patients with a seizure history on an AR inhibitor?

Dr. Traverso:
Yes. I would say certainly it's a discussion. The seizure risk is certainly higher with enzalutamide especially but same with apalutamide, and there is a smaller one with darolutamide, but in that case, abiraterone would probably be the best choice. If your patient also has some cardiac toxicity, it might be more of a discussion, especially with like your attending, but I would say it wouldn't be a blanket no, but certainly you would want to avoid those ones that have a higher risk of seizure and neurocognitive issues.

Dr. Sims:
Sarah, thank you so much. This has been a wonderful presentation, and we've run out of time. The audience has really learned a lot. I know I have, too. Again, thank you, Sarah, again, for a wonderful presentation.

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