

# The Role of Therapeutic Layering in Optimizing Treatment for Patients With Castration-resistant Prostate Cancer (Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence II)



E. David Crawford, Daniel P. Petrylak, Neal Shore, Fred Saad, Susan F. Slovin, Nicholas J. Vogelzang, Thomas E. Keane, Phillip J. Koo, Leonard G. Gomella, Joe M. O'Sullivan, Bertrand Tombal, Raoul S. Conception, Paul Sieber, Nelson N. Stone, Steven E. Finkelstein, and Evan Y. Yu, as the Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence (RADAR II) Group

**OBJECTIVE** To offer recommendations on identification of disease progression, treatment management strategies, and suggestions on timing of initiating and discontinuing specific castration-resistant prostate cancer (CRPC) treatments.

**MATERIALS AND METHODS** The Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence II Working Group convened to provide guidance on sequencing, combination, or layering of approved treatments for metastatic CRPC based on available data and clinical experience.

**RESULTS** A consensus was developed to address important questions on management of patients with metastatic CRPC.

**CONCLUSION** In the absence of large-scale clinical trials, the Working Group recommends that patients may best be managed with a layered approach of approved therapies with unique or complementary mechanisms of action. *UROLOGY* 104: 150–159, 2017. © 2017 Elsevier Inc.

Financial Disclosures: E. David Crawford is a consultant for Amgen, Bayer, Denzire, Ferring, Janssen, Pfizer, Sanofi, and Takeda; Daniel P. Petrylak received consultations fees from Bayer, Becton, Denzire, Sanofi, Amgen, Johnson and Johnson, Janssen, Ferring, Millenium, Medivation, Pfizer, Biondi Laboratories, and Tysco pharmaceuticals and reports ownership interest or ownership for Becton and Tysco; Neal Shore is a consultant for Amgen, Bayer, Denzire, Ferring, Janssen, Pfizer, Sanofi, and Takeda; Fred Saad is a consultant for Janssen, Bayer, Sanofi, Merck, Amgen, and Amgen; Susan F. Slovin is a consultant for Bayer, Sanofi, Janssen, and Amgen; Howard Thaler is an advisor and/or paid consultant for Amgen, Amgen, Bayer, Ferring, Janssen, Medivation, and Sanofi-Genzyme; David S. Conception is a consultant for Denzire, Amgen, Medivation, Janssen, Bayer, Sanofi, Takeda, Amgen, and Bayer/Genzyme; Paul Sieber is a member of the Speakers Bureau for Amgen, Bayer, Amgen, Ferring, and Denzire; Nelson N. Stone is a consultant for Bayer and receives salary as member of KIOlogy, Inc.; Steven E. Finkelstein is a speaker for Bayer, Denzire, Amgen, and Medivation; Evan Y. Yu is a consultant for Denzire, Janssen, Bayer, Merck, Genzyme/Richter, Ferring, Biondi/Genzyme, and Amgen/Genzyme.

Reading Supports: This study was supported by a grant support from Decipher, Ferring, Johnson and Johnson, Millenium, Celgene, Denzire, Sanofi, Amgen, BMS, and Amgen.

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# The Role of Therapeutic Layering in Optimizing Treatment for Patients With Castration-Resistant Prostate Cancer

UROLOGY. 2017;104:150–159

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# Agenda

- ▶ Introduction
- ▶ Current mCRPC Treatment Landscape
- ▶ Redefining Disease Progression
- ▶ Recommendations on Initiating and Discontinuing Therapeutic Agents
- ▶ Clinical Data in mCRPC
- ▶ Focus on Therapeutic Layering
- ▶ Conclusion

# Introduction

# Brief Review of Prior RADAR I Recommendations on Imaging

- ▶ RADAR I faculty included prostate cancer experts from the fields of urology, oncology, and nuclear medicine
- ▶ The faculty made recommendations on the appropriate timing and frequency of imaging among different patient types with prostate cancer to help identify metastatic disease earlier
- ▶ Caution against overutilization of imaging
- ▶ Initiate imaging:

When considering starting therapy

Before changing therapy to establish a new baseline

After completing treatment to monitor progression

- ▶ Importance of PSA trends and clinical context
- ▶ Perform subsequent imaging when clinical or consistent and convincing biochemical progression is identified

# Goal of Imaging: Early Identification of Metastatic Disease

## Newly diagnosed patients

Scan high-risk patient and intermediate-risk patient with at least 2 of the following positive criteria:

- Gleason score >7
- PSA level >10 ng/mL
- Palpable disease (cT2/T3)

## Biochemical recurrent patients

First scan when the PSA level is between 5 and 10 ng/mL

Imaging frequency if negative for previous scan: 2nd scan when **PSA=20 ng/mL** and every doubling of PSA level thereafter<sup>a</sup>

## M0 castrate-resistant patients

First scan when PSA level is  $\geq 2$  ng/mL

Imaging frequency if negative for previous scan: 2nd scan when **PSA=5 ng/mL** and every doubling of PSA level thereafter<sup>a</sup>

<sup>a</sup>Based on PSA testing every 3 months.

Crawford ED, Stone NN, Yu EY, et al. *Urology*. 2014;83(3):664-669.

# Despite Improvement in Survival, mCRPC Continues to Pose Clinical Challenges

Survival with CRPC has improved due to new therapies

Improvement in OS from 19 months prior to sipuleucel-T approval in 2010 to 35 months with abiraterone (COU-AA-302) and enzalutamide (PREVAIL)<sup>1,2</sup>

However, mCRPC continues to be a challenge due to disease heterogeneity and resistance

Despite treatment, mCRPC continues to be a terminal disease with development of multiple pathways of resistance

Optimal use of current therapies to achieve maximum clinical benefit is not well established

Clinical research efforts are ongoing in search of evidence regarding optimal sequencing, combination, and layering approaches

OS, overall survival.

1. Beer TM, Armstrong AJ, Rathkopf DE, et al. *N Engl J Med*. 2014;371(5):424-433.

2. Ryan CJ, Smith MR, Fizazi K, et al. *Lancet Oncol*. 2015;16(2):152-160.

# Objectives of the RADAR II Group

## **Goal of RADAR II:**

To provide a consensus on sequencing, combination, and “therapeutic layering”

# Combination Therapy vs Therapeutic Layering

- ▶ Combination therapy, in which 2 or more therapies are initiated simultaneously, has been the backbone of oncology for many years (eg, breast and colorectal cancer)<sup>1-3</sup>
- ▶ “Therapeutic layering,” as defined by the RADAR II Group, is different from combination therapy in that it represents a clinical point where 1 or more agent(s) are added onto an existing therapy
- ▶ In CRPC, all treatment interventions are technically layering of therapy since agents are added to the foundation of ADT

1. Shannon C, Smith I. *Crit Rev Oncol Hematol*. 2003;45(1):77-90.  
2. Maithel SK, D'Angelica MI *Surg Oncol Clin N Am*. 2010;19(1):163-181.  
3. Koupparis A, Gleave ME. *Curr Oncol*. 2010;17(suppl 2): S33-S37.



