# Cases from the Community: Investigators Discuss Emerging Research and Actual Patients with Prostate Cancer (Part 1 of a 3-Part Series)

**Thursday, February 25, 2021**
**5:00 PM – 6:30 PM ET**

## Faculty

**Tanya B Dorff, MD**
**Fred Saad, MD**
**A Oliver Sartor, MD**
**Matthew R Smith, MD, PhD**

## Moderator

**Neil Love, MD**

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# Faculty

**Tanya B Dorff, MD**
Associate Clinical Professor of Medicine
City of Hope National Medical Center
Department of Medical Oncology and
Developmental Therapeutics
Head, Genitourinary Cancer Program
Los Angeles, California

**A Oliver Sartor, MD**
CE and Bernadine Laborde Professor for Cancer Research
Medical Director, Tulane Cancer Center
Assistant Dean for Oncology
Tulane Medical School
New Orleans, Louisiana

**Fred Saad, MD**
Professor and Chief of Urology
Director of GU Oncology
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University of Montreal Hospital Center (CHUM)
Director, Prostate Cancer Research
Montreal Cancer Institute/CRCHUM
Montréal, Québec, Canada

**Matthew R Smith, MD, PhD**
Claire and John Bertucci Endowed Chair in
Genitourinary Cancers
Professor of Medicine, Harvard Medical School
Director, Genitourinary Malignancies Program
Massachusetts General Hospital Cancer Center
Boston, Massachusetts

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# Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Clovis Oncology, Exelixis Inc, Merck and Sanofi Genzyme.

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| **Contracted Research** | Bayer HealthCare Pharmaceuticals, Pfizer Inc |

# Dr Saad — Disclosures

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# Dr Sartor — Disclosures

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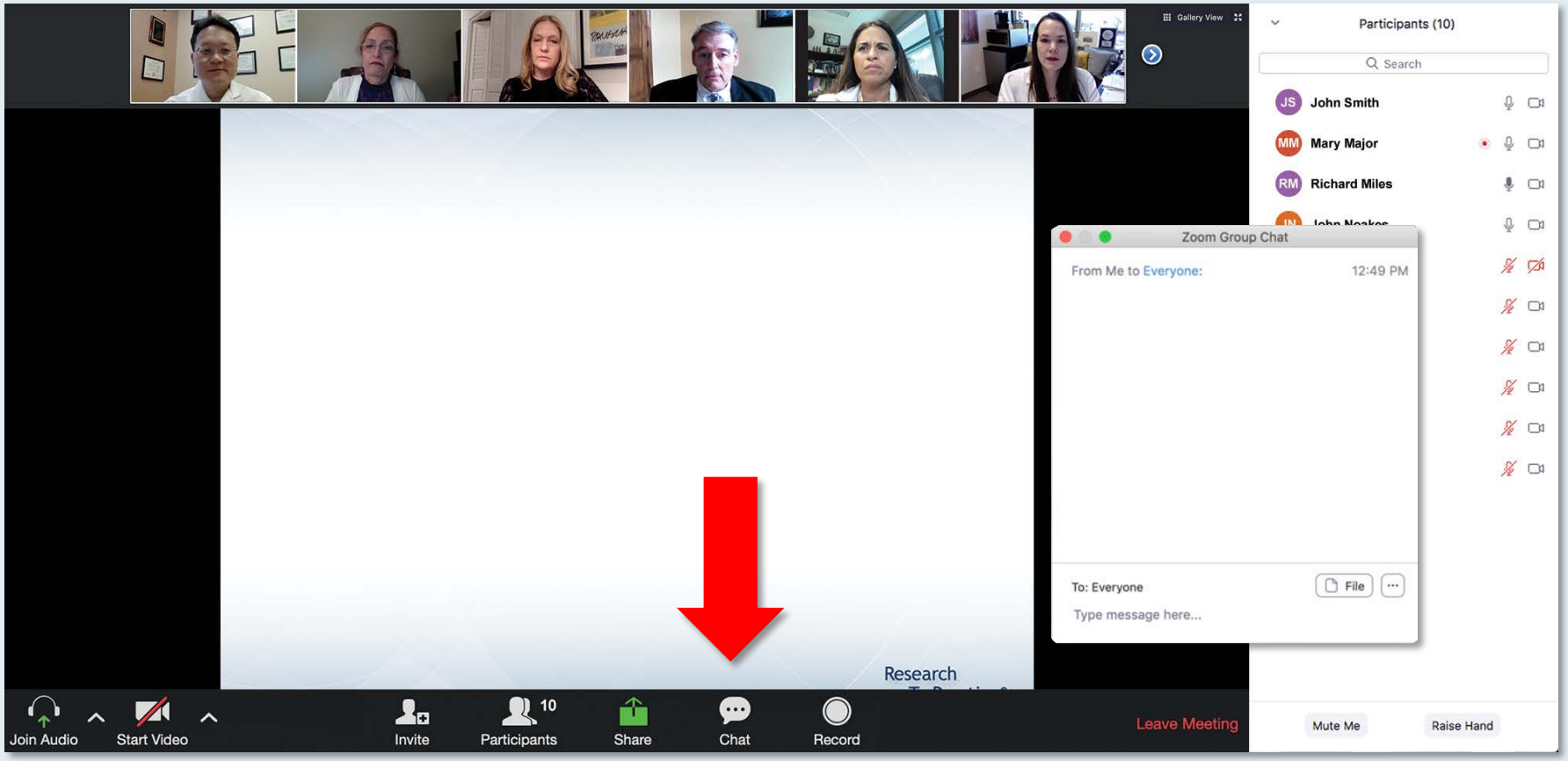
# We Encourage Clinicians in Practice to Submit Questions

