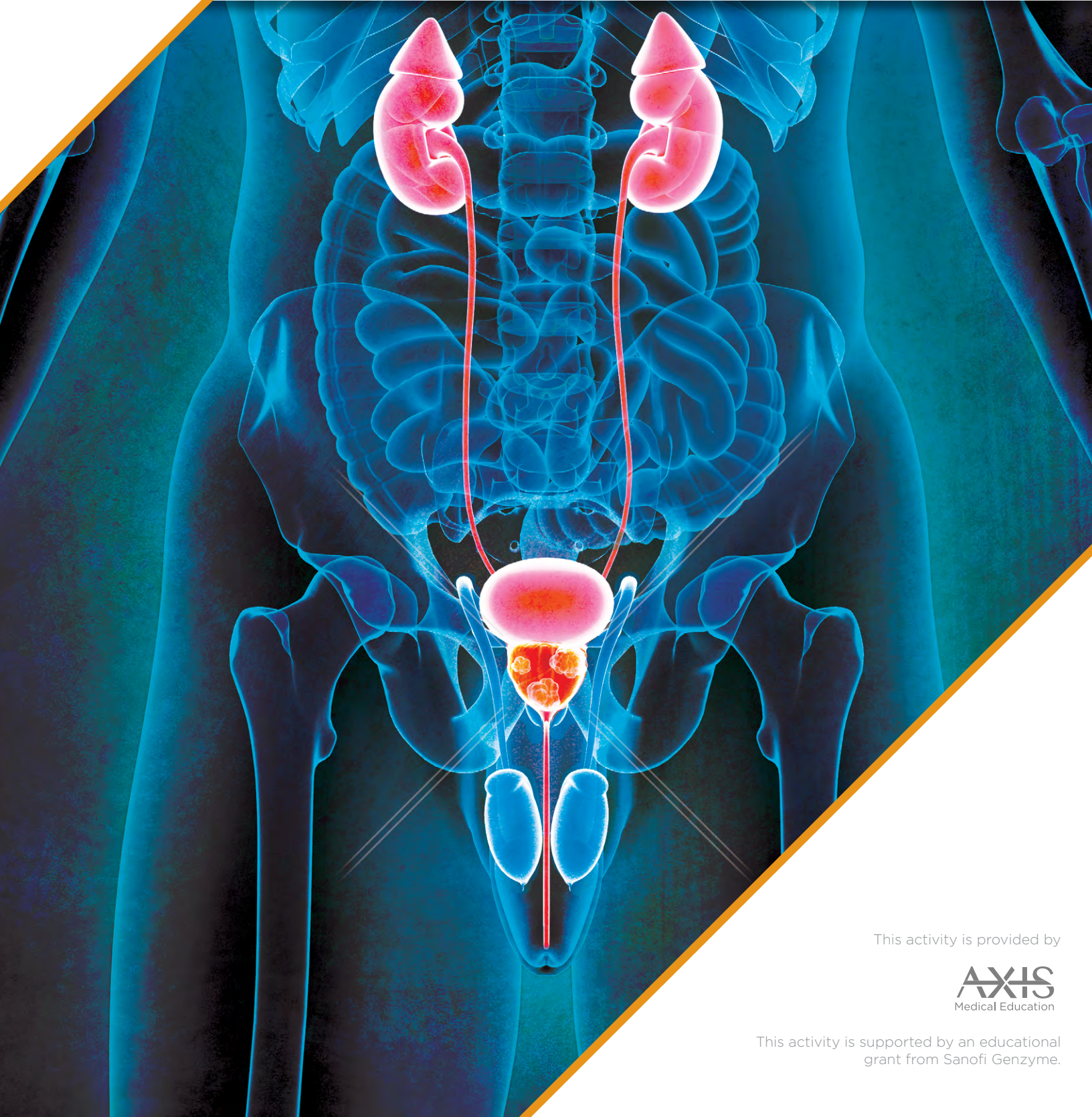


Advancing Interdisciplinary Care in Prostate Cancer:

Clinical Updates for Urology and
Oncology Healthcare Professionals

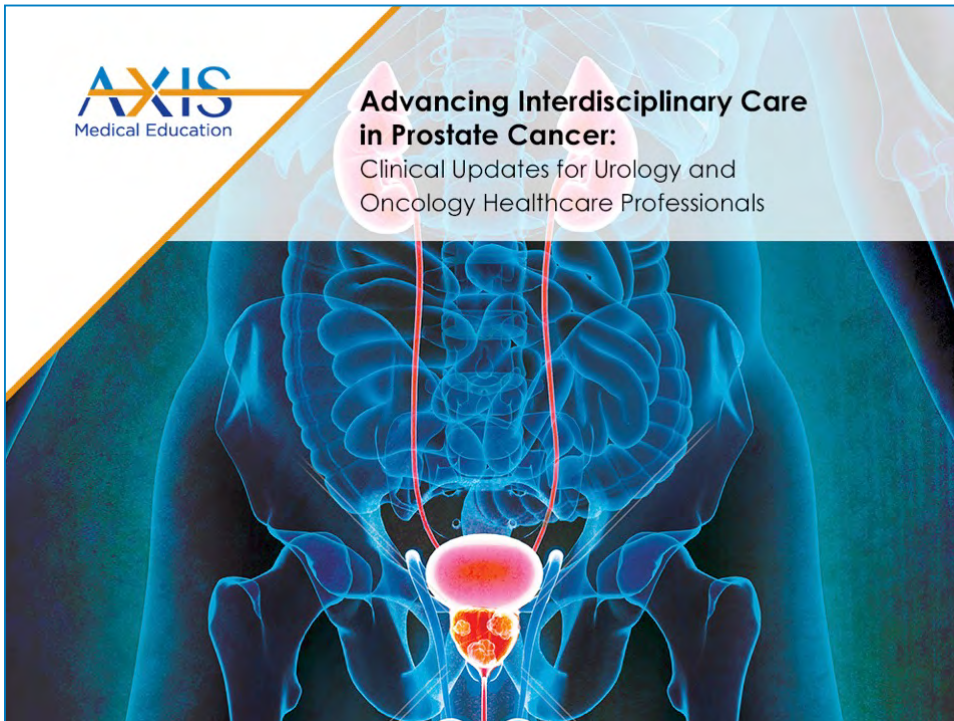
This transcript has been edited for style and clarity and
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Advancing Interdisciplinary Care in Prostate Cancer: Clinical Updates for Urology and Oncology Healthcare Professionals

Oliver Sartor, MD



► Dr. Oliver Sartor:

Hi, I'm Oliver Sartor, and it's my pleasure today to help give you an update on advanced prostate cancer and some of the new concepts that we've been exploring, some of the new data that I think are impactful.

Managing Prostate Cancer

- Current and future management of prostate cancer will likely include the following:
 - Hormonal therapy
 - Targeted therapy
 - Immunotherapy
 - Chemotherapy
 - Surgery
 - Radiation oncology
 - Nuclear medicine
 - Molecular and genetic testing

- And, it's quite interesting—we used to sort of think about prostate cancer in terms of surgery, radiation, hormonal therapy, and chemotherapy. But, we're beginning to introduce new concepts, in particular, the targeted therapies that are being explored in clinical trials, immunotherapy; novel immunotherapy is being explored in clinical trials. We're looking at nuclear medicine in all new ways in terms of both diagnostics, as well as treatment. And we're looking at molecular genetic testing and genetic counseling in a whole new way, as well, so the repertoire of skill sets required to take care of these advanced patients is being expanded.

