# Recent Advances in Medical Oncology: Prostate Cancer

**Wednesday, July 1, 2020**
**5:00 PM – 6:00 PM ET**

## Faculty

**Robert Dreicer, MD, MS**
**Daniel P Petrylak, MD**
**Christopher Sweeney, MBBS**

## Moderator

**Neil Love, MD**

Co-provided by USF Health

RTP RESEARCH TO PRACTICE

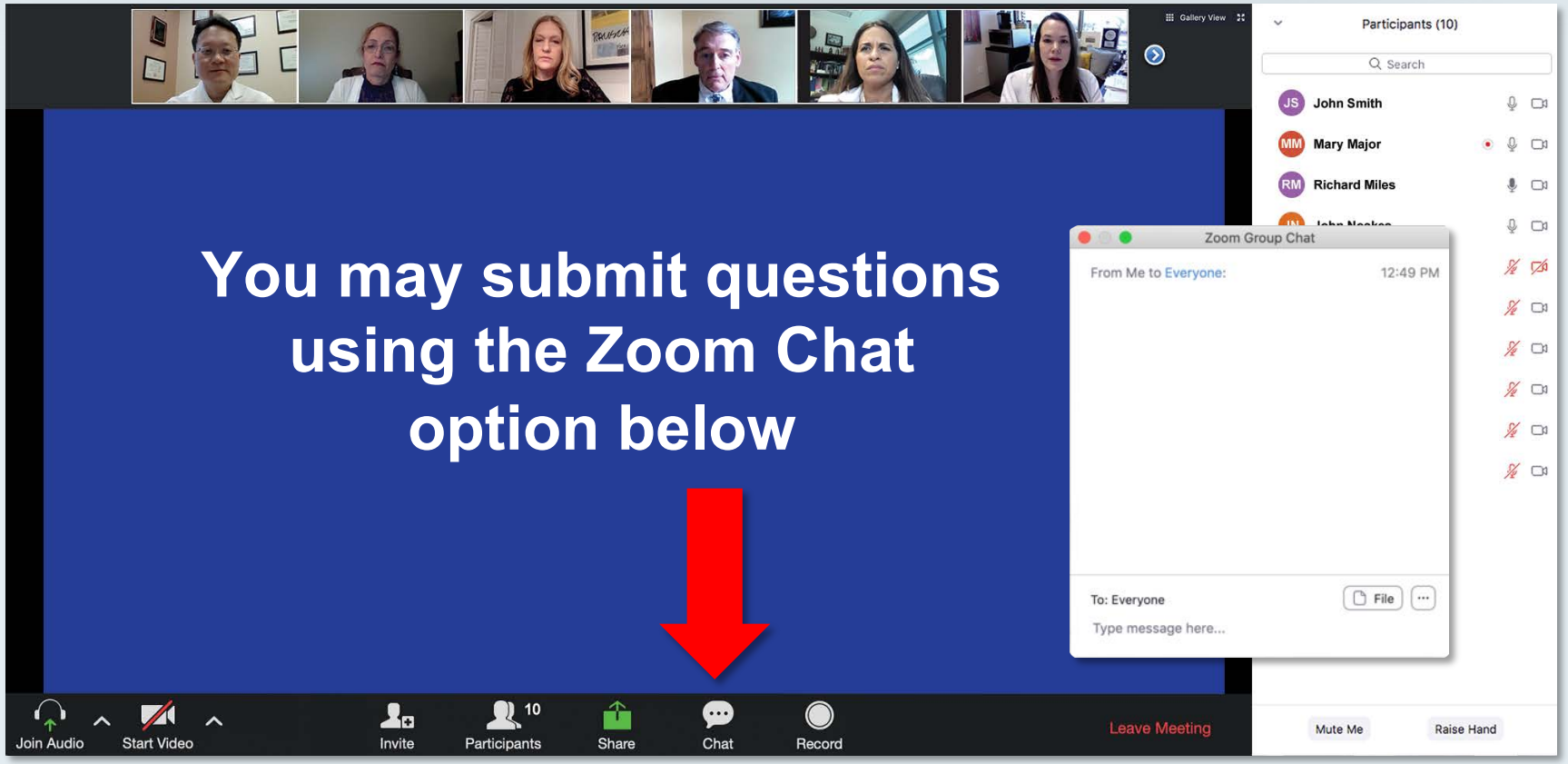
# Faculty

**Robert Dreicer, MD, MS**
Section Head, Medical Oncology
Deputy Director, University of Virginia Cancer Center
Associate Director for Clinical Research
Professor of Medicine and Urology
University of Virginia School of Medicine
Charlottesville, Virginia

**Christopher Sweeney, MBBS**
Professor, Medicine
Harvard Medical School
Medical Oncologist
Dana-Farber Cancer Institute
Boston, Massachusetts

**Daniel P Petrylak, MD**
Professor of Internal Medicine (Medical Oncology) and Urology
Yale University
New Haven, Connecticut

# Dr Love and Faculty Encourage You to Ask Questions




Feel free to submit questions **now before** the program commences and **throughout the program.**

# ONCOLOGY TODAY

## WITH DR NEIL LOVE

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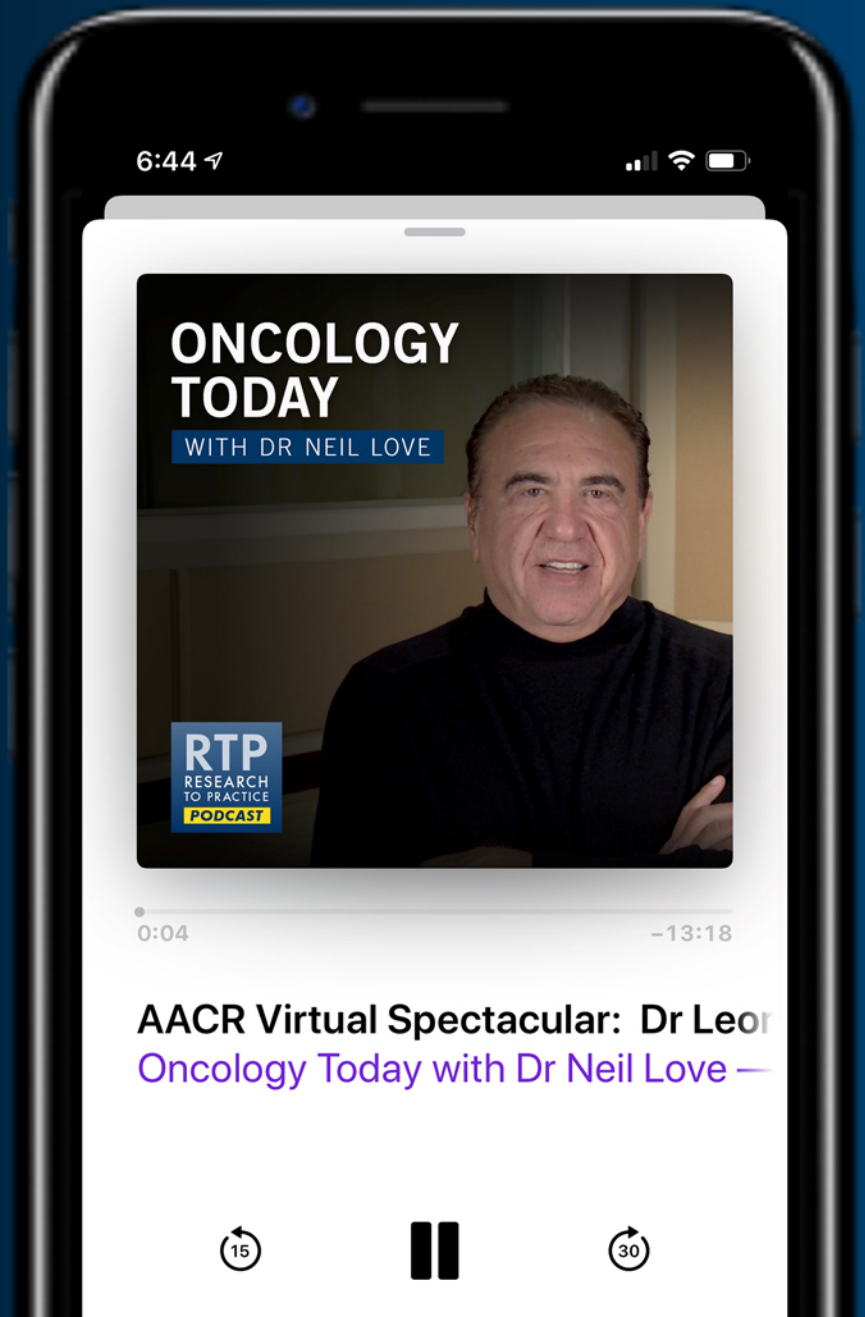

# COVID-19 AND LUNG CANCER

## What We Know, What We Don't Know and What It All Means for Current Patient Care – *A Live CME Webinar*

**Thursday, July 2, 2020**
**12:00 PM – 1:00 PM ET**

**Moderator**
**Neil Love, MD**

**Faculty**
**Leora Horn, MD, MSc**
**Naiyer A Rizvi, MD**
**Lecia V Sequist, MD, MPH**

# Recent Advances in Medical Oncology: HER2-Positive Breast Cancer

**Wednesday, July 8, 2020**
**5:00 PM – 6:00 PM ET**


## Faculty

**Lisa A Carey, MD**
**Ian E Krop, MD, PhD**

## Moderator

**Neil Love, MD**


RTP RESEARCH TO PRACTICE

# What Urologists Need to Know About Immune Checkpoint Inhibitors and Other Novel Approaches for Urothelial Bladder Cancer

**Thursday, July 9, 2020**

**5:00 PM – 6:00 PM ET**


## Faculty

**Arjun Balar, MD**
**Sia Daneshmand, MD**
**Ashish M Kamat, MD, MBBS**
**Jonathan E Rosenberg, MD**

## Moderator

**Neil Love, MD**


RTP RESEARCH TO PRACTICE

# Recent Advances in Medical Oncology: Prostate Cancer

**Wednesday, July 1, 2020**
**5:00 PM – 6:00 PM ET**

## Faculty

**Robert Dreicer, MD, MS**
**Daniel P Petrylak, MD**
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## Moderator

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Co-provided by USF Health

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# Agenda

## Module 1: M0 Castration-Resistant Prostate Cancer (PC) — Dr Petrylak

- Endocrine treatment for patients with cardiovascular disease
- SPARTAN, ARAMIS and PROSPER trials and implications

## Module 2: Metastatic Hormone-Sensitive PC — Dr Sweeney

- Secondary hormonal therapy versus chemotherapy
- LATITUDE, ARCHES, TITAN and ENZAMET trials and implications

## Module 3: Castration-Resistant Metastatic PC — Dr Dreicer

- Cabazitaxel versus secondary endocrine treatment
- Radium-223
- PARP inhibitors

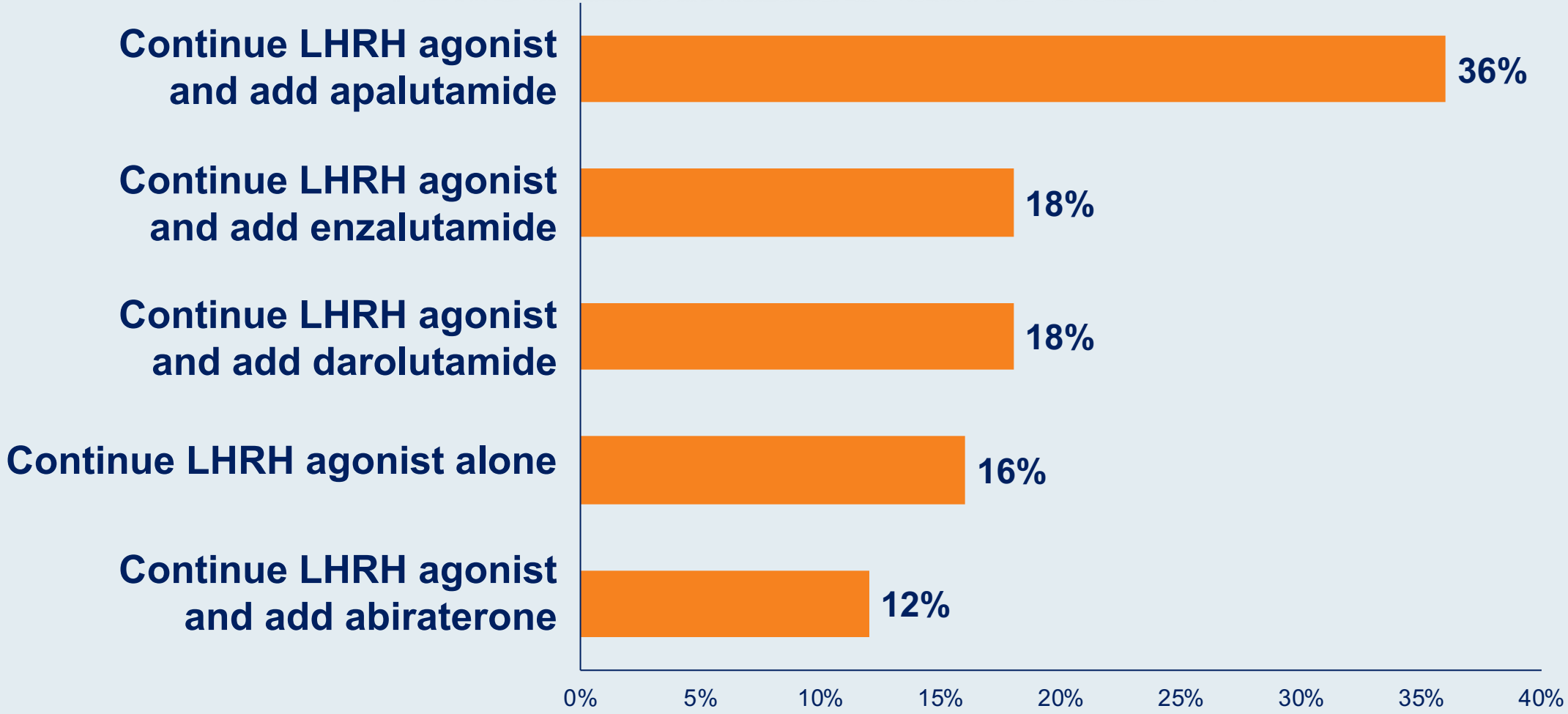
## Module 4: ASCO Journal Club

- ARV-110 PROTAC® degrader (Abstract 3500)
- $^{177}$Lu-PSMA-617 (Abstract 5500)
- PSMA imaging (Abstract 5501)

## Module 1: M0 Castration-Resistant Prostate Cancer (PC) — Dr Petrylak

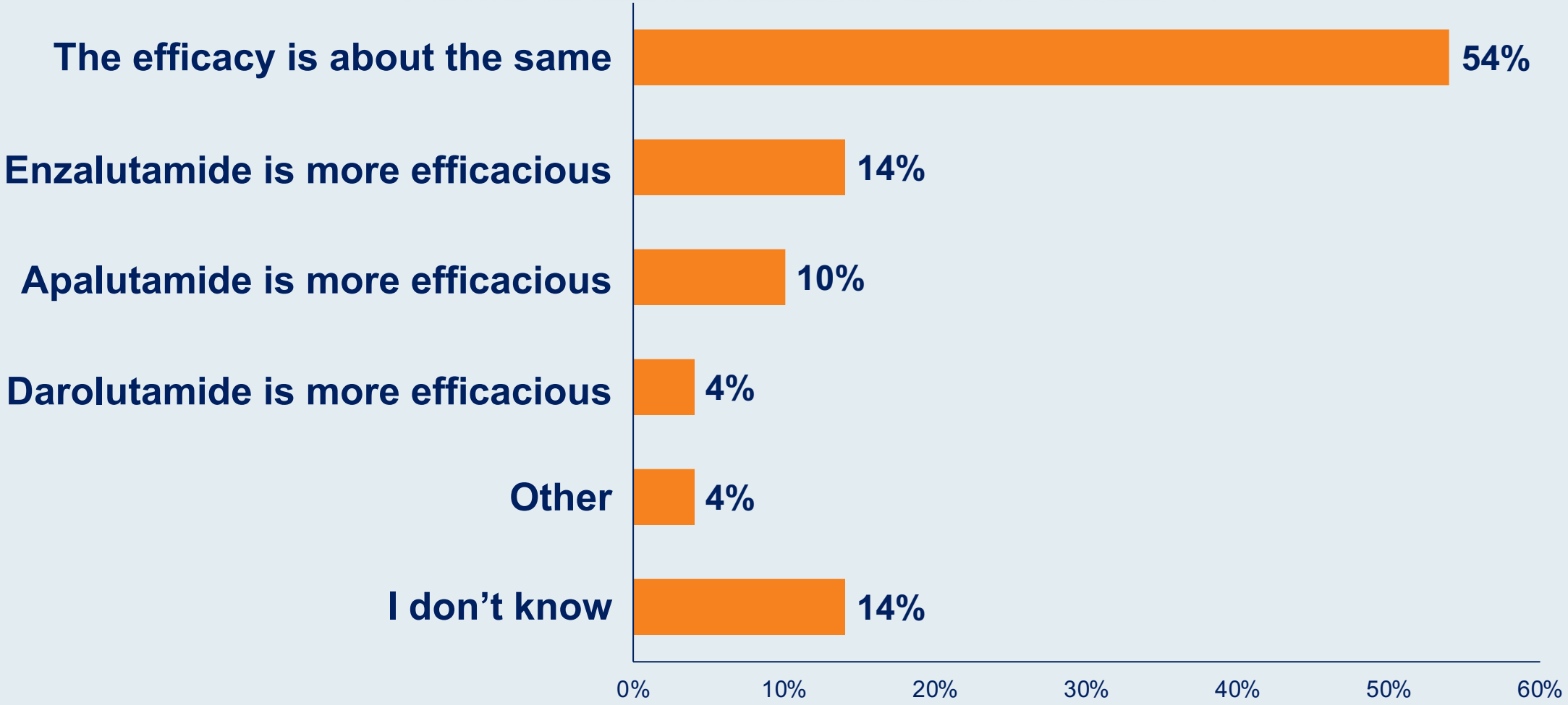
- Endocrine treatment for patients with cardiovascular disease
- SPARTAN, ARAMIS and PROSPER trials and implications

