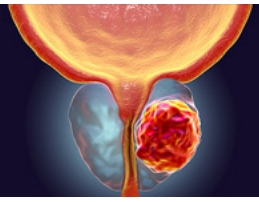
Novel Androgen Deprivation Treatment for

# Advanced Prostate Cancer:

## Optimizing Benefits, Mitigating Risk



## OVERVIEW

Prostate cancer is the most common cancer diagnosed among men in the United States. Considered curable if diagnosed at a localized stage, the survival rate of men with metastatic disease is dramatically reduced. Due to the androgen-dependence of prostate cancer, androgen deprivation therapy (ADT) has been the mainstay and primary therapeutic approach for management of men with metastatic prostate cancer. Join Drs. Robert Dreicer and Michael Cookson as they review the principles of androgen deprivation therapy and discuss the latest clinical data for recently approved ADT agents and studies of ADT-based combination regimens in the treatment of men with metastatic hormone sensitive prostate cancer (mHSPC). The evolving guideline-directed evidence-based approaches for therapeutic intensification in the treatment of mHSPC are also discussed. Listen to the faculty discuss case studies to gain practical insights into choosing optimal therapies that incorporate ADT for individual patients and balance patient preferences with therapeutic goals.

## TARGET AUDIENCE

This activity is intended for a national audience of medical oncologists, nurse practitioners, and other healthcare professionals who care for patients with prostate cancer.

## LEARNING OBJECTIVES

At the conclusion of this activity, participants should be better able to:

- Explain the differences between luteinizing hormone-releasing hormone agonists and gonadotropin-releasing hormone antagonists in terms of mechanism of action and outcomes
- Select optimal therapy to avoid/reduce cardiovascular risk in patients with advanced prostate cancer
- Compare and contrast the latest evidence regarding options for patients with advanced prostate cancer
- Develop treatment strategies incorporating patient-specific factors, including risk factors, concerns, preferences, and adherence information regarding oral vs injectable oncologic therapy

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**Michael S. Cookson, MD, MMHC**

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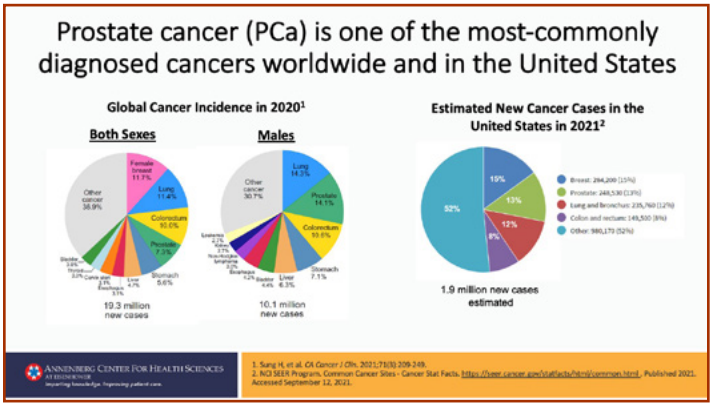
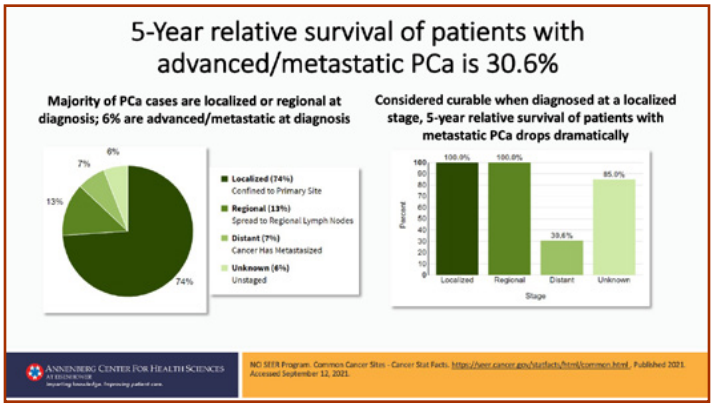
# ANDROGEN DEPRIVATION THERAPY: CLINICAL DIFFERENCES

Michael Cookson, MD

I'd like to go ahead and introduce our topic today on androgen deprivation therapy and I'm going to highlight some of the clinical differences. As we begin the program, I'd like to review some of the epidemiology and disease progression. Now, we know that prostate cancer represents about 7.3% of cancers globally and about 14% of male cancers. In the United States, prostate cancer represents about 13% of new cancers with about 248,530 cases to be diagnosed in 2021.

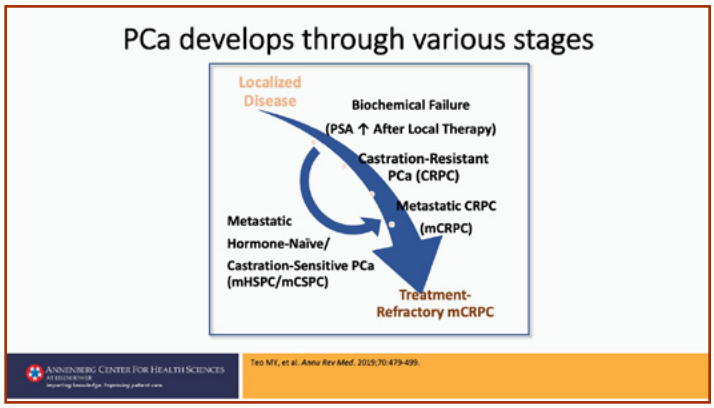



In the United States, prostate cancer is the leading cancer among men and is the second most common cause of cancer deaths. In fact, by statistics, about every 15 minutes a man dies from prostate cancer. Now, we know that for early-stage prostate cancer, survival is quite good. However, for patients with advanced and metastatic disease, the 5-year overall survival for metastatic disease is around 30%.

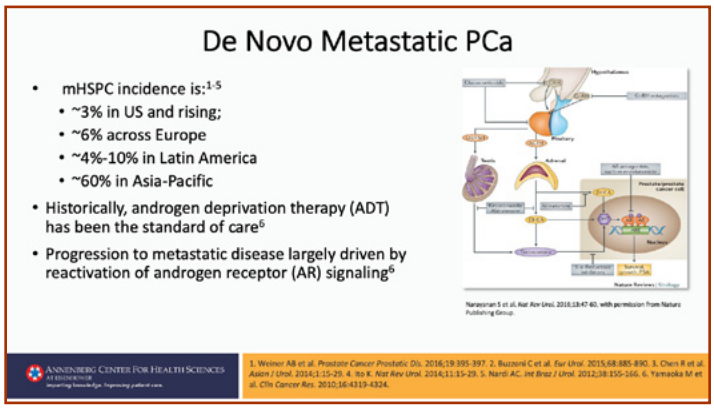



We know that prostate cancer develops through various stages, and these stages of progression are important, and the escape mechanisms for these are both androgen-dependent and non-androgen-dependent pathways.

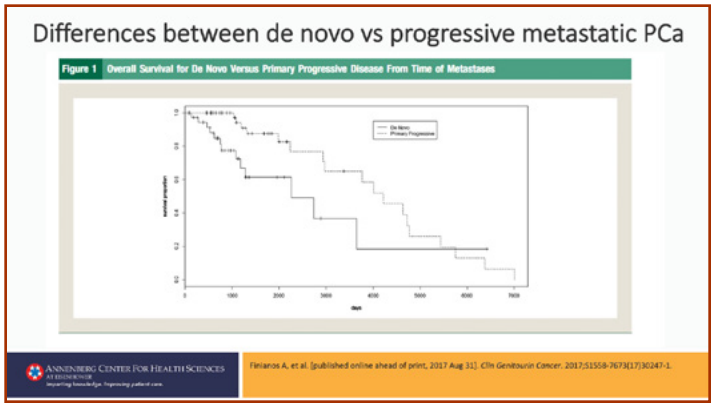
A model of prostate cancer clinical states is an important concept. We know that, at some point, men with localized disease progress through these more advanced stages, and some of them may progress through treatment-related effects and have biochemical failure and progress to a nonmetastatic form of even castration resistance, while the more common scenario would be patients who develop overt evidence for metastatic disease and then progress through to castration resistance.




There has been an awareness of a distinction between the presentation of patients with de novo vs those who present with progressive metastatic prostate cancer, and we know that historically about 3% of patients presented with de novo metastatic disease. And this is, of course, higher numbers in areas of the world where there is less screening and less access to good clinical care and we see this at higher rates in Europe, higher rates in Latin America, and the highest in Asian Pacific areas. We do know, due to a variety of factors in the United States, the development of de novo metastatic disease is unfortunately increasing.

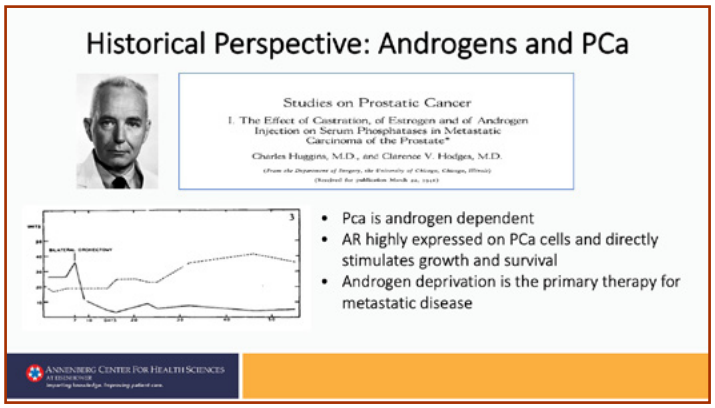



There have been differences, as I mentioned, between de novo and progressive disease and some of these features are illustrated when we look at overall survival rates for patients with de novo vs metastatic disease. In this particular study, there were significant differences in the overall survival of men as to whether or not they presented with metastatic disease or progressed from earlier stage disease. Overall survival was worse in the de novo arm, with a median of around 6.2 years survival compared with that around of 11.6 for patients who had more progressive disease. These distinctions have also been



appreciated in some of the clinical trials that we'll talk about a little later.

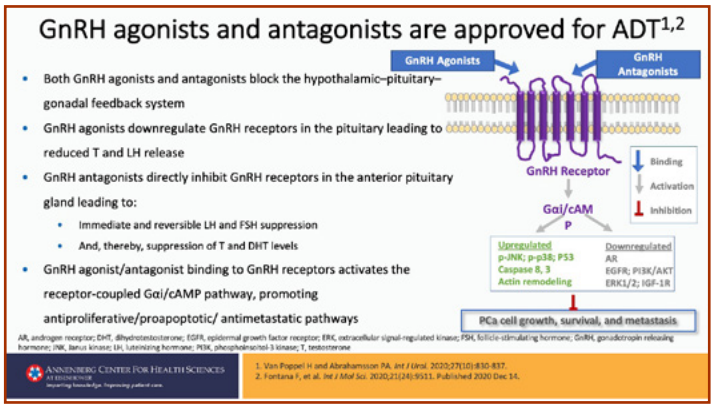
Now we're going to transition to the role of management of patients with androgen deprivation therapy. From a historical perspective, we know that androgens, and their effect on prostate cancer, was a sentinel moment in the history of urology and we know that some of the Nobel Prize-winning work from Dr. Huggins and Dr. Hodges in the 1940, early 1940s, was an important event. We know prostate cancer is androgen dependent. It's highly expressed. The androgen receptor is highly expressed in prostate cancer cells and directly stimulates the growth, and that these androgen deprivation therapy results in a regression in patients with metastatic disease.