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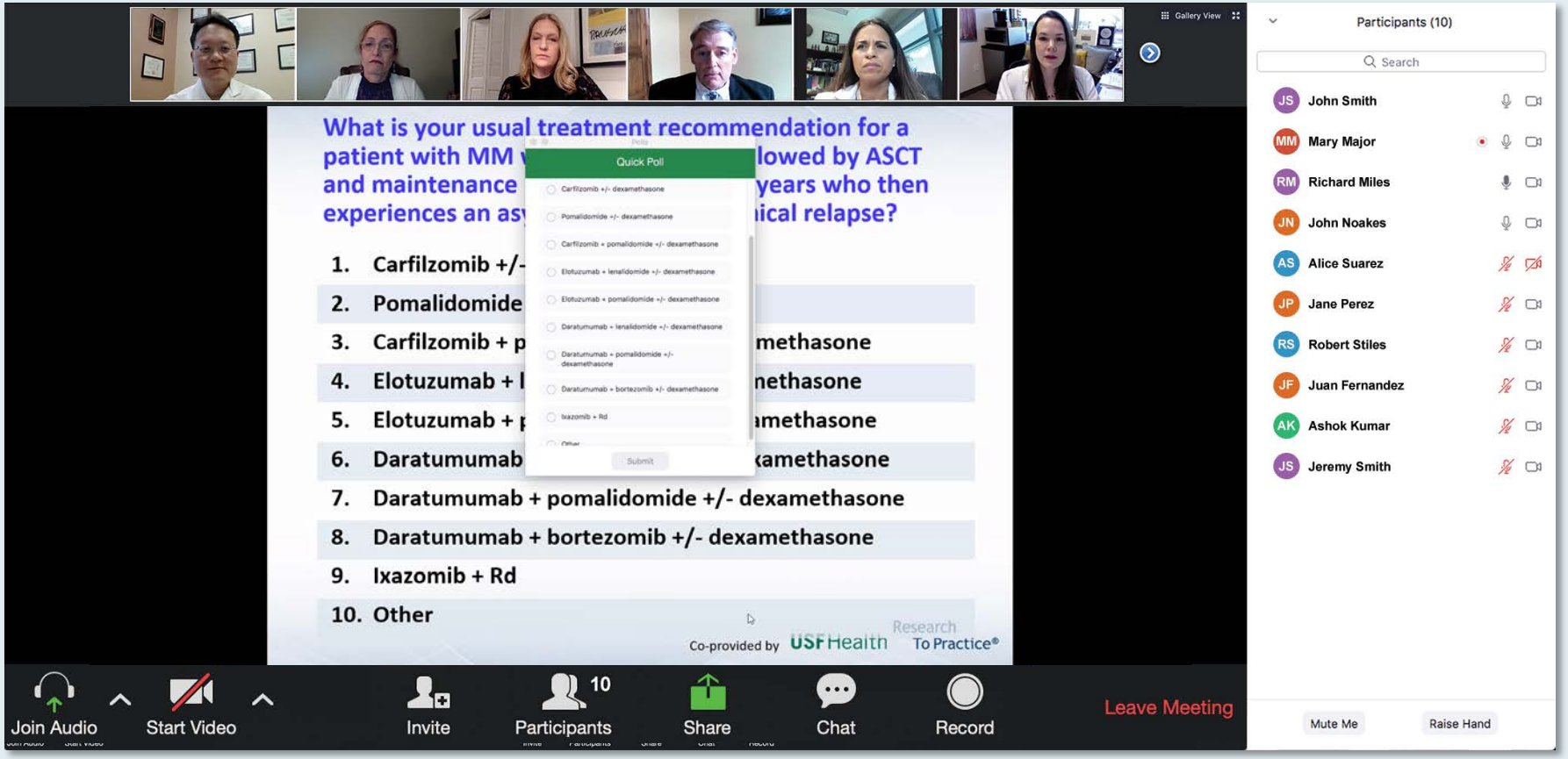
# Familiarizing Yourself with the Zoom Interface