**A 65-year-old man s/p radical prostatectomy followed by radiation therapy for PSA-only recurrence (M0) receives an LHRH agonist for further PSA progression. Regulatory and reimbursement issues aside, what would be your most likely treatment recommendation if the patient responded but then experienced PSA progression to a PSA level of 3.4 ng/dL with a doubling time of 10 months?**



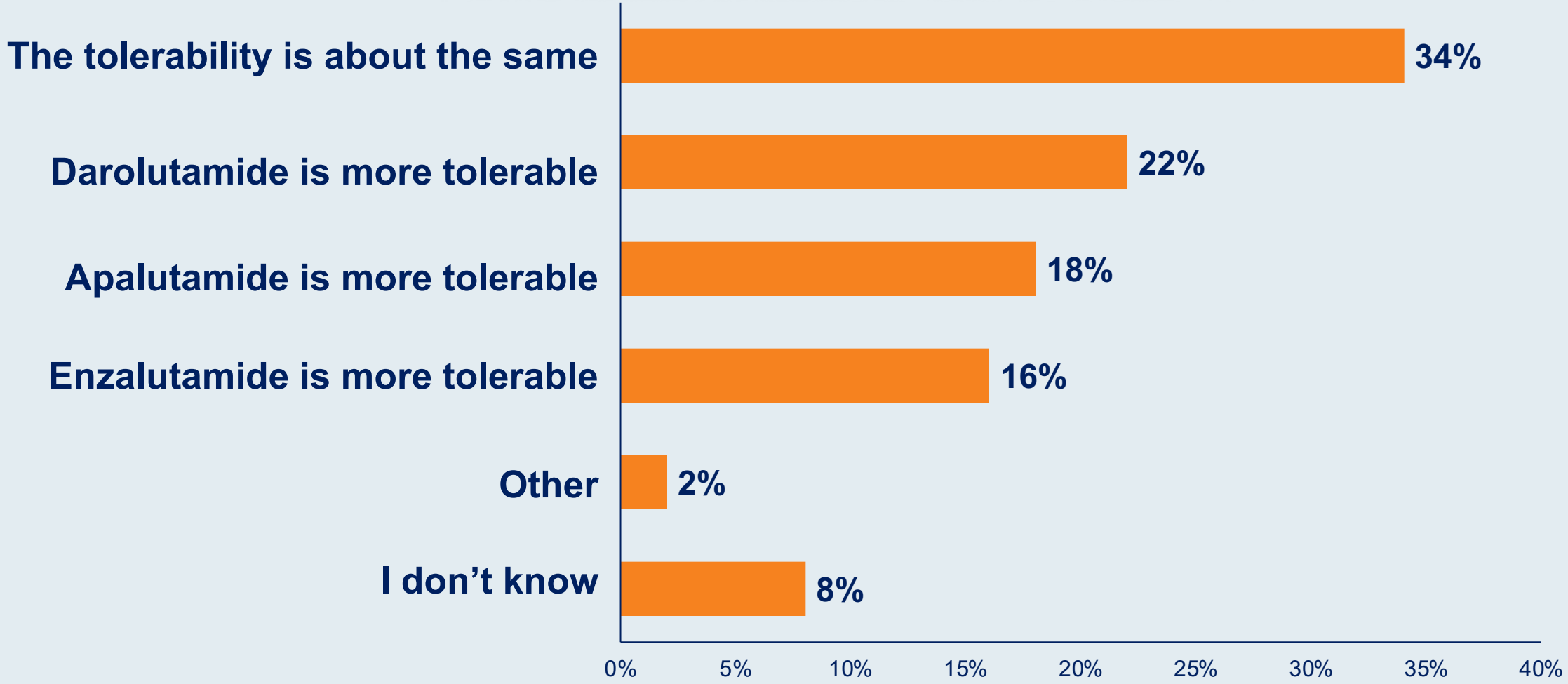

Survey of 50 US-based medical oncologists, June 2020

# How would you compare the efficacy of enzalutamide, apalutamide and darolutamide in patients with M0 prostate cancer?




Survey of 50 US-based medical oncologists, June 2020

# How would you compare the tolerability of enzalutamide, apalutamide and darolutamide in patients with M0 prostate cancer?




Survey of 50 US-based medical oncologists, June 2020

**In general, which endocrine treatment would you prefer for an 84-year-old man with prostate cancer (PC) and a history of atrial fibrillation, sick sinus syndrome, pacemaker placement and hypertension?**

a. Enzalutamide
b. Apalutamide
c. Darolutamide
d. Abiraterone/prednisone
e. Other

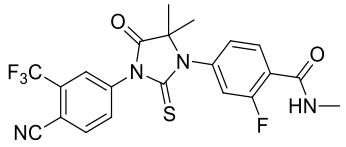
# Case Presentation – Dr Petrylak: A man with M0 prostate cancer

- 84-year-old man
- Past medical history which includes atrial fibrillation, sick sinus syndrome, pacemaker placement, and hypertension.
- Radical prostatectomy in 2010. Gleason 4+3=7. pT3aN0M0
- 2012 status post the placement of a urethral sling for stress incontinence
- PSA rose in 2013, was started on androgen blockade

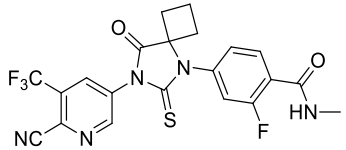
# Case Presentation – Dr Petrylak: A man with M0 prostate cancer (cont)

- PSA 3/18/2019 = 6.99; 9/20/2019 = 9.44; 3/19/2020 = 24.2; imaging negative for metastatic disease
- Started enzalutamide in 4/2020, PSA 6/2020=3

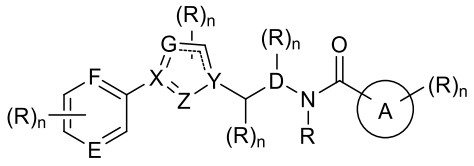
# Next-Generation Antiandrogens



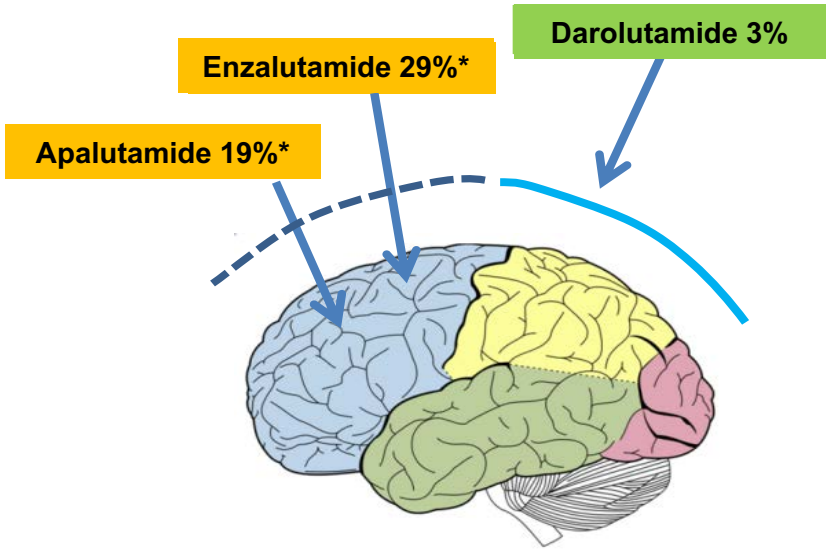
Enzalutamide
(MDV-3100)



Apalutamide (ARN-509)



General chemical structure
for Darolutamide (ODM-201)




**No CYP inhibition or induction with therapeutic doses**

| Compound | AR-WT affinity Ki (nM) | Antagonism AR-WT IC50 (nM) | Antagonism AR T878A IC50 (nM) | Antagonism AR F877L IC50 (nM) | Proliferation VCaP IC50 (nM) |
|---|---|---|---|---|---|
| Enzalutamide | 78 | 155 | 296 | agonist | 400 |
| Apalutamide | 53 | 168 | 1130 | agonist | 300 |
| Darolutamide | 9 | 65 | 700 | 66 | 500 |

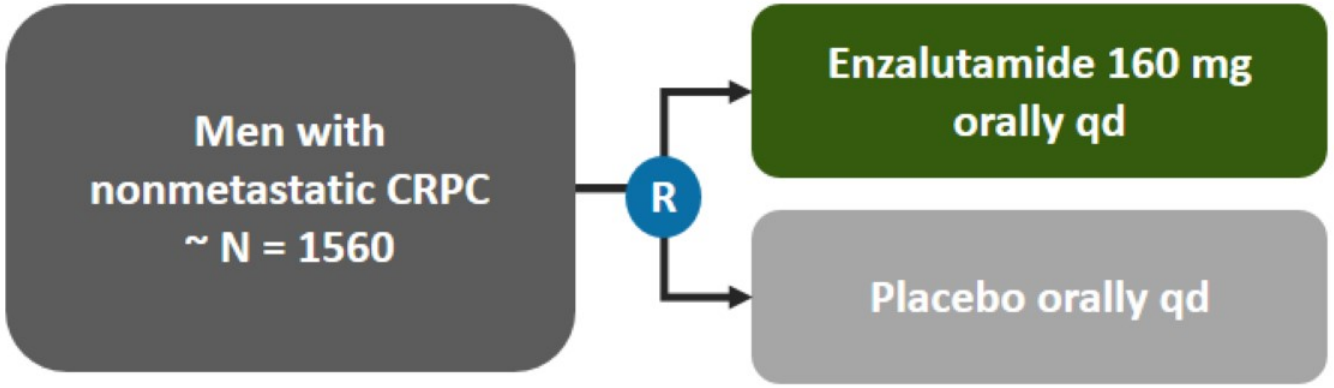


Courtesy of Robert Dreicer, MD, MS

Moilanen A et al. *Sci Rep* 2015; 5:12007. Courtesy of Daniel P Petrylak, MD

# PROSPER

## *Randomized, Double-Blind, Phase 3 Trial of Enzalutamide in Nonmetastatic CRPC*

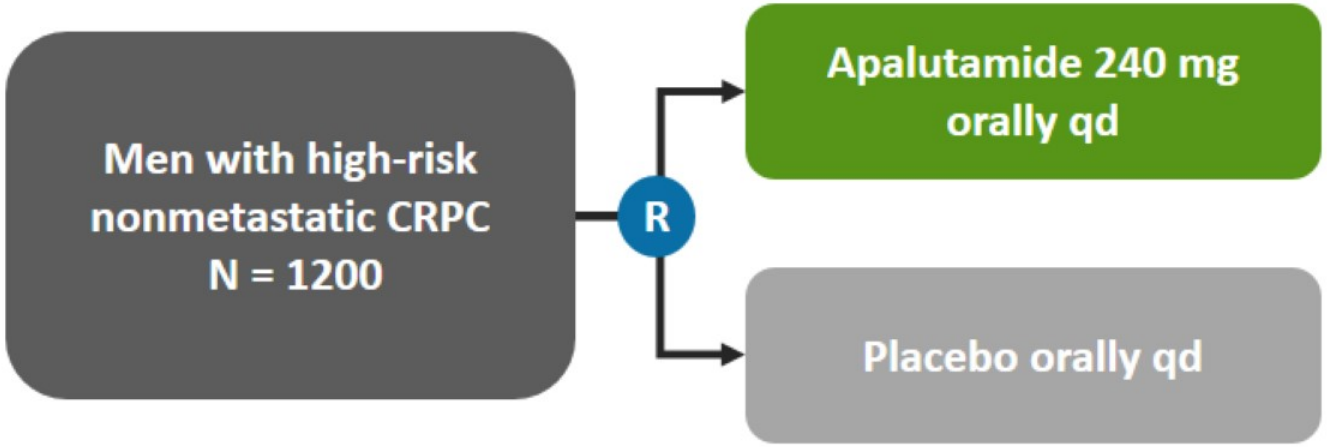



- **Primary endpoint:** metastasis-free survival
- **Secondary endpoints**: time to pain progression, time to first cytotoxic therapy, time to opiate use for cancer pain, time to first antineoplastic therapy, time to PSA progression, FACT-P Global Score, QoL assessment

ClinicalTrials.gov. NCT02003924.

# SPARTAN

## *Randomized, Double-Blind, Phase 3 Trial of Apalutamide in Nonmetastatic CRPC*

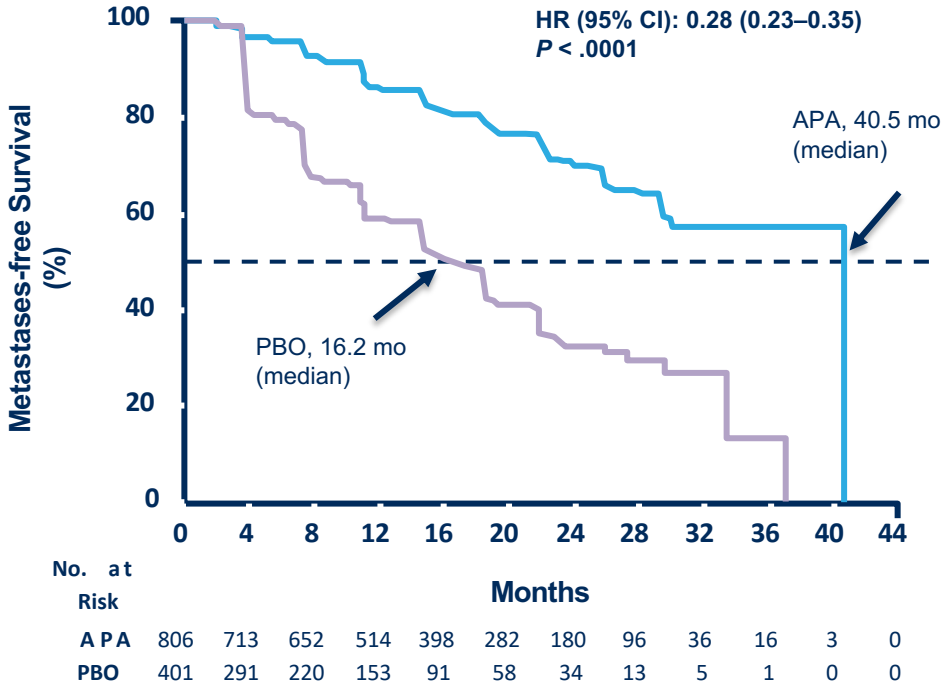



- **Primary endpoint**: metastasis-free survival
- **Secondary endpoints**: OS, time to symptomatic progression, time to first cytotoxic chemotherapy, PFS, time to metastasis, change in FACT-P and EQ-5D scores, AEs, pharmacokinetics

ClinicalTrials.gov. NCT02003924.

# Primary Endpoint – MFS

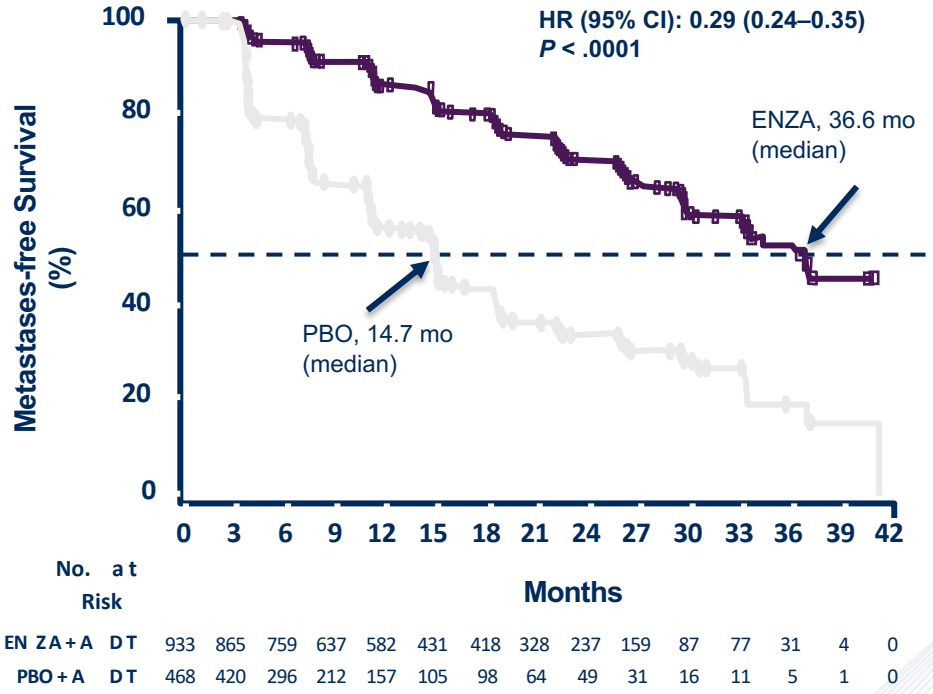
## SPARTAN[1]




| No. at Risk | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| APA | 806 | 713 | 652 | 514 | 398 | 282 | 180 | 96 | 36 | 16 | 3 | 0 |
| PBO | 401 | 291 | 220 | 153 | 91 | 58 | 34 | 13 | 5 | 1 | 0 | 0 |

- **72% reduction of distant progression or death**
- **Median MFS: APA 40.5 months vs PBO 16.2**
- **24-month additional MFS benefit**