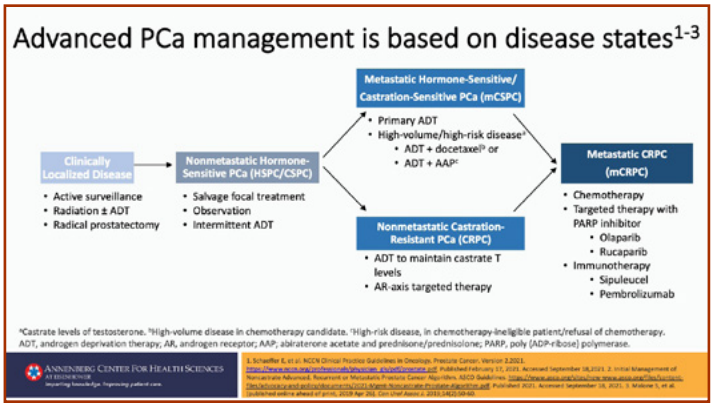

When we think about the management of men with prostate cancer, of course it is dependent on the stage at which they are being treated and the stage at which they are presenting. And so, for localized disease, we have active surveillance, radiation and surgery. As patients progress to more advanced disease, there is more of a reliance on systemic therapies and, for metastatic, hormone-sensitive or untreated hormone-naive patients, androgen deprivation therapy is a primary treatment, and then we layer on top of that additional therapies which we're going to get into in a little bit. As men progress to the metastatic castration-resistant state, additional sequencing and additional layering of therapy and control are added. These include some of our novel antiandrogen therapies, as well as some of the next generation therapies, such as PARP inhibitors and immunotherapies.

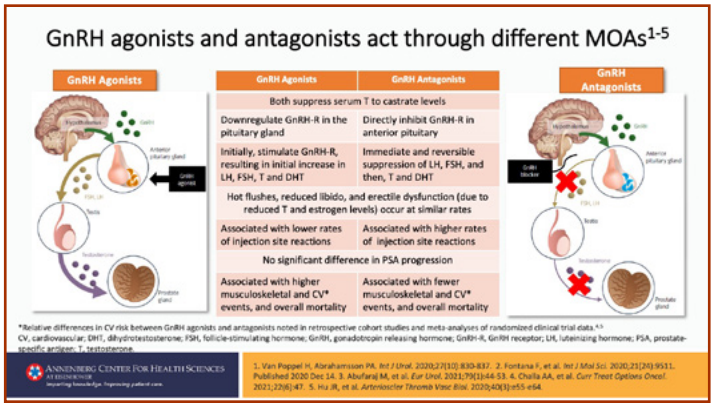
We know that androgen deprivation therapy, however, remains the backbone of cancer control in metastatic disease. This has been a standard of care for more than 75 years. We know that the prostate cancer cells almost always initially respond and are androgen-dependent, however we also know that as these androgen deprivation pressures are placed upon these cancers, the cancers ultimately can develop escape mechanisms.

We're going to talk about some of the distinctions between the GnRH agonists and the antagonists in this next portion. And so we know that there are GnRH agonists and antagonists that are both approved as androgen deprivation therapy, and both of these forms of therapy block the hypothalamic-pituitary-gonadal feedback system. The agonists down-regulated GnRH receptors in the pituitary leading to a reduction in testosterone and LH release whereas the antagonists directly inhibit GnRH receptors in the anterior pituitary leading to an immediate and reversible LH and FSH suppression, and therefore significant suppression in testosterone and subsequently dihydrotestosterone levels. Both agonists and antagonists binding in the GnRH receptors activate receptors that are coupled with cyclic AMP pathway and promote antiproliferative, proapoptotic, and antimetastatic pathways.



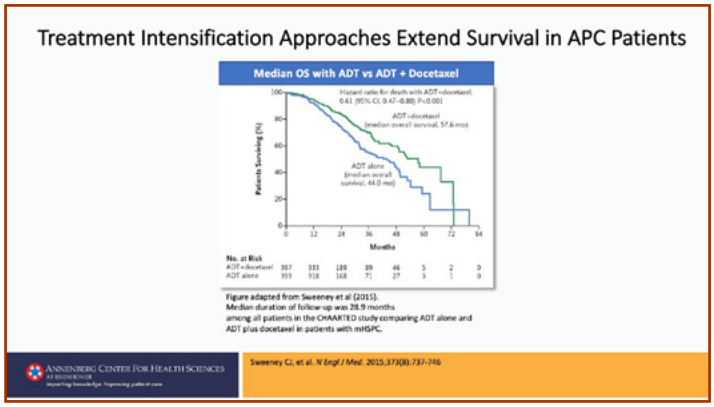

When we look at some of the differences through the mechanisms of action, as I mentioned earlier, both of these suppress testosterone to castrate levels. The agonists down-regulate the GnRH in the pituitary by sort of overstimulating, initially stimulating the receptor and then there's an initial increase in LH, FSH and a surge in testosterone that then suppresses and then reduces the output. When we talk about the antagonists, there is more of a direct inhibition of the receptor in the GnRH pathway and there's an immediate suppression of LH, FSH, testosterone and dihydrotestosterone. Both of these result in the classic side effect profiles that we see in our patients, such as hot flashes, reduced libido, erectile dysfunction and metabolic syndromes that can occur, and there are some subtle differences based on the delivery system for these different mechanisms of action, which we can get into a little bit later.

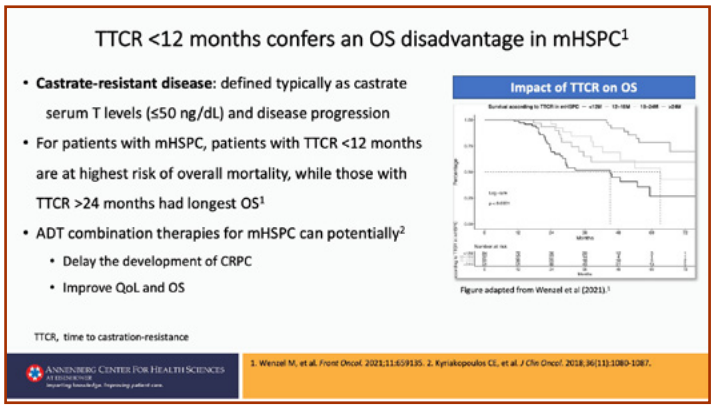


When we talk about some of the clinical differences, the key takeaways are we know that prostate cancer is the most commonly diagnosed male cancer worldwide and certainly prostate cancer is the most common male cancer in the United States. It's the leading diagnosis and the second-leading cause of cancer deaths in men in the United States and while localized staged disease is considered highly curable, the prognosis for advanced and metastatic prostate cancer remains relatively modest, with somewhere around 30% 5-year survival, particularly in de novo presentations.

Prostate cancer progresses through clinical states model from early localized to advanced metastatic and castration-resistance. The incidence of metastatic disease presenting in the United States has been relatively low but is increasing due to a variety of factors. ADT has been and continues to be the mainstay of cancer control, but we know it's not enough and so we need to layer onto it. Both GnR, GnRH agonists and antagonists are currently approved as medical forms of castration and while both classes of agents suppress testosterone, those different mechanisms of action and some variations in their clinical profiles have an impact on the prostate cancer clinical management and, in patients, based on their presentation and goals and desires. And we'll get into that in a little bit with some case presentations.




## CURRENT STATE OF CARE IN ADVANCED PCa

### Robert Dreicer, MD

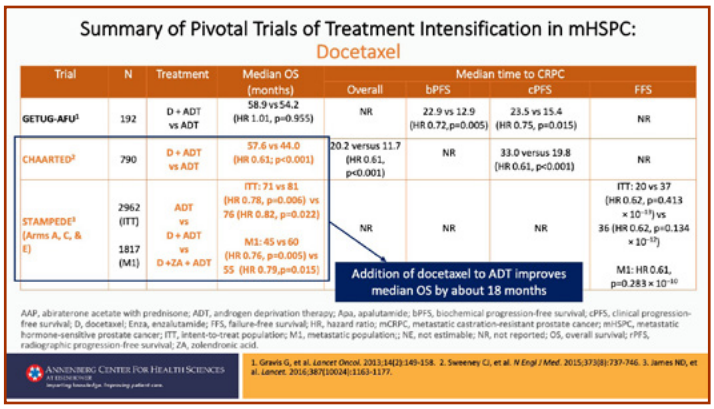
Dr. Cookson has provided us really an excellent overview of the disease state, reminding us that prostate cancer is an androgen receptor-regulated disease. So, now we're going to sort of transition to talking about more advanced disease and I think the best way to describe the current state of care in prostate cancer is to sort of remind us that there's been a lot of progress. Much of it is in AR-directed therapeutics. So, this is sort of the good, the bad and the ugly, right? The good, AR-directed therapy works, right? Eighty years of effective therapy dating back to the Nobel Prize-winning work of Huggins and Hodges. The bad, we're going to look at a lot of data that now should be part of our routine clinical practice, but unfortunately there's evidence that it's not been as widely adopted as it should be. And the ugly, unfortunately ADT, AR-directed therapy, also has side effects. We need to recognize those and be able to try to sort of manage these and involve the patients in their care.

Let's talk about intensification. Sort of the disease state, therapeutic choices, hormone-sensitive metastatic prostate cancer is evolving. Some of the issues that we use in clinical practice, the extent of the disease, sometimes characterized as high vs low volume, sites and metastatic burden, do you see visceral metastatic disease or nodal disease, is the patient symptomatic or not, patient preferences for some therapies. And although genetic testing is listed here, the reality is that while genomic testing, looking at germline somatic mutations, is going to be increasingly relevant probably in the hormone-sensitive setting, it's still more directed in the castrate-resistant setting with regards to the approval of PARP inhibitors. And I think that's it's not going to be much longer that we start thinking about this in terms of management decisions. It is also pretty clear that next-generation sequencing, especially germline testing, is now recommended by AUA guidelines for advanced prostate cancer, NCCN, and a multitude of other advisory boards.

So, standard androgen deprivation therapy. We know that when you take a patient, whether they're de novo metastatic or evolved from local disease, and we use androgen deprivation therapy with monotherapy, be that historically the bilateral orchiectomy, subsequently LH/RH agonist or antagonist therapy, that the vast majority of patients, almost 100% of patients, have an initial response. Back in the day, we used to tell patients that their initial response to primary ADT was 12 to 24 months and then, upon progression to the castrate-resistant setting, survival was a year. Fortunately, that kind of very difficult discussion is evolving pretty rapidly.

We see a survival curve here that comes from the CHAARTED trial, but this is really just calling your attention to the monotherapy arm where the median survival is seen. Again, this is getting better dramatically as we've now evolved to intensification. The concept of time to castrate resistance is a relatively important issue, although it has to be taken into [consideration], you have to look at the big picture here. Castrate-resistant disease is defined typically as a man with castrate levels of testosterone defined as less than or equal to 50 ng/dL and progression. That could be PSA progression, radiographic progression and clinical progression in the context of radiographic progression. But pure biochemical progression, in terms of castration resistance, may not necessarily translate into worse outcomes. So, while this is an important consideration biologically, you have to really look at the entire package of the disease.

