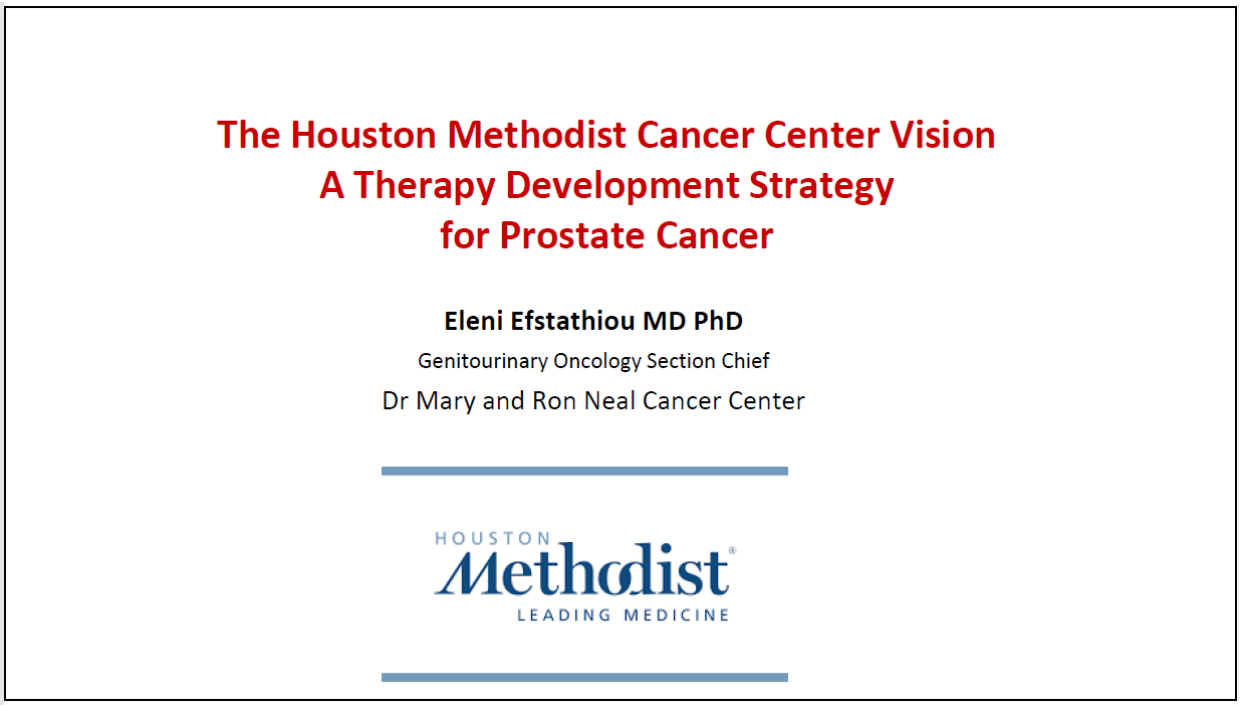
Dr. E on *therapy development* and the patient's voice

Transcript of Dr. Eleni Efstathiou's talk to the AnCan group for High-Risk/Advanced/Recurrent prostate cancer on Dec. 19, 2022. Edited for clarity, omitting Q&A on other topics.

She invited us to share her slides and continue the dialogue.



I'm trying to put together a GU research program geared towards prostate cancer that will allow us to – of course – serve science, as we all want to, but mainly put at the center the patient and his needs while trying to offer cutting-edge options for research.

This is where your views and your thoughts become extremely important.

The view of life, where I was before, was serving science, but not always listening to you guys to make it an improved experience and an outcome that's tangible for you – not something you have to wait for years and years until it reaches you.

You always hear us speak in research about *drug* development; what we're after in this collaboration is *therapy* development – a bigger view of life, the strategy we need in prostate cancer to get to our goal.

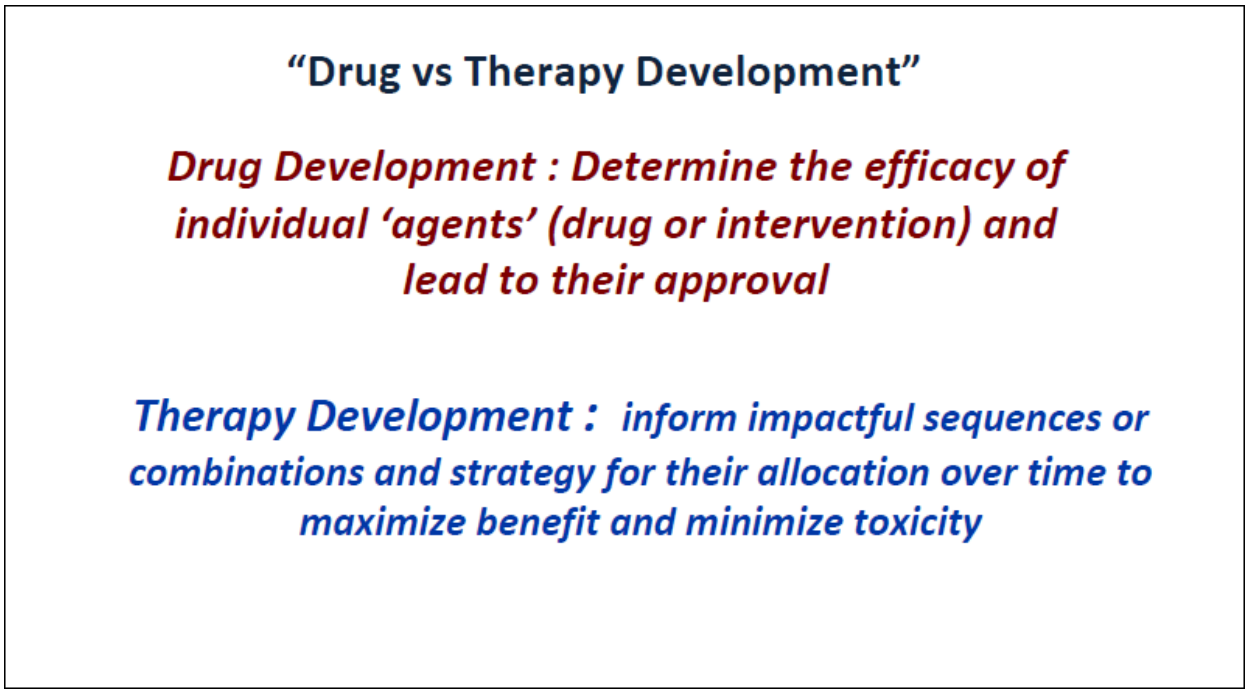
This is the vision of how we would develop this strategy, and this is something we've discussed with our urology team, our radiation oncology team, and the leadership, including Marc Boom, who's our CEO.

The next slide includes my disclosures.

During the coming GU ASCO I'm going to be presenting some updated information from big Phase 3 trial settings that have to do with the use of PARP inhibitors.

This is going to be a very big meeting in GU ASCO, where three trials are going to be presented with updates, and I promise you one of them is going to be extremely positive – kind of changing the way we think of things. We'll have to revisit, probably during 2023, these ideas of how we should combine drugs.