## PROSPER[2]



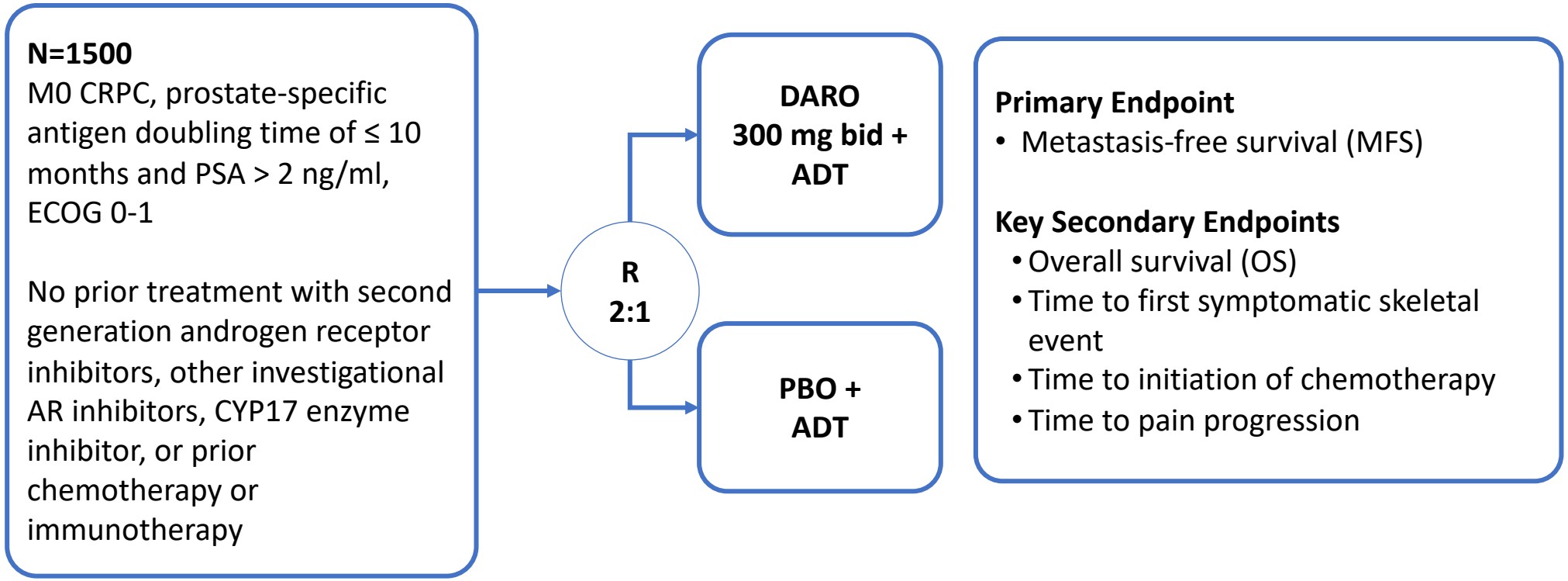

| No. at Risk | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ENZA+ADT | 933 | 865 | 759 | 637 | 582 | 431 | 418 | 328 | 237 | 159 | 87 | 77 | 31 | 4 | 0 |
| PBO+ADT | 468 | 420 | 296 | 212 | 157 | 105 | 98 | 64 | 49 | 31 | 16 | 11 | 5 | 1 | 0 |

- **71% reduction of distant progression or death**
- **Median MFS: ENZA 36.6 months vs PBO 14.7**
- **22-month additional MFS benefit**

**Caveat: Comparing across studies is problematic. This is not a head-to-head comparison.**

1. Smith MR, et al. *N Engl J Med*. 2018; 378:1408-1418; 2. Hussain M, et al. *N Engl J Med*. 2018; 378:2465-2474.

# M0 CRPC - ARAMIS: Darolutamide

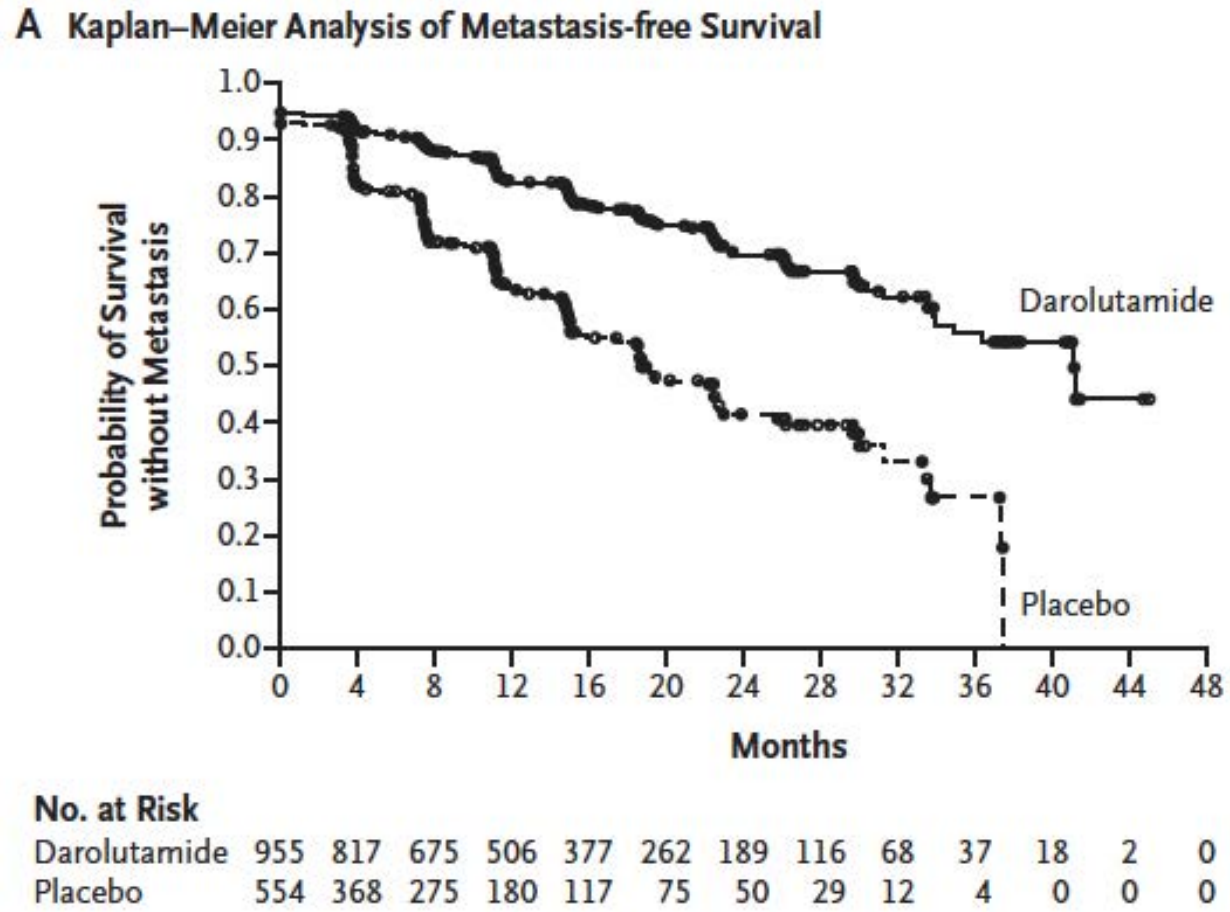



www.clinicaltrials.gov (NCT02200614)

Fizazi et al, NEJM, 2019

Courtesy of Daniel P Petrylak, MD

# M0 CRPC - ARAMIS: Darolutamide




| | Median Metastasis-free Survival (95% CI) |
|---|---|
| | *mo* |
| **Darolutamide** | 40.4 (34.3–NR) |
| **Placebo** | 18.4 (15.5–22.3) |

Hazard ratio, 0.41 (95% CI, 0.34–0.50)
P<0.001

Courtesy of Daniel P Petrylak, MD

Fizazi, et al, NEJM, 2019

# SURVIVAL: PROSPER, SPARTAN, ARAMIS

| | PROSPER[1] | SPARTAN[2] | ARAMIS[3] |
|---|---|---|---|
| Median Follow-up | 47 | 52 | 49 |
| % Died at analysis (control vs experimental) | 31 vs 38% | 34 vs 38% | 19 vs 16% |
| Median OS (Estimated) | 67 vs 56 months | 74 vs 60 months | Not Estimated |
| HR OS | 0.73 | 0.78 | 0.69 |

[1] Sternberg CN et al. *N Engl J Med* 2020;382(23):2197-206; [2] Small EJ et al. ASCO 2020;Abstract 5516; [3] Fizazi et al. ASCO 2020;Abstract 5514.

# Comparison of Toxicities: PROSPER vs. ARAMIS

| Toxicity | Enzalutamide | Placebo | Darolutamide | Placebo |
|---|---|---|---|---|
| Fatigue/Asthenia | 33% | 14% | 16% | 11% |
| Fall | 11% | 4% | 4% | 5% |
| Dizziness | 10% | 4% | 5% | 4% |
| Mental Impairment | 5% | 2% | 1% | 2% |

Hussain M et al. *N Engl J Med* 2018;378(26):2465-74; Fizazi K et al. *N Engl J Med* 2019;380(13):1235-46.



Courtesy of Daniel P Petrylak, MD

# Conclusions and Clinical Implications

- Enzalutamide, apalutamide and darolutamide have similar hazard ratios for metastasis-free survival and overall survival.
- Different toxicity patterns particularly with falls, fatigue and mental impairment in favor of darolutamide

**Which systematic treatment, if any, would you recommend for a 74-year-old man with M0 PC who experiences disease progression with negative imaging while receiving enzalutamide (with ADT)?**

a. None — observation
b. Darolutamide
c. Apalutamide
d. Abiraterone/prednisone
e. Docetaxel
f. Other

# Case Presentation – Dr Petrylak: 74-year-old man with M0 Prostate Cancer

- 74 year old male
- In 2007, the patient had an elevated PSA. The patient underwent a radical robotic prostatectomy on 6/18/2007. Final pathology demonstrated a Gleason 3+4 = 7 adenocarcinoma involving both lobes of the prostate. Tumor extended into the left posterior pseudo-capsule. Tumor was present at the left apical and left posterior soft tissue margins. Intra-prostatic peri-neural invasion was present. The base and seminal vesicle margins were negative for tumor. Stage pT2cN0M0.

# Case Presentation – Dr Petrylak: 74-year-old man with M0 Prostate Cancer (cont)

- PSA started to rise in 1/2013. He could not undergo external beam radiation therapy due to the fact that he had severe incontinence from surgery.
- The patient's PSA subsequently went to 12 in September 2014 and he started androgen blockade with degarelix.
- The patient remained on intermittent androgen blockade until January of 2018, when his PSA did not decline after the initiation of androgen blockade. At that time his PSA was 18. Repeat imaging negative. PSA DT=5 months. Testosterone=20

# Case Presentation – Dr Petrylak: 74-year-old man with M0 Prostate Cancer (cont)

- The patient was started on enzalutamide when his PSA reached 26.
- His PSA doubling time was 8 months at the start of enzalutamide. His PSA reached a nadir of 4 in October 2018 then began to rise again in January 2019 to 11. Repeat imaging negative, patient requested stopping enzalutamide.
- He was then started on apalutamide and discontinued this in December 2019. PSA = 71.
- Repeat imaging in February 2020 demonstrated new progression in bone metastases, and the patient was started on docetaxel in March 2020.

# Agenda

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## Module 2: Metastatic Hormone-Sensitive PC — Dr Sweeney

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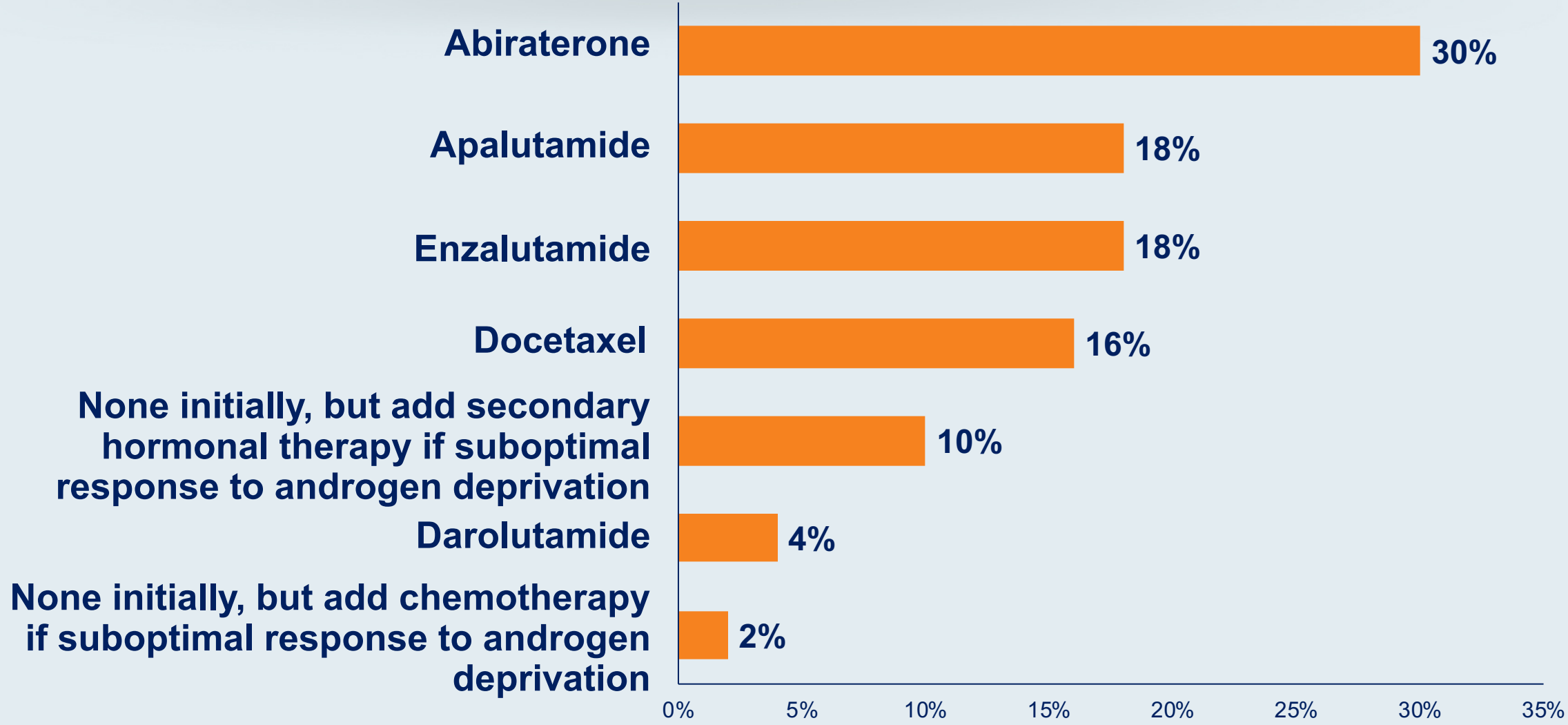
- PSMA imaging (Abstract 5501)

## Module 2: Metastatic Hormone-Sensitive PC — Dr Sweeney

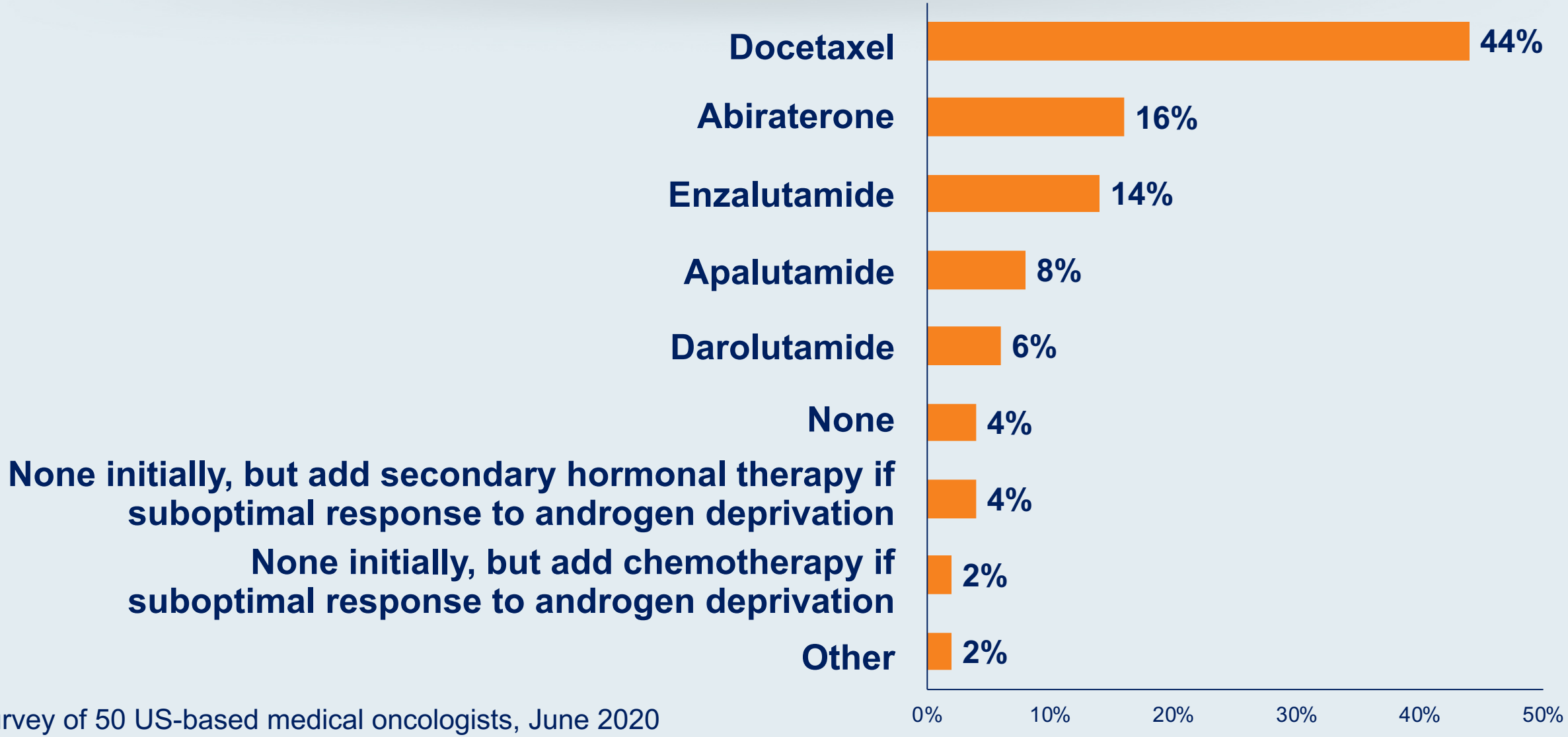
- Secondary hormonal therapy versus chemotherapy
- LATITUDE, ARCHES, TITAN and ENZAMET trials and implications