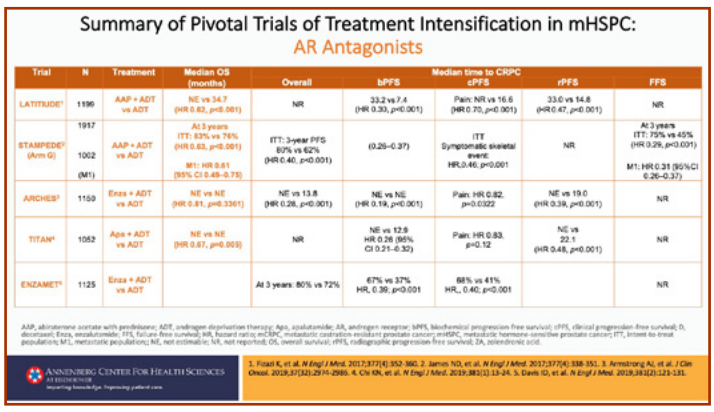
Alright. Intensification defined. Patient starts on testosterone suppression and is now receiving an additional drug. The first trials that demonstrated intensification changed the natural history of the disease were the trials of docetaxel. I'm going to focus primarily on the trials CHAARTED and STAMPEDE. CHAARTED was a US Intergroup trial which simply added 6 cycles of docetaxel to standard ADT and showed its initial interpretation, a striking improvement in overall survival, moving the needle almost a year and a half on a median basis. Subsequent work has really shown us that the majority of patients who still benefit are patients with what were called high-volume disease, and this has to do with the number of sites of bone metastases or the presence of visceral metastatic disease. It's very clear that those patients will unequivocally benefit from docetaxel. The low-volume patients probably not so much.




STAMPEDE is a trial framework done in the United Kingdom which is a really critically important clinical trial mechanism where multiples arms testing different concepts can be added to a framework. The STAMPEDE study that looked at the same docetaxel fortunately found very similar results and actually both studies look almost identical. And it's these 2 studies that really provided the impetus to change the natural history of the disease and began to change how we practice the management of patients with hormone-sensitive metastatic disease.

Similar trials have been done with AR antagonists and these are agents such as abiraterone acetate, a lyase inhibitor, and now a subsequent number of AR antagonists. These are second-generation drugs, bicalutamide being a representative of first-generation drugs like enzalutamide and apalutamide, which are more potent and first-generation ARs.

And here are a series of trials looking at all of these agents which also unequivocally demonstrated benefit to the addition of an AR antagonist or a lease inhibitor in the management of castrate-sensitive disease. These trials have some differences.

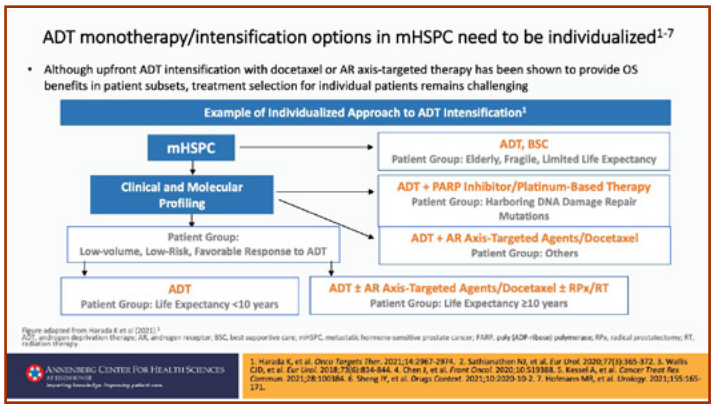



It's important to recognize that, for example, in LATITUDE, they used the definition of high-risk and low-risk, but the more recent trials, looking at apalutamide and enzalutamide, frankly took all comers, all risk groups, and showed that the benefit for intensification held. And you see all of this is now on the basis of overall survival. What's very important to recognize is that the differences in survival seen from intensification. Much of it approaches a year and a half to 2 years of median improvement.

When you think about the improvement in advanced disease, we're talking about improvements in survival of 2 and 3 and 4 and 5 months. This is a dramatic change in the natural history which is why the vast majority of patients who present with castrate-sensitive metastatic prostate cancer need to be intensified, because this data basically provides broad evidence of the benefit.

One of the things that you didn't see in those 2 slides, where we discussed the trials, is comparative data. And simply put, there is no comparative data. We don't know whether or not docetaxel for high-volume patients provides better outcomes compared to abiraterone or apalutamide, etc. STAMPEDE, because of the ability to sort of just do a framework set of studies, has been able to do sort of some indirect comparisons and what I find comforting in that, we've not shown you this data, is that the arms of abiraterone in the STAMPEDE studies compared, and again it's an historical comparison, but again similar patients in a reasonably similar time frame have shown results not terribly dissimilar to that of (inaudible) docetaxel. So, that leaves the clinicians faced with making decisions about how we figure out what therapy to offer what patient in the absence of comparative data.

Each of the trials do have some differences in terms of high- vs low-volume, high- and low-risk, and clinicians need to basically look at some of those and make decisions based on what the evidence showed and then have to look at the patient in individualized therapy.




ADT monotherapy and intensification can be drawn on clinical features and some disease features from the studies. There is the potential over time, not yet available, to begin to look at things from a molecular perspective. There's some very interesting data that's been recently published out of the same group that reported CHAARTED that begins to look at molecular profiling in predicting which patients may or may not benefit from docetaxel in a way distinct from the underpinning clinical parameters. So, there's a lot of work to be done in this area, but in the meantime, ultimately it's about trying to pick the right patient and match them with the right therapy.

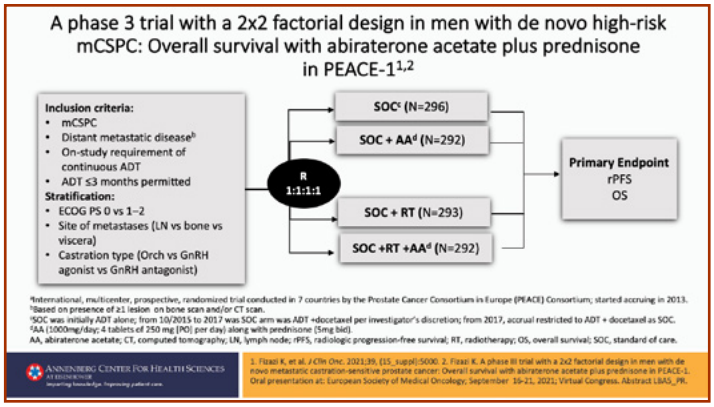
As mentioned earlier, unfortunately what we've found is that ADT intensification is underutilized. We know from work in the VA system, more than half the patients were still receiving monotherapy. In real world studies, 30% to 40% of patients in the US are still being treated with ADT monotherapy despite really very compelling evidence. Whether this represents a degree of nihilism or truly the inability to fully appreciate the benefit of therapy, is unclear. Now this is a reasonable time to just mention something and I'll be asking Dr. Cookson for his thoughts. It's that prostate cancer is a solid tumor that is managed by a range of clinicians that is really unique in oncology. So, we have our colleagues who are urologists who practice in the community, and we have colleagues who practice in large urology group practices, some of which have advanced prostate cancer clinics with a great deal of sophistication and management of disease. There are community medical oncologists, depending on where they are, who see more or less numbers of patients. Radiation oncologists, academic urologists, academic urologic medical oncologists. So there's this diversity of clinicians all engaged in the management of these patients. Dr. Cookson, your thoughts about, why the lack of sort of adoption and what is [the reason for it]? What's it going to take for us to do a better job here?

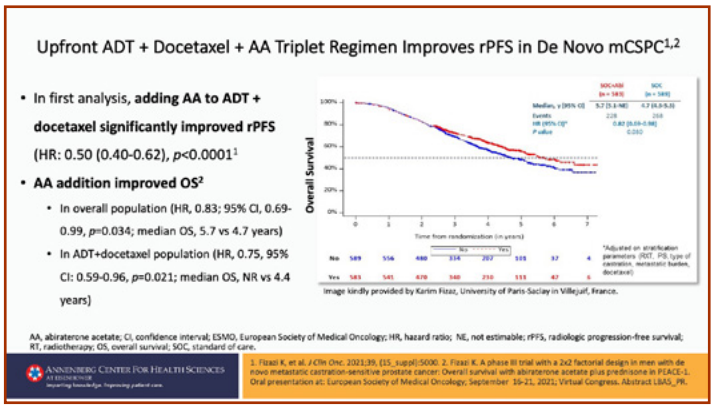
## Michael Cookson, MD

That's a great question. I think that we are all guilty of perhaps a little bit lagging behind in, as the data becomes available, putting it into routine clinical practice. I think efforts by multiple organizations to educate clinicians about this is important and we've certainly made good headway. It's important that patients who present with metastatic disease be presented with options beyond ADT monotherapy which was traditionally the management. So, I think it's happening, Rob. I think the data kind of lags a little bit behind the reality too. I know that most patients are offered advanced therapy, novel anti-androgen therapy, referrals to oncologists for consideration of chemotherapy. I think genetic testing's becoming an important component earlier in the presentation of these patients. But it's an evolution, and these types of programs, I hope, will raise awareness. Every little thing we do to try and, whether it's a national program, whether it's a regional program, it's a CME or there are so many ways in which we have to try and reach our audience and our primary audience, but you're right. There are too many men with prostate cancer and too many patients with advanced disease. There's not enough special to subspecialty trained to take care of them. So, it's really become important for us to make sure that each local area has an expert and has the option to refer to a center where they can get more advanced therapy when they qualify.

## Robert Dreicer, MD

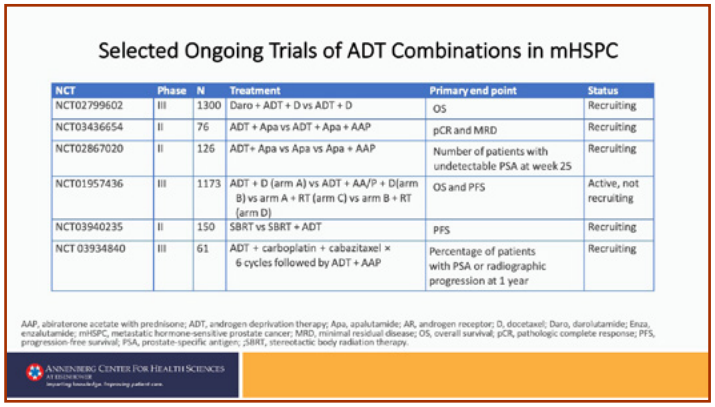
The science moves along. Actually, just about 4 or 5 weeks ago, at the European Society of Medical Oncology, this very important trial was presented. This is called PEACE-1. To summarize, these are patients with de novo high-risk metastatic prostate cancer who were randomized into this 4-arm trial. It's addressing a number of different questions, among them the role of radiation therapy in management. But for this analysis,



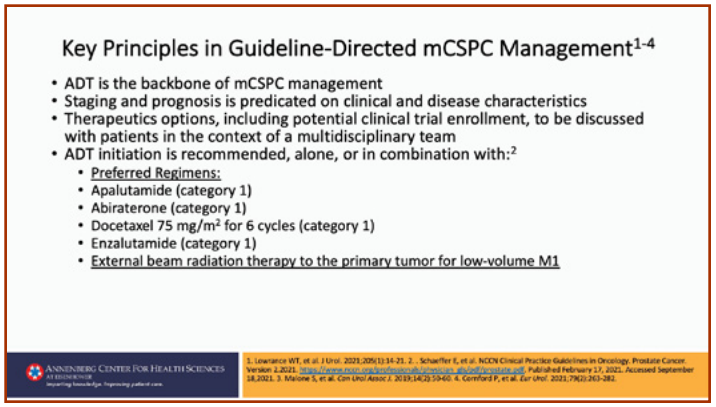

this was patients who were receiving what are called standard of care for their de novo metastatic disease and that would be ADT plus docetaxel. And they were randomized to receive abiraterone or radiotherapy. For the purposes of this analysis, the trial was able to statistically compare patients getting ADT/docetaxel vs ADT/docetaxel followed by abiraterone. This trial showed a very compelling improvement in survival. Remember, ADT/docetaxel, already a standard that shows improvement, and this particular study showed the addition of abiraterone, further intensification, moves the needle by a median improvement in survival of another year, with about 2½ years of improvement in radiographic progression-free survival. This is very compelling data. This will be published in the near term and additional follow-up with regards to the role of radiation therapy will be addressed. So, this tells us that we're not done yet with intensification, and it seems that moving many of these therapies earlier in the disease course may ultimately change the natural history of the disease.