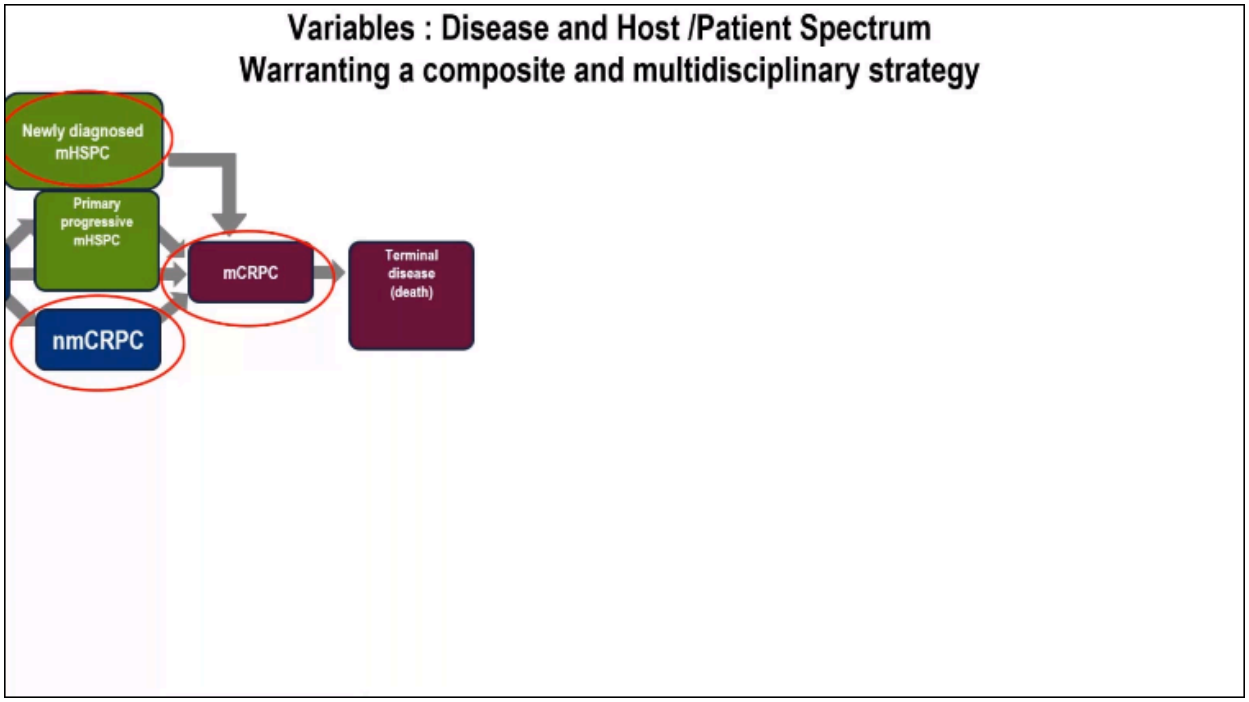
But let's talk a little bit about the difference between drug development and therapy development in medicine.



Drug development essentially is simple – going from point A, which is inception of a drug, to getting the drug FDA approved.

Therapy development is more the **sequence** or **combination,** and the **strategy** for the correct allocation of each treatment at the right time.

It's convoluted and becomes elusive – there's this A, B, C, D, E, F drug approved, but how do we sequence them, and how do we combine them in a way that you maximize the output for yourselves, the individual patient?



We have to consider the variables, and the variables include the disease, and in this slide I've put in a graph of prostate cancer – and I'm talking about the *real* prostate cancer, not low-risk; I'm talking about prostate cancer that is high-risk localized and above.

It may be metastatic hormone-naive de novo, which is what we also like to call synchronous; it could be metastatic based on advanced imaging, which is the PET scans, or it could be based on conventional imaging.

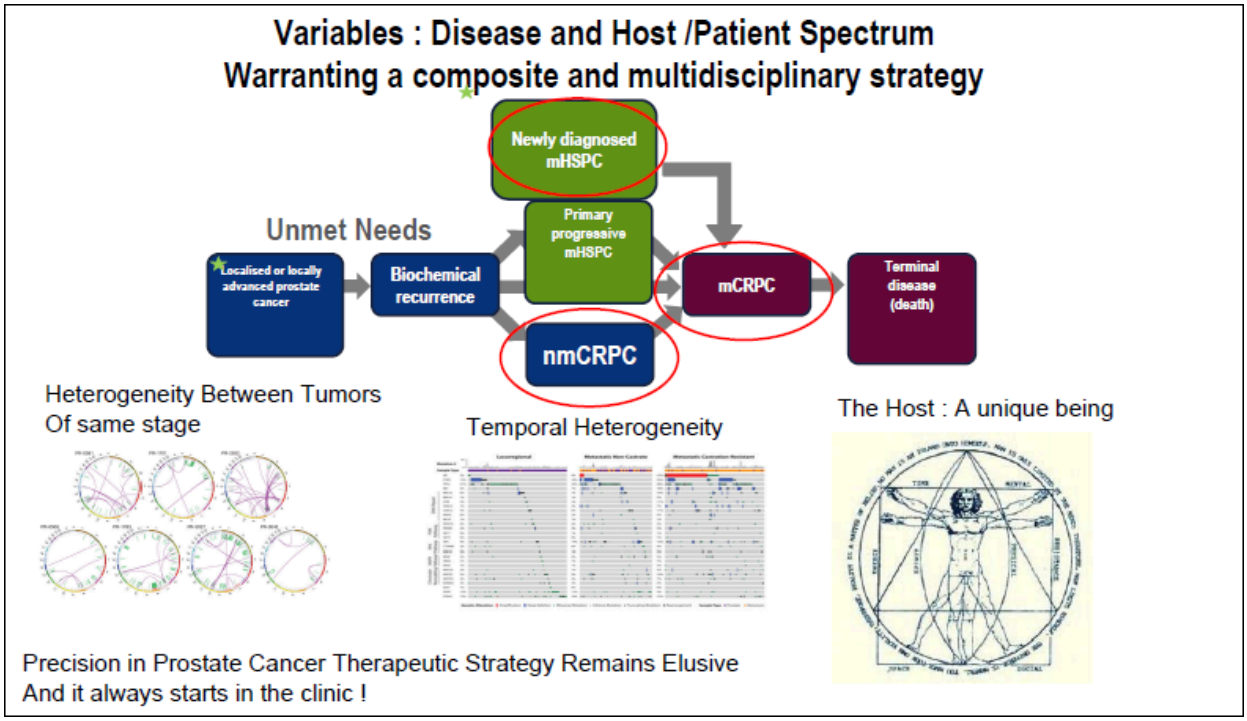
And then you see a cascade of other stages of the disease.

But the biggest unmet need that we have in our world is the one that's on the left – the localized or locally advanced high-risk disease.

And I want you to think of it differently than sometimes even physicians do. High-risk disease is an entity on its own, and it's enriched for a disease that has potential to be dynamically more aggressive. We have not invested enough assets in this disease setting.

Though some people may say metastatic is always worse, I would argue that high-risk localized disease is more enriched for that phenotype that can be imminently threatening. Obviously, "imminently" is a different word when used in the setting of prostate cancer; I mean in several years.

So that's where the big problem comes in – versus a disease that's a Gleason 7, for instance, that was intermediate risk and, years later, might develop into a disease with a few metastases – it's a different disease.



In the bottom here I have put seven genomes of cancers, and if you look at the little circles you see they're very different.

These are from men that have the same Gleason score, the same age, the same clinical characteristics – and the DNA of these tumors could not be more different.

And I want you to think that it's also about the RNA, it's also about other events that lead in the tumor microenvironment to what is the final product, that cancer.