**Regulatory and reimbursement issues aside, what systemic therapy, if any, would you typically add to androgen deprivation for a 65-year-old patient who underwent radical prostatectomy for Gleason 8 prostate cancer but presents 3 years later with 3 asymptomatic bone metastases that are not amenable to ablative therapy?**



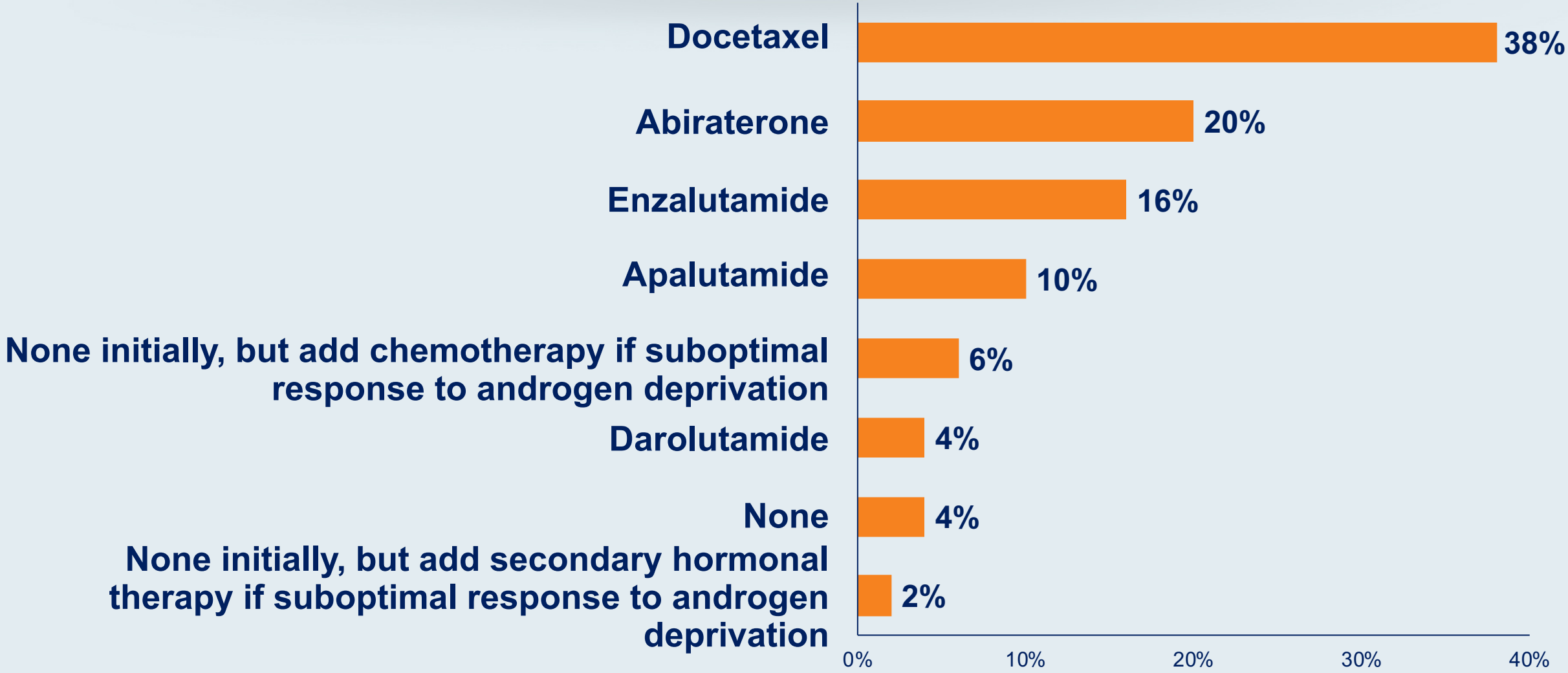

Survey of 50 US-based medical oncologists, June 2020

# What systemic therapy, if any, would you typically add to androgen deprivation for a 65-year-old patient presenting de novo with Gleason 8 prostate cancer and widespread, moderately symptomatic bone metastases?




Survey of 50 US-based medical oncologists, June 2020

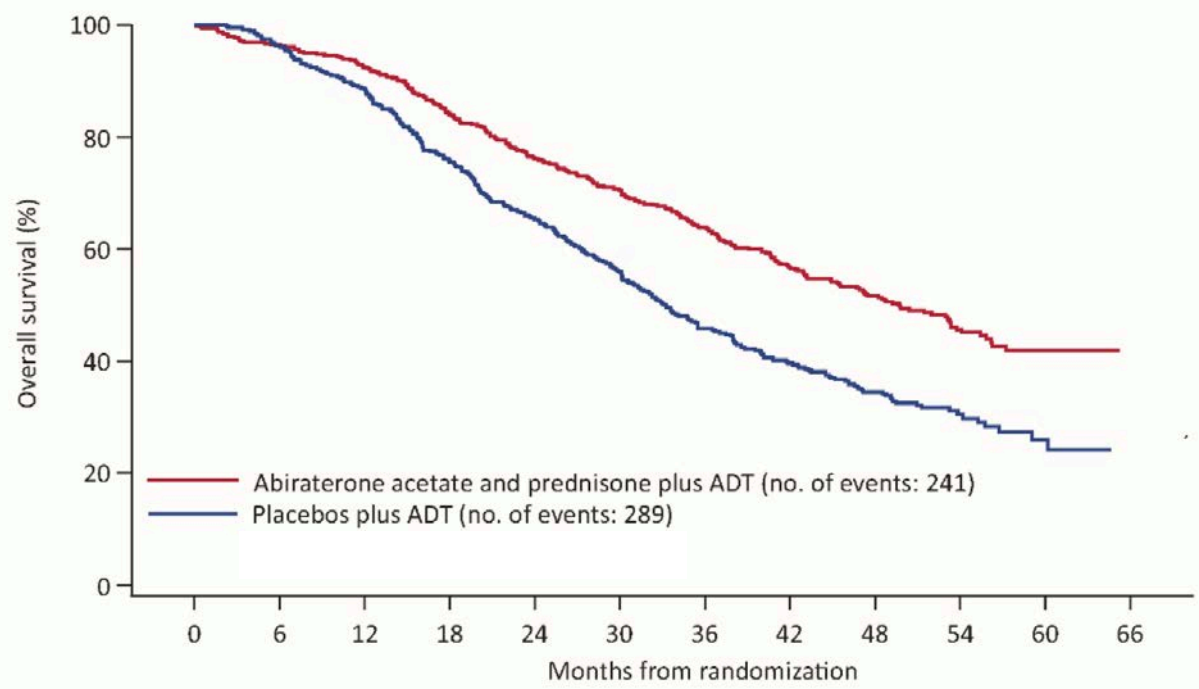
# What systemic therapy, if any, would you typically add to androgen deprivation for a 65-year-old patient presenting de novo with Gleason 8 prostate cancer and asymptomatic liver metastases?




Survey of 50 US-based medical oncologists, June 2020

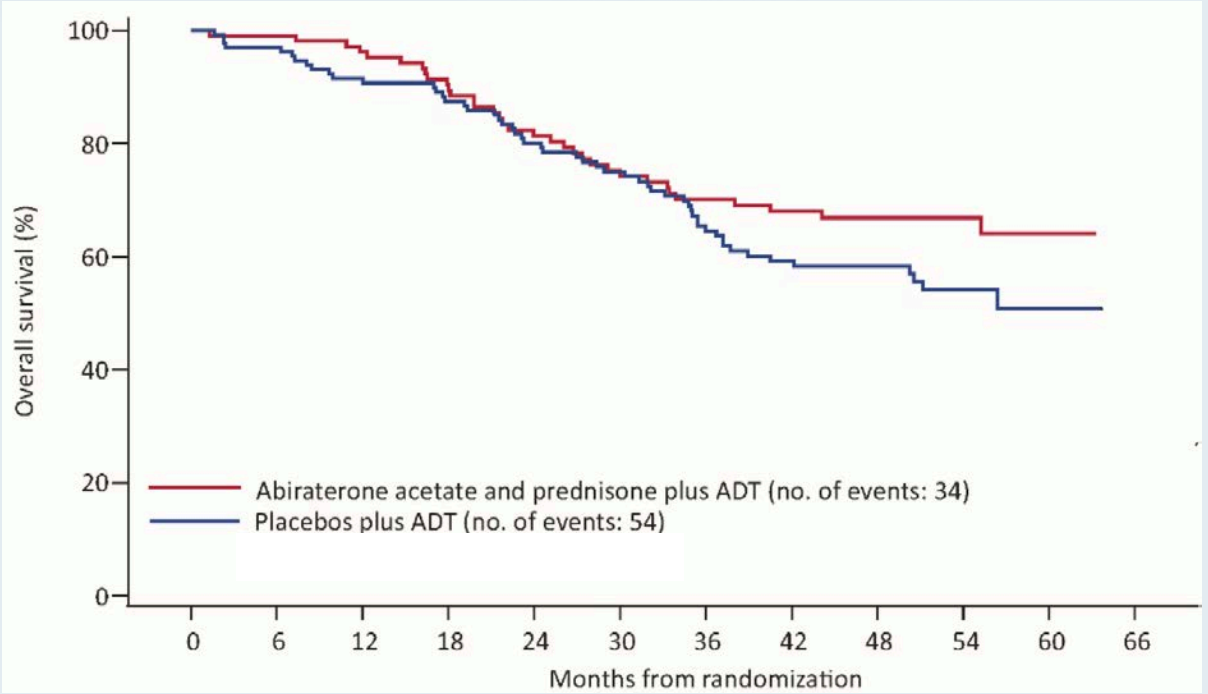
# LATITUDE Final Overall Survival Analysis By Volume of Disease (CHAARTED definition*)

## High-Volume Disease




| | ADT + AA + P (n = 487) | ADT + Placebo (n = 468) | HR | *P*-value |
|---|---|---|---|---|
| mOS | 49.7 mo | 33.3 mo | 0.62 | <0.0001 |

## Low-Volume Disease




| | ADT + AA + P (n = 110) | ADT + Placebo (n = 133) | HR | *P*-value |
|---|---|---|---|---|
| mOS | Not reached | Not reached | 0.72 | 0.1242 |

*CHAARTED definition of low vs high volume: Presence of visceral mets and/or ≥4 bone mets, with one outside the vertebral column or pelvis

Fizazi K et al. Lancet Oncol 2019;20:686-700. *Chi et al 2019 GU Cancers Symposium;* Abstract 141.

# Summary Results for ADT + Enzalutamide (ARCHES) and Apalutamide (TITAN) in Metastatic HSPC

| | ARCHES (N = 1150) | | TITAN (N = 1052) | |
|---|---|---|---|---|
| Characteristics | • 2/3rd High Volume<br>• 17% prior docetaxel<br>• 25% prior RP/XRT | | • 2/3rd High Volume<br>• 10% prior docetaxel<br>• 17% prior RP/XRT | |
| | **ADT + Enzalutamide (n = 574)** | **ADT (n = 576)** | **ADT + Apalutamide (n = 955)** | **ADT (n = 554)** |
| Radiographic PFS | NR | 19.0 mo | NR | 22.1 mo |
| | **HR (overall): 0.39**<br>• HR (prior docetaxel): 0.52<br>• HR (high volume): 0.43<br>• HR (low volume): 0.25 | | **HR (overall): 0.48**<br>• HR (prior docetaxel): 0.47<br>• HR (high volume): 0.53<br>• HR (low volume): 0.36 | |
| Overall Survival | NR | NR | NR | NR |
| | **HR: 0.81 (Immature)** | | **HR (overall): 0.67**<br>• HR (prior docetaxel): 1.27<br>• HR (high volume): 0.68<br>• HR (low volume): 0.67 | |

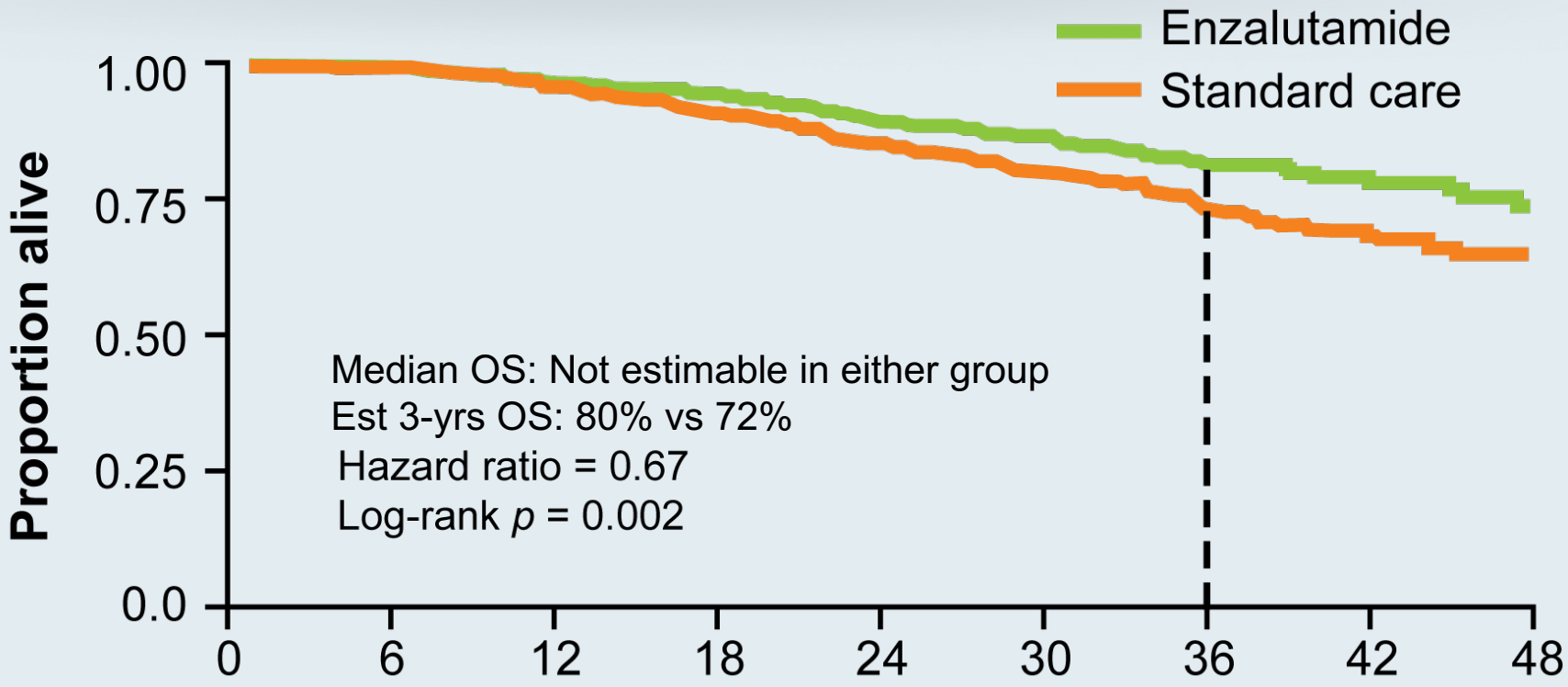
Armstrong AJ et al. *J Clin Oncol* 2019;[Epub ahead of print]. Chi KN et al. *N Engl J Med* 2019;381(1):13-24.

NR, not reached

# ENZAMET: ADT + Enzalutamide or Standard Nonsteroidal Antiandrogen
# Primary Endpoint: Overall Survival

## A Mixed Bag

- High and Low Volume
- *De novo* vs Metach
- Concurrent Docetaxel
- Many Permutations




**Number at risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Standard care | 562 | 551 | 531 | 501 | 452 | 311 | 174 | 86 | 32 |
| Enzalutamide | 563 | 558 | 541 | 527 | 480 | 340 | 189 | 106 | 45 |

Davis ID et al. *N Engl J Med* 2019;381(2):121-31.