# Questions Considered by the RADAR II Group

## Disease progression

- How is progression defined? What is the best way to determine progression while a patient is being treated with therapeutic agents with biologically distinct mechanisms of action?

## Initiating and discontinuing therapeutic agents

- How early should treatment be initiated in patients with mCRPC? Which agents should be considered for use early in the metastatic setting?
- When should therapy be changed? Should treatment continue beyond progression? If yes, with which agents?
- When should treatment be started and when should treatment be discontinued for each specific therapeutic agent?
- Should second-generation androgen pathway inhibitors (abiraterone or enzalutamide) be used sequentially?

# Current mCRPC Treatment Landscape

# Approved Agents for mCRPC

- ▶ Since approval of docetaxel in 2004, 5 new agents have been FDA-approved for mCRPC<sup>a</sup>
- ▶ Goal of CRPC treatment:
  - ▶ Prolong life
  - ▶ Preserve QOL
  - ▶ Prevent complications

**Table 1.** Agents approved for the treatment of mCRPC in the US

Therapy	Sipuleucel-T	Docetaxel	Abiraterone Acetate	Enzalutamide	Radium-223
Indication	M1 CRPC: asymptomatic, minimally symptomatic	M1 CRPC	M1 CRPC	M1 CRPC	M1 CRPC: symptomatic with bone metastases and no visceral metastases
Class of therapy	Autologous immunotherapy	Chemotherapy	Hormonal therapy	Hormonal therapy	Targeted alpha therapy
Efficacy parameter					
OS	✓	✓	✓	✓	✓
PFS		✓	✓ (radiographic)	✓ (radiographic)	
Reduced time to first SSE					✓
Steroids required	No	Yes	Yes	No	No
Liver or kidney monitoring or dose adjustment required	No	Yes	Yes	No	No
Dosing schedule	3 cycles (leukapheresis + infusion) about 2 weeks apart	10 cycles, every 3 weeks	4 tablets once daily with BID concomitant steroids	4 capsules once daily	6 cycles, every 4 weeks
Route of administration	Intravenous	Intravenous	Oral	Oral	Intravenous

BID, twice daily; CRPC, castration-resistant prostate cancer; M1, evidence of metastatic disease; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PFS, progression-free survival; SSE, symptomatic skeletal event; US, United States.

<sup>a</sup>Although cabazitaxel is indicated only for the treatment of patients with mCRPC who have received prior treatment with a docetaxel-containing regimen, the other agents may be employed earlier in the course of therapy.

# Current Guidance for CRPC Treatment

- ▶ Current treatment guidelines provide a list of available agents with **limited recommendations** regarding any order of sequence, combination, or layering<sup>1-5</sup>

**Table 2.** Current guidance for the treatment of CRPC

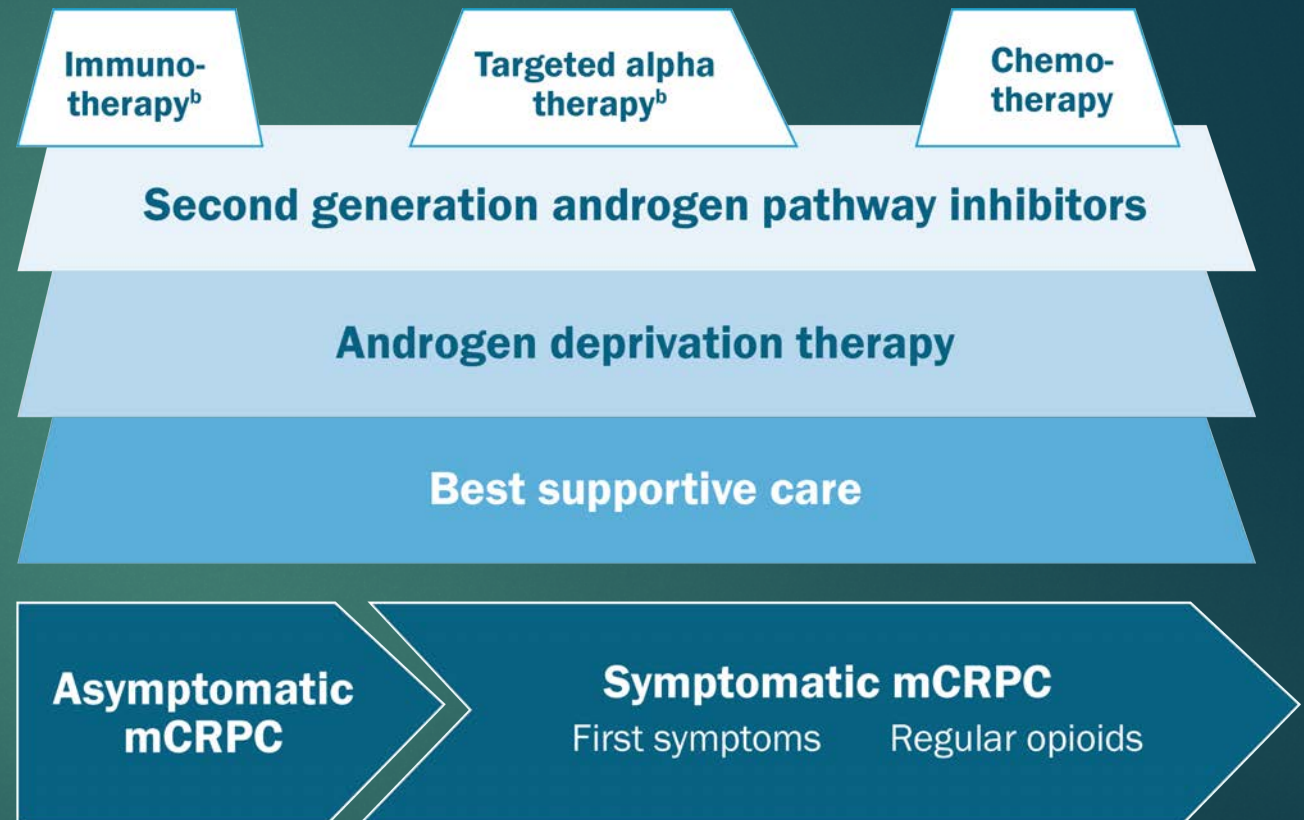
Stage	National Comprehensive Cancer Network (NCCN) <sup>4</sup>	American Urological Association (AUA) <sup>3</sup>	American Society of Clinical Oncology (ASCO) <sup>2</sup>	European Society for Medical Oncology (ESMO) <sup>9</sup>	Canadian Urological Association-Canadian Urologic Oncology Group (CUA-CUOG) <sup>10</sup>
M0				Docetaxel (patients with local progression and no possibility for local treatment)	
M1	Docetaxel Mitoxantrone Sipuleucel-T Abiraterone Enzalutamide Cabazitaxel Radium-223 (with bone metastases)	Docetaxel Mitoxantrone Sipuleucel-T Abiraterone Enzalutamide Cabazitaxel Radium-223 (with bone metastases)	Docetaxel Mitoxantrone Sipuleucel-T Abiraterone Enzalutamide Cabazitaxel Radium-223 (with bone metastases)	Docetaxel Abiraterone* Enzalutamide* Cabazitaxel Sipuleucel-T* Radium-223†	Docetaxel Abiraterone Enzalutamide Cabazitaxel Radium-223 (with bone metastases)

**Abbreviations as in Table 1 .**  
 \* Patients who are asymptomatic or mildly symptomatic with chemotherapy-naive mCRPC.  
 † Patients with bone-predominant, symptomatic mCRPC.