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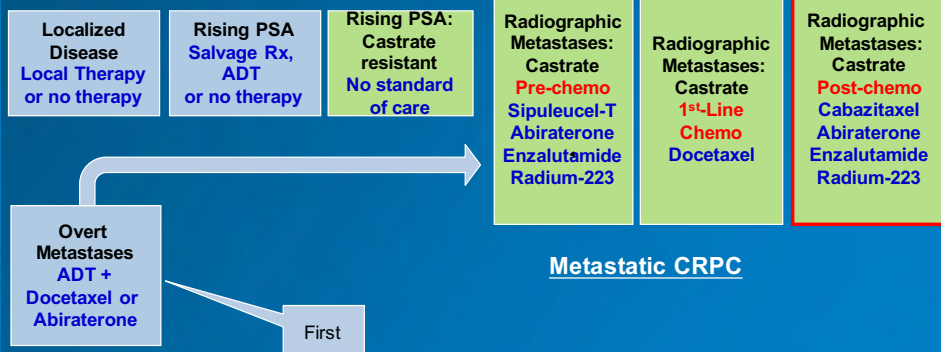
Prostate Cancer Clinical States

Hormone sensitive

Recurrent after initial hormonal therapy

Diagnoses: 200,000

Deaths: 26,000



ADT, androgen deprivation therapy; PSA, prostate-specific antigen.
Courtesy of Oliver Sartor, MD.

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► When we look at the patients with prostate cancer, we can broadly divide them into different disease states. And there's a lot of ways to divide this. I'm going to be starting by talking about metastatic disease.

DNA-Repair Gene Mutations

- 11.8% of men with metastatic prostate cancer

Gene	Mutation (%)
<i>BRCA2</i>	5.8
<i>CHEK2</i>	1.9
<i>ATM</i>	1.6
<i>BRCA1</i>	0.9
<i>RAD51D</i>	0.4
<i>PALB2</i>	0.4

- 4.6% of men with localized prostate cancer

Pritchard et al. *N Engl J Med.* 2016;375:443-453.

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► It's quite interesting that we now have DNA repair gene mutations that are much more commonly found than what was previously anticipated. Almost 12% of men with metastatic prostate cancer will have DNA repair gene mutation, most common of which is *BRCA2*. Other common ones include *CHEK2*, *ATM*, *BRCA1*, *RAD51D*, and *PALB2*. There's definitely a higher incidence of these alterations within men with metastatic disease, as compared to localized disease.

Why Are Germline Mutations Important?

- Poor prognosis and early age of onset for prostate cancer
- Implications for future treatments
 - Today PARP inhibitors, platinum, and PD-1 inhibitors
 - Tomorrow, maybe more?
- Implications for family members may include increasing monitoring at an earlier age and possible prophylactic intervention
- What genetic alterations are important in various ethnic populations?
 - Current data are mainly from European centric populations

PARP, poly (ADP-ribose) polymerase; PD-1, programmed cell death protein 1.

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▶ So, why are these germline mutations important? This is inherited DNA, and there are a couple of things that I'd like to bring out. Number one is these patients have a poor prognosis overall, they have an earlier age of onset, they're more likely to be diagnosed with a metastatic disease. It has implications for future treatments. Today we have PARP inhibitors that can target some of the DNA repair defects, platinum perhaps in PD-1 inhibitors for mismatched repair, and tomorrow there may be much more. There are implications for family members that may need increased monitoring at an earlier age and possibly even prophylactic intervention, particularly for women who have prophylactic mastectomy or prophylactic oophorectomy, which are indicated in a substantial number of women who might have high-risk mutations such as *BRCA1* and *BRCA2*. There are a lot of issues that we don't know. Various ethnic populations are, of course, relatively unstudied. Mainly what we have today in the current datasets are European centric populations.

Prostate Cancer Clinical States

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Localized Disease
Local Therapy
or no therapy

Rising PSA
Salvage Rx,
ADT
or no therapy

Rising PSA:
Castrate
resistant
No standard
of care

Radiographic
Metastases:
Castrate
Pre-chemo
Sipuleucel-T
Abiraterone
Enzalutamide
Radium-223

Radiographic
Metastases:
Castrate
1st-Line
Chemo
Docetaxel

Radiographic
Metastases:
Castrate
Post-chemo
Cabazitaxel
Abiraterone
Enzalutamide
Radium-223

Overt
Metastases
ADT +
Docetaxel or
Abiraterone

Therapy

Metastatic CRPC

ADT, androgen deprivation therapy; PSA, prostate-specific antigen.
Courtesy of Oliver Sartor, MD.

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► So, when we begin to look at these individuals with metastatic disease—understanding that they may be influenced by certain mutations such as DNA repair—what about therapy? And we have some newer data with therapy I'd like to cover with you today.

Consensus, Controversy, and Change in Hormone-Naïve Metastatic Prostate Cancer: 2017

- Consensus: High volume metastatic disease is suitable for ADT + 6 cycles of docetaxel for high-volume, de novo metastatic PC.
- Controversy: Use of ADT + 6 cycles of docetaxel debatable with low-volume metastasis, given lack of data from STAMPEDE and negative data from CHAARTED studies
- Change: STAMPEDE and LATITUDE are game changers, presented at ASCO 2017 and published in *The New England Journal of Medicine*
 - ADT +/- Abiraterone

ADT, androgen deprivation therapy.

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► I titled this next section in terms of consensus and controversy and change. We've known from the CHAARTED studies and the first STAMPEDE reports that high-volume metastatic disease is suitable for ADT and six cycles of docetaxel. And I think we have a lot of consensus on that point. But, we do have controversy in those individuals with low-volume metastatic disease, and that's simply because we have data from CHAARTED that shows no survival benefit. On the other hand, we have data from STAMPEDE that is somewhat agnostic with regard to high or low volume. STAMPEDE guides just say metastasis is appropriate for six cycles of docetaxel, but that is not the case from the CHAARTED studies to date. What's new is

(cont'd on next page)

Consensus, Controversy, and Change in Hormone-Naïve Metastatic Prostate Cancer: 2017

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 - ADT +/- Abiraterone

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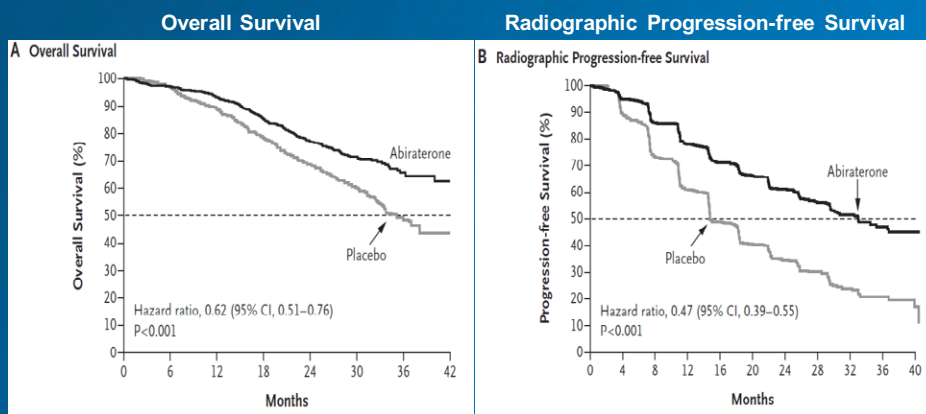
that we have the LATITUDE and the new STAMPEDE, and these were presented at ASCO 2017 with ADT plus or minus abiraterone and simultaneously published in *The New England Journal of Medicine*.

ADT, androgen deprivation therapy.