## How to answer poll questions

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# ONCOLOGY TODAY

WITH DR NEIL LOVE

## The Role of PARP Inhibition in the Management of Prostate Cancer

DR MAHA HUSSAIN
NORTHWESTERN UNIVERSITY FEINBERG SCHOOL OF MEDICINE

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# Cases from the Community: Investigators Discuss Emerging Research and Actual Patients with Renal Cell Carcinoma (Part 2 of a 3-Part Series)

**Monday, March 1, 2021**
**5:00 PM – 6:00 PM ET**

## Faculty

**Thomas E Hutson, DO, PharmD**
**Thomas Powles, MBBS, MRCP, MD**

## Moderator

**Neil Love, MD**

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# *Meet The Professor*
# Management of Ovarian Cancer

**Tuesday, March 2, 2021**
**5:00 PM – 6:00 PM ET**

## Faculty

**Thomas J Herzog, MD**

## Moderator

**Neil Love, MD**

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# *Meet The Professor*
# Management of Multiple Myeloma

**Wednesday, March 3, 2021**
**5:00 PM – 6:00 PM ET**

## Faculty

**Morie A Gertz, MD, MACP**

## Moderator

**Neil Love, MD**

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# Cases from the Community: Investigators Discuss Emerging Research and Actual Patients with Urothelial Bladder Carcinoma (Part 3 of a 3-Part Series)

**Thursday, March 4, 2021**
**5:00 PM – 6:15 PM ET**

## Faculty

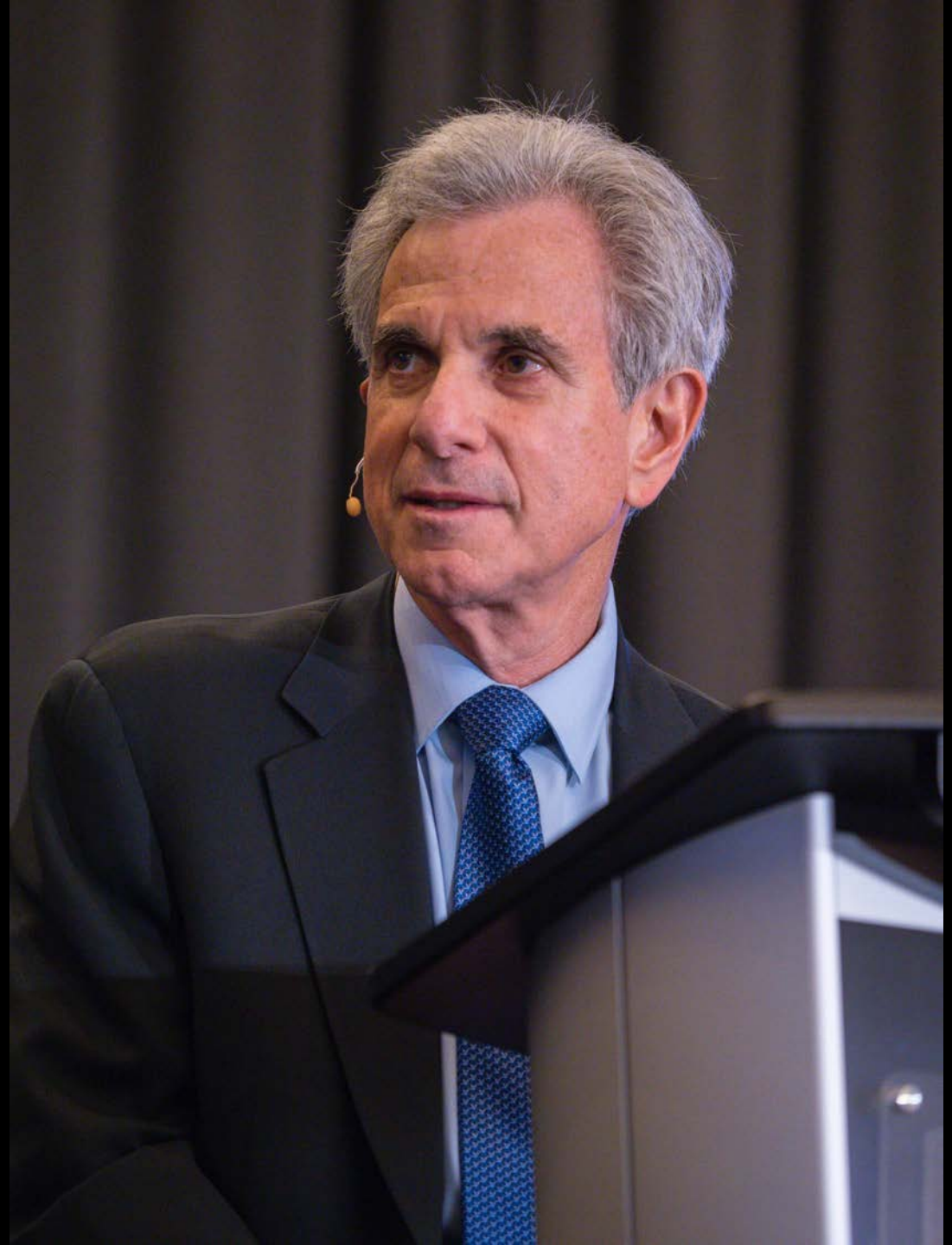
**Arjun Balar, MD**
**Elisabeth I Heath, MD**
**Jonathan E Rosenberg, MD**