1. National Comprehensive Cancer Network. 2016. Prostate cancer (version 3). [http://www.nccn.org/professionals/physician\\_gls/pdf/prostate.pdf](http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf). Accessed July 14, 2016. 2. Cookson MS, Lowrance WT, Murad MH, et al. *J Urol*. 2015;193(2):491-499. 3. Basch E, Loblaw DA, Oliver TK, et al. *J Clin Oncol*. 2014;32(30):3436-3448. 4. Parker C, Gillissen S, Heidenreich A, et al. *Ann Oncol*. 2015;26[suppl 5]:v69-v77. 5. Saad F, Chi KN, Finelli A, et al. *Can Urol Assoc J*. 2015;9(3-4):90-96.

# Opportunities for Therapeutic Layering

- ▶ The RADAR II Group recommends considering therapeutic layering of certain new agents in mCRPC patients when appropriate



<sup>a</sup>ClinicalTrials.gov Identifiers: NCT01487863, NCT01981122, NCT02034552, NCT02288247, and NCT02522715.

<sup>b</sup>Not eligible if visceral metastasis is present.

# Redefining Disease Progression

# Questions Considered by the RADAR II Group: Disease Progression

## Disease progression

- **How is progression defined? What is the best way to determine progression while a patient is being treated with therapeutic agents with biologically distinct mechanisms of action?**

## Initiating and discontinuing therapeutic agents

- How early should treatment be initiated in patients with mCRPC? Which agents should be considered for use early in the metastatic setting?
- When should therapy be changed? Should treatment continue beyond progression? If yes, with which agents?
- When should treatment be started and when should treatment be discontinued for each specific therapeutic agent?
- Should second-generation androgen pathway inhibitors (abiraterone or enzalutamide) be used sequentially?

# Definition of Progression of mCRPC

The RADAR II Group defines progression of mCRPC as:

Convincing and consistent rise in PSA<sup>a</sup>

Evidence of radiographic progression, or

Presence of clinical symptoms while on therapy

<sup>a</sup>Please see the Prostate Cancer Clinical Trials Working Group definition for more specificity.<sup>1</sup>

1. Scher HI, Morris MJ, Stadler WM, et al. *J Clin Oncol*. 2016;34(12):1402-1418.



# RADAR II Group Recommendations for the Treatment of mCRPC

1. **Immunotherapy** with sipuleucel-T should be considered for all newly diagnosed asymptomatic or minimally symptomatic mCRPC patients with low tumor burden
2. **Androgen pathway inhibitors** can be initiated or added upon consecutive PSA rise with consideration after sipuleucel-T on biochemical or clinical progression
3. **Targeted alpha therapy** can be introduced at the first sign of progression on androgen pathway inhibitors for patients with bone metastases and symptoms
4. **Chemotherapy** can be administered after abiraterone or enzalutamide and radium-223

# Recommendations on Initiating and Discontinuing Therapeutic Agents

# Questions Considered by the RADAR II Group: Initiating and Discontinuing Therapeutic Agents

## Disease progression

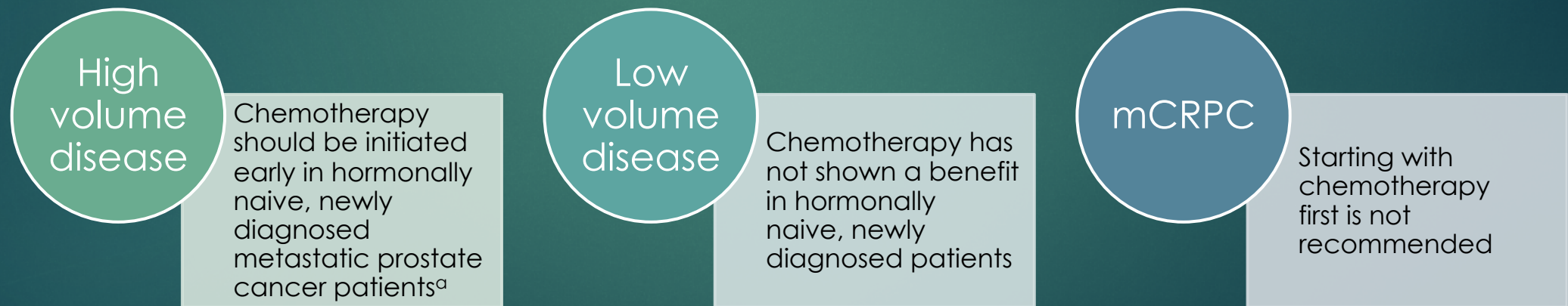
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# Selection of Treatments Vary by Volume and Location of Tumor Burden, Comorbidities, and Prior Lines of Therapy

- ▶ CHAARTED, STAMPEDE, GETUG-AFU-15 have potential to affect subsequent therapy in mCRPC<sup>1-3</sup>
  - ▶ These 3 trials collectively demonstrate that early use of docetaxel in patients with metastatic androgen-sensitive disease significantly improves PFS and OS
- ▶ The RADAR II Group consensus:



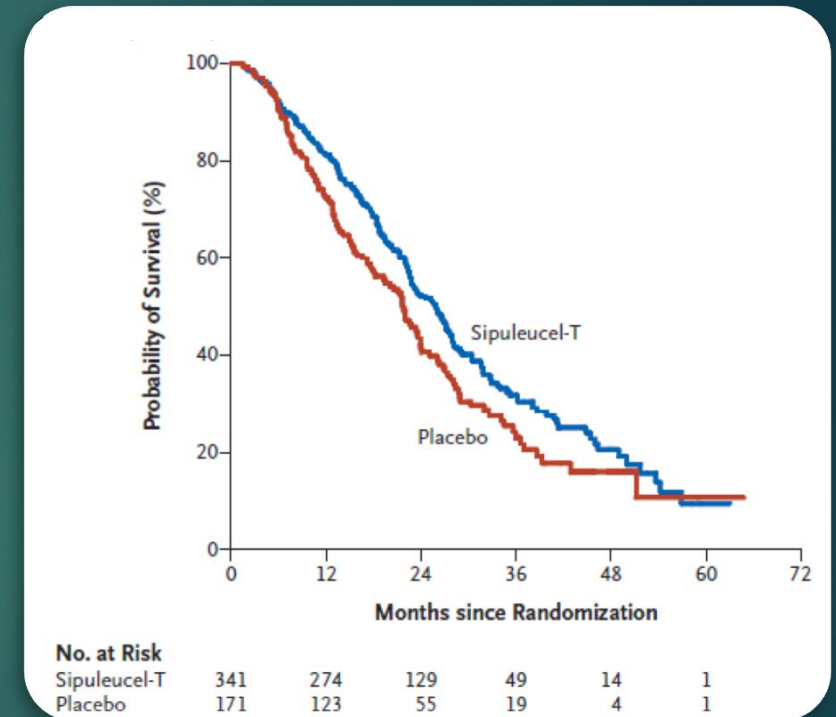
<sup>a</sup>Level 1 evidence for the use of androgen deprivation therapy and second generation androgen pathway inhibitor abiraterone in high volume disease.  
1. Sweeney CJ, Chen YH, Carducci MA, et al. *N Engl J Med*. 2015;373(8):737-746. 2. James ND, Sydes MR, Clarke NW, et al. *Lancet*. 2016;387(10024):1163-1177. 3. Gravis G, Fizazi K, Joly F, et al. *Lancet Oncol*. 2013;14(2):149-158.