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ADT + Abiraterone Acetate + Prednisone vs. ADT + Dual Placebos: LATITUDE Primary Endpoints

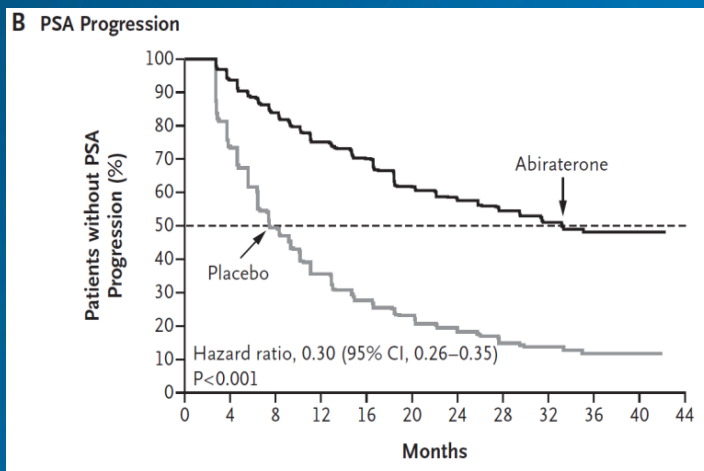
- If we look at the LATITUDE study, and these were typically people who had boney metastatic disease in combination with a high Gleason score that was the most typical entry criteria. If you look at overall survival, there's absolutely no question that the addition of abiraterone can improve the overall survival relative to placebo, and that would be plus ADT, so everybody got ADT. The radiographic progression-free survival was also improved with ADT plus abiraterone, as compared to placebo plus ADT. And the data shown here really emphasize that point.



ADT, androgen-deprivation therapy.
Fizazi et al. *N Engl J Med*. 2017;377:352-360. Used with permission. © 2017 Massachusetts Medical Society.

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LATITUDE PSA Progression



ADT, androgen-deprivation therapy; PSA, prostate-specific antigen.
Fizazi et al. *N Engl J Med.* 2017;377:352-360. Used with permission. © 2017 Massachusetts Medical Society.

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▶ One of the things that was, to me, a little bit surprising was the degree of improvement in the PSA progression. If you look at conventional ADT in this population—admittedly a pretty tough population to treat—the median time to PSA progression was about 8 months in the regular ADT arm plus placebo; but with abiraterone, it was stretched out to the 34-month range. So, this is really a tremendous difference with a hazard ratio of 0.3.

LATITUDE Adverse Events

Graded Adverse Events	ADT + Abiraterone Acetate + Prednisone (n = 597)			ADT + Placebo (n = 602)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Hypertension	219 (37)	121 (20)	0	133 (22)	59 (10)	1 (<1)
Hypokalemia	122 (20)	57 (10)	5 (1)	22 (4)	7 (1)	1 (<1)
ALT increased	98 (16)	31 (5)	2 (<1)	77 (13)	8 (1)	0
Hyperglycemia	75 (13)	26 (4)	1 (<1)	68 (11)	18 (3)	0
AST increased	87 (15)	25 (4)	1 (<1)	68 (11)	9 (1)	0
Bone pain	74 (12)	20 (3)	0	88 (15)	17 (3)	0
Cardiac disorder						
Any	74 (12)	15 (3)	5 (1)	47 (8)	6 (1)	0
Atrial fibrillation	8 (1)	2 (<1)	0	2 (<1)	1 (<1)	0
Anemia	54 (9)	12 (2)	3 (1)	85 (14)	26 (4)	1 (<1)
Back pain	110 (8)	14 (2)	0	123 (20)	19 (3)	0
Fatigue	77 (13)	10 (2)	0	86 (14)	14 (2)	0
Spinal cord compression	14 (2)	12 (2)	0	12 (2)	7 (1)	3 (<1)

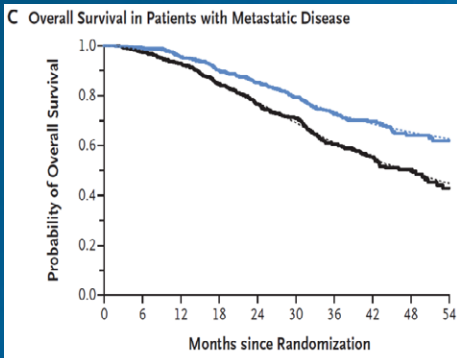
ADT, androgen-deprivation therapy; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
Adapted from Fizazi et al. *N Engl J Med.* 2017;377:352-360.

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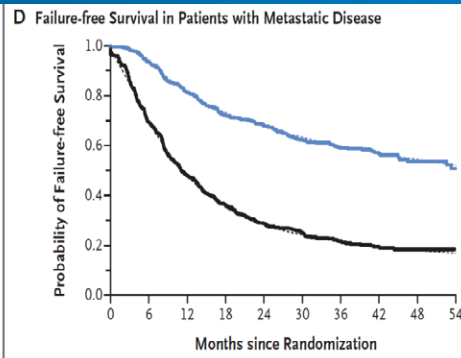
▶ Looking at the adverse events, I think they're the same adverse events that we would have been associating with the abiraterone and prednisone in the more advanced studies such COUGAR 301 and 302. There's some hypertension, hypokalemia, some liver function changes being the predominant issues, and those definitely are things that you need to be monitoring when you're treating these patients. Interestingly, I'll point out that in the LATITUDE studies, they were using only 5 mg of prednisone, not the 5 mg twice daily that has been used in COUGAR 301 and 302.

ADT Alone Versus ADT + Abiraterone Acetate + Prednisone: STAMPEDE Overall and Failure-free Survival in Metastatic Disease

Overall Survival in Patients with Metastatic Disease



Failure-free Survival in Patients with Metastatic Disease



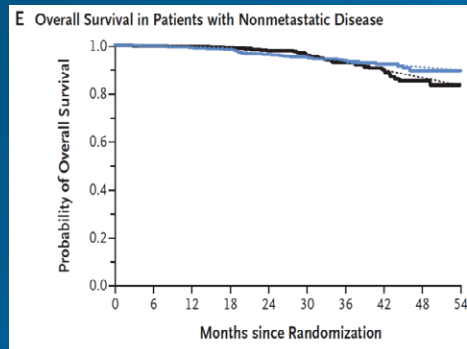
ADT, androgen-deprivation therapy. James et al. *N Engl J Med.* 2017;377:338-351. Used with permission. © 2017 Massachusetts Medical Society.



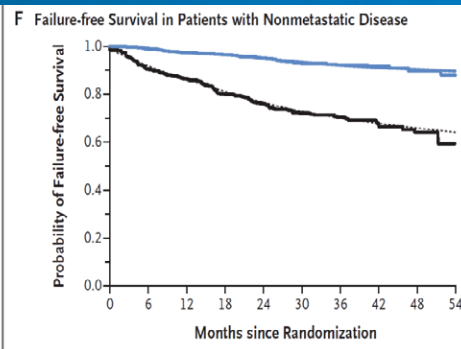
► Now the data from STAMPEDE is also very, very similar showing in the metastatic patients an improvement in overall survival and failure-free survival, which included PSA progression. Clearly, very, very distinct between the ADT plus abiraterone arms versus the ADT alone arms. So, that's again, data that I think you could take to the bank.

ADT Alone Versus ADT + Abiraterone Acetate + Prednisone: STAMPEDE Overall and Failure-free Survival in Nonmetastatic Disease

Overall Survival in Patients with Nonmetastatic Disease



Failure-free Survival in Patients with Nonmetastatic Disease



ADT, androgen-deprivation therapy. James et al. *N Engl J Med.* 2017;377:338-351. Used with permission. © 2017 Massachusetts Medical Society.