## Moderator

**Neil Love, MD**

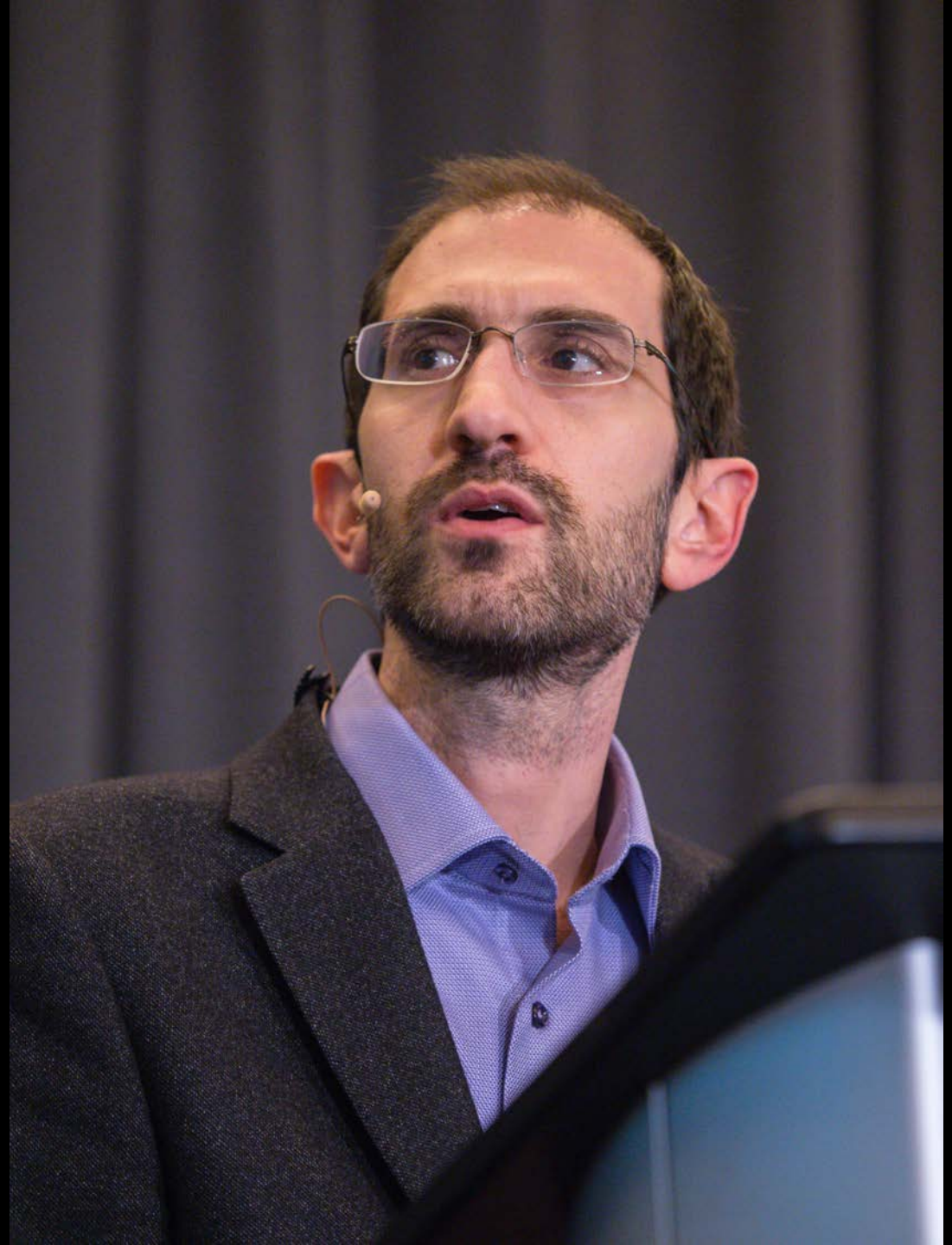
RTP RESEARCH TO PRACTICE


A 65-year-old man s/p radical prostatectomy follows
PSA-only recurrence (M0) receives an LHRH agonist
to a PSA level of 14 ng/dL with a doubling time of 3
imaging are negative. The patient has asked you to
diagnosed with metastatic disease in 3 years if he c
alone. How would you respond?
MARRIOTT MARQUIS SAN FRANCISCO