# Clinical Data in mCRPC

# Immunotherapy in Select mCRPC Patients

- ▶ Immunotherapy as first-line therapy can be considered in mCRPC patients with the following<sup>1,2</sup>:
  - ▶ Asymptomatic
  - ▶ Low disease burden, and
  - ▶ Indolent disease characteristics
- ▶ Early data showed patients with lower baseline PSA achieved a greater magnitude of OS benefit with sipuleucel-T<sup>3</sup>
- ▶ In postchemotherapy setting, sipuleucel-T can have survival benefit but in a unique subset of patients<sup>4</sup>
- ▶ Recent clinical trials combined sipuleucel-T with:
  - ▶ Enzalutamide<sup>5</sup>
  - ▶ Abiraterone<sup>6</sup>
  - ▶ Radium-223<sup>7</sup>

Overall Survival Benefit of Sipuleucel-T<sup>2</sup>



1. Crawford ED, Petrylak DP, Higano CS, et al. *Can J Urol*. 2015;22(6):8048-8055. 2. Kantoff PW, Higano CS, Shore ND, et al. *N Engl J Med*. 2010;363(5):411-422. 3. Schellhammer PF, Chodak G, Whitmore JB, et al. *Urology*. 2013;81(6):1297-1302. 4. Higano CS, Armstrong AJ, Cooperberg MR, et al. *J Clin Oncol*. 2013;31(suppl): 5034. 5. A study of sipuleucel-T with administration of enzalutamide in men with metastatic castrate-resistant prostate cancer. ClinicalTrials.gov Identifier: NCT01981122. Accessed October 30, 2017. 6. Concurrent vs sequential sipuleucel-T & abiraterone treatment in men With metastatic castrate resistant prostate cancer. ClinicalTrials.gov Identifier: NCT01487863. Accessed October 30, 2017. 7. Park JC, Sartor AO, Sullivan R, et al. *J Clin Oncol*. 2015;33(suppl):TPS5076.

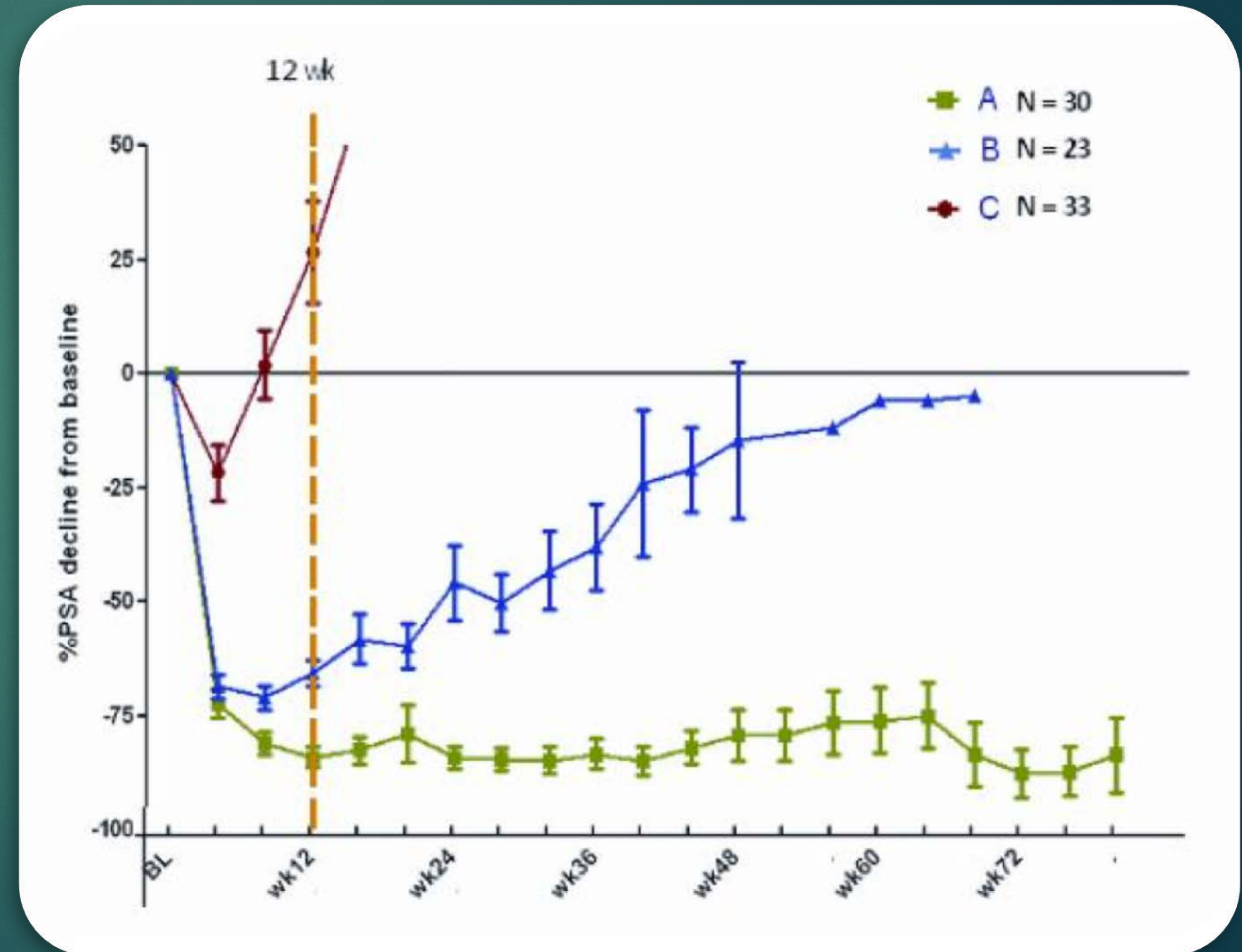
# Second Generation Androgen Pathway Inhibitors Following Immunotherapy

- ▶ Current guidelines recommend early initiation of androgen pathway inhibitors (ie, abiraterone or enzalutamide) for patients with or without minimal symptoms in the prechemotherapy setting<sup>1</sup>
- ▶ The RADAR II Group recommends initiating second-generation androgen pathway inhibitors following immunotherapy in the setting of biochemical or clinical progression
- ▶ Start first with a second-generation androgen pathway inhibitor if immunotherapy is not appropriate for the patient

1. National Comprehensive Cancer Network. 2016. Prostate cancer (version 3). [http://www.nccn.org/professionals/physician\\_gls/pdf/prostate.pdf](http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf). Accessed July 14, 2016.