► With regard to the overall survival in non-metastatic disease, there's really no question that the overall survival has a favorable trend, but it's too early to really make a call. These are non-statistically significant changes. The failure-free survival, however, does show a strong benefit. And whether or not that'll translate into improvements in survival will require more time and study.

Some Implications of LATITUDE and the “New” STAMPEDE

- Upfront abiraterone/prednisone and ADT changes the biology of the tumor
- The effectiveness of subsequent therapies are altered in undefined ways
 - That said, cross-resistance between abiraterone and enzalutamide are well documented
- The meaning of CRPC is now changing...post-ADT or post-ADT + docetaxel or post-ADT+ abiraterone/prednisone?
- Should we be using ADT + docetaxel or ADT + abiraterone/prednisone or triple therapy?
 - ESMO 2017 data by Sydes et al LBA31_PR indicates OS same for docetaxel and abiraterone

ADT, androgen-deprivation therapy; CRPC, castrate-resistant prostate cancer; OS, overall survival.

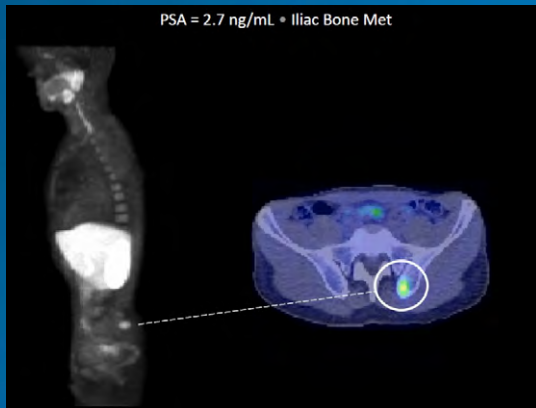


▶ So what are the implications of the LATITUDE and new STAMPEDE? I think that upfront abiraterone and prednisone are going to be appropriate for standard of care, but I think it could change the biology of the tumor; what we call castrate-resistant disease is going to be a new castrate-resistant disease because when you treat with ADT/abiraterone it's going to be different than just ADT alone. There are going to be cross-resistance, there's going to be an issue here. We already know about the strong cross-resistance between abiraterone and enzalutamide in advanced disease, and I think it'll hold here as well.

It really changes what we mean about CRPC. You know, castrate-resistant prostate cancer has been a monolithic variety where it's just post-ADT. But now, we have to define what type of CRPC we're treating. Is it just post-ADT? Is it post-ADT/docetaxel, or post-ADT/abiraterone/prednisone? So there's, again, perhaps a little bit of controversy over what might be appropriate. I'm sure you're aware that docetaxel is now a generic drug; abiraterone is not. It's hard to know from a cost perspective which one is better, but we do have the ESMO 2017 data, which indicates that the overall survival is the same for docetaxel and abiraterone. And, whether or not the six cycles of chemotherapy or the abiraterone until progression ought to be used I think ought to be left to individual decision making. And, in many cases, the cost will drive people into docetaxel.

Treating Limited and/or Oligometastatic Disease

What Happens if You Have Very Few Metastases? Oligometastatic?



PSA, prostate-specific antigen.
Courtesy of Oliver Sartor, MD.

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► Now one of the things that's been quite commonly detected now, as we move into more scanning with the novel nuclear medicine agents—and this could be things like choline, it could be PSMA-PET, it could be fluciclovine-PET (now I'm not covering all of those here just with limitations of time)—but the new nuclear medicine imaging is important. We're defining more and more patients with oligometastatic disease; meaning just a few areas of metastases. How do we treat those patients is really becoming very controversial.

Current Approach to Olig-Mets Following Surgery and/or Radiation to the Prostate

- Observation
- SBRT to mets (delay systemic therapy)
- ADT “old” or “new” ...how long???
 - New ADT might include abiraterone/prednisone
- ADT + SBRT to mets
- ADT + docetaxel
- ADT + docetaxel + SBRT to mets
- Something for everyone...a true “dealer’s choice”
- No one knows the right answer and current trials are limited!

ADT, androgen deprivation therapy; mets, metastases; SBRT, stereotactic body radiation therapy.

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► First of all, I'll start off by saying that nobody really knows the right answers. A lot of times we're using stereotactic body radiotherapy, or SBRT, to the metastases, and that may delay systemic therapy. You can use kind of “old” ADT, which is the testicular suppression alone; or maybe the “new” ADT, which may involve abiraterone, but there are controversies over which one you should use and how long. Should you be using combinations of ADT and SBRT? And some people may even argue about docetaxel. Or maybe you ought to do all the above but, of course, we don't have data for that. What I'll say is that we have something for almost every predilection. We have a true “dealer’s choice,” but we have no comparative trials, so we don't really know the right answer. It depends on the goals, importantly.

Prostate Cancer Clinical States

Hormone sensitive

Recurrent after initial hormonal therapy

Diagnoses: 200,000

Deaths: 26,000

Localized Disease
Local Therapy
or no therapy

Rising PSA
Salvage Rx,
ADT
or no therapy

Rising PSA:
Castrate
resistant
No standard
of care

Radiographic
Metastases:
Castrate
Pre-chemo
Sipuleucel-T
Abiraterone
Enzalutamide
Radium-223

Radiographic
Metastases:
Castrate
1st-Line
Chemo
Docetaxel

Radiographic
Metastases:
Castrate
Post-chemo
Cabazitaxel
Abiraterone
Enzalutamide
Radium-223

Overt
Metastases
ADT +
Docetaxel or
Abiraterone

NEXT

Metastatic CRPC

ADT, androgen deprivation therapy; CRPC, castration-resistant prostate cancer; PSA, prostate-specific antigen.
Courtesy of Oliver Sartor, MD.



► So next I'd like to go into the metastatic CRPC setting, which is a setting that involves a lot of deaths each year in the United States; it's about 26,000 deaths; it's the third leading cause of cancer death in American men with lung cancer and colon cancer being slightly more prevalent. We have a lot of trials that have been ongoing in this space, and I don't mean to cover them.

mCRPC Clinical Trials

TRIAL	FIRST LINE	HR	Survival (mo)*
TAX 327 ¹	Docetaxel/prednisone vs mitoxantrone/prednisone	0.79	19.2 vs 16.3
IMPACT ²	Sipuleucel-T vs placebo	0.78	25.8 vs 21.7
COU-AA-302 ³	Abiraterone/prednisone vs placebo/prednisone	0.81	34.7 vs 30.3
PREVAIL ⁴	Enzalutamide vs placebo	0.77	35.3 vs 31.3
TRIAL	POST-DOCETAXEL	HR	Survival (mo)*
TROPIC ⁵	Cabazitaxel/prednisone vs mitoxantrone/prednisone	0.70	15.1 vs 12.7
COU-AA-301 ⁶	Abiraterone/prednisone vs placebo/prednisone	0.74	15.8 vs 11.2
AFFIRM ⁷	Enzalutamide vs placebo	0.63	18.4 vs 13.6
TRIAL	FIRST LINE and POST-DOCETAXEL	HR	Survival (mo)*
ALSYMPCA ⁸	Radium-223/supportive care vs placebo/BSC	0.70	14.9 vs 11.3

*Final analysis.
BSC, best standard of care; mCRPC, metastatic castration-resistant prostate cancer.

- Berthold et al. *J Clin Oncol*. 2008;26:242-245.
- Kantoff et al. *N Engl J Med*. 2010;363:411-422.
- Ryan et al. *Lancet* 2015;16:152-160.
- Beer et al. *European Urology* 2017;71:151-154; Tombal et al. 2015 European Association of Urology Congress.
- de Bono et al. *Lancet* 2010;376:1147-1154.
- Fizazi et al. *Lancet Oncol*. 2012;13:983-992.
- Scher et al. *N Engl J Med*. 2012;367:1187-1197.
- Parker et al. *N Engl J Med*. 2013;369:213-223.