There are other trials ongoing and this is just a selection of trials. And what you see is further intensification using other ARIs,


Selected Ongoing Trials of ADT Combinations in mHSPC

| NCT | Phase | N | Treatment | Primary end point | Status |
|---|---|---|---|---|---|
| NCT02799602 | III | 1300 | Daro + ADT + D vs ADT + D | OS | Recruiting |
| NCT03436654 | II | 76 | ADT + Apa vs ADT + Apa + AAP | pCR and MRD | Recruiting |
| NCT02867020 | II | 126 | ADT+ Apa vs Apa vs Apa + AAP | Number of patients with undetectable PSA at week 25 | Recruiting |
| NCT01957436 | III | 1173 | ADT + D (arm A) vs ADT + AA/P + D(arm B) vs arm A + RT (arm C) vs arm B + RT (arm D) | OS and PFS | Active, not recruiting |
| NCT03940235 | II | 150 | SBRT vs SBRT + ADT | PFS | Recruiting |
| NCT 03934840 | III | 61 | ADT + carboplatin + cabazitaxel × 6 cycles followed by ADT + AAP | Percentage of patients with PSA or radiographic progression at 1 year | Recruiting |

AAP, abiraterone acetate with prednisone; ADT, androgen deprivation therapy; Apa, apalutamide; AR, androgen receptor; D, docetaxel; Daro, darolutamide; Enza, enzalutamide; mHSPC, metastatic hormone-sensitive prostate cancer; MRD, minimal residual disease; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival; PSA, prostate-specific antigen; ;SBRT, stereotactic body radiation therapy.
Annenberg Center For Health Sciences at Eisenhower

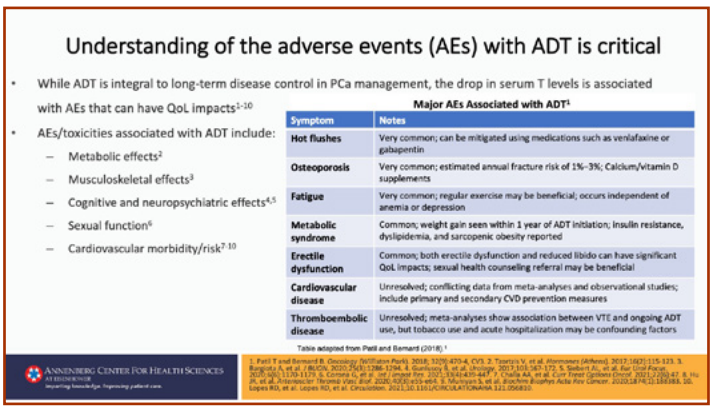



asking the question about platinum-based chemotherapy, as well as the role of radio surgery.

So, guidelines basically help frame reference. There are a number of guidelines, the most recent are the American Urologic Association Advanced Prostate Cancer Guidelines which were published earlier this year, NCCN guidelines, and basically what we see is that all of these regimens that we've just discussed provide evidence of improvement in overall survival. There is a little bit of a provocative suggestion that, for patients with low-volume metastatic disease, external beam radiotherapy to the primary should be considered, and there are studies, including PEACE-1 that I just briefly mentioned, that will also provide additional information. So, all of this is guideline-directed therapeutic options.

We are going to transition now to some of the ugly parts of what we do, but it's clinically important. And that's really to focus on the adverse effects of androgen deprivation therapy. You know, back in the day when hormonal therapy was in its early days with medical therapy because obviously orchiectomy had been a standard of care for a number of decades until the development of the LH/RH agonists, and, subsequently, the antagonists. Men who have a decline in testosterone have immediate effects. We're all aware clearly that libido is associated with testosterone. We also recognize the impact on hot flushes which can be very common. And, for a long time, to be honest with you, because hormonal therapy tended to be used really in advanced disease, the full impact of these were not particularly well appreciated because the survival of patients was limited.

PSA was introduced into clinical practice around 1986, '87, and then more widespread use of ADT was brought to bear, again perhaps in the absence of evidence, but still brought to bear exposing a much larger [number] of men. And over the last couple of decades, we have increasingly recognized some very




important changes. We know about the metabolic effects and we'll talk about them in a minute with regards to increase in weight and the risk of diabetes, the loss of muscle mass, increased risk of osteoporosis, and the issue about cardiovascular morbidity and risk which remains controversial, but certainly an important consideration as our population ages and as more men are exposed to ADT.

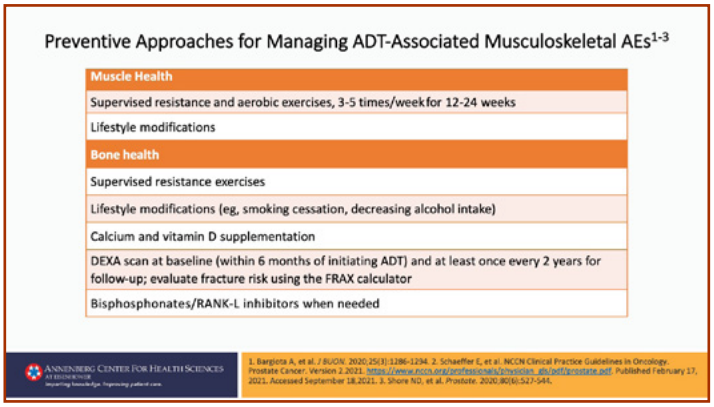
So, focusing a bit on the metabolic complications, first things first, the rule of 10%. So, there is reasonable evidence that many men, if not educated appropriately, are at risk to gain 10% of their body weight in year 1. Many of our patients, unfortunately, are a little bit on the heavy side. You take a 220 lb man, 10% of that is not inconsequential. So, therefore one of the things that we must do when we begin to see patients starting on therapy is to advise them of these risks. We recognize that there's unequivocally level 1 evidence to support an increased risk of diabetes. So, blood sugar control, which is associated with weight, the metabolic changes associated with dyslipidemia, and the increased risk for metabolic syndrome, and the downstream risk of increased cardiovascular complications, is unequivocal.

Among the strategies that many of us use is, one, somebody has to talk to the patient, be it the physician, a physician extender, a nurse clinician, a nurse. We have to review the risk of weight gain and metabolic changes, advising caloric control, some form of regular exercise which impacts not only weight but also the risk of osteoporosis and muscle mass loss. This is probably the most critical thing we do. I think it's also pretty clear that we don't do this as well as we might.

Musculoskeletal effects, again muscle mass loss and overall long-term decrease in or increased risk of osteoporosis. Again, many of these changes happen within the first 6 to 12 months of ADT, therefore this isn't necessarily a long-term issue. Again, recognizing these risks and engaging the patient in terms of exercise, again, even if it's low-volume sort of weights, if it's regular walking or swimming, whatever the patient's other comorbidities will allow, this becomes increasingly important that we, as the primary clinician driving the ADT, review.

We know that there is a whole range of good science that suggests why and what the background with regards to osteoporosis and muscle mass loss is. And again, the routine use of assessment of osteopenia and osteoporosis with DEXA scans is a little controversial but certainly patients who have long exposure, people who may have been treated in the context of nonmetastatic disease, this has to be part of what we think about, vitamin D and calcium supplementation, a relatively simple thing, is part of the standard of care of management. All of this is really incorporated, and again, in counseling of our patients, but ongoing. Again, as we manage these patients, we have to ask about the weight, we have to ask about exercise, about supplementation. It's not a sort of a 1-stop shop where you do it 1 time and there's no further discussions of these issues.

So again, preventative approaches. Lifestyle modifications. Again, it's got to be about caloric control because exercise alone is not going to work. While there's not level 1 evidence to support it, many of us find advising patients for low carbohydrate diets, like Mediterranean diets, can be attractive ways to try to, again, allow patients to do lifestyle changes over which they have control. Remember, these are people with diseases that are now out of



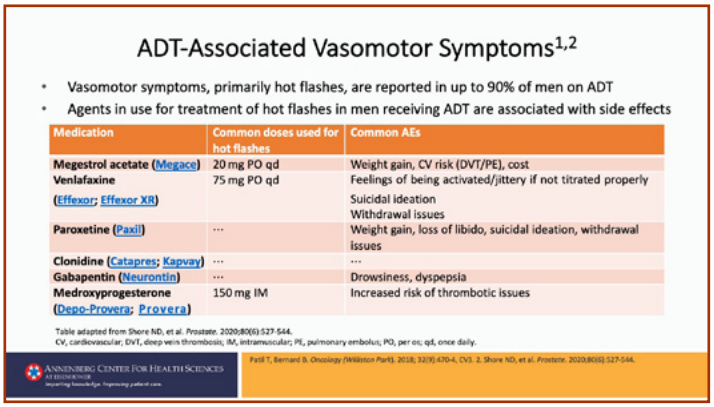

their control in terms of what the disease is doing, so what do they have control of? They have control of what they put in their mouth and many of these patients have some control over the ability to do some exercise. So again, engaging them. I find that for men, being somewhat competitive, encouraging them to look at steps, to get a pedometer, to use their smart phones, to begin to set goals for themselves so that they can build on that, is a way to get them to sort of be competitive with themselves. And when those patients are engaged, I'll ask them about how they're doing when I see them because, in a sense, it provides a way for them to have some control over what's going on.

Again, the calcium and vitamin D supplementation is relatively straightforward. Most of these men, if they're not taking a multivitamin, that'll work, or an over-the-counter vitamin D [supplement] 2 times a day [with] 1,000 mg of calcium. Relatively simple things. The DEXA scan at baseline is not necessarily covered by insurance and I think you have to look at patients who may be at increased risk for osteoporosis and maybe be a little bit more aggressive in evaluating them. Again, patients who have unequivocal significant risk for osteoporotic fracture, supplementation with bisphosphonates or frank ligand inhibitors may be appropriate.