# Not All Patients Respond to Second Generation Androgen Pathway Inhibitors

- ▶ Although second generation androgen pathway inhibitors provide benefit to many, not all patients respond
- ▶ Among these responders, there is limited durability of response
- ▶ Patterns of response for patients on enzalutamide include:
  - ▶ Dramatic declines in PSA with durable radiographic control (**green**)
  - ▶ Intermediate response characterized by a slowly rising PSA (**blue**)
  - ▶ Those who do not respond (**red**)

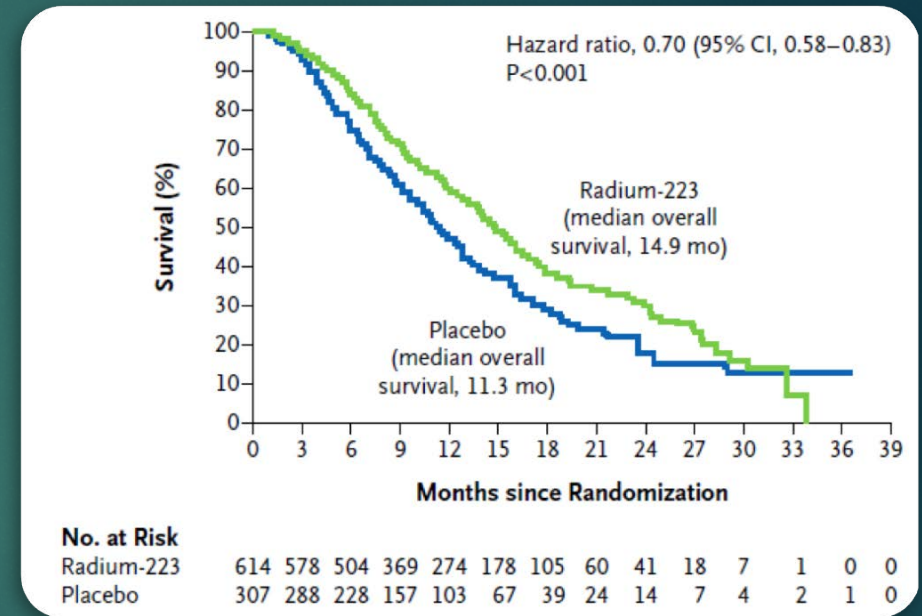




# Targeted Alpha Therapy for mCRPC Patients With Bone Metastases

- ▶ Following a second-generation androgen pathway inhibitor, consider radium-223 for patients with bone metastases on emergence of signs and symptoms
  - ▶ Risk of bone metastatic disease can be independently predicted by alkaline phosphatase and PSA<sup>1</sup>
- ▶ Phase 3 trials of enzalutamide and abiraterone showed a subsequent decrement in QOL soon after PSA progression, even in the absence of radiographic progression<sup>2,3</sup>
  - ▶ Therefore, radium-223 should be considered during or soon after PSA progression on those agents
- ▶ RADAR II Group recommends adding (therapeutic layering) radium-223 to androgen pathway inhibitors in patients with bone metastases and symptoms

Overall Survival With Radium-223<sup>4</sup>



1. Moslehi M, Cheki M, Salehi-Marzijarani M, et al. *Rev Esp Med Nucl Imagen Mol.* 2013;32(5):286-289. 2. Beer TM, Armstrong AJ, Rathkopf DE, et al. *N Engl J Med.* 2014;371(5):424-433. 3. Ryan CJ, Smith MR, de Bono JS, et al. *N Engl J Med.* 2013;368(2):138-148. 4. Parker C, Nilsson S, Heinrich D, et al. *N Engl J Med.* 2013;369(3):213-223.

# Questions Considered by the RADAR II Group: Initiating and Discontinuing Therapeutic Agents

## Disease progression

- How is progression defined? What is the best way to determine progression while a patient is being treated with therapeutic agents with biologically distinct mechanisms of action?

## Initiating and discontinuing therapeutic agents

- How early should treatment be initiated in patients with mCRPC? Which agents should be considered for use early in the metastatic setting?
- **When should therapy be changed? Should treatment continue beyond progression? If yes, with which agents?**
- When should treatment be started and when should treatment be discontinued for each specific therapeutic agent?
- Should second-generation androgen pathway inhibitors (abiraterone or enzalutamide) be used sequentially?

# Consideration of MOA and Type of Progression

Changes in therapy should depend on careful consideration of MOA with type of progression

- eg, sipuleucel-T and radium-223 offer survival benefit without consistent PSA declines since they do not directly induce tumor cell apoptosis or inhibit the androgen axis

Changes based on PSA alone are not generally recommended, particularly in the setting of favorable PSA kinetics

- St. Gallen Advanced Prostate Cancer Consensus Conference cautioned against stopping treatments with a proven survival benefit on the basis of PSA progression alone<sup>1</sup>
- Prostate Cancer Clinical Trials Working Group 3 emphasized importance of distinguishing between first evidence of disease progression (perhaps by PSA rise) and stopping treatment when there is no longer a clinical benefit<sup>2</sup>

Symptomatic or radiographic progression is a more reliable trigger for either therapeutic layering or change

PSA progression alone should prompt re-imaging and may be a more reliable biologic indicator for therapeutic alteration or layering for the androgen pathway inhibitors

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# Recommendation to Augment Rather Than Switch

- ▶ Consider augmentation rather than switching treatment
  - ▶ This recommendation is based on clonal diversity of mCRPC
  - ▶ Sequencing<sup>a</sup> may allow clones suppressed by the current treatment clones to re-emerge or expand
- ▶ Similar to therapeutic layering of (adding) a new agent to ADT with the development of CRPC, the RADAR II Group also considers therapeutic layering with agents used for known mCRPC

<sup>a</sup>Sequencing here is defined as discontinuing current treatment when a new therapy is initiated.

# Questions Considered by the RADAR II Group: Initiating and Discontinuing Therapeutic Agents

## Disease progression

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## Initiating and discontinuing therapeutic agents