Consensus or Controversy?
Clinical Investigators Provide
Perspectives on the Current and Future
Management of Prostate Cancer
Thursday, February 14, 2019
6:45 PM – 8:45 PM
San Francisco, California
Moderator
Neil Love, MD
Faculty
Emmanuel S Antonarakis, MD
A Oliver Sartor, MD
Howard I Scher, MD
Matthew R Smith, MD, PhD
Cora N Sternberg, MD
Research
to Practice


of your patients with prostate cancer?
Yes (biochemical recurrence with rapid PSA doubling time)
Yes (M0 disease)
Yes (no significant metastatic disease or high-grade
Yes (PSA-only disease
of nodal metastases)
ASUS




MARRIOTT VISTA
SAN FRANCISCO


Case 2: 57-year-old
History of PaTCH-1 deficiency (Gorlin, Marfan syndrome) and multiple recurrent basal cell cancers; currently on hedgehog inhibitor vismodegib; also asymptomatic myeloma
2018: PSA 15, core needle biopsy, radical prostatectomy/bilateral pelvic lymph node dissection = Gleason 4 + 3 = 7 pT3aN0 (0/7) Stage IIIB prostate adenocarcinoma
Postop PSA rose within 8 months of surgery. Not a candidate for RT, hence treated with GnRH. Failure 1 year later; started on enzalutamide, continuing GnRH. Current PSA undetectable.
Questions for the faculty:
In a more typical situation, how do you decide whether to add in another hormone in a patient on ADT with a rising PSA? How do you balance doubling time, time since original surgery, time on ADT and PSA level?
How do you choose which antiandrogen?


MARRIOTT MARQUIS
SAN FRANCISCO

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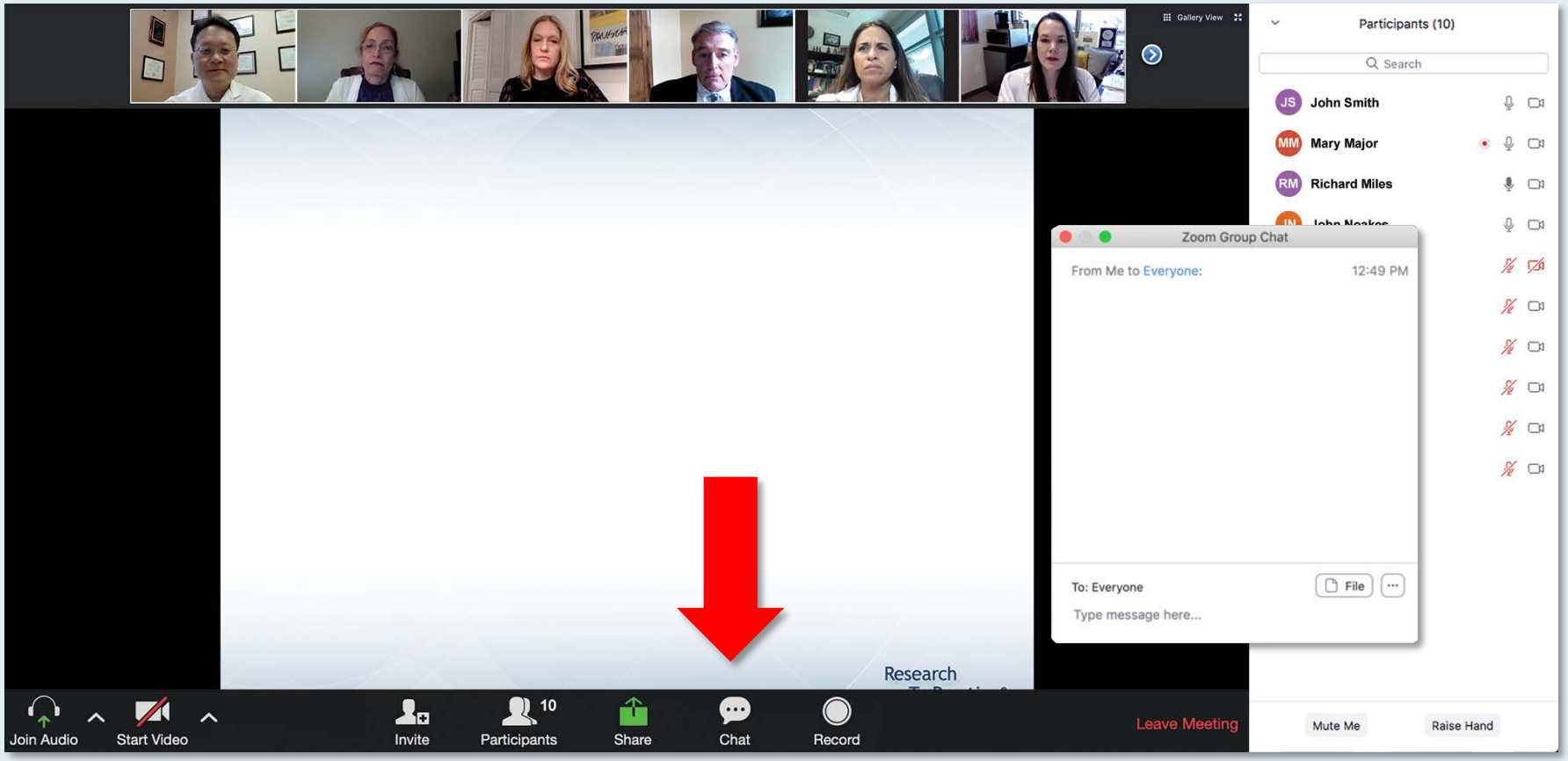