# The many versions of mHSPC - polymetastatic *de novo* presentation

| Clinical Setting | CT A/P; Tc Bone Scan (possible pelvic LN) | PSMA PET Status (beyond pelvic LN) |
|---|---|---|
| High-risk localized | None (but micromets possible) | None or minimal or extensive |
| Low volume / Low Risk ("oligometastatic": surgery/ SBRT) | 3 or fewer bone mets (+/- LN) | Few or many more lesions |
| Low volume / Low Risk* *(surgery / SBRT not viable)* | 3 or fewer bone mets but extensive nodal involvement | Few or many more lesions |
| High volume / High Risk* | 4 or more bone mets &/or visceral mets | Many lesions |

* CHAARTED and LATITUDE definitions

Courtesy of Christopher Sweeney, MBBS

# The many versions of mHSPC - polymetastatic *metachronous* presentation

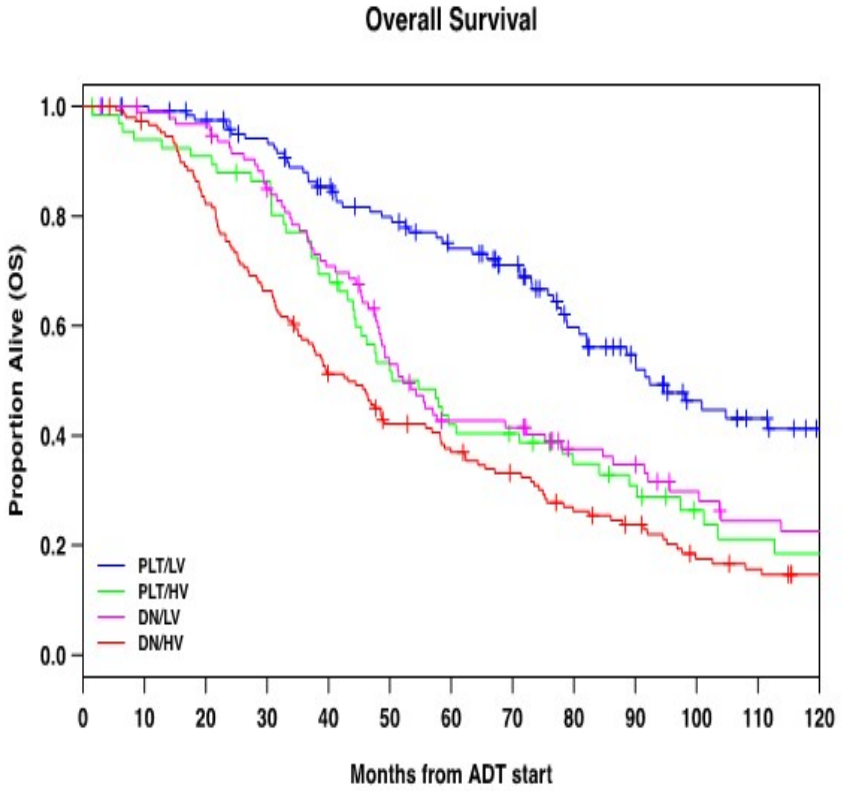
| Clinical Setting | CT A/P; Tc Bone Scan (possible pelvic LN) | PSMA PET Status (beyond pelvic LN) |
|---|---|---|
| Rising PSA post RP or XRT | None | None or minimal or extensive |
| Low volume* ("oligometastatic": surgery/ SBRT) | 3 or fewer bone mets and/or isolated nodal | Few or many more lesions |
| Low volume* (surgery/ SBRT not viable) | 3 or fewer bone mets but extensive nodal involvement | Few or many more lesions |
| High volume * | 4 or more bone lesions, visceral mets | Many lesions |

* CHAARTED definition volume only; LATITUDE/STAMPEDE *high vs low risk* *only de novo*

Courtesy of Christopher Sweeney, MBBS

# Different Prognoses by:
# Type of presentation / Extent of metastases

| CHAARTED & GETUG-15 (TS alone) | Median OS (years) |
|---|---|
| Metach and low volume | ~8 |
| Metach and high volume | 4.5 |
| De Novo and LV | 4.5 |
| De Novo and HV | 3 |




| Groups | N (% events) | Median OS yrs (95%CI) |
|---|---|---|
| Prior Tx+LV | 125 (50) | 7.7 (6.7,10.6) |
| Prior Tx+HV | 67 (75) | 4.6 (3.7,6.7) |
| De-novo+LV | 96 (70) | 4.3 (4,6.5) |
| De-novo+HV | 148 (84) | 3.6 (3.1,4.7) |

***High volume:*** *visceral mets and/or 4 or more bone mets*
*With at least one beyond vertebra and pelvis*

*Francini et al Prostate 2018; Gravis et al Eur Urol 2018*
*(Prior Tx: metachronous metastases)*

56% of mHSPC low volume in hospital registry are metachronous; found by surveillance with rising PSA

Courtesy of Christopher Sweeney, MBBS

## Which systemic treatment would you likely recommend for a 55-year-old man with no comorbidities and high-volume de novo metastatic PC?

a. ADT alone
b. ADT + docetaxel
c. ADT + abiraterone
d. ADT + enzalutamide
e. ADT + apalutamide
f. ADT + darolutamide
g. Other

**Which systemic treatment, if any, would you most likely recommend for an 82-year-old man with a history of congestive heart failure and coronary artery disease who presents with 2 asymptomatic biopsy-proven rib metastases 10 years after undergoing prostatectomy?**

a. None — observation
b. ADT alone
c. ADT + docetaxel
d. ADT + abiraterone
e. ADT + enzalutamide
f. ADT + apalutamide
g. ADT + darolutamide
h. Other

# Spectrum of patients with mHSPC and the disease

**One extreme: 55 yo with no co-morbidities and high volume *de novo* metastatic disease**

**versus**

**Other extreme: 82 yo with CHF and CAD and 2 bone metastases 10 years after prostatectomy**

Courtesy of Christopher Sweeney, MBBS

# Guidance for polymetastatic HSPC

**Based on data as of July 2020: docetaxel versus 'amide versus abiraterone depends on**

- **Fitness for chemotherapy**
- **Fitness for apa/enzalutamide (no seizure, no frailty)**
- **Fitness for abiraterone (blood sugar, hypertension, liver function)**

**Evidence of consistent overall survival benefit for a given setting with use of a given agent**

- **with no decrement in QOL on therapy**

**If chemofit and high volume (and not in COVID pandemic):**

- **Docetaxel either at time of TS start or at CRPC after abiraterone or 'amide**
- **Consider giving docetaxel first (when most fit; less 'amide or abiraterone "costs"/"exposure")**

**If chemofit and low volume not amenable to surgery/SBRT**

- **At time of TS start: Clear evidence for 'amide, abiraterone; less consistent for docetaxel but do not forget about docetaxel for mCRPC**

Courtesy of Christopher Sweeney, MBBS

# Score-card of *direct* consistent data to help choose the right mHSPC Rx[1]

| Patient co-morbidity | Burden and Presentation of Mets | Agent to add to testosterone suppression |
|---|---|---|
| **Chemofit[3]** | **High volume[2]** | **Docetaxel / Abiraterone / Apalutamide/ Enzalutamide** |
| **Not Chemofit** | **High volume[2]** | **Abiraterone / Apalutamide / Enzalutamide** |
| **Chemofit and Not Chemofit** | **Low volume[2] / *De-Novo* Metastatic** | **Abiraterone / Apalutamide / Enzalutamide or Radiate primary[4] *(Docetaxel mixed results if chemofit)*** |
| **Chemofit and Not chemofit** | **Low volume[2] / Prior local therapy[6]** | **Apalutamide[7] / Enzalutamide[7] *(no data from abiraterone studies no evidence of benefit with docetaxel)*** |

[1] **Choice based on patient-physician discussion and availability/affordability**; [2]CHAARTED definition; [3]Able to tolerate 75mg/m$^2$ of docetaxel every 3 weeks; [4]**Unknown if docetaxel or new hormonal therapies add to radiation or radiation adds to docetaxel or new hormonal therapies**; [6]Prior prostatectomy or radiation with curative intent; [7]Very immature

Courtesy of Christopher Sweeney, MBBS

# Conclusions polymetastatic HSPC

- **When deciding on which systemic therapy for which patient with mHSPC**
  - **Are they chemo-fit or not chemo-fit?**
  - **Do they have a low or high burden of mHSPC?**
  - **Look at all the data to define treatment burden vs treatment benefit for a given subgroup**
  - **Engage the patient in treatment choice**
    - **Some chemofit pts with high vol mHSPC might want to get chemo out of the way**
    - **Avoid chemo in COVID pandemic**
    - **Avoid personal biases (eg: “chemophobia - hormonophilia”)**

Courtesy of Christopher Sweeney, MBBS

# Case Presentation – Dr Sweeney: 66-year-old man with de novo low volume metastatic HSPC

- 66 yo in 2010 with left hip pain & sciatica and MRI pelvis bone met -> PSA 1244 + Prostate mass.
  - Tc bone scan uptake in left pubic bone only
  - CT C/A/P craggy prostate; pubic bone lesion only
  - Prostate biopsy: high volume Gleason 8
- Treatment
  - Dec 2010 ADT commenced
  - Apr 2011 radiation to bone met and prostate
  - ADT completed Jan 2013.
- Surveillance off ADT:
  - June 2014: PSA 0.05 with testo 340.
  - Mar 2018: 0.05 ng/mL; testo 190 ng/dL
  - 76 yo May 2020: PSA < 0.02; testo 60 with elevated LH and FSH; working full time.

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- Radium-223
- PARP inhibitors

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- PSMA imaging (Abstract 5501)

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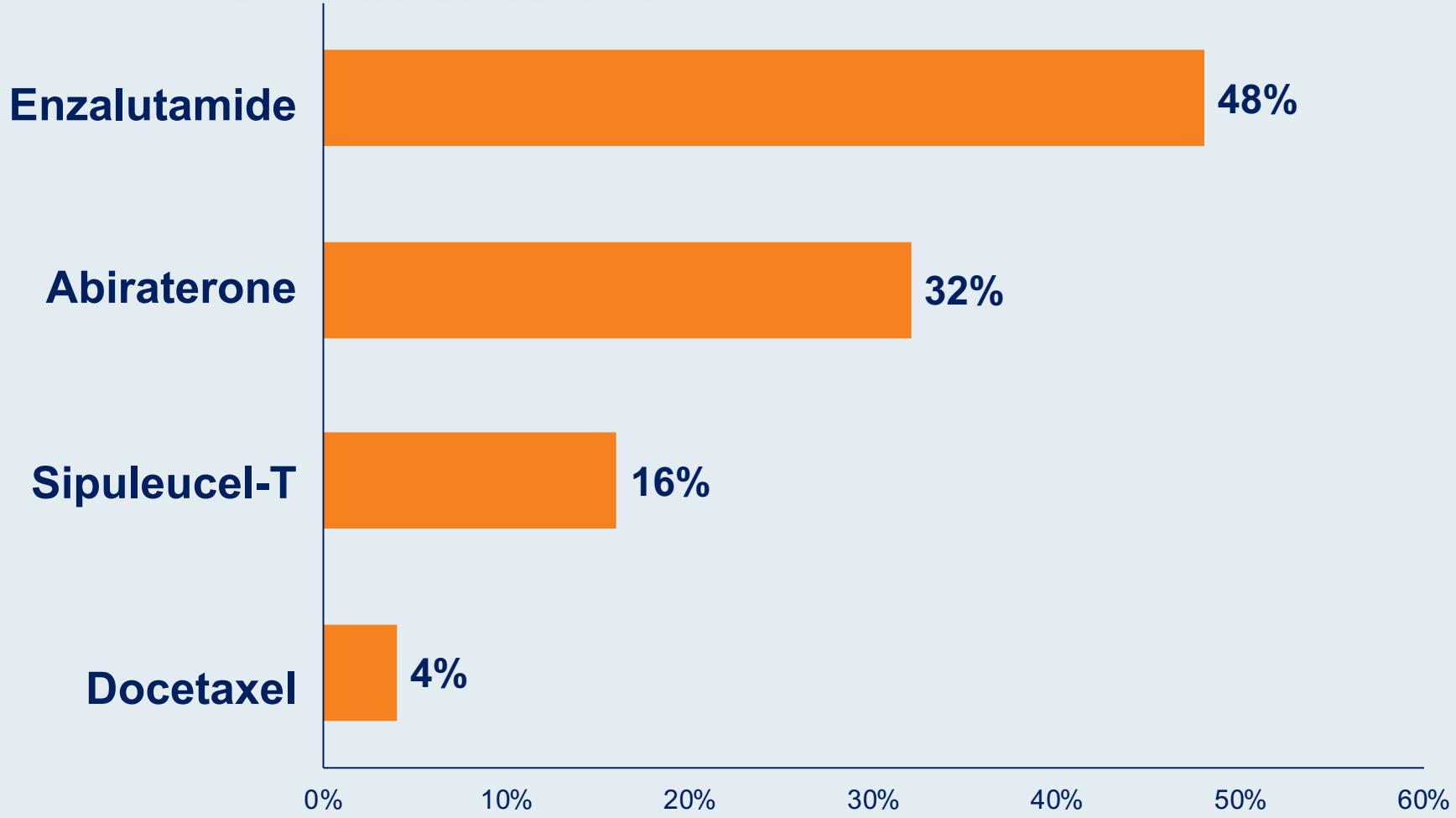
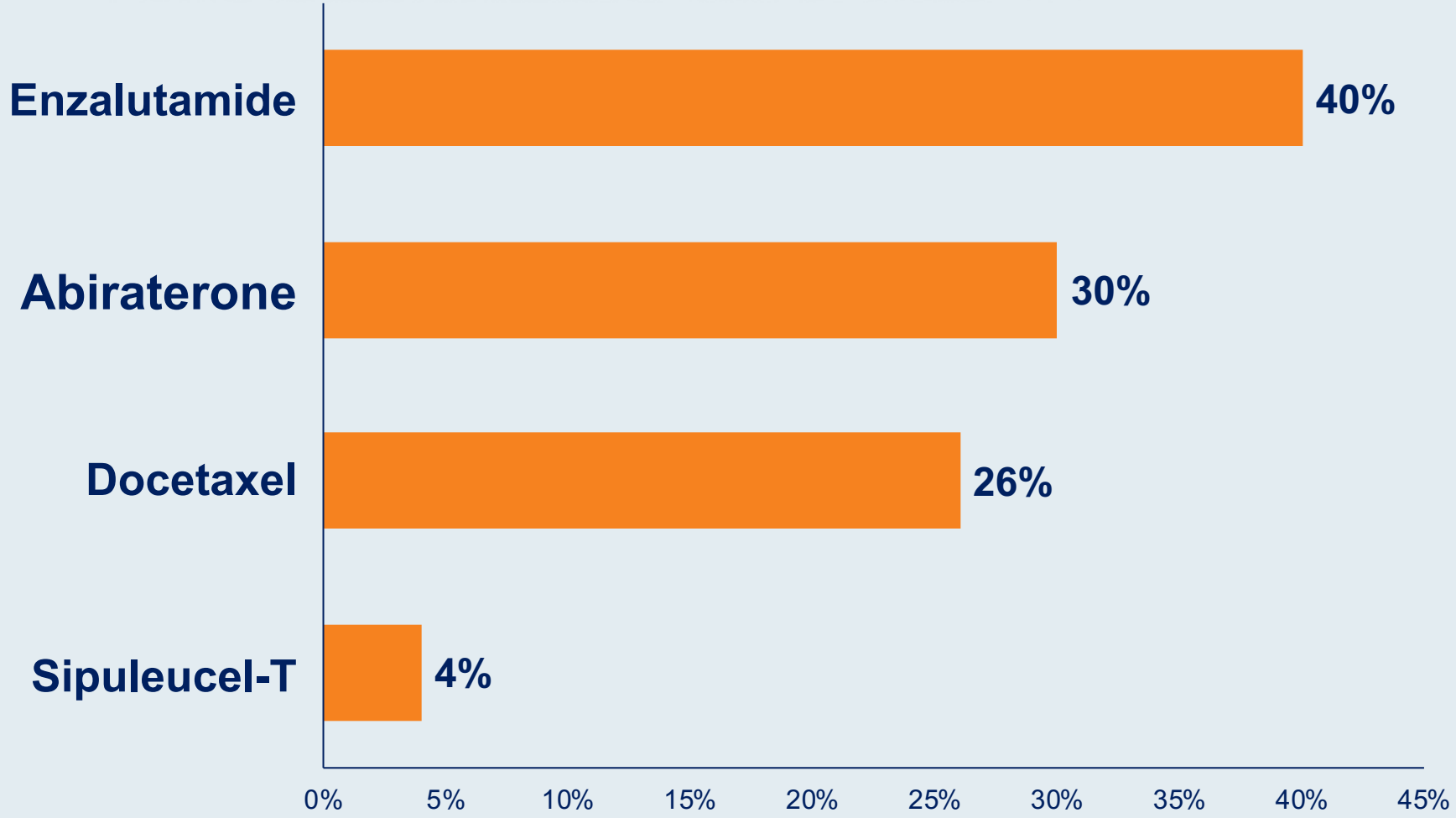
- PARP inhibitors

# A 65-year-old man receiving androgen deprivation therapy (ADT) for M0 disease after radical prostatectomy is found to have asymptomatic bone metastases. What systemic treatment would you most likely recommend?



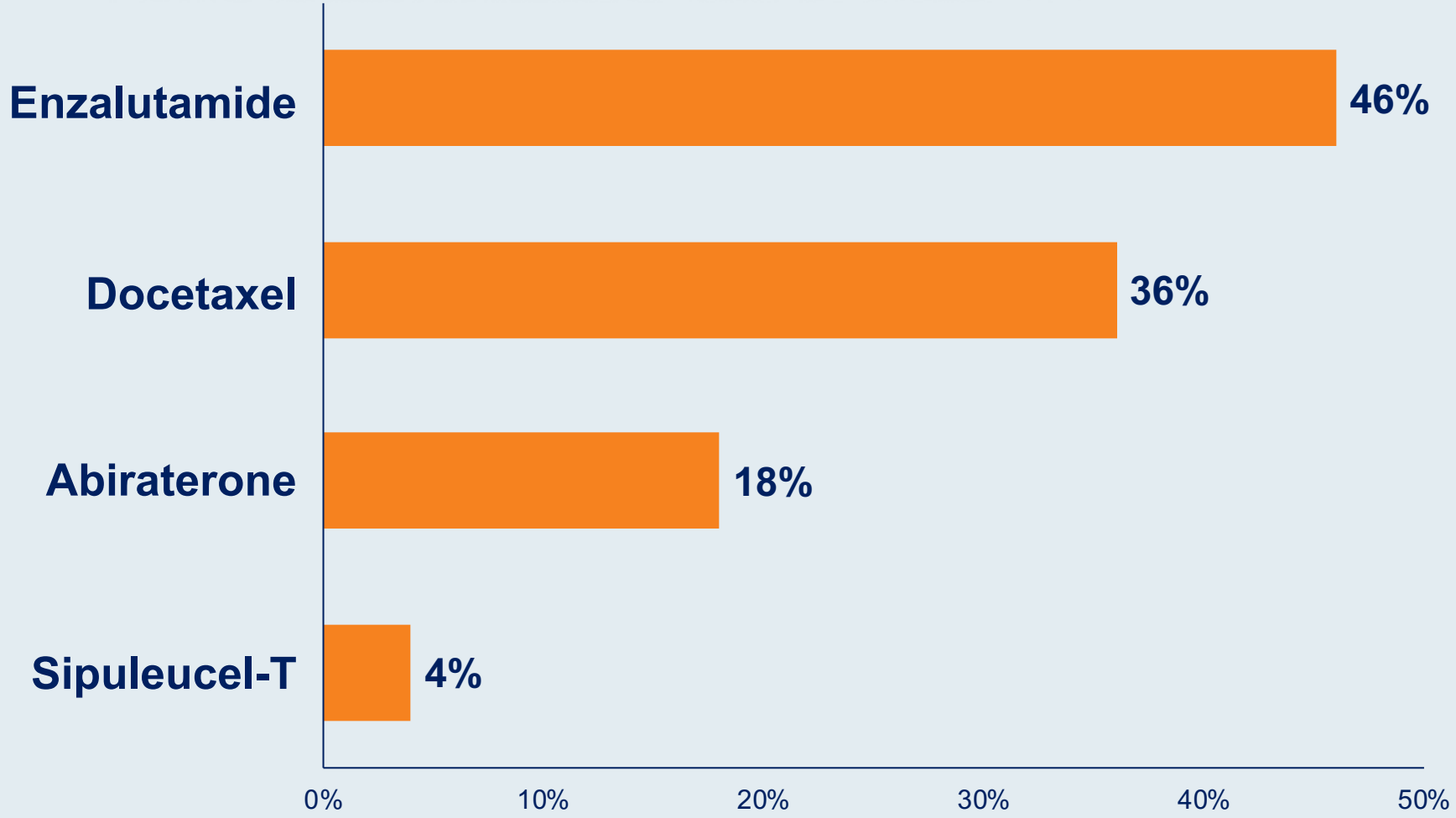

Survey of 50 US-based medical oncologists, June 2020

# A 65-year-old man receiving ADT for M0 disease after radical prostatectomy is found to have widespread, moderately symptomatic bone metastases. What systemic treatment would you most likely recommend?