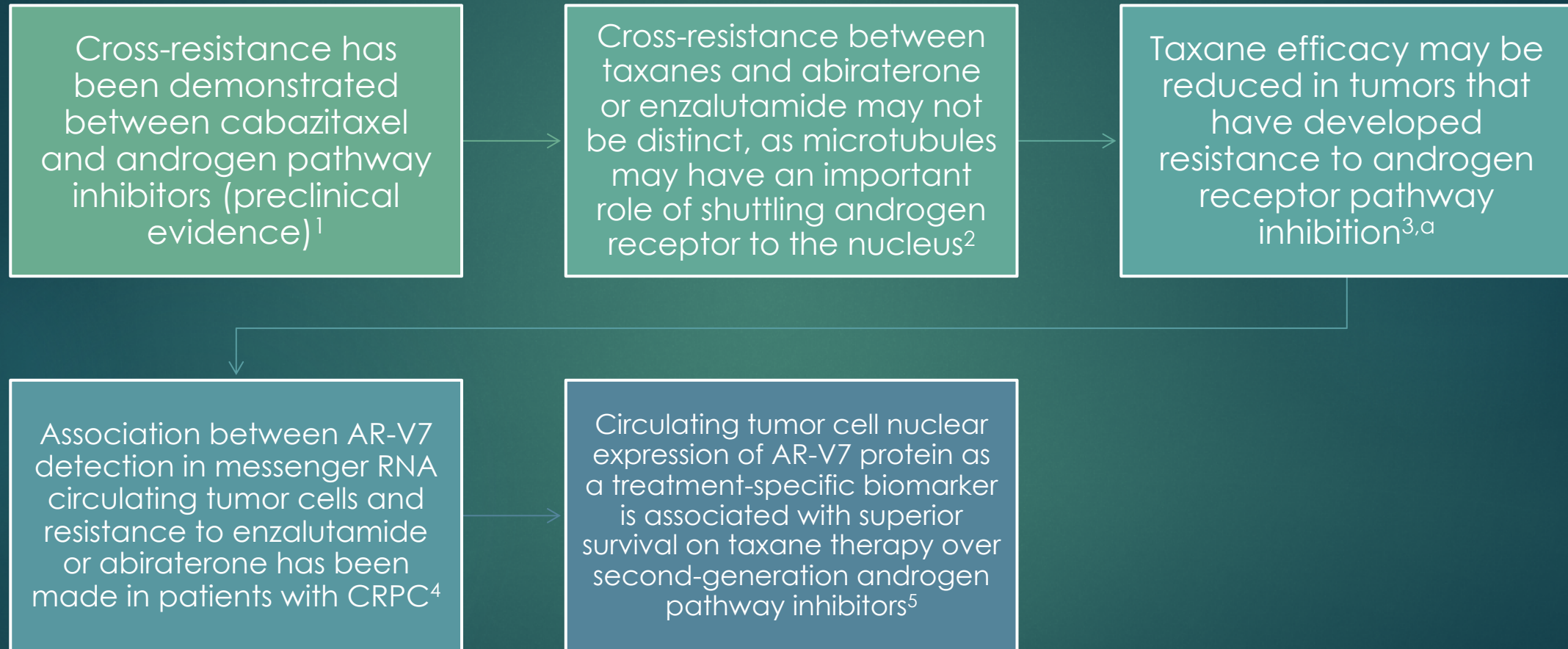
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- **Should second-generation androgen pathway inhibitors (abiraterone or enzalutamide) be used sequentially?**

# Sequential Administration of Second-Generation Androgen Pathway Inhibitors May Reduce Antitumor Activity

- ▶ Ideal sequence of abiraterone and enzalutamide has not been established<sup>1</sup>
- ▶ Sequential administration may reduce antitumor activity<sup>2-4</sup>
- ▶ Even with PSA responses, magnitude and duration of response may be diminished with second-line androgen pathway inhibitor relative to first androgen pathway inhibitor
- ▶ In the prechemotherapy setting, enzalutamide has shown limited activity when administered subsequent to abiraterone<sup>3</sup>
- ▶ St. Gallen Advanced Prostate Cancer Consensus recommends against sequencing enzalutamide and abiraterone<sup>5</sup>

1. National Comprehensive Cancer Network. 2016. Prostate cancer (version 3). [http://www.nccn.org/professionals/physician\\_gls/pdf/prostate.pdf](http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf). Accessed July 14, 2016. 2. Lortot Y, Bianchini D, Ileana E, et al. *Ann Oncol*. 2013;24(7):1807-1812. 3. Cheng HH, Gulati R, Azad A, et al. *Prostate Cancer Prostatic Dis*. 2015;18(2):122-127. 4. Omlin A, Pezaro C, Gillessen Sommer S. *Ther Adv Urol*. 2014;6(1):3-14. 5. Gillessen S, Omlin A, Attard G, et al. *Ann Oncol*. 2015;26(8):1589-1604.

# Consideration of Cross-Resistance Between Taxanes and Second-Generation Androgen Pathway Inhibitors



<sup>a</sup>The RADAR II Group, however, noted that shorter efficacy of subsequent therapy to docetaxel may also be due to more advanced disease rather than prior therapeutic exposure.

AR-V7, androgen receptor splice variant 7.

1. van Soest RJ, van Royen ME, de Morrée ES, et al. *Eur J Cancer*. 2013;49(18):3821-3830. 2. Darshan MS, Loftus MS, Thadani-Mulero M, et al. *Cancer Res*. 2011;71(18):6019-6029. 3. Huillard O, Albiges L, Eymard JC, et al. *J Clin Oncol*. 2013;31(suppl):5075. 4. Antonarakis ES, Lu C, Wang H, et al. *N Engl J Med*. 2014;371(11):1028-1038. 5. Scher HI, Lu D, Schreiber NA, et al. *JAMA Oncol*. 2016;2(11):1441-1449.



# Switching From One Second-Generation Androgen Pathway Inhibitor to Another After Progression Is Not Recommended in Most Situations

- ▶ Based on the current state of the data, switching therapy from one second-generation androgen pathway inhibitor to another after progression on the first agent is not recommended in most situations
- ▶ However, a switch may be considered if there is the following:
  - 1) Prolonged treatment response (>12 months) to the first agent, or
  - 2) If the patient is a poor candidate for, or declines on, taxane therapy
- ▶ As an option, radium-223 can be layered to a second-generation androgen pathway inhibitor on first sign of progression
- ▶ If chemotherapy is administered between one novel hormonal agent and another, there may be resensitization of the patient's tumor to second generation androgen pathway inhibitors

**Focus on Therapeutic Layering**

# Most Effective Sequence, Combination, or Therapeutic Layer in mCRPC

- ▶ Potential benefit of combining agents for patients with mCRPC were assessed in several small-scale studies, with larger trials ongoing to determine the following:
  - ▶ Optimal timing
  - ▶ Sequence
  - ▶ Combination of agents

# Most Effective Sequence, Combination, or Therapeutic Layer in mCRPC (cont'd)

## Androgen pathway inhibitors

- Easiest agent to layer with ongoing trials with chemotherapy

## Radium-223

- Concurrent administration of radium-223 and second-generation androgen pathway inhibitors appears to be well tolerated with similar toxicities compared with radium-223 alone
- Significantly longer OS with radium-223 and abiraterone (vs radium-223 alone), and radium-223 and denosumab (vs radium-223 alone)
- Ongoing trials of radium-223 and abiraterone or enzalutamide

## Sipuleucel-T

- Successfully administered during concurrent administration of abiraterone plus prednisone without altering immunologic effects or parameters correlated with survival benefit from sipuleucel-T
- Also being studied with enzalutamide as well as radium-223

# Conclusion

- ▶ Despite great strides in mCRPC management, selecting a treatment to optimize outcomes remains a challenge
- ▶ mCRPC is best managed with different agents, especially those with unique and complementary MOA to avoid inducing cross-resistance
- ▶ Optimal treatment selection may depend on molecular characterization and genotyping as well as patients' clinical characteristics
- ▶ Clinical trials remain an important need to provide additional evidence on the efficacy, safety, and tolerability of combination regimens and patient identification
- ▶ The RADAR II Group recommendations are based on available trial literature and real-world experience, but optimal patient care continues to depend on the clinical judgment of each treating physician