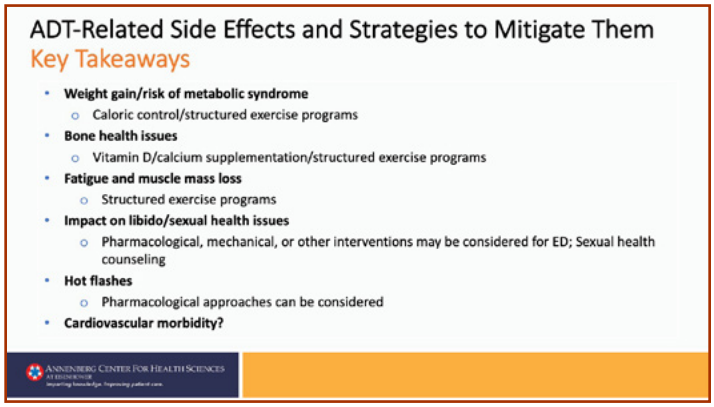
One of the interesting challenges that we all see with patients is the issue about cognitive impact. When you treat enough patients with ADT, you will get a subset of patients who will tell you that they somehow don't feel quite as sharp, or they feel a little bit of brain fog. There's been a lot of work done in this area. These are obviously very difficult studies to do. It's unclear that a clear link has been made. One of the challenges about intervening is when you don't necessarily know it's directly related. Again, these are men in their sixth, seventh, eighth decades of life. There are comorbidities at work here. So, it's not always absolutely clear. One of the things that obviously has to be taken into consideration is the potential for concomitant presentation of depression. It's the most common medical illness and therefore it would not be uncommon then in these patients who are complaining of these issues that depression represents an important sort of part of the evaluation. If men have primary care physicians, it's good to engage them in sort of helping work these because they frequently know these patients well. But unfortunately, a lot of times when you take over prostate cancer management, sometimes you become the doc and therefore some of these evaluations may fall to us, as clinicians managing the disease.

One of the things that doesn't get discussed enough is the impact on sexual function of ADT and this is, again, in the context of many of these patients receiving intensification. We talk about the loss of libido associated with testosterone decrease. However those men whose primary treatment is not impacted on erectile function, can still attain erections and therefore counseling, especially partner counseling, may be very important to maintain the emotional well-being of our patients and their partners. So again, in those centers where there is expertise here, sometimes it's very useful to bring those to bear because it doesn't get discussed unless we raise it a lot of times. And, most of the time, again, we're talking about men and many men will just not raise this issue because they're embarrassed or if their partner is not present they'll just sort of pass over this. But this remains something that we need to continue to focus on.

Hot flushes, again 90% of men will have hot flushes, 5% of men will not have any issue and then 5%, in my experience, have what I call just intolerable issues. One of the things that we have found is that, over time, there's a little bit of experiential, sort of therapeutic management and there's some now randomized trials that give us insight. Drugs that have been used, over time, include drugs like megestrol acetate (Megace) which, while in a subset of patients, are effective, is associated with an increased risk of thromboembolic disease as well as weight gain, already in the context of patients who are already struggling with their weight. Venlafaxine (Effexor) at either 37.5 or higher doses, have been used. Sometimes a higher dose might be appropriate in the context of also managing depression. Low-dose, it's been my experience that although randomized trial evidence is a little less compelling to suggest benefit, but about 1 or 2 out of 5 patients with low-dose Effexor will say there are fewer hot flushes or the intensity is less. There is randomized trial evidence of some utility of gabapentin, but there are side effects associated with it, even at low dose. Again, these are strategies to be used. Most men will not want to add additional drugs to their regimen, but in those men where their quality of life is really impacted, it's important that we discuss these and then give patients therapeutic trials. It's typical for me to give a patient 2 or 3 weeks of a drug and say, if this has not helped, just wean yourself off and we're done. We'll think about something else. And if you get benefit, we'll continue. So, it's not a forever therapy if it's not working.

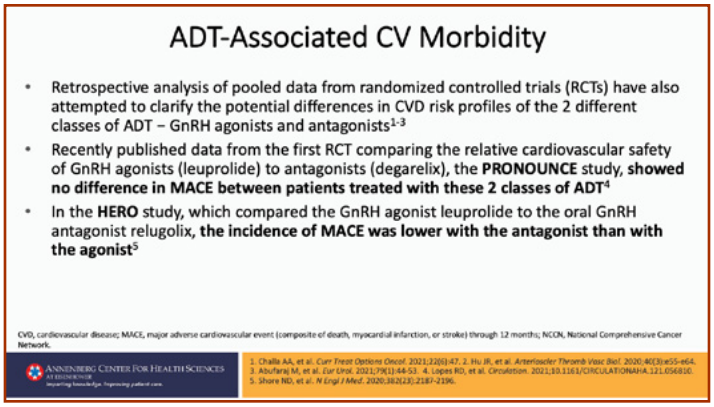



Alright, sort of high-level issues about AR-related side effects and strategies. Again, weight gain and the risk of metabolic syndrome, we have to talk about it, we have to have a change in caloric intake and there's got to be some form for them

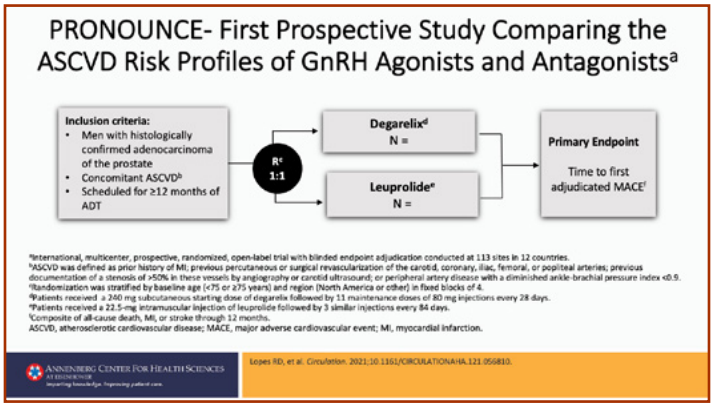



of a structured exercise program. Vitamin D and calcium supplementation. Again, discussions about sexual health issues, reminding men that if there's not underlying reasons for ED, that men can achieve erections and therefore that may be part of their partner's satisfaction. And again, you have to ask about hot flashes, because a lot of men, unless it's really desperate, will not complain, but certainly might be impacted in a positive way by intervention.

Alright, let's transition into the difficult challenges about concerns of cardiovascular risk. It's been recognized for a number of decades that older patients receiving ADT might have some impact on cardiovascular risk. To be honest with you, a large number of cohort studies have been done and the reality is that no compelling data from many of those well-done meta-analyses, as well as observational cohort studies, that has demonstrated a firm association between ADT and cardiovascular morbidity and mortality. There is, I think, reasonably compelling evidence that the metabolic changes that occur from ADT have a link with cardiovascular disease and I think that that is increasingly an accepted sort of state of the science in this area.

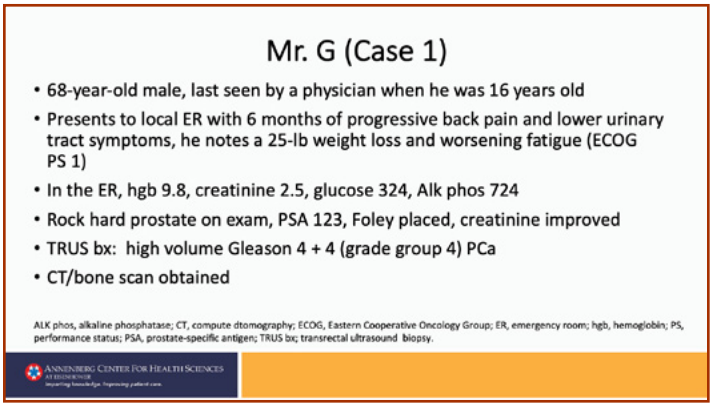



Again, a large number of analyses looking at a variety of things, cardiovascular morbidity and high-level MIs, thromboembolic, stroke or other cardiovascular-related issues. Major adverse cardiovascular event, MACE, is increasingly a term that you will hear used as we think about these studies. Again, one of the other things that's temporally important about this in this discussion, as we've talked about the differences potentially between drugs that are GnRH agonists and antagonists, is some interesting data from 2 studies that we'll briefly discuss that show some differences, potentially, in these different classes of agents with regards to CV risk.

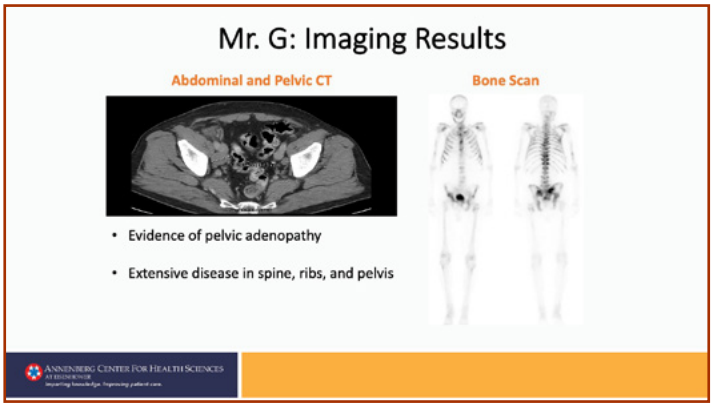



The most recent study actually published, we're going to come back and talk about the study that led to one of the AR antagonist's approval, but this is PRONOUNCE. This is actually the first prospective study which looked at cardiovascular risk or MACE, major adverse cardiovascular events, comparing an agonist and an antagonist, degarelix vs leuprolide. And this study was powered to look at first adjudicated by review by cardiology, major adverse cardiovascular events. This study, basically this study was closed early because of relatively slow accrual, showed no difference at 1 year in the major adverse cardiovascular events between the agent degarelix and leuprolide.

We're going to talk about the HERO study which showed us a little bit different data, but again this was a prospectively designed trial to look at these. Now, there are some issues with this study that time does not allow, but again this sets the baseline for some of the controversies that we're going to discuss.




Let's talk about a case at this point. I'm going to ask Dr. Cookson to join me as we think about how we might manage this gentleman. Mr. G., 68-year-old gentleman, it's been a long time since he saw a physician, goes to the ER, has not been feeling well for half a year with lower back pain, increasingly having problems with lower urinary tract symptoms, 25 lb weight loss. He's more fatigued, even though he continues to work. He's anemic. His creatinine's 2.5, his blood sugar's 324, his alkaline phosphatase is elevated. On exam, he has a rock-hard prostate. He has a foley placed, his creatinine gets better. His PSA is checked, it's 123. Ultimately seen by a urologist, has a high-volume grade group 4 prostate cancer. Has a metastatic evaluation and appears to have both bone and pelvic nodes, worrisome for the presence of metastatic disease.




Dr. Cookson, back in your clinic now, you've ordered this stuff up. He's got metastatic disease. He's got a reasonably good performance status and he wants to know what you think is the best way to take care of him.

## Michael Cookson, MD

There's a lot in this patient, but I think you have to, of course, alleviate his urinary obstruction. So, I'm not sure the foley catheter may have been a temporizing maneuver, but he may need more from an outlet. You'd want to really make sure his kidneys are unobstructed, etc. Moving forward with just the management of his de novo metastatic presentation, you referred to those initial trials, like the CHAARTED, and I believe he would be a high-volume presentation based on the number of bony metastases that he represents. So, this would be a patient who would certainly be offered androgen deprivation therapy and you would want to layer on that additional therapy. Docetaxel would be appropriate. The PEACE study gives the opportunity to consider combining Zytiga. In the past it was usually like a choice between the androgen pathway and the chemo pathway on top of the backbone of androgen deprivation, but going forward there may be an opportunity to combine both. But I would definitely consider this gentleman for docetaxel in addition to ADT.