In the middle of that bottom section I also have put a graph from a paper that's about 5 years old now that shows genomic differences in whether the cancer is

hormone-sensitive and just diagnosed, or later when it relapses, or even later when it's been exposed to different drugs.

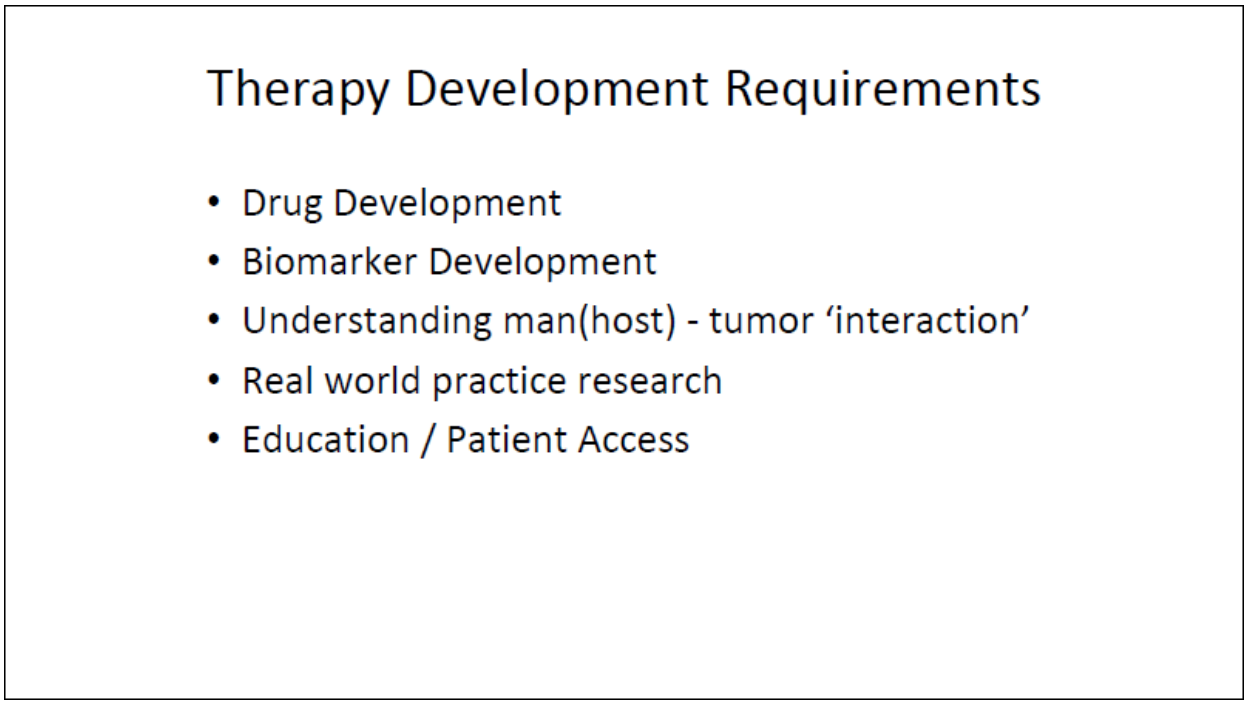
The little dots and colors – you don't have to understand all that – you need to look at how many more dots you see on the far right; that means that the cancers that are more advanced, that have been exposed to more drugs, are enriched for more DNA aberrations, more mutations. This is common sense.

Another problem as the disease progresses is temporal heterogeneity.

So you have heterogeneity within each tumor, you have temporal heterogeneity over time, and finally you have heterogeneity within the host – and that defines your immune response, that defines the interactions within the tumor microenvironment, that defines the alternate growth factors that are going to be potentially employed by the malignancy.

So just by going over this, you understand immediately how convoluted the issue is, especially with prostate cancer.

And we have discussed with a lot of you how much the metabolic syndrome comes into play, and how much it can take over when we have completely depleted the androgens.



We need drugs, but what we really need and we have not achieved is biomarker development.

Your biopsy says Gleason 7, 8, 9, 10 (because Gleason 6 is not a real cancer, right? – it's a cancer wannabe), but it's just somebody looking in a microscope at the morphology – unlike the case for breast cancer, where from that biopsy you already have a very clear understanding of all the biomarkers that may be implicated in deciding the therapeutic plans.

And then of course beyond biomarker development we need to understand that interface between the host and the tumor, and it's not trivial.

This is where you come into play: What is the real-world practice, and how can we translate what is in the research to the real world. And you know who has been very good about it are the British.

They were the ones who developed about 15 years ago this STAMPEDE program, as a lot of you may have heard. With STAMPEDE we have been delivered a lot of data, including data on high-risk disease that is moving the needle to favor better survival, better outcomes – better everything.

The trials they are running are real-world trials – they're nothing more than patients who go to community practices and enter that research, and that is why it has been so successful, and it has been like wildfire for the UK.

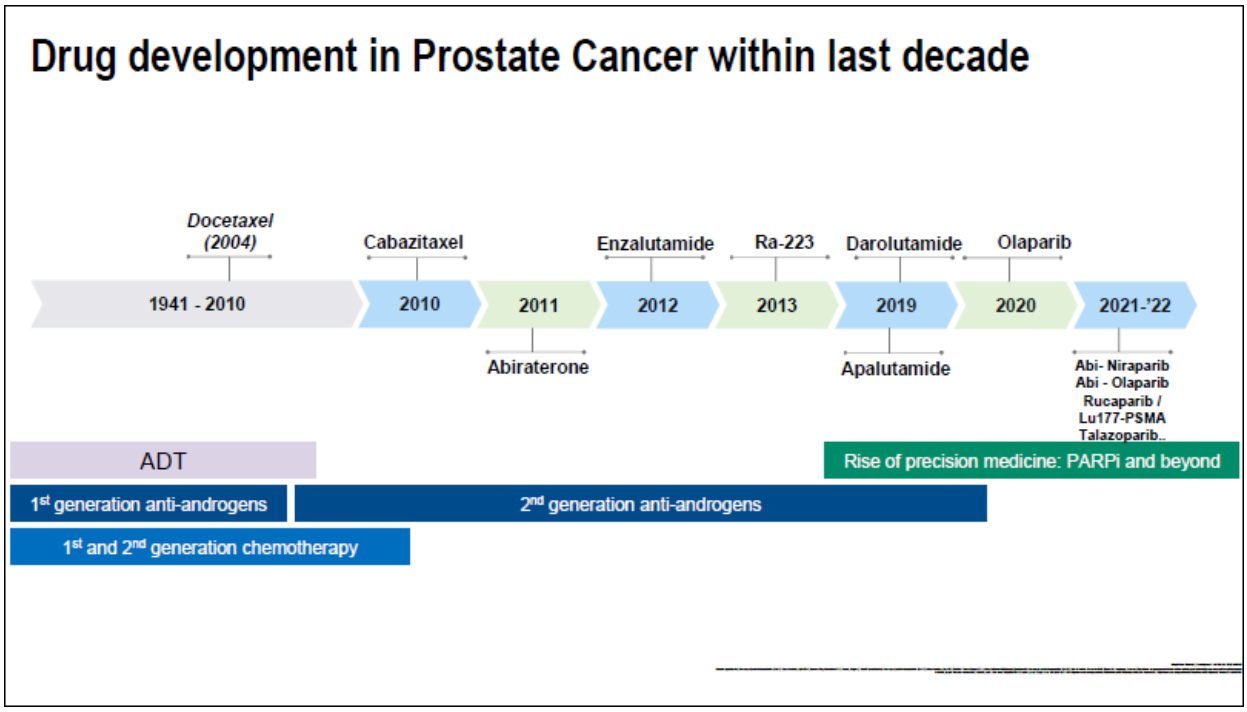
And finally, maybe one of the most important considerations: the fact that there is a drug approved doesn't mean that it is accessible to you, for many, many reasons.