**Thank You**

**Back Up**

# Treatment Recommendations for Patients With mCRPC: Immunotherapy

**Table 3.** Treatment recommendations for patients with mCRPC TxNx-M1

<b>Immunotherapy (sipuleucel-T)</b>	<b>Initiate or Add</b>	<b>Imaging or Biomarkers to Follow</b>	<b>Stop-Switch-Add Treatment</b>	<b>Consensus Commentary</b>
	<ul style="list-style-type: none"> <li>Should be considered for all newly metastatic CRPC patients with low tumor burden (asymptomatic or minimally symptomatic patients)                             <ul style="list-style-type: none"> <li>Can be used after other therapies if patient had an outstanding response to the prior therapy</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>PSA &lt;22 before initiation may provide best survival outcomes<sup>12</sup></li> <li>Improvements in PSA or imaging should generally not be expected</li> </ul>	Duration of therapy is fixed to 3 doses	<ul style="list-style-type: none"> <li>Anti-PAP antibody may be detectable for 8-10 years post vaccination<sup>13</sup></li> </ul>

ADT, androgen deprivation therapy; ALP, alkaline phosphatase; AR, androgen receptor; LDH, lactate dehydrogenase; PAP, prostatic acid phosphatase; PARP, poly ADP ribose polymerase; PSA, prostate-specific antigen; other abbreviations as in Table 1.

\*PSA alone should not be used.



# Treatment Recommendations for Patients With mCRPC: Androgen Pathway Inhibitors

**Table 3.** Treatment recommendations for patients with mCRPC TxNx-M1

<b>Androgen pathway inhibitors (abiraterone acetate and enzalutamide)</b>	<b>Initiate or Add</b>	<b>Imaging or Biomarkers to Follow</b>	<b>Stop-Switch-Add Treatment</b>	<b>Consensus Commentary</b>
	<ul style="list-style-type: none"> <li>• Upon consecutive PSA rises</li> <li>• Early initiation is associated with greater benefit<sup>4</sup></li> <li>• Consider initiating therapy following sipuleucel-T on biochemical or clinical progression</li> <li>• If patient is not a good candidate for sipuleucel-T, start with abiraterone or enzalutamide</li> </ul>	<ul style="list-style-type: none"> <li>• Consecutive rise in PSA levels* indicative of resistance</li> <li>• AR full length and AR splice variant expression in circulating tumor cells are potential biomarkers still under evaluation and requiring validation</li> </ul>	<ul style="list-style-type: none"> <li>• Symptomatic progression</li> <li>• Radiographic progression</li> <li>• Consider reimaging with consecutive and convincing PSA rises and either proceed with therapeutic layering or switch</li> </ul>	<ul style="list-style-type: none"> <li>• Therapeutic layering with radium-223 as appropriate</li> <li>• Switch to taxane-based therapy</li> <li>• PSA and ALP may rise before falling with abiraterone (wait 3 months before making decision on these markers)</li> <li>• Bone scan healing flare has been described<sup>14</sup></li> </ul>

ADT, androgen deprivation therapy; ALP, alkaline phosphatase; AR, androgen receptor; LDH, lactate dehydrogenase; PAP, prostatic acid phosphatase; PARP, poly ADP ribose polymerase; PSA, prostate-specific antigen; other abbreviations as in Table 1.

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# Treatment Recommendations for Patients With mCRPC: Targeted Alpha Therapy

**Table 3.** Treatment recommendations for patients with mCRPC TxNx-M1

	<b>Initiate or Add</b>	<b>Imaging or Biomarkers to Follow</b>	<b>Stop-Switch-Add Treatment</b>	<b>Consensus Commentary</b>
<b>Targeted alpha therapy (radium-223)</b>	<ul style="list-style-type: none"> <li>• Can be introduced at the first sign of progression on androgen pathway inhibitors for patients with bone metastases and symptoms</li> <li>• Strong consideration for use before chemotherapy                             <ul style="list-style-type: none"> <li>– Favorable safety profile and low risk for adverse effects on hematopoiesis</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• PSA changes do not correspond with survival outcomes</li> <li>• ALP is a potential response biomarker</li> </ul>	<ul style="list-style-type: none"> <li>• May be therapeutically layered onto abiraterone or enzalutamide</li> <li>• All 6 cycles should be given for maximal benefit</li> <li>• If given just with ADT, therapeutic layering of abiraterone or enzalutamide can be considered with:                             <ul style="list-style-type: none"> <li>– appearance of new symptoms</li> <li>– rapid growth of lymph nodes</li> <li>– emergence of visceral disease</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Consider radium-223 earlier in therapy</li> <li>• Palliative radiotherapy can be used before, during, or after radium-223</li> </ul>

ADT, androgen deprivation therapy; ALP, alkaline phosphatase; AR, androgen receptor; LDH, lactate dehydrogenase; PAP, prostatic acid phosphatase; PARP, poly ADP ribose polymerase; PSA, prostate-specific antigen; other abbreviations as in Table 1.

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# Treatment Recommendations for Patients With mCRPC: Chemotherapy