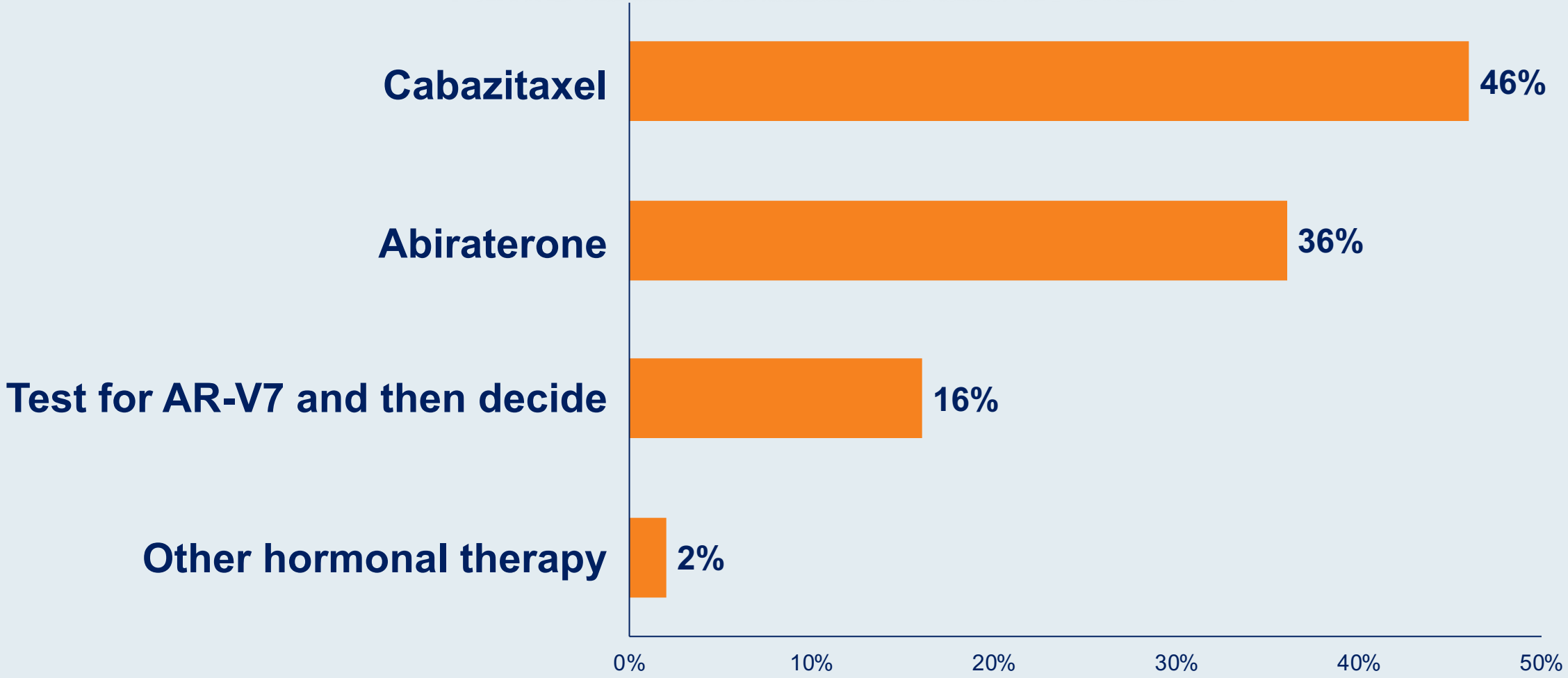

Survey of 50 US-based medical oncologists, June 2020

# A 65-year-old man receiving ADT for M0 disease after radical prostatectomy is found to have asymptomatic liver metastases. What systemic treatment would you most likely recommend?



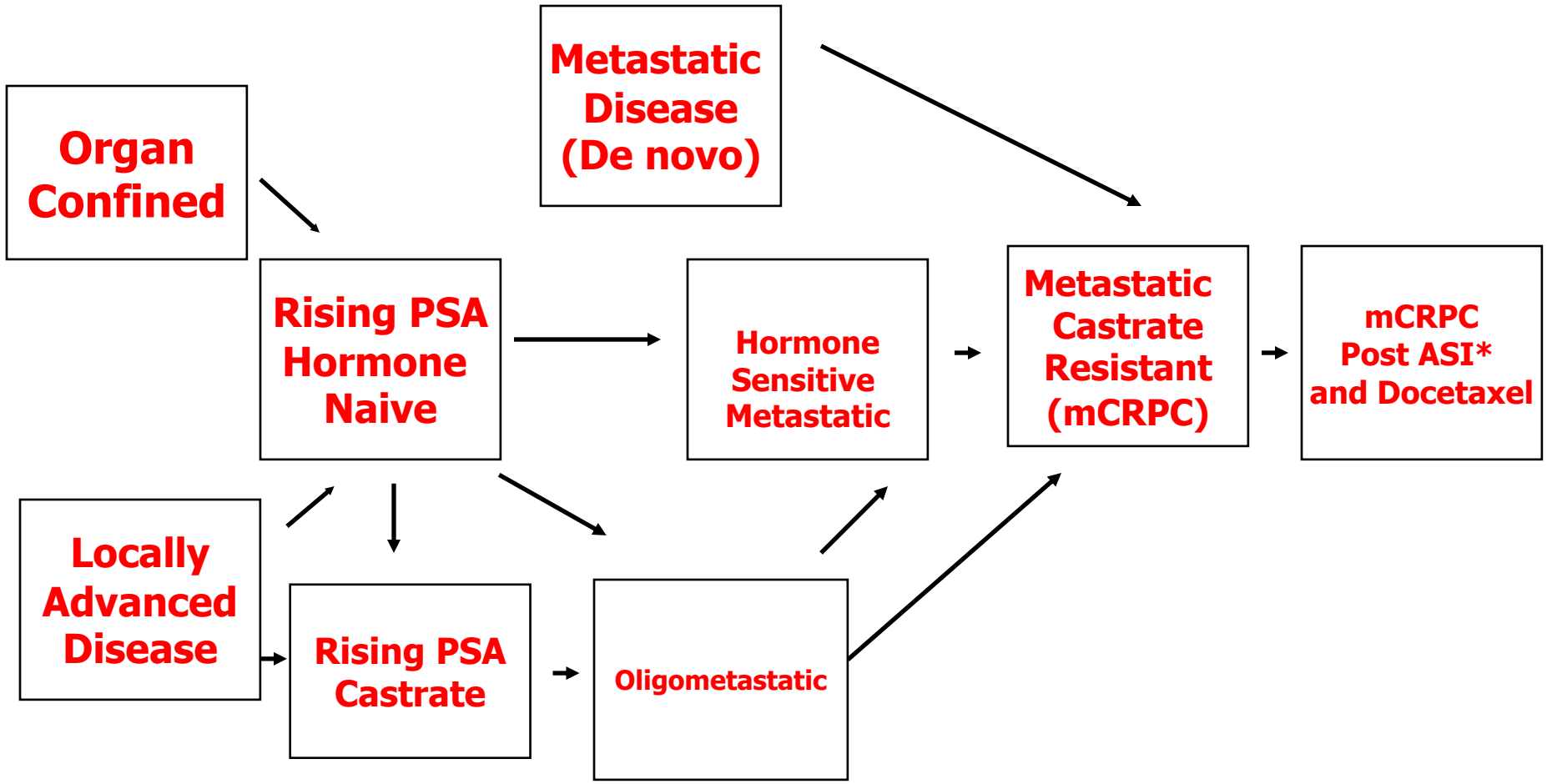

Survey of 50 US-based medical oncologists, June 2020

**A 65-year-old man presents with minimally symptomatic metastatic prostate cancer (BRCA wild type) to the nodes and bone and receives docetaxel and androgen deprivation with response followed by progression. The patient is started on enzalutamide but experiences further disease progression after 18 months. What would you recommend?**




Survey of 50 US-based medical oncologists, June 2020

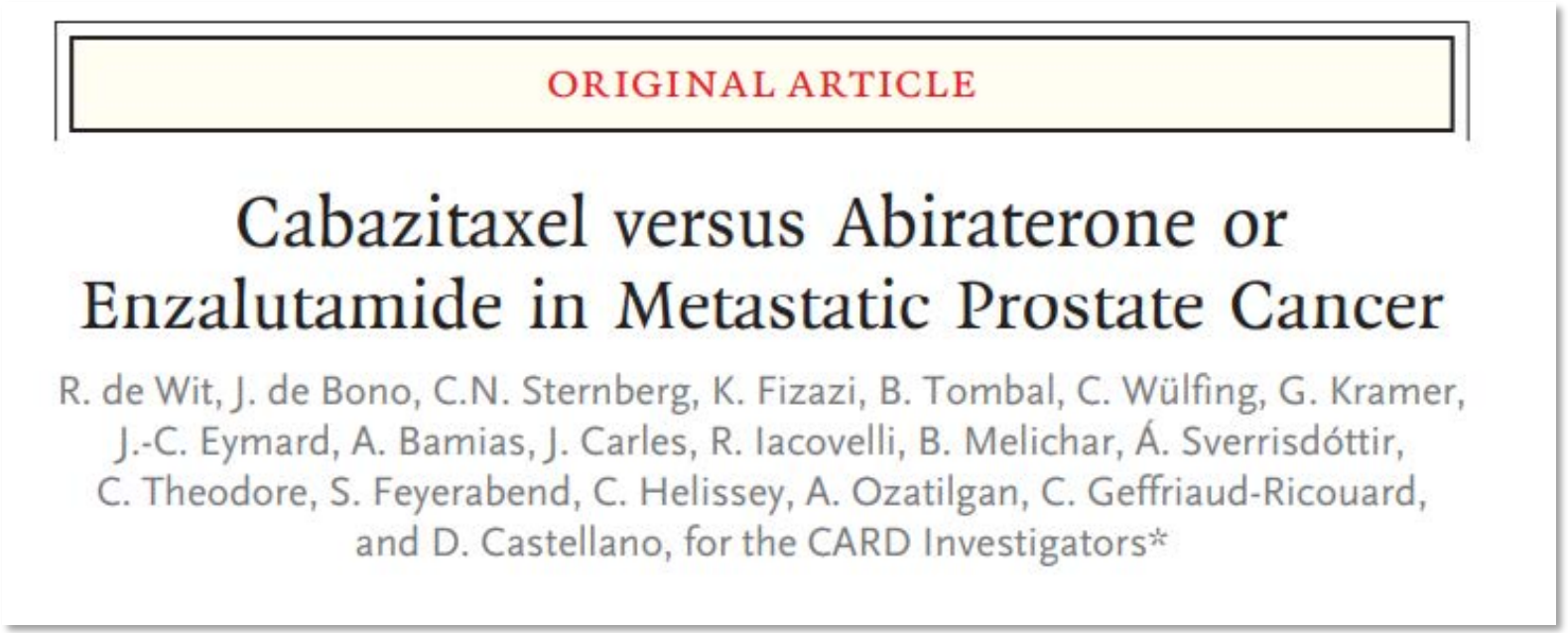
# Clinical States In Prostate Cancer (Circa 2020)




Modified from Scher H, et al. Urology 2000; Courtesy of Robert Dreicer, MD, MS

* ASI: androgen signaling inhibitor

# CARD Trial



ORIGINAL ARTICLE

## Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer

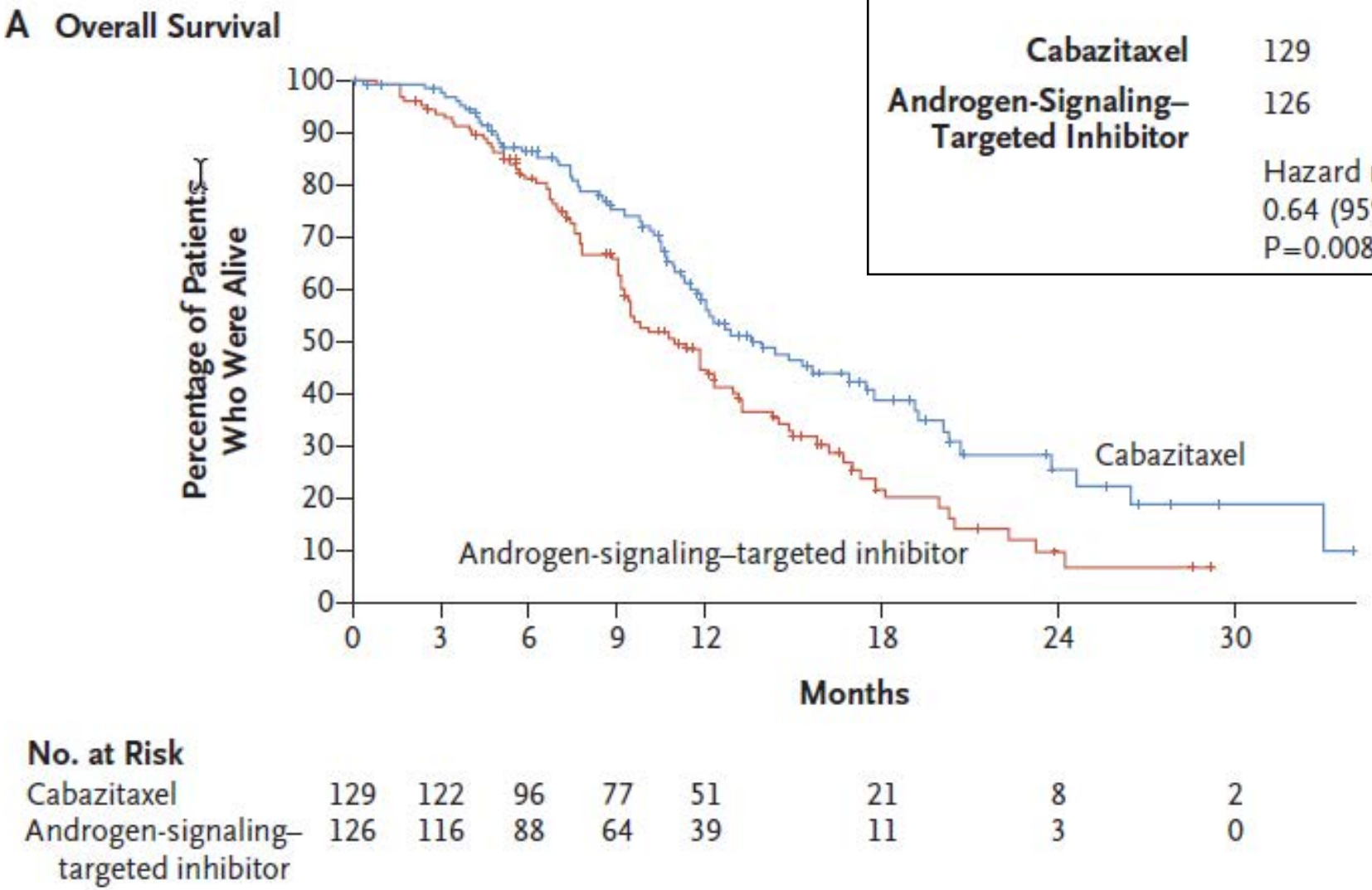
R. de Wit, J. de Bono, C.N. Sternberg, K. Fizazi, B. Tombal, C. Wülfing, G. Kramer, J.-C. Eymard, A. Bamias, J. Carles, R. Iacovelli, B. Melichar, Á. Sverrisdóttir, C. Theodore, S. Feyerabend, C. Helissey, A. Ozatilgan, C. Geffriaud-Ricouard, and D. Castellano, for the CARD Investigators*

- mCRPC patients previously treated with docetaxel and had progression within 12 months of receiving either abiraterone or enzalutamide
- Randomized 1:1 to receive either cabazitaxel (25 mg/m$^2$ plus growth factor) OR alternative agent either abiraterone or enzalutamide
- Primary end point imaging-based progression free survival

de Wit, et al. *N Engl J Med* 2019 381:2506-2518; Courtesy of Robert Dreicer, MD, MS

# CARD Trial

| | No. of Patients | Median Overall Survival (95% CI) *mo* |
|---|---|---|
| Cabazitaxel | 129 | 13.6 (11.5–17.5) |
| Androgen-Signaling–Targeted Inhibitor | 126 | 11.0 (9.2–12.9) |
| | Hazard ratio for death, 0.64 (95% CI, 0.46–0.89) P=0.008 | |




de Wit, et al. *N Engl J Med* 2019 381:2506-2518; Courtesy of Robert Dreicer, MD, MS

ARTICLE

Clinical Research

# Concurrent or layered treatment with radium-223 and enzalutamide or abiraterone/prednisone: real-world clinical outcomes in patients with metastatic castration-resistant prostate cancer

Neal Shore[1] · Celestia S. Higano[2] · Daniel J. George[3] · Cora N. Sternberg[4] · Fred Saad[5] · Bertrand Tombal[6] · Kurt Miller[7] · Jan Kalinovsky[8] · XiaoLong Jiao[9] · Krishna Tangirala[9] · Oliver Sartor[10]

*Prostate Cancer and Prostatic Disease* 2020 May 13; [Epub ahead of print]

- Retrospective study (N = 625) of patients with mCRPC treated with radium-223
- Treatment with radium-223 plus abiraterone/prednisone or enzalutamide was defined as concurrent if both drugs started within 30 days of one another, or layered when the second drug started ≥30 days after the first

# A retrospective analysis of treatment patterns in metastatic castration-resistant prostate cancer patients treated with radium-223

Sartor AO et al.
Genitourinary Cancers Symposium 2019; Abstract 180.