► But, starting off with TAX 327, SWOG 9916 with the docetaxel data; the IMPACT data with sipuleucel-T; COUGAR 302, 301; PREVAIL; TROPIC; AFFIRM; ALSYMPCA. Each of these trials have been done in a particular space—either the previously chemotherapy naïve, the post-docetaxel space, or a combination like ALSYMPCA. So, there's really a lot of data out there. But, at the same time, there's a lot of things that we don't know.

Sequencing, Combinations, and Utility of Molecular Biomarkers

The Great Unknowns

▶ Among the things we don't know are what are called sequencing and combinations and molecular biomarkers. I'm going to label these as the great unknowns.

NCCN Guidelines: M1 CRPC

First Line*

- Sipuleucel-T**
- Abiraterone + prednisone
- Docetaxel + prednisone
- Enzalutamide
- Alternative chemotherapy (mitoxantrone + prednisone)
- Radium-223 for symptomatic bone metastases
- Clinical trial
- Secondary hormone therapy

Progression After Abiraterone, Enzalutamide*

- Docetaxel + prednisone
- Abiraterone + prednisone
- Enzalutamide
- Radium-223 for symptomatic bone metastases
- Sipuleucel-T**
- Clinical trial
- Other secondary hormone therapy
- Best supportive care

Progression After Docetaxel*

- Enzalutamide
- Abiraterone + prednisone
- Radium-223 for symptomatic bone metastases
- Cabazitaxel + prednisone
- Sipuleucel-T**
- Clinical trial
- Docetaxel rechallenge
- Alternative chemotherapy (mitoxantrone + prednisone)
- Other secondary hormone therapy
- Best supportive care

▶ If you look at the NCCN Guidelines®, we have a variety of choices in terms of first-line therapy. We have a variety of choices after progression on abiraterone or enzalutamide. We have a variety of choices after progression on docetaxel. And you can see within the NCCN Guidelines large listings that, quite frankly, are not particularly helpful for the physicians. There are no comparative trials, there are no real combination trials that have been reported to date. So we're stuck with sort of questions over how should we manage these patients.

*Depending on visceral metastases, yes or no. See full guidelines.

**If asymptomatic or minimally symptomatic, no liver metastases, life expectancy >6 months, ECOG 0-1.

Adapted from NCCN Guidelines Version 2.2017 Prostate Cancer.

Data Comparing Various Sequential Therapies is Limited Outside of the Post-Docetaxel Space

- Randomized trials show clear life-prolonging activity for abiraterone/prednisone, enzalutamide, cabazitaxel, and radium-223 in the post-docetaxel space
- No level 1 evidence for any therapy in the post-abiraterone, post-enzalutamide, post-sipuleucel-T, post-cabazitaxel, or post-radium-223 space

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▶ Now, what I'll say is that when we look at sequential therapies, we do actually have a lot of data about what happens post-docetaxel. And, there we have FDA approvals for abiraterone, enzalutamide, cabazitaxel, and radium. But again, no level 1 evidence for comparing these particular agents to one another. And so that leaves us with a bit of a conundrum.

Considerations

- Many articles can be cited but huge cross-resistance between abiraterone and enzalutamide when used sequentially
- Whichever you use first, will likely last
- Whichever you use second, not likely to last
 - First choice has a much better chance of producing a lasting response than second-line AR inhibitor therapy
- **Back-to-back** oral hormonal agents might not be the best option

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▶ So what are some of the considerations? Number one, there are many articles that can be cited. But I'll say that there's huge cross-resistance between abiraterone and enzalutamide when used sequentially. Whichever you use first will likely last a while. Whichever one you use second is not going to be a treatment that lasts very long. And, you're always going to have a better chance of having a lasting response with your first-line as opposed to your second-line androgen receptor inhibitor therapy. In fact, I'll even go so far to say is that back-to-back hormonal agents might not be the best option, particularly if you're using enzalutamide first, going to abiraterone; the response rate is extremely low. If you go from abiraterone first and enzalutamide second, you do have a little higher response rate, but rarely are those responses durable.

Prospective Second-Line Therapy: Abiraterone Acetate > Docetaxel From COU-AA-302

Maximum PSA decline

- o 40% of patients with a PSA decline of 50% or more

PSA, prostate-specific antigen.
de Bono et al. *Eur Urol*. 2017;71:656-664.

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- ▶ So what about chemotherapy here? And I'll quote data from the COUGAR 302 trial where they looked at docetaxel post-abiraterone, about 40% of the patients had a PSA decline of 50% or more.

Third-Line Cabazitaxel Therapy: Docetaxel > Abiraterone > Cabazitaxel

- o $\geq 50\%$ PSA decline: 28/79 patients (35.0%) med OS: 14.3 mo
- o $\geq 50\%$ PSA decline in TROPIC study (39.2%)
- o No correlation between response to cabazitaxel and duration on docetaxel or abiraterone

Cabazitaxel remains active in pts. progressing after docetaxel and novel AR-pathway targeted therapies, arguing against cross-resistance

OS, overall survival, PSA, prostate-specific antigen.
Nakouzi et al. *Eur Urol*. 2015;68:228-235.

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- ▶ If you look at the third-generation cabazitaxel, here there's some interesting data with docetaxel first, then abiraterone, followed by cabazitaxel. And here you end up with a PSA response rate of about 35%, median OS about 14.3 months. And that compares very favorably to the TROPIC study, which was just post-docetaxel, with a PSA decline right at greater than 50% of around 39% of patients. And it would appear that cabazitaxel does seem to retain activity in this third-line setting. And, that is an interesting finding; there may be a little less cross-resistance with cabazitaxel.

FIRSTANA: Cabazitaxel vs. Docetaxel as First-Line Therapy

- Assessed whether cabazitaxel 20 mg/m² (C20) or 25 mg/m² (C25) is superior to docetaxel 75 mg/m² (D75) in terms of OS
- 1,168 patients with chemotherapy-naïve mCRPC randomly assigned 1:1:1 to receive C20, C25, or D75 IV every 3 weeks plus daily prednisone
- Median OS
 - 24.5 months with C20
 - HR for C20 versus D75: 1.01 (95% CI, 0.85 to 1.20; *P* = .997)
 - 25.2 months with C25
 - HR for C25 versus D75: 0.97 (95% CI, 0.82 to 1.16; *P* = .757)
 - 24.3 months with D75
- C20 and C25 did not produce superior OS versus D75 in patients with chemotherapy-naïve mCRPC

IV, intravenously; OS, overall survival; PFS, progression-free survival. Oudard et al, 2017.

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► Now, what about comparing cabazitaxel to docetaxel in the first-line metastatic setting? And, what I'll say is that there is a cabazitaxel trial. And this was very recently published by Stephane Oudard and colleagues in the *Journal of Clinical Oncology* looking at two doses of cabazitaxel versus the conventional dosing of docetaxel. And, it turns out that the median survival was really no different among the various arms. And you can see here on this slide for the FIRSTANA trial that the survival, in terms of median, was 24.5, 25.2, 24.3 for the various arms. And, there really were no differences in survival. There were, however, some differences in the adverse event ratio with having some less neuropathy, a little less alopecia, perhaps less edema associated with cabazitaxel. So, there were some different toxicity profiles.