## Robert Dreicer, MD

I think that's an excellent suggestion and I think you're bringing up the PEACE study is actually important because, frankly, this patient probably would have been eligible for that study and I think if this patient walked in today, I mean you'd have to have that conversation. Now, that's not to suggest that if you offered docetaxel alone, if you offered apalutamide or enzalutamide or abiraterone, now, interestingly enough even though, again, we don't have comparative data, but this is a patient already walking in with a blood sugar of 324, so suggesting that there's some work afoot there. That CT scan shows a little bit of a fat pad, suggesting he might be a relatively large gentleman. So, perhaps a drug like abiraterone might not be a great therapy where other drugs, like enzalutamide or apalutamide, might certainly be very reasonable or docetaxel. So again, one of the [things that] this already shows us [is] that you can make certain sort of decisions based on the volume of disease, in this case putting him sort of as a good candidate for any of the approved therapies. Perhaps shying away from one that requires more risk of metabolic complications and the need for at least 5 mg of prednisone. So, those are the kinds of decisions that clinicians need to make, but there's unequivocal suggestion that this patient not only will benefit from therapy, but the reality is that intensification will probably, or at least likely, improve his survival.

## Michael Cookson, MD

You brought up and when you see a case like this it's easy to focus solely on the cancer treatments, but as you mentioned, there's other things going on with this gentleman so I think having a framework within your practice of how you don't get distracted by the elephants in the room, the potential for impact on what's the duration of therapy, likely it's lifetime for this gentleman, what is the status of his baseline presentation for bone health, assessing his other comorbidities and the cardiovascular part is also becoming evident. So, getting these things done at baseline, throw in genetic testing, there's a lot to do, and so I think it's really helpful to try and construct, whether it's your notes or your EMR system, a nice framework. You might not accomplish everything on the first visit, but I think there's a lot to do because we're talking about somebody you're going to be managing for years, hopefully, not days or weeks. And so getting all of those things in place is an important component, like you mentioned.

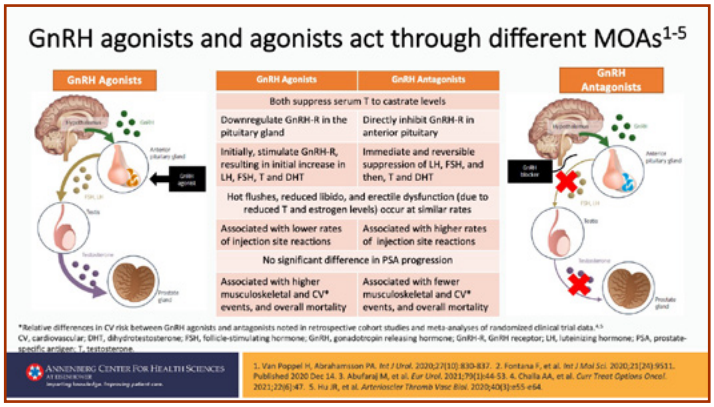
## Robert Dreicer, MD

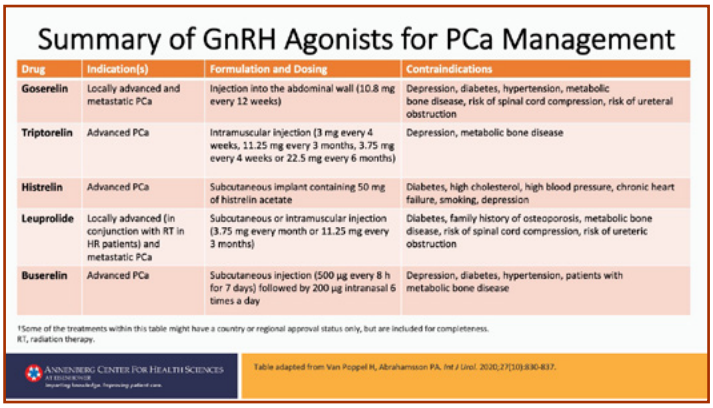
And I agree. And I think that, to expand just a little bit further on the excellent points you made, I think in a patient like this—if I was seeing this patient in the office—so this work has been done and he's now sitting down and we're about to review, we have his biopsy results, we have his imaging results. The first thing, in addition to talking to him about sort of the therapeutic options and the natural history, is I need him to get a primary care doc, right? I mean, this is a man who has multiple comorbid problems and, as you well know, a lot of the patients we take care of, even with advanced disease, sometimes the risk of dying of other diseases during the time frame is not inconsequential. So, here's a guy who unequivocally probably has diabetes. He may or may not have cardiovascular disease, we don't really know because he's not really been assessed. So, I'm going to work hard to get him a primary care doc. That's part of my responsibility to this gentleman. I'm going to recommend that we do germline testing. I'm going to ask him if he's got children, but even if he doesn't have children I think germline testing is now a standard of care. It may not make a choice for me today, but certainly it will impact on how I think about the disease going forward.

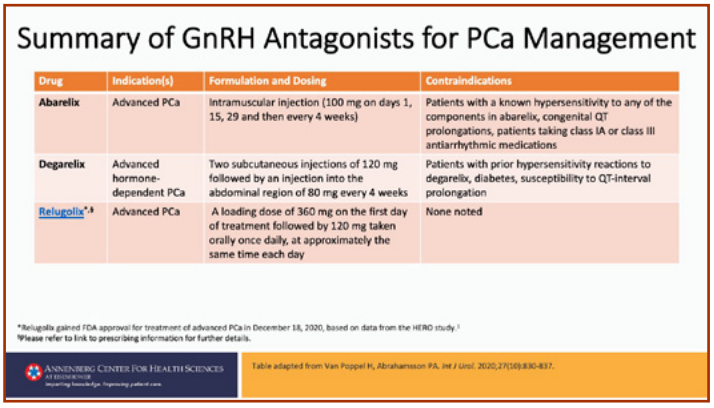
We have to talk about caloric control, but part of that is in the context of managing a blood sugar disorder. And again, as a medical oncologist, I don't really want to manage his blood sugar disorder. I want to get a clinician involved and, again, part of the team. He's probably going to need, to benefit, to be seeing a dietician about his blood sugar issues, hopefully. He's got type 2 diabetes and maybe he can be put on an appropriate diet, maybe started on a drug like metformin. I mean, again, as you point out, it's, it's sort of the whole-body work-up that we've got to take care of, and we can't make up for 50 years of no healthcare.

But we now are sort of obligated to sort of take him forward, making sure that he's on vitamin D and calcium replacement. And I think your suggestion about having sort of a checklist to make sure that we capture all of the critical issues because a lot of times these patients are just overwhelmed with what we're doing. And when I talk about intensification, my strategy—and I've talked to a lot of colleagues, both on the urologic oncology side and the geo-med-onc side, and I've heard similar things—is I tend to introduce the subject during that first visit, but I don't go into great detail. Because, as you know, our patients, they're overwhelmed at this point, right? So, how much are they going to remember? I point out to them that this is just the first part of the discussion and I typically bring them back in about a month. And, at that point, we can then sit down, things have settled down a little bit, they've been started on their therapy, and now we can talk about that intensification. And I find that strategy works reasonably well.

Let's, again at a high level, and this case is sort of representative of it, is we've talked about how you think about making choices in the metastatic hormone-sensitive setting, but the fact that we have a lot of things to do and that a lot of that has to do with management, not only of the disease, the appropriate use of intensification, but really the recognition that what we're about to do has potential downstream impacts in terms of toxicity. And that we need to be proactive in discussion of these issues and we need to follow through on discussions of these issues. It doesn't mean we, the clinician who's managing the disease, has to do everything, but it does mean in a sense, we have to oversee the management. So, we're going to ask our colleagues in nutrition to help us. We're making that referral. We're making sure that happens. If we're doing genomic testing, some of us in prostate cancer, we see a lot of this disease, become increasingly comfortable with interpreting genomic results, but if a patient comes back, like this gentleman that we just talked about, and is a BRCA-2 carrier and has 2 sons, well we may want to engage genetic counseling in involvement of not only the patient per se, but really more the family and the larger issues. If you're managing this disease, you have to be the content expert. That means we need to basically direct how these things go, and we need to be aware of the implications, both of the known side effects, but, increasingly, of really some very serious side effects, like potentially cardiovascular disease.




in a variety of depo formulations and if we have time, we can talk about some of the controversies, sort of tale of the depo recovery of testosterone, and those kinds of issues. And again, one of the things that's important as we look at the antagonists and the approved agents, including relugolix, the most recently approved, which is an oral agent, as well as the parenteral agents, recognizing that all of these agents, the agonists and antagonists, received FDA approval on the ability to suppress testosterone. That is the critical issue here. And there is no controversy as to the ability of agonists vs antagonists to suppress testosterone. There are mechanistic differences, and we'll touch on some of them, but again approval is granted not on the anti-prostate cancer properties of these drugs, but the downstream impact of suppression of testosterone.

Given that, there are no differences that are known in terms of oncologic outcomes. And again, the key driver here is testosterone suppression and therefore, as long as these agents can effectively obtain castrate levels of testosterone, you would not expect there to be any difference in disease activity, the antitumor activity. But there are other differences, potentially, in other sort of more nuanced ways of assessing disease.

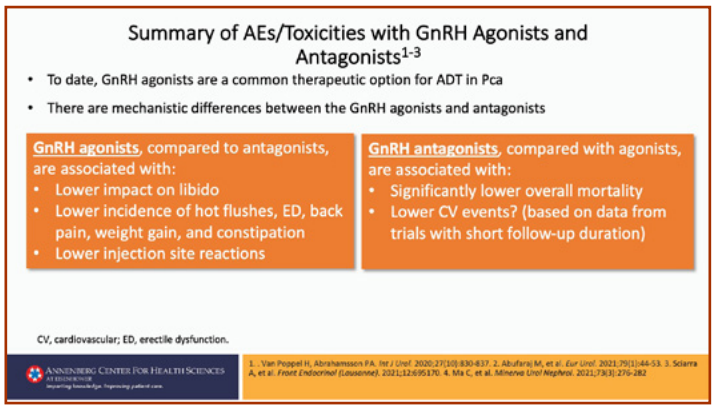
## EXPLORING OPTIMAL THERAPEUTIC OPTIONS

### Robert Dreicer, MD

Now we're going to really move on to sort of a nuanced part of the discussion and focus a little bit more on some of the differences between the GnRH agonists and antagonists in advanced prostate cancer, looking at some of the available data and some of the ongoing controversies.

Just again, reviewing the mechanism of actions. You saw this earlier from Dr. Cookson's discussion and this just sort of level sets us again. There are a number of agents approved in terms of GnRH agonists. All of these are essentially leuprolide derivations. They're administered differently sometimes in terms of into the abdominal wall subcutaneously, intramuscularly, etc. They come

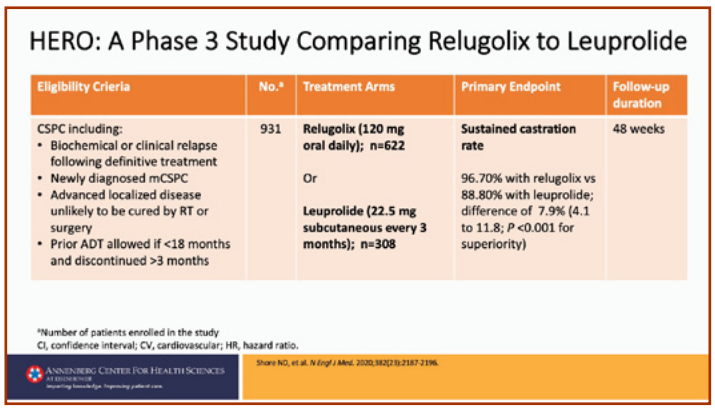
We know that when you look at the whole sort of summary of agents, that include even bilateral orchiectomy, there have been some trials that have suggested subtle differences. One of the challenges, of course, is that there are no comparative studies that are powered to address all these in detail. I think that many of these studies are historical. So, for example, the concept that a bilateral orchiectomy decreases the risk of cardiovascular-related complications. Again, we spent some time during this session talking about the concern and the relationship between ADT and complications and the data suggesting orchiectomy, which of course just decreases testosterone, perhaps is a little bit less compelling in the big picture. So, it's not clear that any of these are less risky with regards to toxicities of concern.