First, there's a lag time from the approval to integration in the clinic.

For instance, we know that since 2017 we've had approval for use of enhanced androgen signaling inhibitors such as abiraterone and enzalutamide, more recently apalutamide and now darolutamide in the hormone setting, but only 50% of patients, 50 in this country, are given the opportunity to be exposed to these drugs as early as they should.

And that is not a criticism to the physicians and their practices, this is a criticism of how the system works, right? There's not enough time, which is the biggest commodity to integrate in the clinic, and they're usually battling insurance co-pays and what have you – you all know how it goes.

So these are the requirements, and each is equally important to get to the product, the deliverable which is getting, in every clinic around the world, the same level of treatment for the patient.



OK – drug development – we've done it, we're there essentially. Remember we started back in the 1940s with surgery and then they moved on to using chemotherapies because that's what was understood as an anti-cancer approach.

But more recently you see this slew of different drugs approved, and you've probably heard that combinations of enhanced androgen signal inhibitors and PARP inhibitors – the FDA just approved the one of abiraterone and plus olaparib – regardless of presence of BRCA mutation. The same happened with Europe, it's even approved in Brazil.

Now, this is what's going to be a big discussion next year.

We also got last year the approval of lutetium and PSMA, with all the limitations of access that a lot of you have experienced, but we are moving in the right direction from a drug perspective.

What remains elusive is how we should prioritize this.

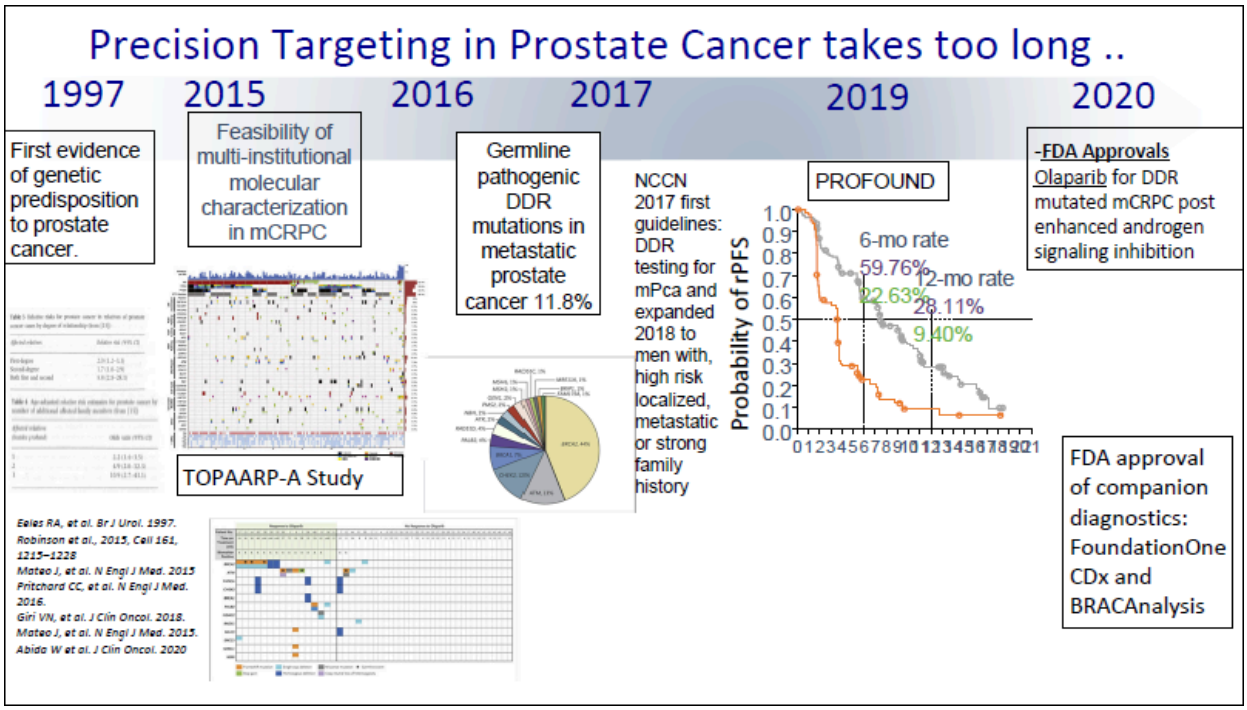
We have understood that enhanced androgen signal inhibition should come early in the disease setting, but we don't know, for instance – and I was just having a meeting over that today – how early we should include PARP inhibitors, or, for instance, lutetium and PSMA.

The trials happening right now are not comparing active agents. You may remember trials using as their control moving from abiraterone to enzalutamide or from enzalutamide to abiraterone. That approach is erratic, it is not correct, it is not even, I daresay, ethical, because we know that for 80 percent of patients who fail on one of the two drugs, or of the four, the other is not going to offer more.

There's only one exception where this can be of great benefit, and we can discuss it later, but that's a very small minority.

So the FDA is doing better this past year and mandating better control arms. This is going to be an opportunity to run trials that are real to life and develop therapy better.

Okay, so we've got the drug development.



So when it was 1997 and I was a kid finishing medical school – you know, in Europe, we go when we're like 17 years old – there were the first data – you will not believe it, this is 25 years – when we had the first data reported to suggest that there is genetic predisposition to prostate cancer, by Rosalind Eeles.

This woman is a medical oncologist and a geneticist in Great Britain; 25 years later she still has not convinced her country to have genetic testing for men with prostate cancer.

This is how hard it has become in some countries with more socialized systems, but even here it took us 20 years to understand there is a genetic predisposition for prostate cancer, especially when you identify mutations such as BRCA and the BRCA families.

From 1997 it took us 18 years to report in a big trial that there is a high incidence of events within the tumor that are BRCA or BRCA-like, even if there is no germline event, and this fast-forwarded to the trials that led to the approval of olaparib. We're probably going to hear soon about talazoparib and niraparib in the field.

This [process] is way too long. This is what we need to create a shortcut to.