PROSELICA: Reduced Dose Cabazitaxel in Postdocetaxel Patients

- Assessed noninferiority of cabazitaxel 20 mg/m² vs cabazitaxel 25 mg/m² in postdocetaxel patients with mCRPC
- 1,200 patients randomly assigned (20 mg/m², *n* = 598; 25 mg/m², *n* = 602)
- Estimated median OS:
 - 13.4 months for 20 mg/m²
 - 14.5 months for 25 mg/m²
 - HR: 1.024
 - Upper boundary of HR CI: 1.184 (less than 1.214 noninferiority margin)
- Efficacy of cabazitaxel in postdocetaxel patients with mCRPC confirmed
- Noninferiority end point met: 20 mg/m² maintained ≥50% of OS benefit of 25 mg/m² versus mitoxantrone in TROPIC
- Major safety findings, myelosuppression, infections, and increased toxicity, occurred with greater frequency on 25 mg/m² arm compared to lower dose
- **Sept 2017**: FDA approved lower dose of 20 mg/m² every 3 weeks in combination with prednisone for the treatment of patients with mCRPC previously treated with a docetaxel-containing treatment regimen

OS, overall survival. Eisenberger et al, 2017; FDA News Release, 2017.

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► It was the second trial that I think is important, and this is a practice-changing trial, PROSELICA, showing that a slightly reduced dose of cabazitaxel, 20 mg/m², was noninferior to 25 mg/m². The overall median OS was no different, 13.4 versus 14.5 months in these patients with cabazitaxel after docetaxel. And, it turns out that in my opinion this is a little better tolerated therapy and one that can be used in practice given the noninferiority for OS. There was less myelosuppression, less infections that were occurring at the slightly lower dose. And the FDA has now approved the 20 mg/m² dosage of cabazitaxel.

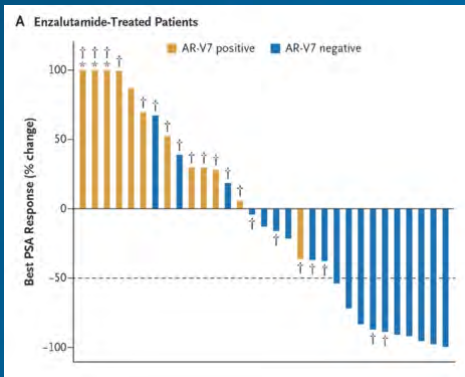
► What about biomarkers and molecular stratification?

Biomarkers: Molecular Stratification

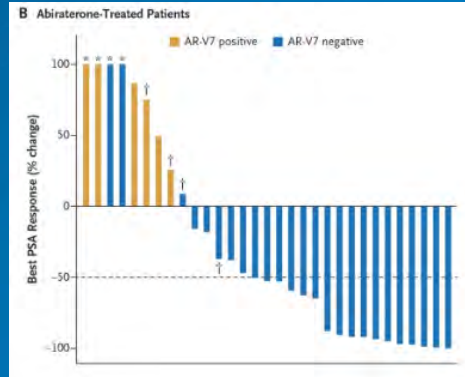
PSA Responses in Abiraterone/Enzalutamide Treated Patients Stratified by AR-V7 RNA Status in CTCs

► What I'll say is that the V7 variant of antigen receptor has gotten a lot of publicity coming from the Hopkins group, *The New England Journal*, back in 2017 being able to classify people perfectly by AR-V7 measurements into resistant or sensitive patients, particularly the resistant patients. But, that has not held up in a perfect manner, but nevertheless it is important. AR-V7 is a splice variant of antigen receptor that translates into a receptor that has a deletion of the ligand binding domain, but it still binds DNA and stimulates transcription. So, it's something that is quite problematic.

Best PSA Responses According to AR-V7 Status
Enzalutamide-Treated Patients



Best PSA Responses According to AR-V7 Status
Abiraterone-Treated Patients

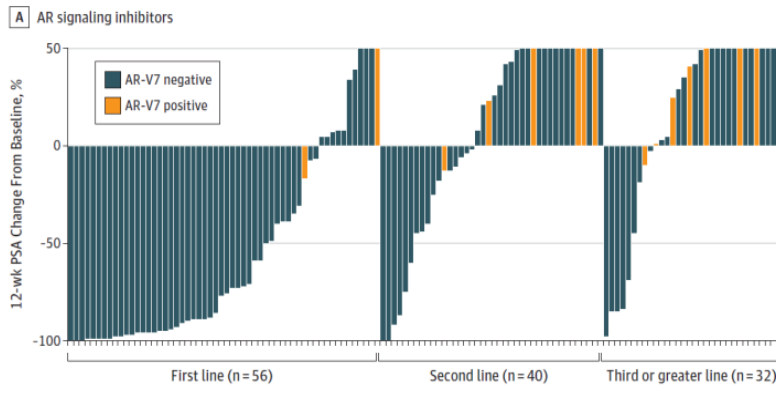


AR-V7, androgen-receptor splice variant 7 messenger RNA; CTC, circulating tumor cells; PSA, prostate-specific antigen. Antonarakis et al. *N Engl J Med.* 2014;371:1028-1038. Used with permission. ©2014 Massachusetts Medical Society.

Nuclear AR-V7 (antibody) and Abiraterone/Enzalutamide Responsiveness

Presence of AR-V7-Positive CTCs and Response to AR Signaling Inhibitors
Percent PSA Change from Baseline at 12 weeks on AR Signaling Inhibitors

Figure 3. Presence of AR-V7-Positive CTCs and Response to AR Signaling Inhibitors



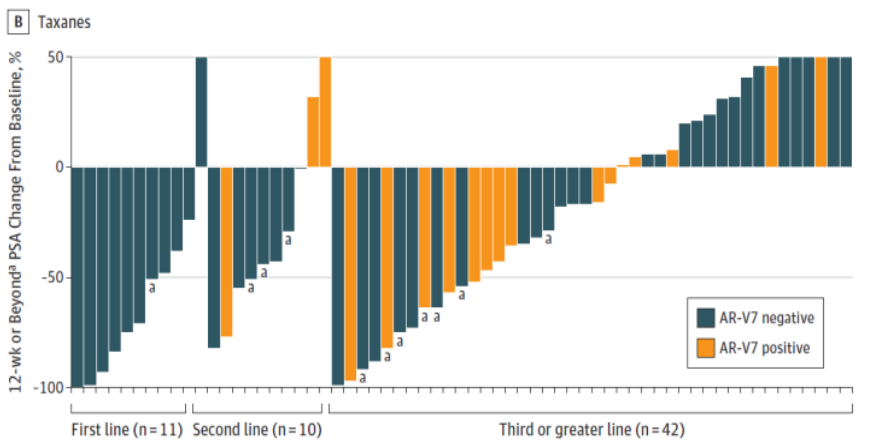
AR, androgen receptor; AR-V7, nuclear androgen-receptor splice variant 7; CTCs, circulating tumor cells; PSA, prostate-specific antigen. Scher et al. *JAMA Oncol*. 2016;1:1441-1449.

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- ▶ And if you look here at the measurement of AR-V7 in CTCs from the Epic Sciences group, what you can see is that there is an accumulation of AR-V7 in resistant patients to second- or third-line therapy with antigen receptor signaling inhibitors such as abiraterone and enzalutamide. But, these are very rare in the first-line. So they typically are associated with a resistant pattern.