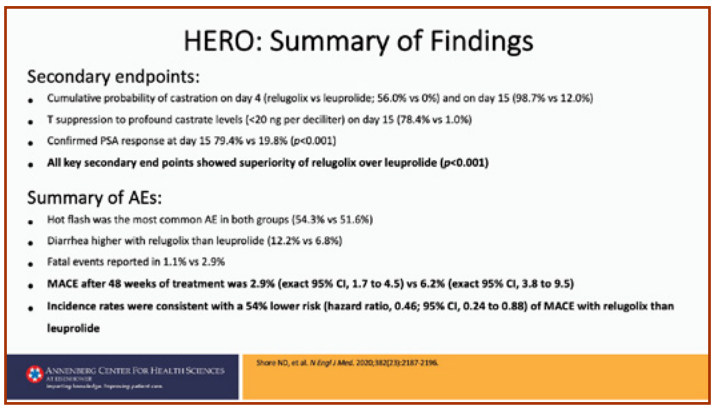



We do know that there are mechanistic differences. We know that, and I think this is a relatively straightforward issue, the antagonists as a class are cleaner molecules. They're also chemically challenging molecules which is why they were not developed first. Had they been developed first, we probably would use these agents routinely, but the agonists were developed first. Direct comparisons between these agents and many of the toxicity profiles that we've talked about are frankly really not existent, but there are mechanistic differences.

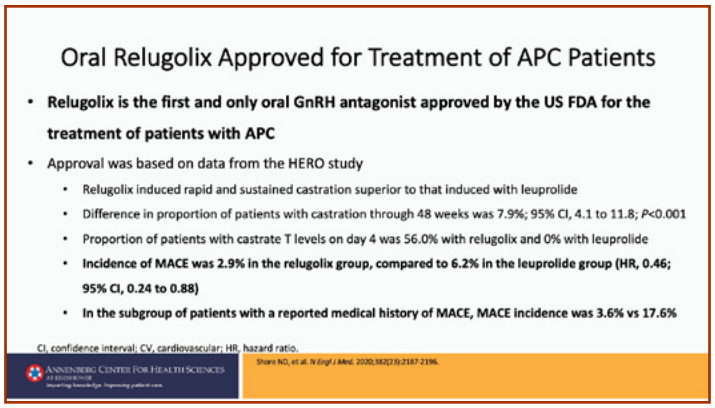
So, the HERO study, which is the trial that led to the regulatory approval of the oral agent relugolix is shown here and basically these are patients with castrate-sensitive prostate cancer, some with metastatic disease, others without. Again, the primary endpoint was testosterone suppression, sustained castration rate. Relugolix compared to leuprolide basically as seen there. Relugolix, an oral drug, effective FDA approval on the basis of testosterone suppression.

These are some of the secondary endpoints and adverse events noted and, again, this is from the *New England Journal of Medicine* publication from last year.




Again, oral relugolix, because of its mechanism, it's an oral antagonist, causes more rapid testosterone suppression mechanistically. That's the way antagonists work compared, or antagonists vs agonists work, and that's well recognized. These are the findings, so approval of relugolix, similar, rapid castration and somewhat improved compared to leuprolide. Again, that was not the primary endpoint to prove that it was better than leuprolide, but the fact that castration was sustained through week 48. And you see some of the differences.




The HERO study was also an interesting study in that it also, as a secondary endpoint, looked at the incidence of major adverse cardiovascular events, the MACE. And, interestingly enough, in the HERO study, that rate was statistically lower in those patients treated with relugolix compared to leuprolide and I think this created some really significant interest in this particular study. Again, to place things into context, this study was published prior to PRONOUNCE, which we've already discussed. That was a study that was specifically powered to look at MACE and the differences between a different antagonist, that of degarelix vs an LH/RH agonist, and there were no differences at one year in MACE. So, we see somewhat different findings. I think it's pretty safe to say that we don't have definitive evidence with regards to this issue with regard to these 2 classes of drugs.

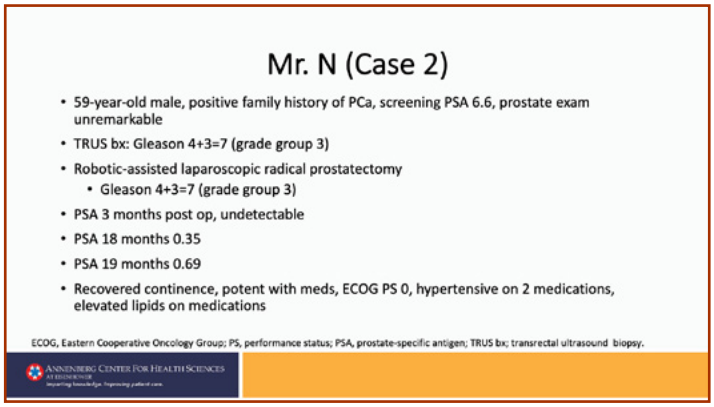
## Michael Cookson, MD

One of the things, if I could comment on that which you highlighted, I think is that the HERO study excluded patients who'd had a recent cardiac event, but they had patients with cardiovascular disease. There was certainly no mandate in the HERO study to be under the care of a cardiologist and so there were differences, and you can see those are particularly different in those patients who had a preexisting cardiovascular

history and that was shown in one of the tables. I think it was like 17% event rate in the leuprolide arm. The PRONOUNCE study was unique in that those patients were under the care of a cardiologist and so, almost a Hawthorne effect, if you will. We know, I think, from looking at that, that patients who are under the care of a primary care or a cardiologist, somebody who's paying attention, managing their lipids, managing baby aspirin, making those interventions, that what I've learned from this is that the patients that are under good clinical care are probably going to be okay. But many patients, as your clinical scenario, present without a primary care doctor, let alone good cardiac care. And so I think this has raised an awareness about the potential impact if they're not under good care. And so, again, I want to bring out those distinctions between the way those trials were conducted.

## Robert Dreicer, MD

I think that's actually a really critical point and many have commented on exactly that issue. One of the challenges that we have is that, again, I think the data for both these trials, with all of the limitations, is provocative, right? It may be that these agents, this class of agents, antagonists, may provide a better alternative. I think it's challenging to take away that with some degree of confidence. What is clear is your point. Whatever therapy you opt to consider and, again, there are differences in these agents, the attention to cardiovascular risk is something that we need to change. Again, we don't do this as a routine and I think one of the things that follows from the discussion earlier about the number of different clinicians who manage advanced prostate cancer, one of the things I think that most folks understand, but we probably should state, is that the number of patients who need therapy for advanced prostate cancer across the spectrum, as we begin to look at much more aggressive management for locally-advanced disease with intensification, has gone up. The number of newly minted urologists is not going up to keep pace. The number of oncologists is not keeping up. We increasingly are stretched. These conversations that we're talking about—it's easy for us to talk about this—but if you're in clinic and you're trying to work through your very busy clinic and you're seeing 2 new patients with this disease, it's really hard to carve out the kind of time that's required or to coordinate the kind of care. It points out that we're going to have to figure this out, again, however, you do it because the reality is although the data may not be 100% tied into CV risk, I think we all recognize that there is an increased CV risk at some level when we use these therapies for patients and that risk happens early. This is all, typically, within a few months of exposure. Again, this program has really been focused more on metastatic disease. One of the interesting issues that we're probably not going to talk about, but we have a minute or 2, is that in the locally advanced patients where there might be a defined period of testosterone suppression, one of the potential benefits of the antagonists is sort of rapid testosterone recovery and the attractiveness for its use in the setting of locally advanced disease where you're going to give a finite period of therapy. But one of the challenges, again, is that even if you're talking about a finite period of therapy, it's still likely to be 18 months or 2 years, and therefore the cardiovascular risk from that is still going to be an issue.




This is a 59-year-old gentleman. He has a positive family history of prostate cancer. His dad, a brother, both had prostate cancer, one had de novo mets and one had a bad local prostate cancer that apparently was challenging for the patient. So, it impacted on his psyche. So, he's being followed more carefully. Screening PSA of 6.6, exam's unremarkable, so a T1C, Gleason grade 3 as you see. He undergoes robotic-assisted lap prostatectomy, confirmed a grade group 3. Uneventful recovery from the surgery. Post-op PSA is undetectable. But about 18 months, he has a detectable rising PSA, as you can see, from .35 to .69. Good recovery of continence. He's actually potent, using meds. Good performance status. He's hypertensive and he's got elevated lipids, but he's on drug.

So, biochemical failure. How do we think about managing this patient?

## Michael Cookson, MD

He would certainly categorize as a high-risk by European stratification given that the grade group 3 with a 4/3 predominance would put him in a high grade. His doubling time, albeit his PSA is low, is rapid, and so I think that shows you that he will declare himself. You know, there was a lot of debate in the day certainly about adjuvant vs early salvage, but we've seen several trials come forward now, raves, radical, meta-analysis, artistic, demonstrating the benefit of early salvage that allows you to selectively treat those patients when they're really declaring themselves, as opposed to just giving it and maybe overtreating a third of patients, subjecting them to the complications.

I think this patient would be a good candidate for early salvage radiation therapy, given the numbers and the handwriting on the wall, and that's probably where I would head with him.

## Robert Dreicer, MD

Now your radiation oncologist sees the patient and he says to you, "I'd like to add 6 months of ADT based on evolving data that suggests that salvage radiotherapy and ADT works." The patient comes back to you for conversations. What are your thoughts and how would you go about doing that, assuming you agree with your radiation oncologist?

### Michael Cookson, MD

The data's still to come forward about the true benefit here for adding that ADT in this particular setting, but I would agree that that's probably a good idea. So far, all of the studies with more intermediate- to high-risk patients show benefit of that addition. There is probably synergy there. On the other hand, these are patients that really don't want to be on therapy for a long time. And so, when you showed the HERO trial, definitely one of the things there was a tail on that study where patients were monitored for their recovery in a subset and there was a much more rapid recovery with relugolix in patients once they came off the therapy. We know that with traditional leuprolide, for example, there is a 9-, 12-month period before recovery. I think it would be attractive to consider an antagonist if this patient was going to get combination therapy.