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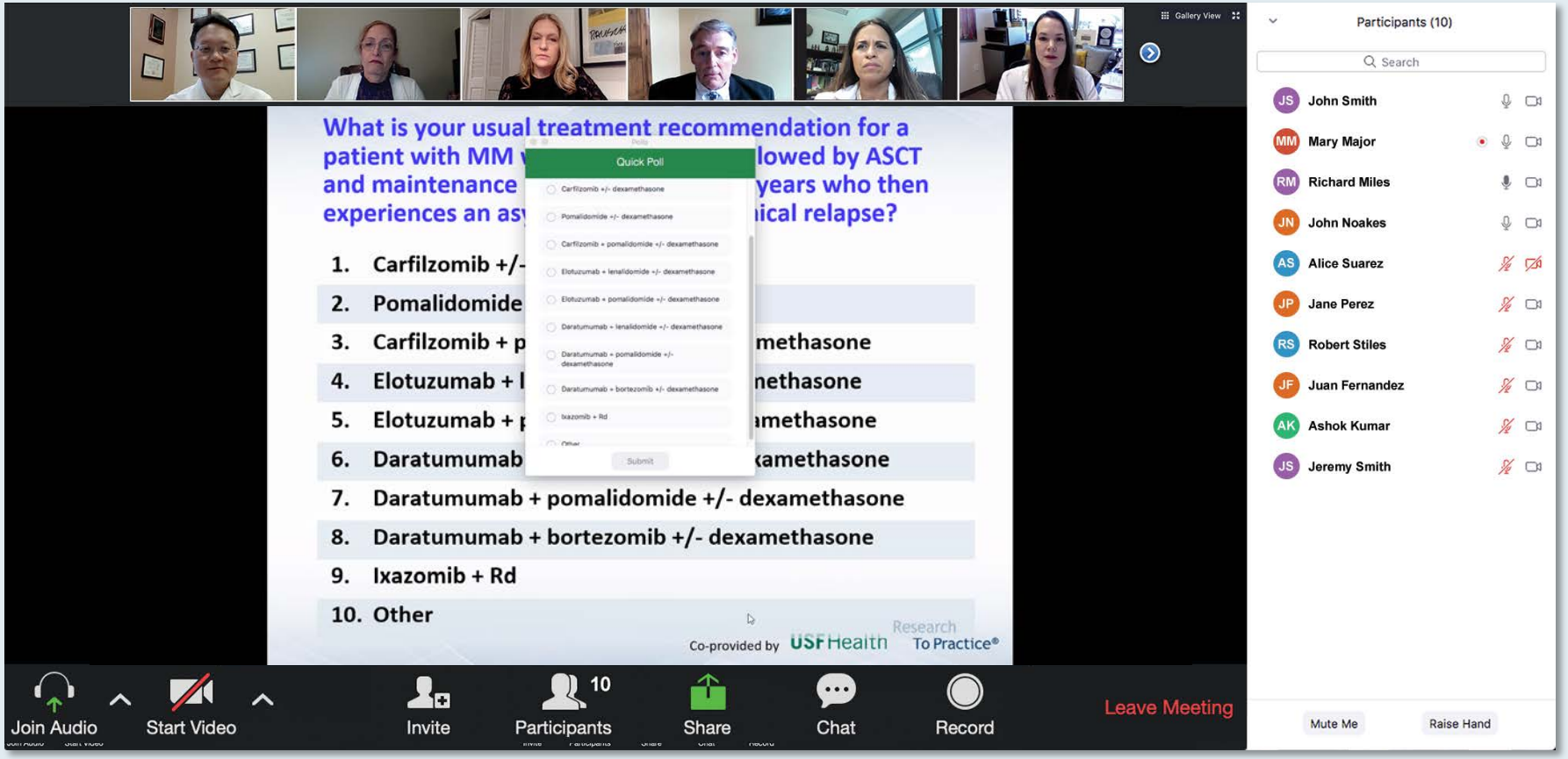


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**Philip L Brooks, MD**
Hematologist/Medical Oncologist
Cancer Care of Maine, Northern
Light Eastern Maine Medical Center
Brewer, Maine

**Nasfat Shehadeh, MD**
Medical Oncologist
Oncology Specialists of Charlotte
Charlotte, North Carolina

**Philip Glynn, MD**
Director, Medical Oncology
Mercy Medical Center
Springfield, Massachusetts

**Syed F Zafar, MD**
Hematologist and Medical Oncologist
Florida Cancer Specialists and
Research Institute
Chief, Division of Hematology
and Oncology, Lee Health
Fort Myers, Florida