# Era of Genomic Targeted Therapy in Prostate Cancer Has Arrived

- mCRPC is molecularly heterogeneous; up to 30% of mCRPC harbor deleterious alterations in DNA damage repair genes, including those with direct or indirect roles in homologous recombination repair (HRR)

- These gene alterations can confer sensitivity to poly(adenosine diphosphate–ribose) polymerase (PARP) inhibition and platinum agents

    - *BRCA1*, *BRCA2* and *ATM* are the most well characterized

Courtesy of Robert Dreicer, MD, MS

# FDA Approved PARP Inhibitors For Prostate Cancer

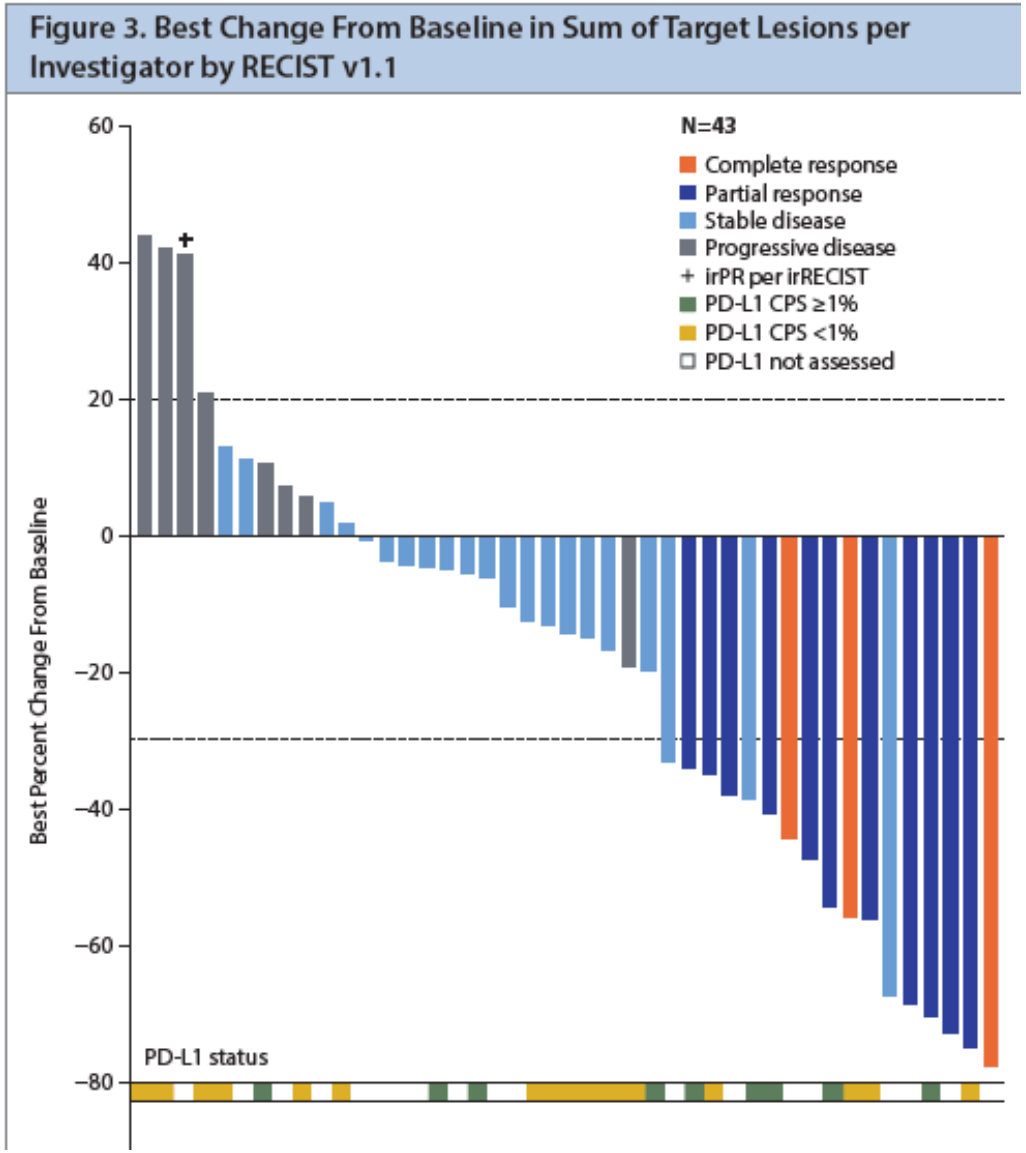
"On May 19, 2020, the Food and Drug Administration approved olaparib for adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC), who have progressed following prior treatment with enzalutamide or abiraterone."

"On May 15, 2020, the Food and Drug Administration granted accelerated approval to rucaparib for patients with deleterious *BRCA* mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy."

Courtesy of Robert Dreicer, MD, MS

# Cabozantinib in combination with atezolizumab in patients with metastatic castration-resistant prostate cancer: results of cohort 6 of the COSMIC-021 study

- Atezolizumab/cabozantinib
- ORR was 32% per RECIST v1.1 with a median DOR of 8.3 months
- Median duration of exposure in all patients was 6.9 months
- Most common grade 3 toxicities
  - Fatigue, diarrhea, nausea, PPE

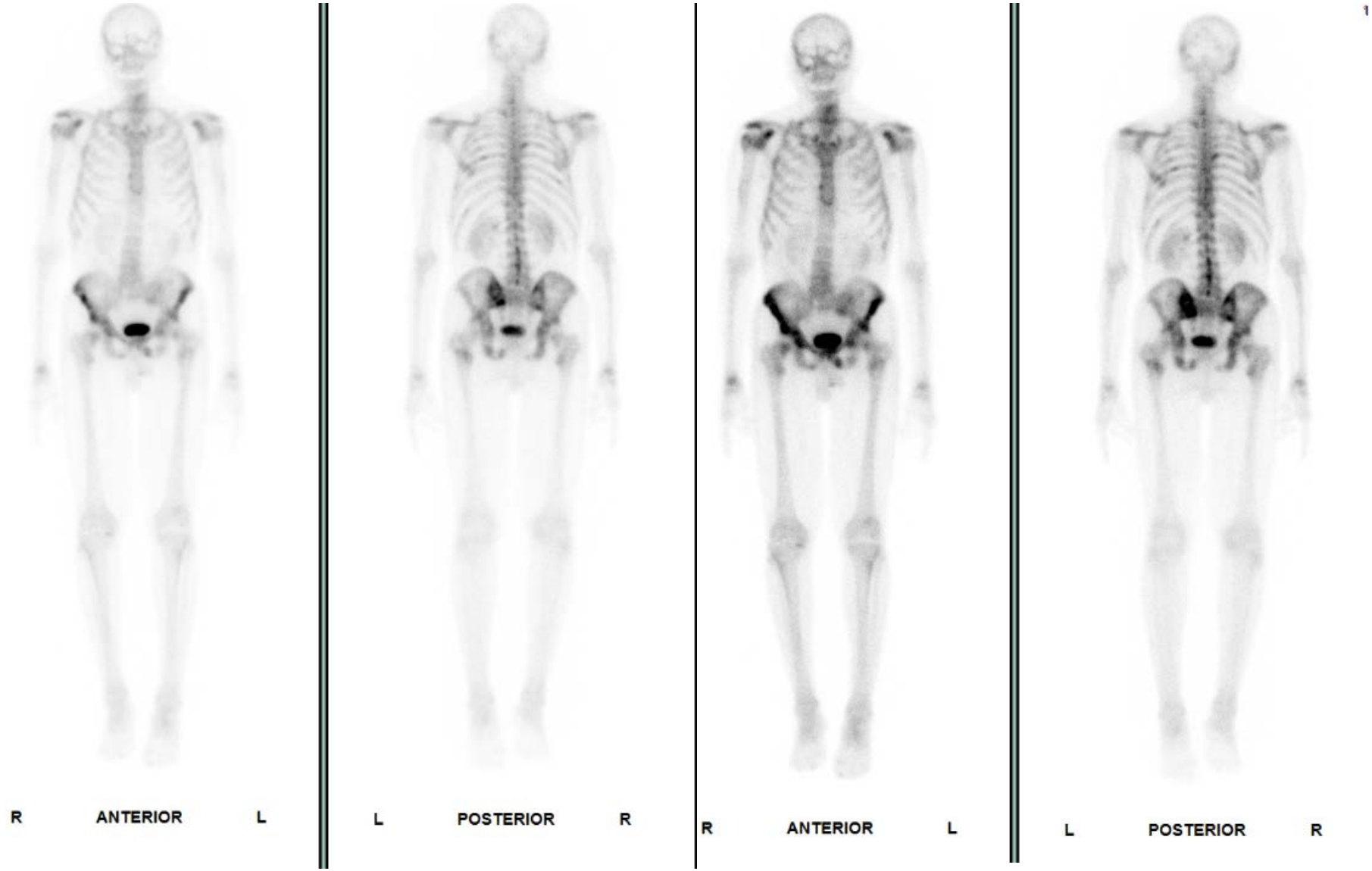



Agarwal N, et al. JCO 38, no. 6 suppl (February 20, 2020) 139-139; Courtesy of Robert Dreicer, MD, MS

# Case Presentation – Dr Dreicer: 72-year-old man with mCRPC

- 72 year old man 5 years out from RRP Gleason 4 +3 , iPSA 8.5
- 12 months post op, detectable rising PSA (0.45), salvage EBRT administered
- PSA progression, pelvic bone mets
- ADT/abiraterone, progression at 18 months
- Some limited bone pain, no weight loss, ECOG 1
- NGS: no actionable DDR germline/somatic mutations

# Case Presentation – Dr Dreicer: 72-year-old man with mCRPC




baseline

progression

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# First-in-human phase I study of ARV-110, an androgen receptor (AR) PROTAC degrader in patients (pts) with metastatic castrate-resistant prostate cancer (mCRPC) following enzalutamide (ENZ) and/or abiraterone (ABI)

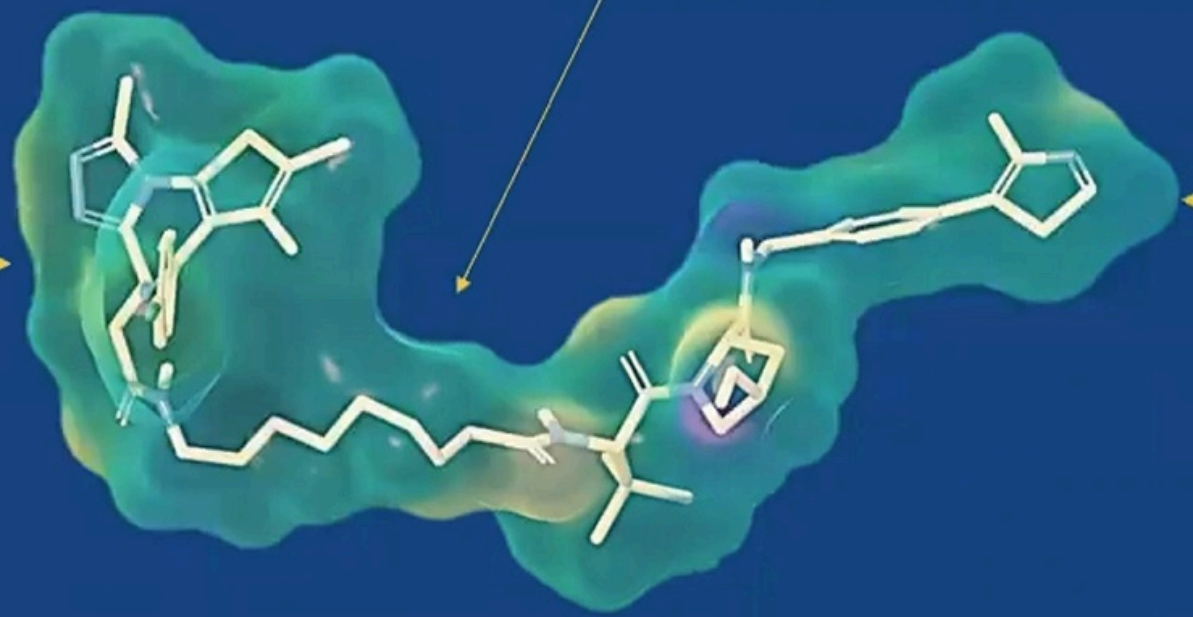
Petrylak DP et al.
ASCO 2020; Abstract 3500.
Developmental Therapeutics—Molecularly Targeted Agents and Tumor Biology

# PROTAC® Protein Degraders

A proteolysis-targeting chimera (PROTAC®) degrader is a chimeric, modular small molecule engineered to induce the degradation of disease-causing proteins via the ubiquitin-proteasome system

A linker region orients the target protein and E3 ligase to enable activity

Protein ligand domain ("warhead") targets a specific protein



Ligase ligand recruits a specific E3 ubiquitin ligase

All three regions of the PROTAC® protein degrader play a role in the specificity and potency of target degradation





Petrylak DP et al. ASCO 2020; Abstract 3500.

# ARV-110 Phase 1 Study

## Design

- "3 + 3" dose escalation; starting dose = 35 mg, orally, once daily with food
- Dose increases dependent on toxicities
  - Range 25% to 100% based on severity of AEs

## Inclusion criteria

- Men with mCRPC, regardless of AR status
- At least two prior systemic therapies, at least one of which was abiraterone or enzalutamide
- Disease progression on most recent therapy
  - Rising PSA or 2+ new lesions upon bone scan

## Endpoints

*Primary*

- Define the maximum tolerated dose and recommended phase 2 dose

*Secondary*

- Pharmacokinetics
- Anti-tumor activity (PSA50, RECIST criteria)

*Exploratory*

- Biomarkers
  - ctDNA mutational profiling
  - AR levels in optional paired biopsies
  - AR and AR-V7 levels in circulating tumor cells (CTCs)

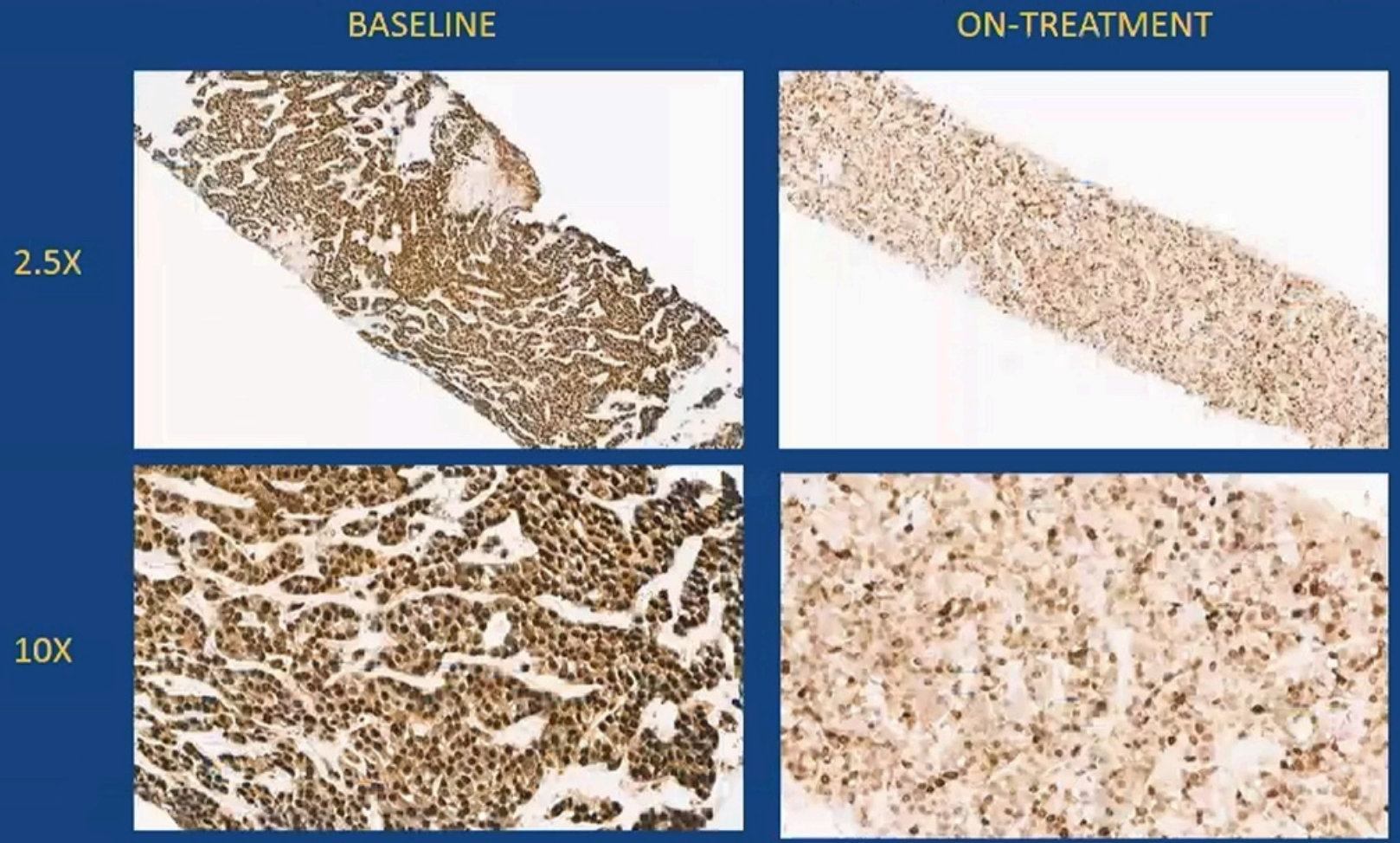
RECIST, Response Evaluation Criteria in Solid Tumors ctDNA, circulating tumor DNA





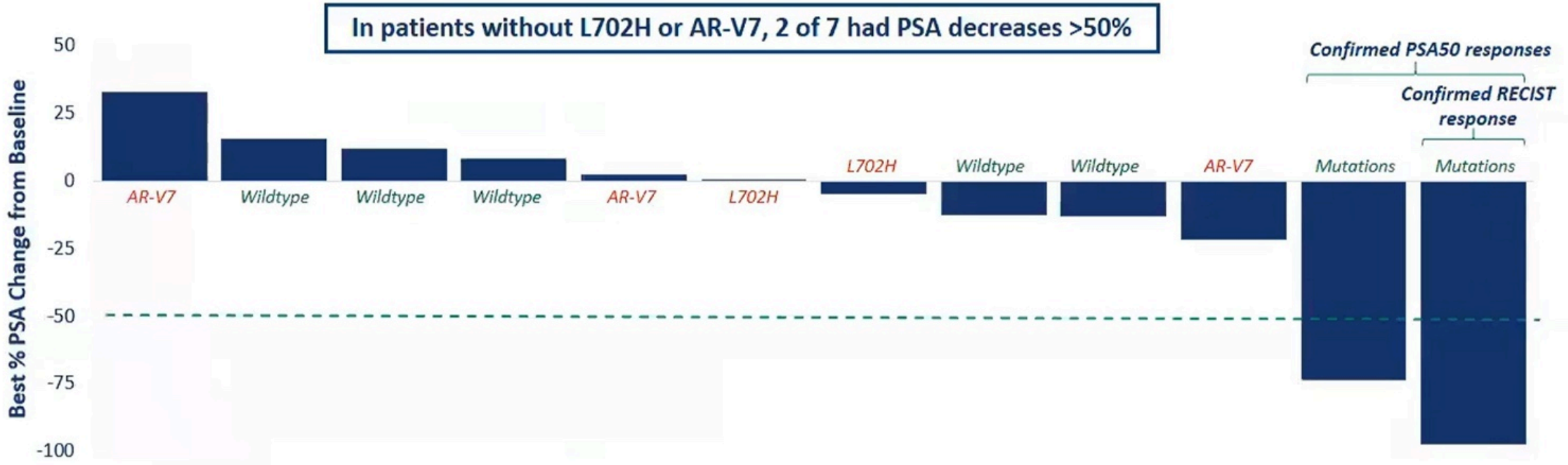
Petrylak DP et al. ASCO 2020; Abstract 3500.