### Robert Dreicer, MD

That's an interesting issue. One of the things that I find, it's annullable right now, but the challenge is that. I mean, I think in many ways the use of an antagonist and a drug like relugolix would be very attractive because, again, you could say you're going to be on testosterone suppression for 6 months and basically that's it and you're going to be better. But some of my radiation oncology colleagues and some of yours also will say, yeah while that's very attractive, now again we've already now extrapolated the data, the biochemical failure settings with hormone, so we're not even going to extrapolate further. They'll point out that all of that data was extrapolated from the context of using antagonists where the recovery time was more than 6 months. In many ways, even though we talk about 6 months of therapy, the reality might have been that those patients were getting 9 months or 12 months or longer. This isn't a moving target, right, because in all of the disease subsets that we're talking about, whatever timeframe we use and if you're talking about using the agonists, the real true time of testosterone suppression was much longer. It's unknowable and I'm not sure it's a reason to do or not to do something, but it is something that is a little bit up in the air of concern. What are your thoughts about that?

### Michael Cookson, MD

I'm a guidelines guy and I'm guidelines driven and there is a data-free zone here, so it's all going to be the art vs true science. I do think, when you introduce things like PSMA scan, the duration of therapy, we may have to redo a lot of trials, and this would probably be a prime area. Imaging, with PSMA scanning, would probably be a component for this gentleman. He's in that range where we might expect to see something that could add additional guidance to where we're going to aim our beam and how we're going to treat him. I think we're in an exciting time, but we don't have all the answers. And so, in a gentleman like this, I think the point is if you're going to go for a more defined 6-month roll, let's give him 6 months of therapy. Some of these men never recover their testosterone after a year or more of therapy and that's really difficult for them. I think, if we have a reversible agent and we have a defined goal, why not use it?

### Robert Dreicer, MD

Would you do next-generation sequencing on this patient based on his family history or would you, and I'm actually specifically asking about germline testing? That's one question. And the second question, you raised the issue very appropriately of PSMA PET CT. At my institution, literally this week, we started doing routine PSMA PET commercially, so we finally hit the big time. So, you inferred that, based on his PSA, that a PSMA PET CT might be reasonable, and we recognize the limits of detection become more useful around 1, but perhaps even lower. So, would you do a PSMA PET CT because you do have access to it at your shop? Would you do next-generation sequencing with germline now or would you wait?

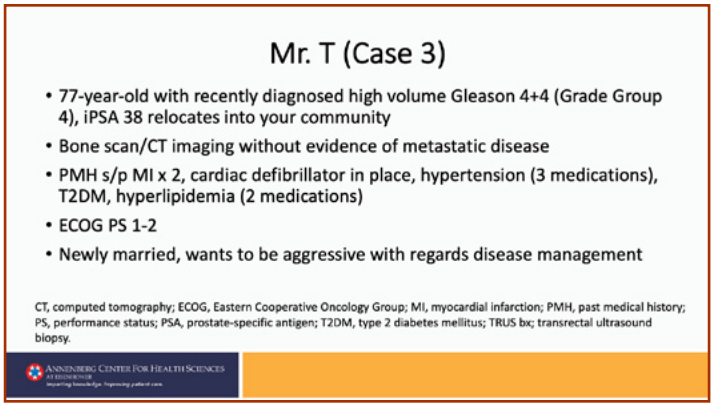
### Michael Cookson, MD

Yes, I think genetics in this guy's family history and we really just kind of contained it to prostate. All of us have become aware of this sort of basket of genes that are connected. And so breast cancer, colon cancer, ovarian, lung, those are all important components too. But just based on his family history of prostate, I think he would qualify for germline testing and we would offer it. Again, it's not going to really change today how we would manage him since those agents are really approved in the more advanced, castration-resistant setting. But I think over the next 5 years we're going to see some differences there too. So, yes to germline testing. Yes, I think it would be reasonable to offer him PSMA PET or an Axumin. Again, PSMA is going to probably detect at a lower level than an Axumin scan, but a lot of people don't have that available to them yet. And it's reasonable. We are seeing things like lymph nodes up by the kidney and areas that we didn't really recognize before. So, it's worth it to get it if you can. Certainly, conventional imaging would not be of any real benefit with such low PSA numbers. I think both of those things are very reasonable to introduce in this particular case.

## PATIENT PREFERENCES: PRESERVING WELLNESS AND OPTIMIZING TREATMENT

### Robert Dreicer, MD

We are going to move on to our last case and try to bring some of the issues of toxicity into focus and how we think about management. This is actually a patient of mine. He's a 77-year-old gentleman who recently presented to me with high-volume, grade group 4 disease. This was a TRUS biopsy done in the northern reaches of our country, with an initial PSA to his primary care doc of 38. He moves into town and says, I need help. So, a bone scan and a CT scan is done. There's no evidence of metastatic disease. He is avascular path, status post MI x 2. He's got a cardiac defib in place. He's on 3 drugs for his hypertension. He's a type 2 diabetic, he's on, I think, 2 drugs for his type 2 diabetes. And he's on 2 drugs for his elevated lipids. So, again, he's a man who screams I've got cardiovascular disease.




His ECOG performance status is sort of like a 1.8-ish. He's a little bit on the sedentary side and part of that is because he's a little overweight and I think that his cardiac disease has impacted on his overall status. Now, good for him, complicating for us, is he's newly married. He wants to be around. He's got stuff to do. He now shows up in your office because he is looking for a really smart doctor.

## Michael Cookson, MD

You did conventional imaging. Now you've got a PSMA. Historically, Axumins were really approved for those patients who recurred after primary failed therapy. The PSMA scans are available for patients for staging. So, you might want to add that to the staging mix because it could impact on the duration of androgen deprivation therapy. I think he's a little over the age, and certainly over the profile, for the average surgical patient, so I'm going to lean him more towards IMR radiation therapy and I'm going to combine that with ADT. The duration, again, somewhere in that 18- to 24-month range unless we were able to discover metastatic disease. But I think he might be a good patient to take the best of the studies you presented. Put him under the care of a cardiologist, so that's your PRONOUNCE. Maybe we can reduce the risk of a cardiac death if you we can cure him of his cancer or certainly delay progression of his disease for years. And then why not introduce relugolix, for example, where we know there's less incidence of, at least in a one-year period, a major cardiac event using that form of therapy. So, we may have 2 reasonable reasons to suggest to him an antagonist may be better and if all things can line up, radiation plus that might be the way to go.

## Robert Dreicer, MD

In fact, this gentleman presented about 2 months after relugolix was FDA-approved. PSMA PET was not yet available, although I think I would agree this patient, by definition, would get this today because of concern based on his PSA and his grade group that there's a lot more disease than might meet the eye. But he was advised that radiation therapy would be a standard of care and he was, in fact, started on relugolix based on the HERO data. He has not 1, but 2 cardiologists. He has an EP doctor as well as sort of a generic cardiologist to try to manage his disease. And so far, he's done well.

But I think this kind of patient is a little bit, obviously, perhaps more the atypical patient in terms of the degree or the confluence of both the really bad disease parameters as well as his cardiovascular risk. But I think the other issue, and again we touched on it but really didn't emphasize it very much, if a patient comes to us and either doesn't have a primary care doc or the last time he saw her or him was 3 years ago, we don't really know what most of these patients' cardiovascular risk is. So, let me ask you, Dr. Cookson, well let me first acknowledge my deficit in practice and then I'll ask about yours. While I clearly work hard to get folks into primary care and get them hooked up with primary care docs so that I don't have to be sort of the driver, I do not routinely, for every patient that I start on ADT—irrespective of where they are in their disease course—recommend cardiology assessment. We, like I'm sure your academic center does, have oncocardiology and our colleagues are willing to see these patients, although our GU group would overwhelm them if we sent every patient that we're starting on ADT. What's your practice? What do you think about that?

## Michael Cookson, MD

I am using some tools because I am not the sharpest in the tool shed, so I like the NCCN ABCDE framework. I think that helps me. I simplify it a little bit, but you know, we've gotten a lot better at just basic bone health and that was really through education and awareness. So, using PRAX tools, getting those baseline DEXAs which are not very expensive, even if they're not covered. And that can kind of set the tone. Looking at their [guidelines], we order lipid panel, hemoglobin A1C, along with their baseline labs, then I guess I sort of triage that. When I see things that are looking bad, if it's an unknown, I'll send it to their primary care. We too have cardio-oncology and if we see some real red flags, then we're going to make that referral too. So, we're selective about what we do, but all of our patients with newly presenting metastatic disease are going to get that panel and then that panel is going to help decide what really is their risk and where we go from there. At the same time, we're looking at their exercise. You mentioned it. You would think that would be kind of a basic thing, but it's not and so we're trying to encourage them, whether [it's] nutrition, I probably under-utilize nutritionists, but I'm trying to do better with that. I don't know how much of a difference it makes, but you try to point them in the right direction. But we do realize that these non-cancer deaths, there's a high rate of cardiac disease in these patients, even not as extreme as the one you presented, and so I think we're doing a better job of paying attention to it, but at the end of the day, we want to extend the length of their life, the quality of their life and pay attention to the whole person, not just the PSA or not just our cancer control. I think we're getting better at it. These types of conversations and the angle for cardiac, the metabolic syndrome, the awareness of bone health, I think it's all helping us to manage them better. Throw in the genetics, we're saving lives of their daughters now, you know. We're getting a BRCA-2 mutation, some of my patients are telling me, oh yeah, my daughter's off having her prophylactic mastectomy. We help them with that because we got that ball rolling. So, there's so many ways that I think we're doing better and can do better in the future. I'm all about sharing secrets, tips and tricks, anything that we have that are tools that are easily available to try and improve them.

This case introduces the opportunity to think more about the cardiac status and considering the data from PRONOUNCE where patients did better regardless of their therapy when they were under the care of a cardiologist, this gentleman sounds like he has that, so that's great. And then taking the results of the HERO study, where we saw a significant reduction in major cardiac events in that first year of therapy using the antagonist, I think using relugolix may be an option for this patient. You know historically, and prior to the release of the oral antagonist, really all we had was the injectables and one of the difficulties with degarelix was the fact that it was a monthly injection and that really was a little burdensome for patients in terms of their time in coming into the clinic. In addition to that, there's also some histamine reaction, site reaction, at the injection that was also a dissatisfier. So, the opportunity to provide an oral agent avoids that burdensome monthly visit as well as the possibility that we can avoid that injection-site reaction that was traditionally found with the injectable antagonist. I think there's some options here and while it's an oral medication, we have to really make sure that they're maintaining their suppression. So that's going to be through periodic testosterone PSA monitoring. But, in the study which I participated in, and you probably did too Rob, the HERO study, compliance was quite good with the use of the oral medication.

### Robert Dreicer, MD

In addition to the points that Dr. Cookson made, when we communicate with patients about management, much of what we're talking about is obviously somewhat out of their control. Bad disease, the evidence is complicated so I'm not going to ask patients necessarily for their choice about intensification in the context where that needs to be done, frankly, because it places an unfair burden upon them. However, in those patients where management, such as this case where there is some suggestion that an approach like the use of an oral antagonist may decrease cardiovascular events, I think the conversation about the role of an agent that is injectable with depo formulations—be it an agonist or an antagonist, vs an oral drug—should be discussed. The oral drug is attractive in some ways, although for some men, especially like this man who's on multiple medications, an additional oral medication may not be really exciting. Alternatively, there are men who may provide or may have interest in using this agent. They may have done some reading and say that this seems to be an attractive strategy. The compliance issue, again, that Dr. Cookson mentioned, which was excellent in the clinical trial, you get into the real world and we do need to sort of monitor this more carefully. Many men figure out pretty quickly, based on the data, you stop the oral agent and in a relatively short period of time your testosterone has recovered. So, compliance is really important, but I think that engaging in conversation in those areas where there is perhaps patient preference certainly makes sense to me.

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