**Yanjun Ma, MD**
Tennessee Oncology
Murfreesboro, Tennessee

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# Agenda

***Case Presentations***

- Dr Glynn: An 88-year-old man with metastatic hormone-sensitive prostate cancer (mHSPC)
- Dr Ma: Comments and questions – LHRH agonists vs antagonists; injections vs oral agents
- Dr Brooks: A 69-year-old man with mHSPC

***GU Cancers Journal Club – Part 1***

***Case Presentations***

- Dr Ma: An 87-year-old man with hormone-sensitive M0 prostate cancer

***GU Cancers Journal Club – Part 2***

***Case Presentations***

- Dr Shehadeh: A 60-year-old man with metastatic castration-resistant prostate cancer (mCRPC) – gBRCA2 mutation
- Dr Zafar: A 77-year-old man with mCRPC – Somatic BRCA2 mutation
- Dr Brooks: A 72-year-old man with mCRPC – gBRCA2 mutation

***GU Cancers Journal Club – Part 3***

***Case Presentations***

- Dr Glynn: A 72-year-old man with mHSPC
- Dr Brooks: A 69-year-old man with mHSPC – MSS, TMB 1, PTEN mutation
- Dr Ma: An 86-year-old man with mCRPC

***GU Cancers Journal Club – Part 4***

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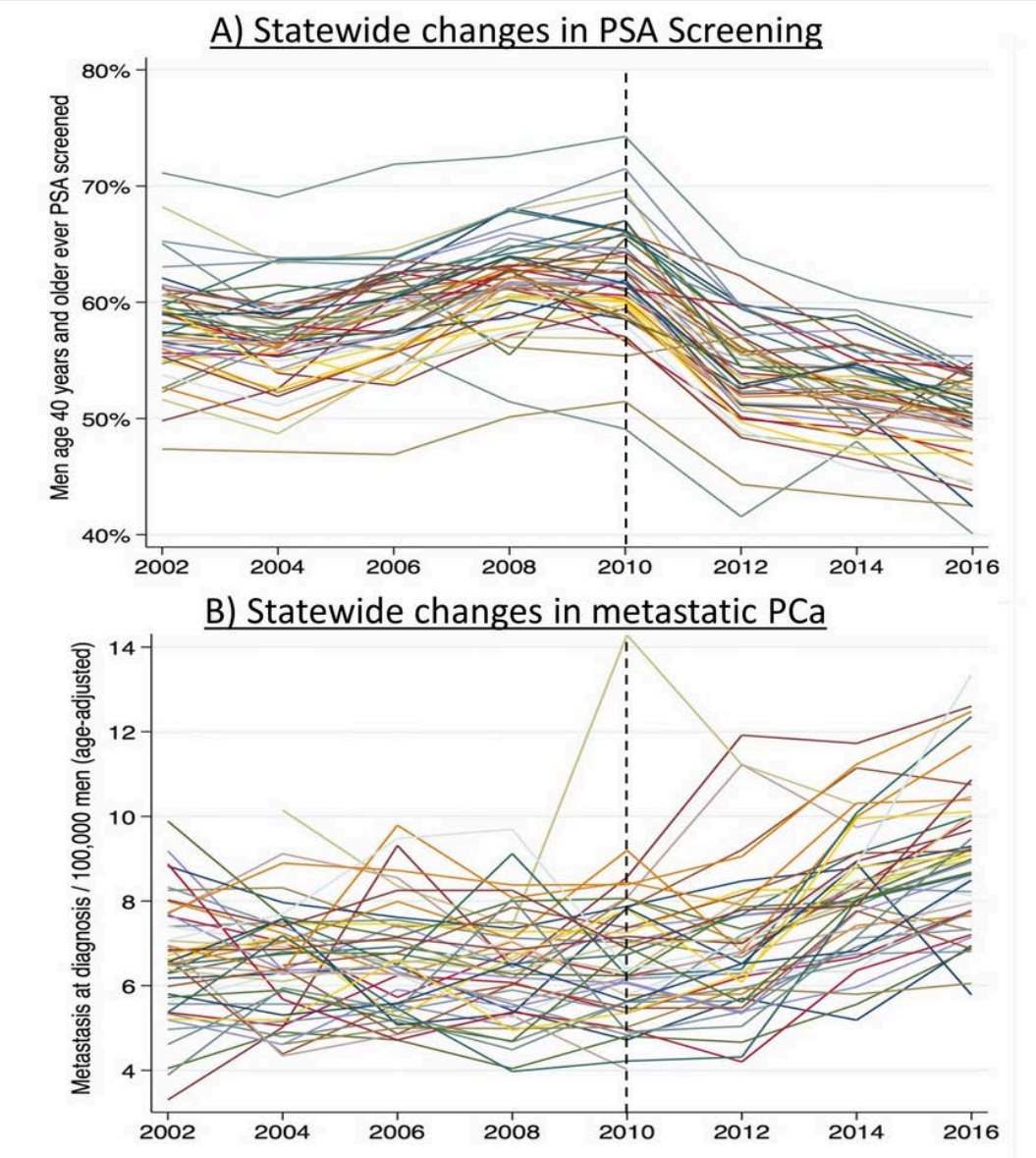
# Association of Reductions in PSA Screening Across States with Increased Metastatic Prostate Cancer in the United States

Sharma V et al.
Genitourinary Cancers Symposium 2021;Abstract 228.