# Preliminary Evidence of ARV-110-mediated AR Degradation in Tumor Tissue




Decreased AR protein levels in an AR wildtype/amplified tumor from a patient following 6 weeks of ARV-110 dosing (280 mg)

# AR Biomarker Status and Best % PSA Change in Patients at ≥140 mg (Excludes DLT Patient; N=12)†




| AR Status: | AR-V7 | Wildtype Amplif. | Wildtype | Wildtype Amplif. | AR-V7 | L702H T878S W742C | L702H | Wildtype | Wildtype | T878A Amplif. AR-V7 | T878A H875Y | T878A H875Y |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

†1 patient discontinued after 2 weeks due to DLT associated with rosuvastatin.
AR status based on assays from Epic Sciences, Foundation Medicine (RUO), and OHSU/KDL





Petrylak DP et al. ASCO 2020; Abstract 3500.

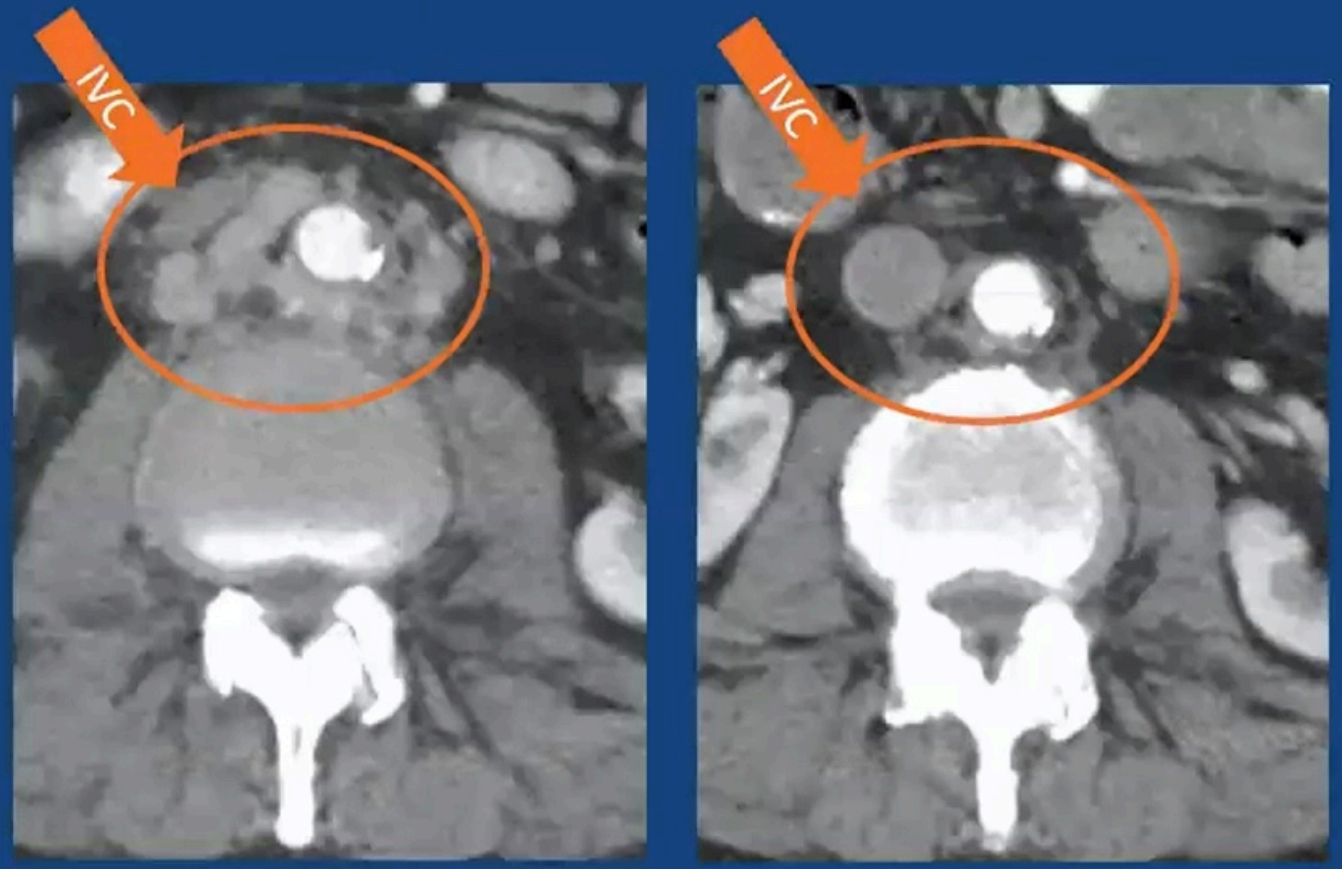
# Confirmed RECIST Partial Response in a Patient with a PCWG3 PSA Response

**Patient history:**
- 72 y.o. male
- Diagnosed 2010 with metastatic prostate cancer (mHSPC)
- Metastatic sites: adrenal gland, aortocaval nodes, bone-spine, pelvis

**Prior therapy:**
- Bicalutamide
- Enzalutamide
- Sipuleucel-T
- Abiraterone
- Cabazitaxel

**Biomarker status:**
- AR H875Y and T878A mutations (associated with resistance to abiraterone and enzalutamide)

**Response:**
- PSA reduction 97%
- Duration of ARV-110 18 weeks and ongoing




BASELINE CT SCAN

AFTER 4 CYCLES

IVC, inferior vena cava



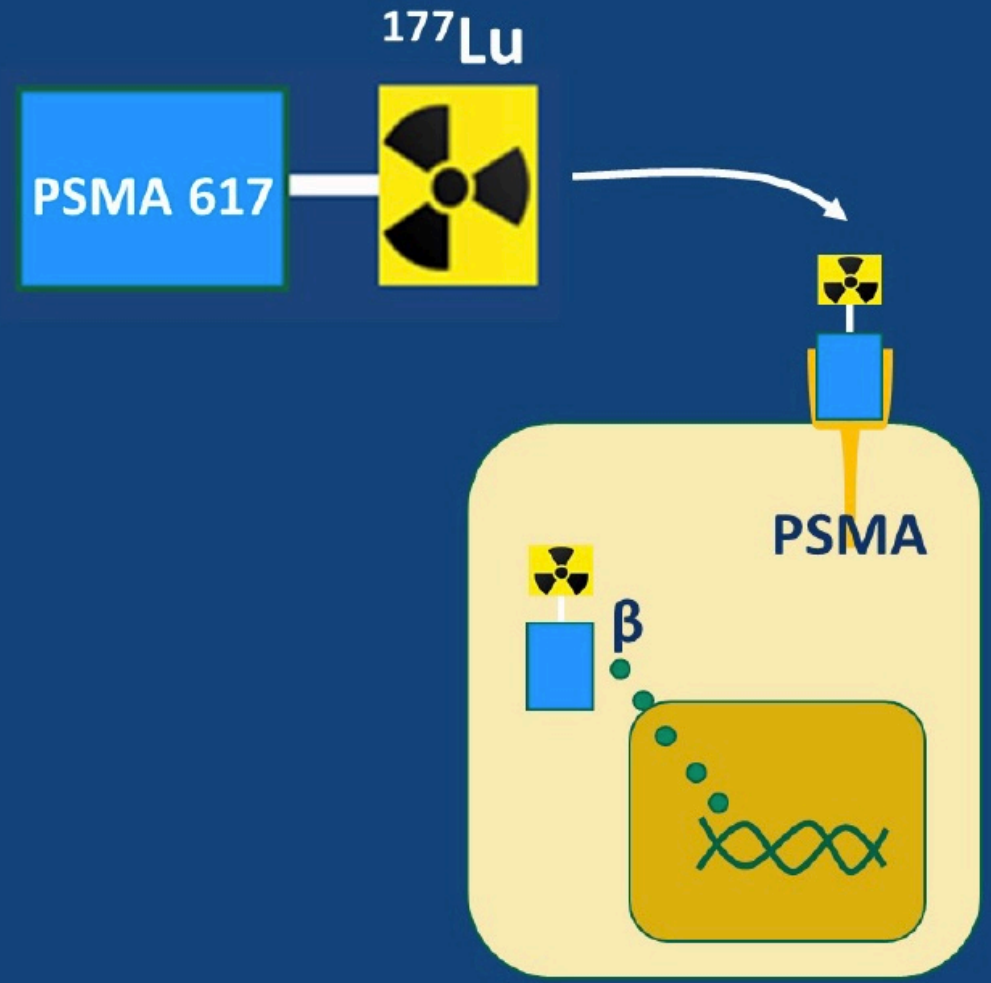


Petrylak DP et al. ASCO 2020; Abstract 3500.

# TheraP: A randomised phase II trial of $^{177}$Lu-PSMA-617 (LuPSMA) theranostic versus cabazitaxel in metastatic castration resistant prostate cancer (mCRPC) progressing after docetaxel: Initial results (ANZUP protocol 1603)

Hofman MS et al.
ASCO 2020; Abstract 5500.
Genitourinary Cancer (Prostate, Testicular, and Penile) Track

# $^{177}$Lu-PSMA-617 is a small molecule RLT targeting PSMA

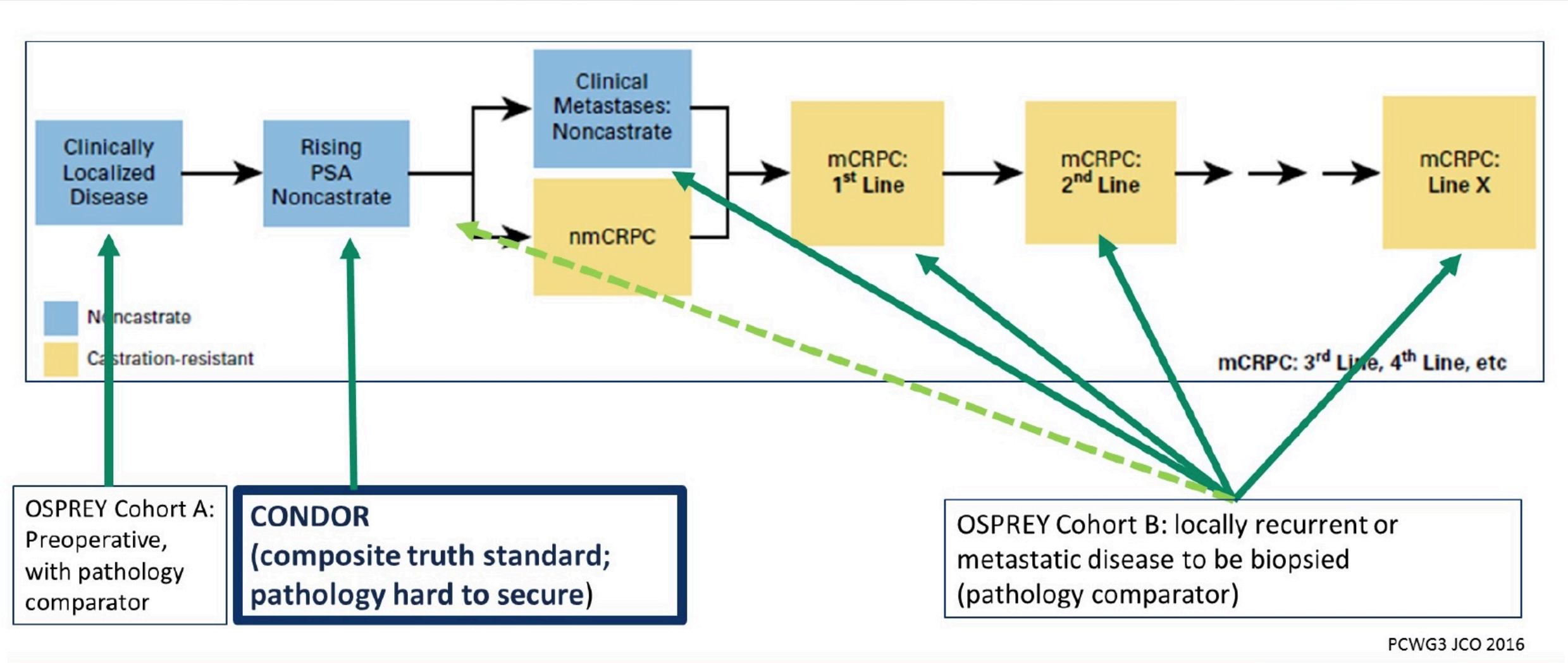



Wise DR. ASCO 2020 Highlights of the Day: Genitourinary Cancer (Prostate)

# Impact of PSMA-targeted imaging with 18F-DCFPyL-PET/CT on clinical management of patients (pts) with biochemically recurrent (BCR) prostate cancer (PCa): Results from a phase III, prospective, multicenter study (CONDOR)

Morris MJ et al.
ASCO 2020; Abstract 5501.
Genitourinary Cancer (Prostate, Testicular, and Penile) Track

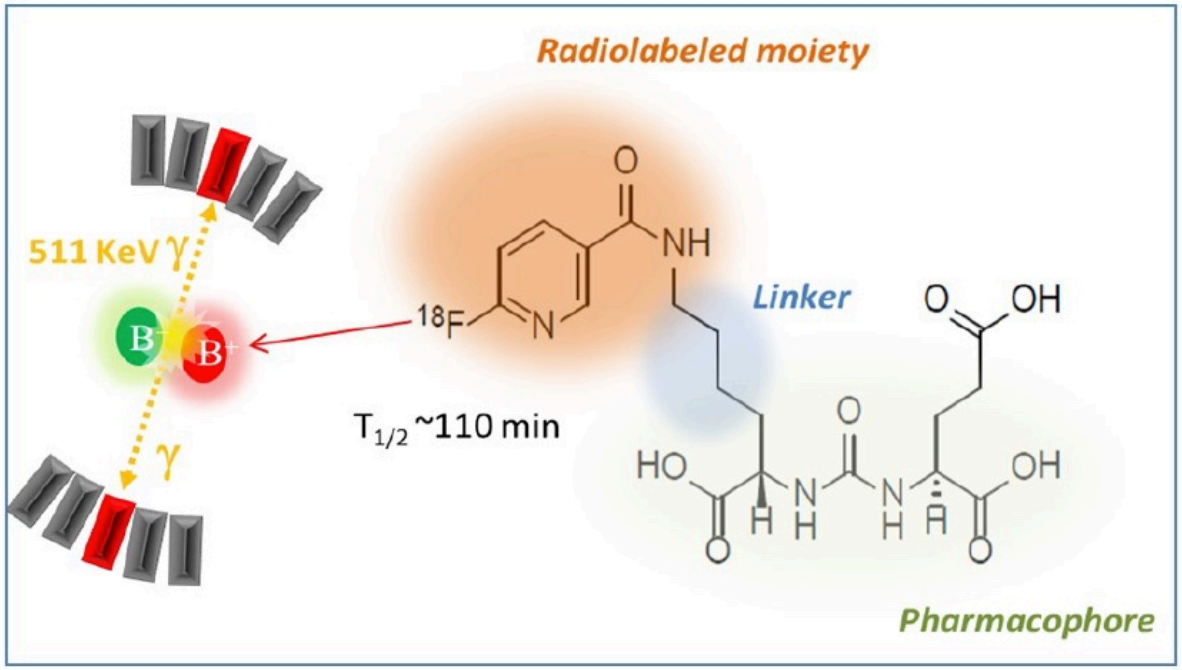
# $^{18}$F-DCFPyL Clinical Development Program




Morris MJ et al. ASCO 2020; Abstract 5501.

# $^{18}$F-DCFPyL

- Lysine-linked, urea-based small molecule
- Targets the extracellular domain of PSMA
- High specific activity
- 9 (±20%) mCi administered intravenously as bolus injection
- Imaging performed 1-2 hours following administration




Chen et al. Clin Cancer Res 2011; laboratory of Martin G. Pomper, MD, PhD

Morris MJ et al. ASCO 2020; Abstract 5501.

**Thank you for joining us!**

**CME and MOC credit information will be emailed to each participant within 5 days.**