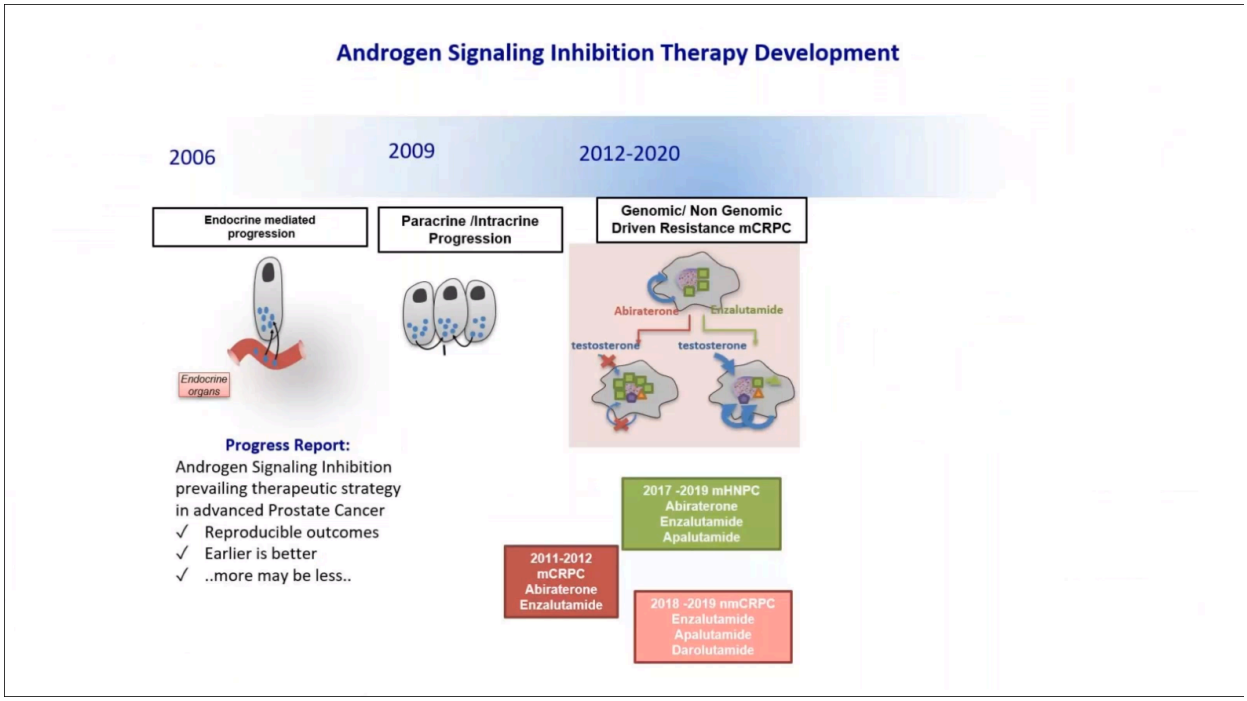
Even to this day, if you take a wild guess, only 5% of men with high risk or metastatic disease are offered germline testing.

And sequencing of the tumor in most cases happens later in the disease rather than early on.

Many physicians say, “I don’t do it early because there’s no access to drug earlier.”

But I would argue that a lot of those findings in early disease can define whether the disease is highly aggressive and may have a bad prognostication, or a disease that might be suitable to treat with enhanced androgen signal inhibition – so a lot of information to get out of it.

But the problem here is cost – that is getting better – time, access, and understanding – understanding even in community practices whose the physicians are not in tune with doing these types of tests.



This is of course where you guys become your best advocates.

Let’s talk a little bit about this whole androgen signal inhibition.

I am guilty as charged – if you go back and look at what I did when I was finishing up my training, I was doing a lot of these initial trials looking at molecular biomarkers for how to best treat with drugs like abiraterone and enzalutamide, apalutamide, and the like.

So what we did back then is, if you were in training in 2006-2007 as I was, and you showed up and said, “I truly believe that there is room to treat this disease past castration,” people would laugh at you. They would say, “No, no, the disease becomes androgen independent.”

So I’ll tell you a little story. When I was presenting my first poster discussion at ASCO – really proud, jumping around like a thyrotoxic bunny, because it was my first presentation and you're top of the world – there was this guy sitting next to me presenting this data that was amazing about an oral drug, abiraterone, that had been sitting on a shelf somewhere in the UK, and a small company had picked it up called Cougar Biotechnology.

I approached the guy and I’m like, “What is this? This looks good! I mean people are getting better, they’re living so

long," and and he's like "Yeah, but I told my chair, 'Then can we do something with that?' He's like, "You're crazy, but okay, if you can get a little drug, you can do a trial."

Fast forward: This was a time when with a small biotech you could do trials. Within a month I was running a trial for people who had failed chemo, failed everything, and we were getting these *amazing* results. And this kind of changed the world on what we were doing with drugs like abiraterone, and research moved away from looking for chemos and chemos and combinations with chemos.

But when we started reporting this data we invariably saw that 30 percent – *30 percent* – of tumors were highly resistant from the beginning, from the get-go, to drugs like abiraterone and enzalutamide.

And I can guarantee you, because we did the trials in the new adjuvant setting, in the high-risk localized setting, that that even happens when you come earlier in the disease.

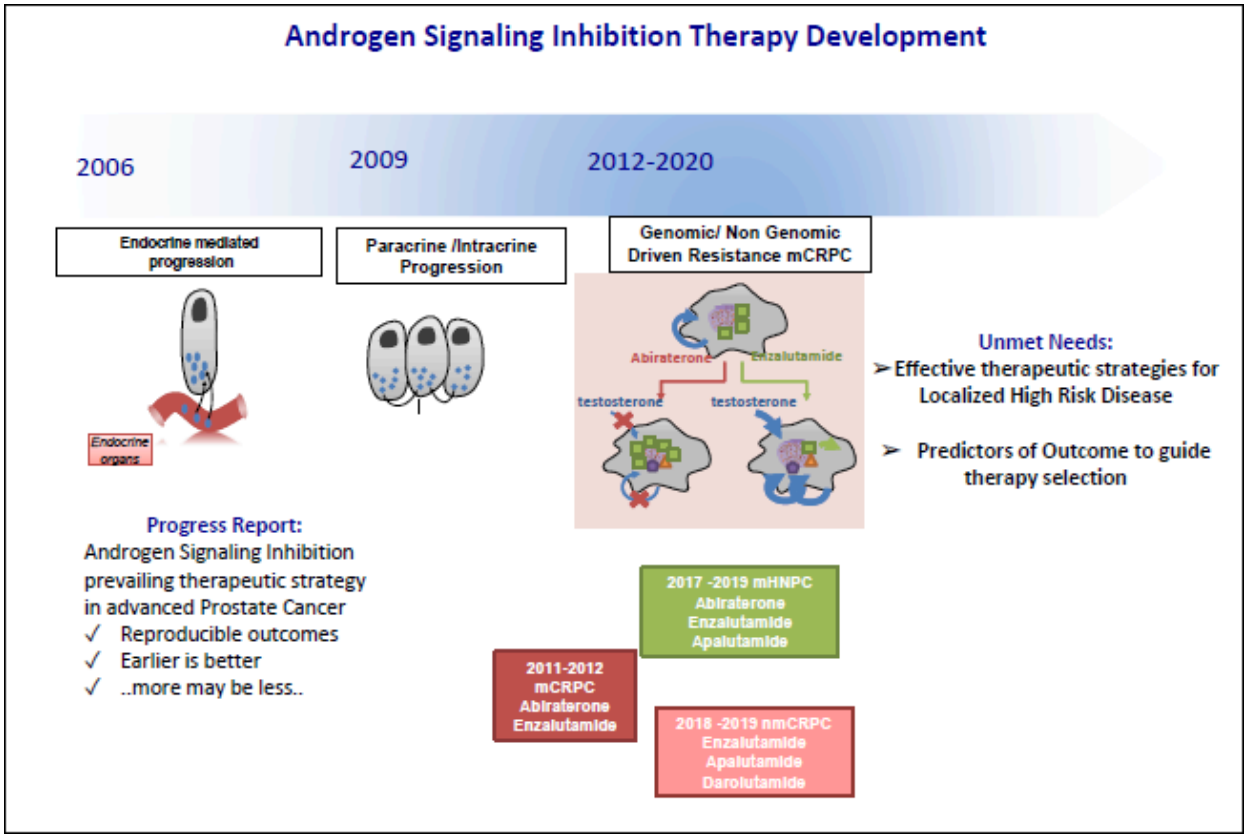
So these first studies really showed us that there can be, even in this early disease setting, resistance to these enhanced androgen signaling inhibitors.