Nuclear AR-V7 and Taxane Responsiveness

Presence of AR-V7-Positive CTCs and Response to AR Signaling Inhibitors
Percent PSA Change from Baseline at 12 Weeks (or best decline if after 12 weeks) on Taxanes



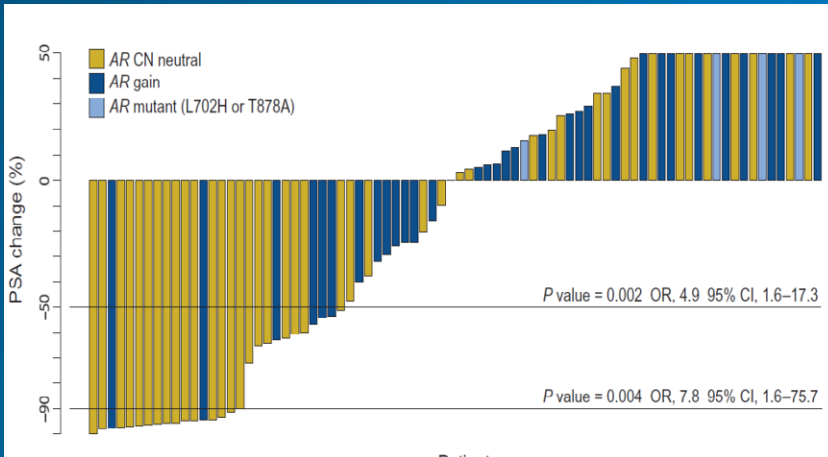
AR, androgen receptor; AR-V7, nuclear androgen-receptor splice variant 7; CTCs, circulating tumor cells; PSA, prostate-specific antigen. Scher et al. *JAMA Oncol*. 2016;1:1441-1449.

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- ▶ Interestingly, however, when we look at taxane responsiveness, taxanes are not sensitive to the AR-V7. So if you have AR-V7 or not, it turns out pretty much to be the same.

AR Copy Number Gain or Selected Mutations in Cell-free Plasma DNA in Abiraterone-Treated Patients

Association of AR Gene Status Before Abiraterone with Treatment Outcome
PSA Decline in Patients with AR Gain



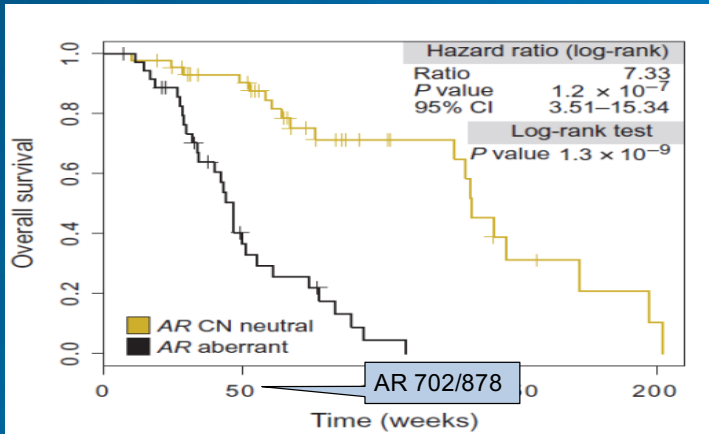
Romanel et al. *Sci Transl Med.* 2015;7:312re10.

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► If we look at another dataset, this is from the Royal Marsden, they're looking at antigen receptor amplification from circulating free DNA or certain antigen receptor mutants, particularly the 702 and the 878 mutant. And what I'll say is that you can see that there's an accumulation of these mutants in patients that are resistant to abiraterone. And, if you are having one of these mutations or copy number gains, you're more likely to be resistant; so that's an important finding, as well, and particularly since the circulating free DNA is starting to be more and more available.

Overall Survival: AR Copy Number Gain or Selected Mutations in Plasma-free DNA Prospectively Tested With Abiraterone

Association of AR Gene Status Before Abiraterone with Treatment Outcome
OS for AR Copy Number Neutral versus AR Aberrant cancer



AR, androgen receptor; CN, copy number; OS, overall survival.
Romanel et al. *Sci Transl Med.* 2015;7:312re10.

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► I'll also say that overall survival of the study from the Royal Marsden indicates that if you do have an androgen receptor aberrancy—in this particular case it's the 702 mutation, the 878 mutation, or the copy number gain—that your survival is much shorter in an abiraterone-treated patient population.

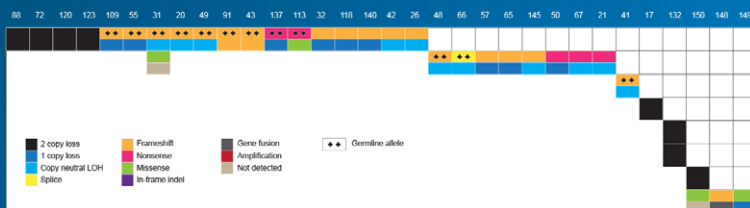
► So how do we get to this kind of new era where we choose the right drug for the right patient at the right time, sort of our precision medicine approach?

Which Drug For Which Patient?

Choosing Which Drugs Might Be Effective, Not Just Predicting Resistance

DNA Repair Defects Can Be Inherited, Somatic, or Both

Aberrations in the DNA Repair Pathway Found in mCRPC



► We need to really have some positive selection parameters, and we have that—we believe—but we need to prove it in more clinical trials. Some DNA repair defects can be inherited, somatic, or both. I already covered some of the inherited mutations. I mentioned the DNA repair pathway, particularly *BRCA2*.

HELC, helical domain; OB, oligonucleotide binding fold; FAT, FRAP-ATM-TRRAP domain; PIK3C, PI3 kinase domain; CC, coiled coil; BRC, Brc repeat.
Adapted from Robinson et al. *Cell* 2015;161:1215-1228.

DNA Repair Defects and Olaparib

- PARP inhibitors in those with DNA repair defects under investigation in multiple clinical trials
- After small trial suggested potential benefit in 14/16 pts

▶ And it turns out that PARP inhibitors seem to be preferentially effective in those with DNA repair defects. A small trial suggested benefit in 14 out of 16 patients, so clearly this needs to be expanded, clearly this needs to be done in a multicenter fashion. But at the same time, the PARP inhibitors do look promising for those with DNA repair defects, particularly the *BRCA1* and *BRCA2* and ATMs.

Mateo et al. *N Engl J Med.* 2015;373:1697-1708. Used with permission. © 2015 Massachusetts Medical Society.

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Biallelic Inactivation of *BRCA2* in Platinum-Sensitive mCRPC

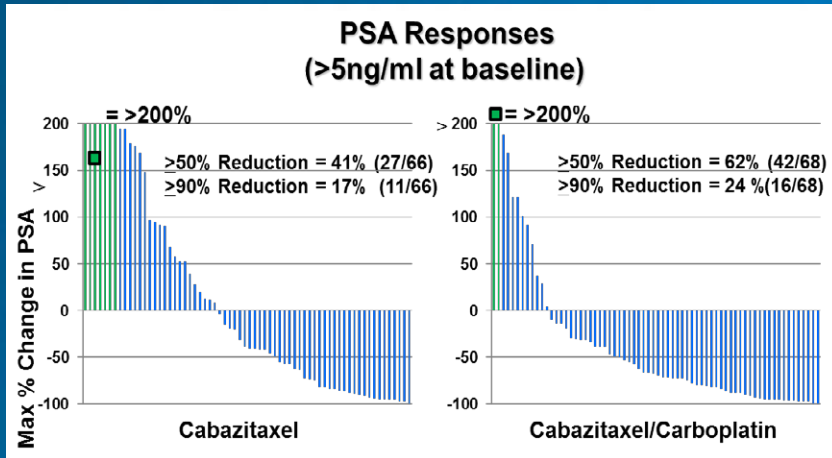
- Selected patients treated with docetaxel/platinum have a very favorable clinical course

▶ Now, what about alternatives? Well we do have platinum sensitivity demonstrated for those with biallelic inactivation of *BRCA2* alterations. And there's been various very small studies showing that the combination of docetaxel and platinum patients would have a favorable clinical course, particularly if they had *BRCA2* alterations.