**Table 3.** Treatment recommendations for patients with mCRPC TxNx-M1

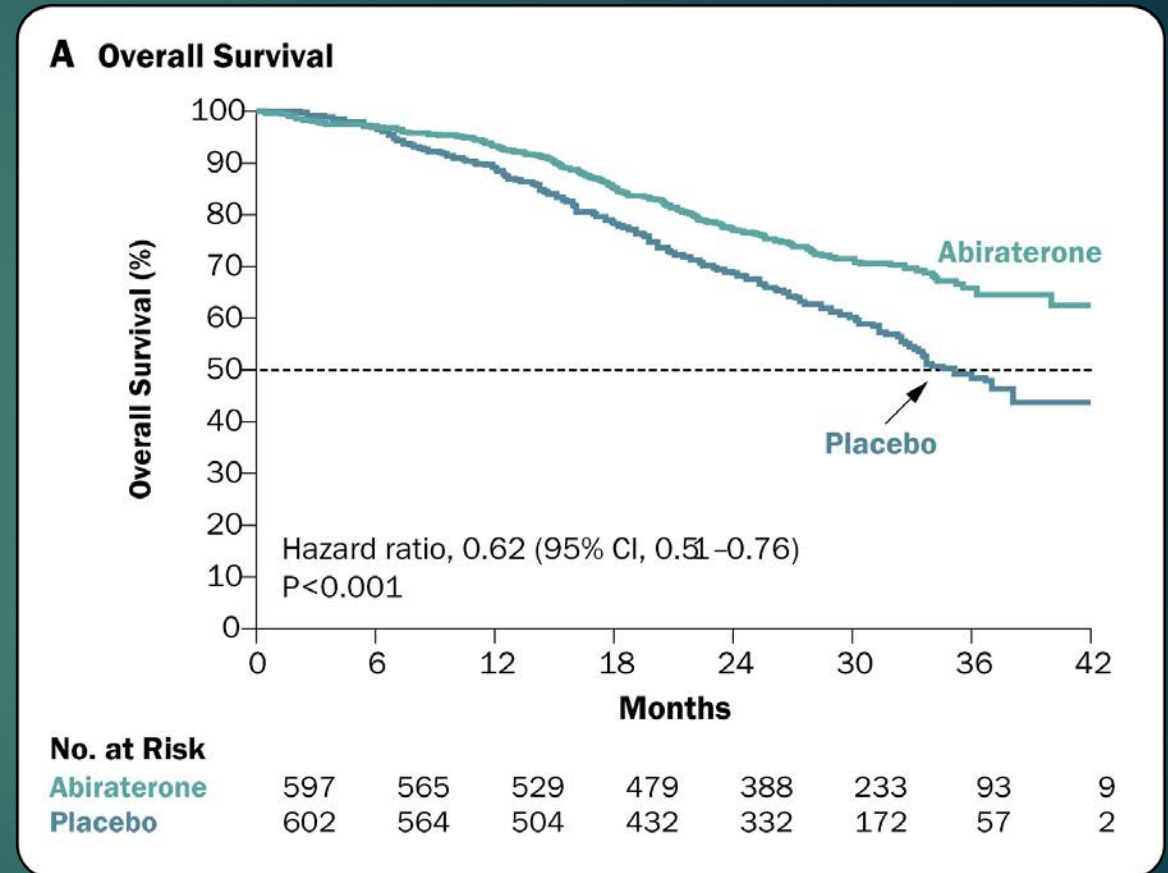
<b>Chemotherapy</b>	<b>Initiate or Add</b>	<b>Imaging or Biomarkers to Follow</b>	<b>Stop-Switch-Add Treatment</b>	<b>Consensus Commentary</b>
	<ul style="list-style-type: none"> <li>• Generally administer after abiraterone or enzalutamide and radium-223</li> <li>– Consider starting earlier in patients with visceral metastases, rapidly progressive symptomatic disease, or those with no or very short response to ADT or second-generation androgen pathway inhibitors</li> <li>– Early chemotherapy may influence the efficacy of latter lines of treatment</li> <li>• For neuroendocrine or small cell carcinoma or aggressive variants, use platinum combination chemotherapy regimens</li> </ul>	<ul style="list-style-type: none"> <li>• Imaging, PSA, ALP, LDH should be obtained before therapy</li> <li>• Imaging if clinical deterioration, regardless of PSA<sup>5</sup> <ul style="list-style-type: none"> <li>• For patients with a known DNA damage repair alteration (eg, BRCA1 or 2),<sup>15,16</sup> agents that induce double-strand DNA breaks should be considered (eg, platinum, radium-223, or mitoxantrone).<sup>17</sup> PARP inhibitors are being explored in this setting (ClinicalTrials.gov Identifier NCT01972217; NCT02500901).</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Stopping point is with radiographic or clinical progression, but it is unclear if PSA progression should be used as well</li> <li>• Phase 3 docetaxel trials allowed up to 10 cycles<sup>18,19</sup></li> <li>• Cabazitaxel should be administered in patients who previously progressed or were intolerant of docetaxel</li> </ul>	<ul style="list-style-type: none"> <li>• May have activity in patients with AR splice variants<sup>20</sup></li> <li>• PSA may first rise before falling</li> </ul>

ADT, androgen deprivation therapy; ALP, alkaline phosphatase; AR, androgen receptor; LDH, lactate dehydrogenase; PAP, prostatic acid phosphatase; PARP, poly ADP ribose polymerase; PSA, prostate-specific antigen; other abbreviations as in Table 1.

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# LATITUDE Study

- ▶ Double-blind, placebo-controlled, phase 3 trial of 1199 patients with newly diagnosed, metastatic, castration-sensitive prostate cancer randomized to either:
  - ▶ ADT plus abiraterone acetate plus prednisone
  - ▶ ADT plus dual placebos
- ▶ Primary endpoints:
  - ▶ OS and radiographic progression-free survival (rPFS)
- ▶ After a median follow up of 30.4 months at a planned interim analysis, the median OS was significantly longer in the abiraterone group than in the placebo group (not reached vs. 34.7 months)
- ▶ Study's authors concluded:
  - ▶ "The addition of abiraterone acetate and prednisone to androgen-deprivation therapy increased overall survival and radiographic progression-free survival in men with newly diagnosed, metastatic, castration-sensitive prostate cancer"

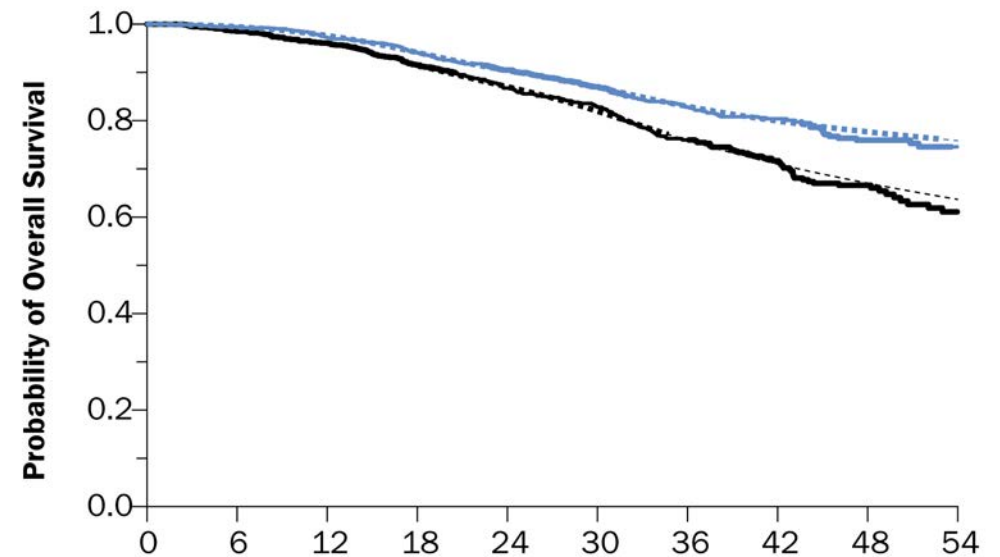


Dashed line in figure represents median.

# STAMPEDE Study

- ▶ 1917 men starting long-term ADT were randomly assigned in a 1:1 ratio to
  - ▶ ADT alone or ADT plus abiraterone acetate and prednisolone
- ▶ Primary endpoint:
  - ▶ Overall survival
- ▶ Median follow-up was 40 months
- ▶ Hazard ratios:
  - ▶ Overall, 0.63; 95% CI, 0.52 to 0.76;  $P < 0.001$
  - ▶ Among patients with non-metastatic disease, 0.75
  - ▶ Among patients with metastatic disease, 0.61
- ▶ Study's authors concluded:
  - ▶ "Among men with locally advanced or metastatic prostate cancer, ADT plus abiraterone and prednisolone was associated with significantly higher rates of overall and failure-free survival than ADT alone"

**A Overall Survival in All Patients**



**No. of Patients  
(no. of deaths)**

**Months since Randomization**

Combination therapy	960 (26)	917 (63)	840 (67)	541 (25)	161
ADT alone	957 (37)	909 (88)	806 (92)	491 (36)	123