Now you're going to say – "Well, wait a minute, 70% of people are responding, why do we care about 30%?"

Well, that’s what precision is all about. That is what therapy development is all about.

So over the years we managed to get a lot of reproducibility, because when 70% of patients respond, that’s when you get 16 trials that are all positive – 16 trials with abiraterone, enzalutamide, darolutamide, apalutamide, all positive.

But there is that 30% that is highly resistant, and they are enriched for high-risk localized disease. I'm going to come to that. We know that earlier is better, but we also know that using more castration leads to less – right? That’s the downside of it – you can actually curtail your survival by causing other adverse events.

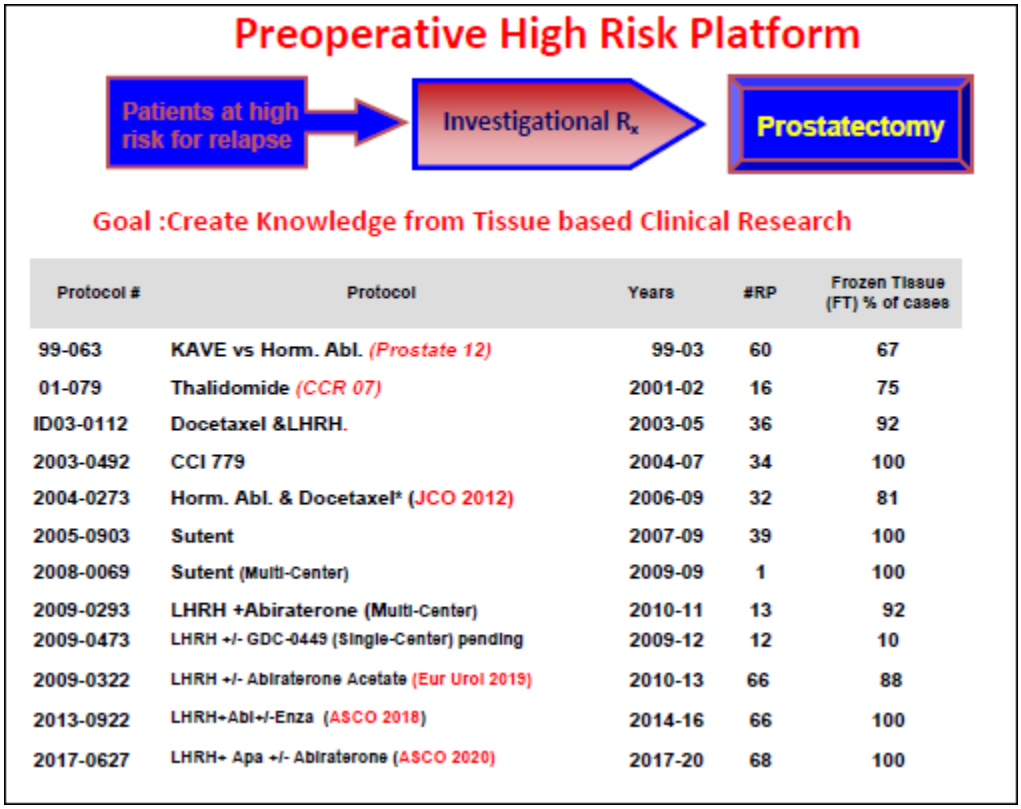


So what haven't we done? We have not reached any therapeutic strategy that is effective for localized high-risk disease, and we have not yet put in stone, written it up, predictors of outcome to guide therapy selection.

That's not because anyone's lazy. It's very hard to come up with validation strategies, because – I will show you – we have explored, we have identified candidates, but unless you validate it, you will not be able to use it in that expanded scale that I was referring to earlier.

It's different when somebody comes to institutions such as the one I was at before, or other big institutions, where we can within our tumor boards discuss and say, "Hey, we've got the STAMPEDE data, we've got these young men, let's discuss new adjuvant strategies, because we can put them within a trial, we can put them within a triple protocol, and the like."

Imagine all the big community practices. We don't even *want* to take such risks unless it's validated.



Protocol #	Protocol	Years	#RP	Frozen Tissue (FT) % of cases
99-063	KAVE vs Horm. Abl. *(Prostate 12)*	99-03	60	67
01-079	Thalidomide *(CCR 07)*	2001-02	16	75
ID03-0112	Docetaxel &LHRH.	2003-05	36	92
2003-0492	CCI 779	2004-07	34	100
2004-0273	Horm. Abl. & Docetaxel* (JCO 2012)	2006-09	32	81
2005-0903	Sutent	2007-09	39	100
2008-0069	Sutent (Multi-Center)	2009-09	1	100
2009-0293	LHRH +Abiraterone (Multi-Center)	2010-11	13	92
2009-0473	LHRH +/- GDC-0449 (Single-Center) pending	2009-12	12	10
2009-0322	LHRH +/- Abiraterone Acetate (Eur Urol 2019)	2010-13	66	88
2013-0922	LHRH+Abi+/-Enza (ASCO 2018)	2014-16	66	100
2017-0627	LHRH+ Apa +/- Abiraterone (ASCO 2020)	2017-20	68	100

These are all the trials that I have conducted, with some that I inherited. Somewhere around 2004 I was doing my training

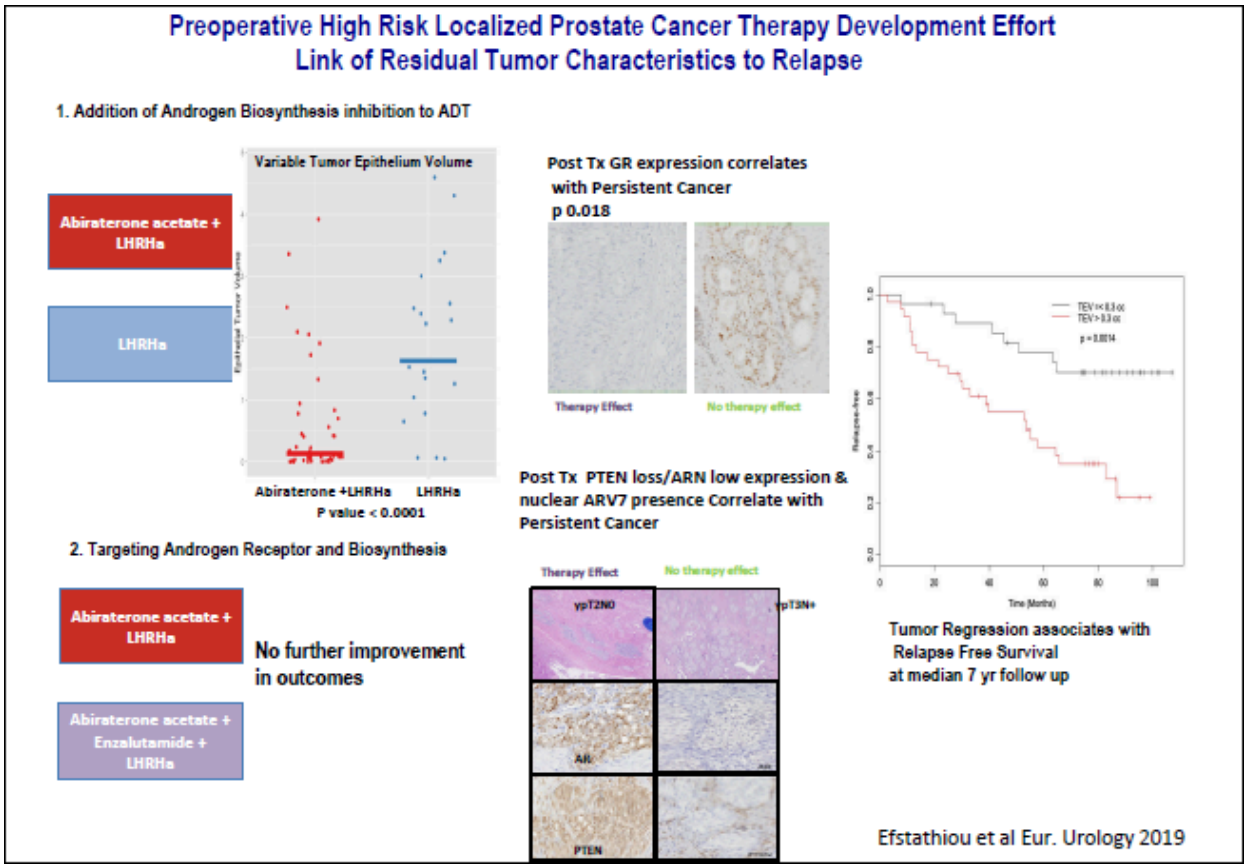
at Anderson [MD Anderson Cancer Center], but before that I inherited and reported because I did the analysis.