DOC, docetaxel; ABI, abiraterone; ENZ, enzalutamide; CAR, carboplatin; DOX, doxorubicin; CIS, cisplatin; ETO, etoposide; PAC, paclitaxel; PSA, prostate-specific antigen.
Cheng et al. *Eur Urol.* 2016;69:992-995.

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Cabazitaxel/Carboplatin/G-CSF in “Aggressive Variant” Prostate Cancer



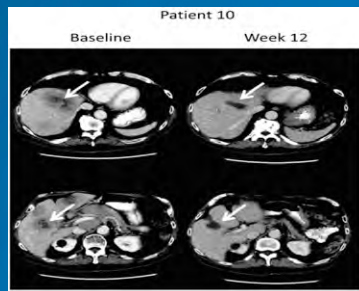
G-CSF, granulocyte colony-stimulating factor; PSA, prostate-specific antigen.
Corn et al. *J Clin Oncol*. 2016;34:5020-5020.

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► There's data with cabazitaxel and carboplatin used with G-CSF, I might add, in “aggressive variants” in prostate cancer. These are liver metastases, high LDH, a variety of sort of criteria went into aggressive variants. It's seven different criteria, not all of which are sort of widely accepted, but these include lytic lesions, low PSA, liver metastases, high LDH. And it looks like that a cabazitaxel/carboplatin regimen may be better than a cabazitaxel regimen alone. We still need more data here, we still need prospective analysis, and so there's going to be more to the story.

Pembrolizumab Trials in CRPC With Enzalutamide: Mismatch Repair or More?

Patient Number	Date of Cycle 1	PSA (ng/mL) baseline to nadir	Measureable Disease at Baseline	Best Radiologic Response	MSI	Prior Treatment of mCRPC
1	April 2015	70.65→0.08	Yes	PR	present	abiraterone, enzalutamide
7	October 2015	46.09→0.02	No	N/A	N/A	abiraterone, enzalutamide
10	January 2016	2502.75→<0.01	Yes	PR	absent	enzalutamide



MSI
Noted

*All responding patients remain on study.
MSI, microsatellite instability; N/A, not applicable (ie, no baseline biopsy done); PR, partial response.
Graff et al. *Oncotarget* 2016;7:52810-52817.

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► What the new immunotherapies? Pembrolizumab is one that is an important new immunotherapy, a PD-1 inhibitor similar to nivolumab. There have been some initial data suggesting that pembrolizumab may be a quite active agent in a subset. We're still struggling to define the subset. Some of these seem to have the MSI high or mismatched repair alteration that we associate with PD-1 sensitivity, but not all patients do. So this is going to have to be more exploratory. It is important to note that the response rate here is probably in the 10% range for meaningful responses; probably not higher than 20%. But again, we need clinical trials to be able to define this further. Because right now, it's an area of lots of exploration.

PTEN Loss as Predictive Biomarker for the Akt Inhibitor Ipatasertib + Abiraterone in mCRPC

N = 253	PTEN Loss			Non-PTEN Loss		
	Ipatasertib-400 + Abiraterone (n = 25)	Ipatasertib-200 + Abiraterone (n=25)	Placebo + Abiraterone (n=21)	Ipatasertib-400 + Abiraterone (n = 32)	Ipatasertib-200 + Abiraterone (n = 27)	Placebo + Abiraterone (n = 35)
rPFS events n (%)	15 (60)	16 (64)	18 (86)	20 (63)	20 (74)	26 (74)
Median, mo	11.5	11.1	4.6	7.5	4.6	5.6
Unstratified HR	0.39	0.46		0.84	1.13	
90% CI	0.22-0.70	0.25-0.83		0.51-1.37	0.69-1.85	
P	.0064	.0285		.5647	.6762	

PTEN, phosphatase and tensin homolog; rPFS, progression-free survival. de Bono et al. *Ann Oncol*. 2016;27: abstract 7180.



► What about PTEN loss? This is one of the more common genetic factors that is associated with advanced prostate cancer. Now this is a somatic mutation or alteration or deletion, not a germline. And it turns out that an Akt inhibitor, ipatasertib, has been found in preliminary trials to have activity. This is now being explored in larger phase 3 trials. And, the *P* value for those with PTEN loss is significant; whereas the *P* value for those without PTEN loss is not. So this is maybe another attempt at precision medicine with Akt inhibitors and the PTEN loss subset.

PSMA Upregulation With Abiraterone/Enzalutamide Treatment

- Enzalutamide and abiraterone demonstrated robust, statistically significant synergy when combined with PSMA ADC

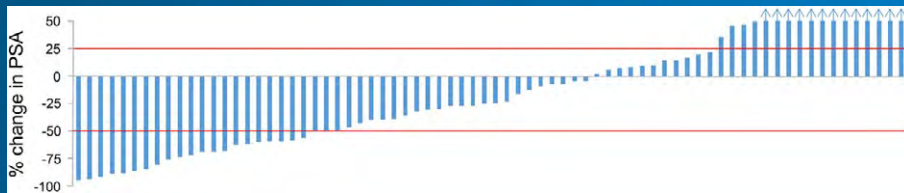
► So, when we look at another thing that is quite interesting, we note that PSMA, which is prostate-specific membrane antigen, gets upregulated. And there is some preclinical data—not clinical data—that demonstrates that you may have synergy when enzalutamide or abiraterone are combined with PSMA-targeted therapy.

AR, androgen receptor; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen. Murgu et al. *Prostate* 2015;75:242-254.



PSMA Lu-177 Clinical Trials: Waterfall Plots for PSA

Waterfall Curve Showing Percentage Change in PSA Values



▶ This needs to be proven in the clinic, but we do have some preliminary activity coming from a variety—particularly German sources, Australian sources—about PSMA Lutetium-177 and the activity for waterfall plots, as shown in the PSA response rate here can be quite impressive.

PSA, prostate-specific antigen.
Rahbar et al. *J Nucl Med.* 2016;57:1334-1338.

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Summary

- CRPC is evolving into a molecularly targeted disease for a significant subset of patients
- The AR remains an important target and much can be gained from treating CRPC with new AR targeting agents, although cross resistance is a major issue
- Taxanes still have an important role to play
- Much progress has been made but there is much more progress to be made

▶ So in summary, what we have is a CRPC that we've been able to treat with hormones and radiopharmaceuticals and chemotherapies and immunotherapies like sipuleucel-T in the past. It's evolving, it's a little more molecularly targeted disease. There's no question that the androgen receptor remains probably the most important target. But we still have a lot of exploration to do. I want to emphasize that taxanes still have a very important role to play; they can work even in the context of prior abiraterone/enzalutamide exposure. And what I'll say is that we have made a great deal of progress over the past several years, but there's so much more progress that we need to make. And that's going to be up to the clinical investigators and

AR, androgen receptor; CRPC, castration-resistant prostate cancer.

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Summary

- CRPC is evolving into a molecularly targeted disease for a significant subset of patients
- The AR remains an important target and much can be gained from treating CRPC with new AR targeting agents, although cross resistance is a major issue
- Taxanes still have an important role to play
- Much progress has been made but there is much more progress to be made

AR, androgen receptor; CRPC, castration-resistant prostate cancer.

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(cont'd from previous page)

individuals who'll be pushing these therapies forward over the next few years.

So thank you very much. It's my pleasure to be able to present this update in advanced prostate cancer today. I'm Oliver Sartor.

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