And you can see they were using chemotherapy for neoadjuvant.

But if you scroll down, you'll see that all the most recent drugs have to do with abiraterone, with apalutamide, with enzalutamide. We're planning with darolutamide which we consider to be safer.

So let me give you an overview of what this data has shown.

This slide is a lot – I'm gonna try to explain it.



We did a bunch of trials where we were using on one arm just castration, on the other arm castration plus abiraterone or castration plus enzalutamide, and more recently apalutamide and the like.

And we saw that if you give for 3 to 6 months, to a man who has high-risk localized disease, one of the new agents plus, of course, limited castration – that's it! 3 to 6 months no more, not beyond – and you go on to surgery, you will get a prostate out and the lymph nodes, and you will be able to assess how much tumor volume is left inside.

I want you to understand that when you take out a prostate in a man who has high-risk localized disease, you will see that within this prostate there is a percentage of cancer cells and a percentage of normal tissue.

Prostate cancer does not usually create what we call a solid sheet – it has pockets and foci of cancer, and those pockets have different extents of cancer cells.

So with a pathologist we developed a strategy where we're not reporting only Gleason score, only pathology stage, but also the cancer volume that's left behind.

The dots that you see in red and blue here are showing the different volumes of cancer. The red is men who have been exposed to one of the new drugs; the blue is only if you use androgen deprivation, old-school castration, for 3 to 6 months

The tumors in the red seem to be smaller overall, but you can see that some red dots are high up there – these are the resistant tumors, these are the tumors that we need to focus on.

I'm not trying to make a negative comment here, I'm trying to say that these are the cases where you need to better understand why they are resistant.

Because I guarantee you – and I've discussed this with a lot of you – when you treat the cancer initially with androgen deprivation plus a new drug, PSA is going to go to zero, it's going to go to zero, but you take that prostate out and you may see almost no cancer left behind or you may see 80% cancer volume in there – even though there's no PSA – and very happy cancer.

So that's exactly the resistant form of it.

If you go to the Kaplan-Meier plot that I have on the right you will see this shows those men who responded very well to even 3 months of hormones – I kid you not – and got organ-confined disease and very small volume of cancer left behind, they were cancer-free 7 years later.

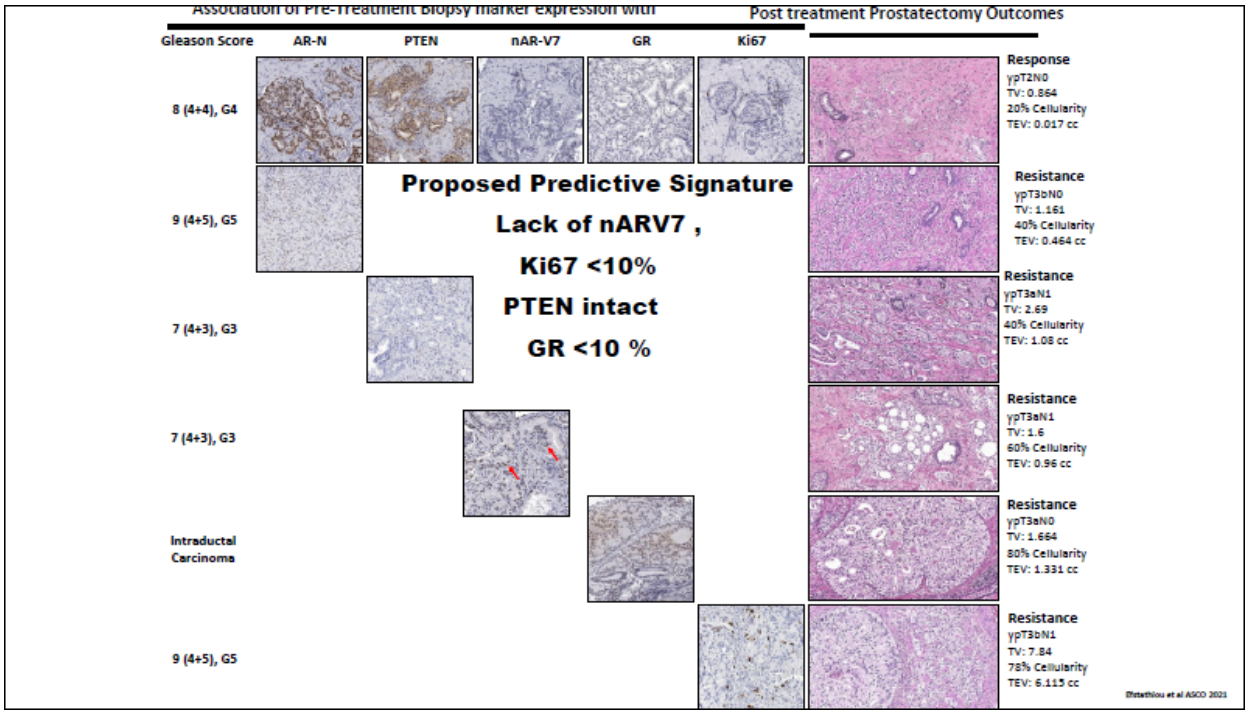
The ones who, even though they had a PSA zero, had quite a bit of resistant prostate cancer, those were the ones that relapsed faster.

There is a Phase 3 trial that I'm participating in that is using this approach with apalutamide. I fear that this trial is setting too high a bar and it's looking for a cancer volume of zero or almost zero to call it a success.

We will know in about a year. It will report whether the treatment with apalutamide can lead to almost undetectable cancer upon prostatectomy.

I would argue you don't need undetectable, you need small volumes, and *that* will be the success.

This is ongoing, and as I said we're also striving to identify what could be drivers of resistance.



This is work we did in the middle of Covid. Patients who had tumors that had a lack of expression such as PTEN, or high expression of a marker called the glucocorticoid receptor, or

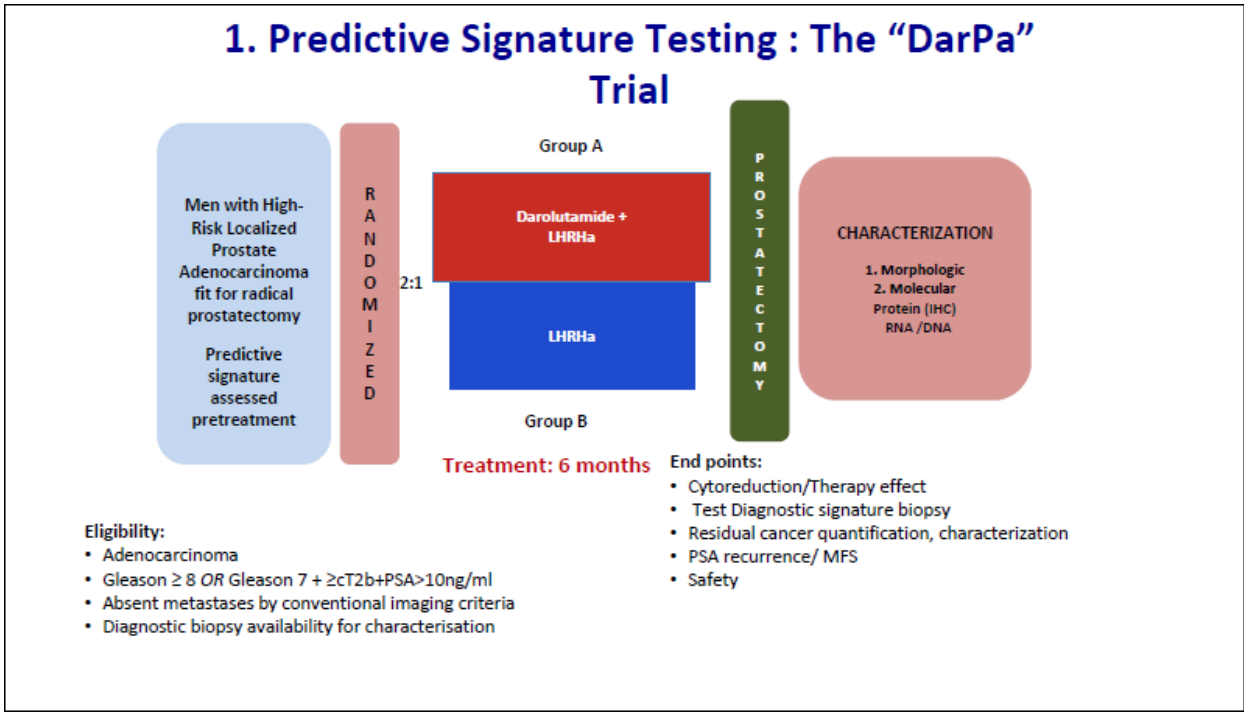
presence of a splice variant of the androgen receptor, these were the ones that belong in this category.

Patients could be Gleason 8 and respond wonderfully well or be Gleason 7 and not respond well. So that is where the genomic players come in.

We're going to test in a prospective trial whether we can identify men who will perform wonderfully with the simple combination for six months and then surgery.

The other option that there is – and it has now been tested with the STAMPEDE data –
is to use hormones for 2 or 3 years and combine it with radiation

Our goal is as I said to limit the exposure to hormones. They think that this strategy combined with surgery – and of course you all know the limitations there – may be more appropriate for men who do not want long-term exposure to castration.



This is going to be with darolutamide. Some of you who've discussed it with me have shared their impressions of the different drugs. I personally have experienced a very good safety profile with darolutamide. it's a little harder to get, but it's not insurmountable, and I think in the coming year it's going to be easier to prescribe.

In my combination with Orgovyx – relugolix – it has been quite well-tolerated, and with the exception of just a couple of people, I have not had to tweak doses at all.

My slide says LHRH but I'm trying to convince the IRB [Institutional Review Board] to allow me to use relugolix. There's a little bit of kickback because of drug interactions. I

like relugolix because it allows for faster testosterone recovery and has shown half the risk for cardiovascular events even when given for a whole year.

I'm going to stop here and get your thoughts.

Some of you are high-risk localized. I wanted your thoughts on a trial that's going to limit exposure to hormones and try to get you the best outcome.

The fact that a man comes in to see us and he may not have these metastases doesn't mean that he does not have a phenotype that may turn aggressive.

This is dynamic. This is the moment in time where it was diagnosed. We assume we're picking up, just by looking at scans, the more aggressive subtype of disease. The scans are only what we call a surrogate of aggressiveness. The real aggressiveness should come through molecular characterization. Gleason 9 and 10 could be enriched for that, but it turns out that Gleason is not enough.

I'm trying to get your quality of life – going under the knife with a 6-month treatment, versus at least 2 years of exposure to hormones, which is the current standard. And I'm talking about ADT plus abi or enza or whichever plus radiation, so that's kind of the question.

[Participants vote.]

From what I could see it was half-half.

I like that, I like that! Because I want to ask next, what would convince folks? Because I think the fear is the surgery, that's the big fear. Everybody wants less hormones, right? That's a given.

Here's the question: how can we make – I bet you've had this discussion – the surgery more failproof, right? The fear is the incontinence, I'm assuming.

[Rick Davis: I think it's both the incontinence but it's also the ED as well.]

The problem with radiation, and I bet you radiation oncologists don't speak about it when you get those 76 Grays, the problem is that 2 to 3 years later there's a high chance you will lose erectile function because of that late effect of radiation.

The other problem is not for the youngsters here, it's for the older folks – unfortunately, after 2 to 3 years of exposure to hormones, there's a 10% to 20% chance that you will not recover your testosterone and then you're stuck.

We have a GU ASCO meeting where it's going to be 5 of us having a debate where I've been asked to talk about supplementation with testosterone. You all know that that's a big, big debate. A lot of physicians are afraid to give testosterone in prostate cancer-history patients.

[John Antonucci: And what are you going to say?]

I don't know yet, I'm thinking about it. We're going to talk about bipolar androgen as well, but I think if it's been a few years I would dare say I would offer with a lot of caution, a lot of monitoring. You can't deny somebody the opportunity to get back their testosterone if you feel comfortable they're cured.

[Rick Davis: We have a few guys who are supplementing testosterone, not many. I don't know if there's anybody on right now, but we do have guys that are supplementing their testosterone who had high-risk recurrent disease, but they've been clear for a while.

I think one of the things with surgery and high-risk disease is to what extent, if you go through the surgery, do you think you're going to need radiation as well. I use the MSKCC nomogram. If you now have better predictive methods from the pathology of the removed prostate, maybe a nomogram

will be developed that will assure people that if they have the surgery they won't need radiation as well – if they have hormone therapy and surgery.]

We agree, and a lot of it, as you know, is very personalized. If you have, let's say, margin positivity, and you've got low-volume disease, and you've got an undetectable PSA with a full-throttle testosterone – not 300s, 400s, normal testosterone – you can give that man the benefit of waiting, as long as you are really monitoring, and you want that healing process of at least 5 to 6 months.

Just being anxious and jumping up and down and saying, let's go for radiation closely after surgery, is not going to cut it if you're going to cause irreparable damage. But having said that, we're all human. When a surgeon sees there's positive margin or lymph node positivity, they take it as a personal failure though it's not, and they get anxious and sometimes pull the trigger a little bit too fast to get things done, and this is what we need to fix.

this is what I was saying earlier education patients rethink it

and this is what I was saying you got to be your best Advocates

you got to be partnering up with that practice that you're in and be patient with them too because they're pretty anxious, I can tell you that, when they see such outcomes you