# Longitudinal Changes by State




**After 2010, PSA screening declined in most states while metastatic disease increased**

Sharma V et al. Genitourinary Cancers Symposium 2021;Abstract 228.

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***GU Cancers Journal Club – Part 4***

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# Case Presentation – Dr Glynn: An 88-year-old man with metastatic hormone-sensitive prostate cancer

**Dr Philip Glynn**

- 2/2019: Significant pain and diffuse arthralgias
  - CT: Extensive pelvic adenopathy, obstructive uropathy, perianal abscess
  - Bone scan: Extensive bony involvement
  - PSA: 273 ng/mL
- Patient skeptical of systemic therapy
- Bicalutamide → ADT, abiraterone/prednisone, denosumab
- 2/2021: PSA: 0.1 ng/mL

**Questions**

- After he's had such a great response, would anybody consider just leaving him on LHRH agent and dropping the abiraterone and prednisone? Could we use intermittent therapy, or modify the treatment to make his life simpler and reduce his cost burden?
- What about using an LHRH antagonist, such as degarelix or the newer, oral agent relugolix?

# Preferences for the use of LHRH agonists versus antagonists, injections versus oral agents

**Dr Yanjun Ma**

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# Case Presentation – Dr Brooks: A 69-year-old man with metastatic hormone-sensitive prostate cancer

**Dr Philip Brooks**

- 2003: Gleason 9 prostate cancer s/p radical prostatectomy
- 2007: Rising PSA → RT → Rising PSA → leuprolide and bicalutamide
- 2013: Severe mood swings, discontinued treatment (PSA <0.1 ng/mL)
- 2015: PSA: 11, but patient dropped out of care due to personal problems
- 10/2016: PSA: 19, Bone scan: Lesion in 9$^{th}$ rib, MRI pelvis: Suspicious lesions
- 3/2017: PSA 39, MRI: PD lesions increasing and now convincing for metastatic disease
- Discussed leuprolide plus abiraterone but due to concerns of fatigue he only proceeded with leuprolide
- 2/2021: PSA: Stable at 0.25 but has now risen in 3 months to 0.39
- Discussed additional imaging or treatment and he would like to wait another 3 months

**Questions**

- Soon I will need to make a decision about further treatment. How should I use either fluciclovine F18 or PSMA PET to aid in that decision?
- In this patient who's already had prostate radiation, is there any role for treating oligometastatic disease with radiation therapy along with systemic therapy?

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# What is your most likely treatment approach for a 75-year-old man presenting de novo with prostate cancer with multiple symptomatic bone metastases and 2 lung metastases?

1. ADT alone
2. ADT and enzalutamide
3. ADT and apalutamide
4. ADT and abiraterone
5. ADT and docetaxel
6. ADT with docetaxel and endocrine treatment

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***GU Cancers Journal Club – Part 4***

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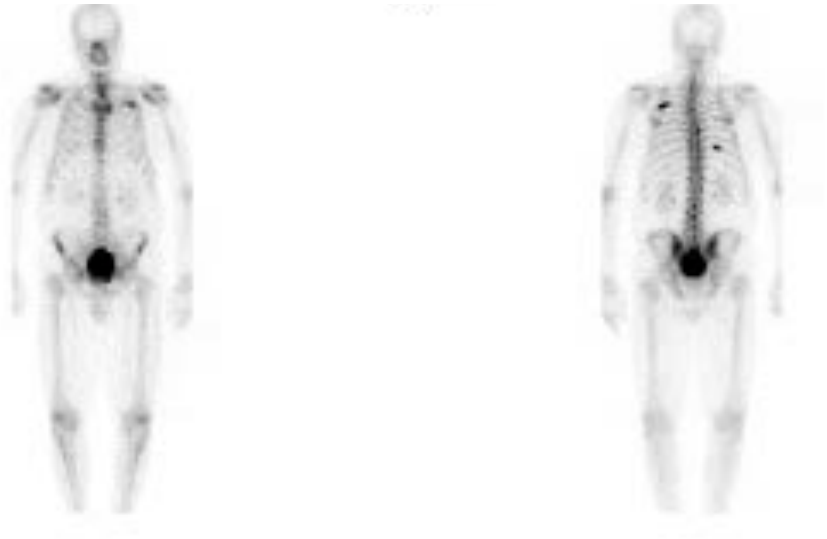
# Case Presentation – Dr Saad: 68-year-old man with mHSPC

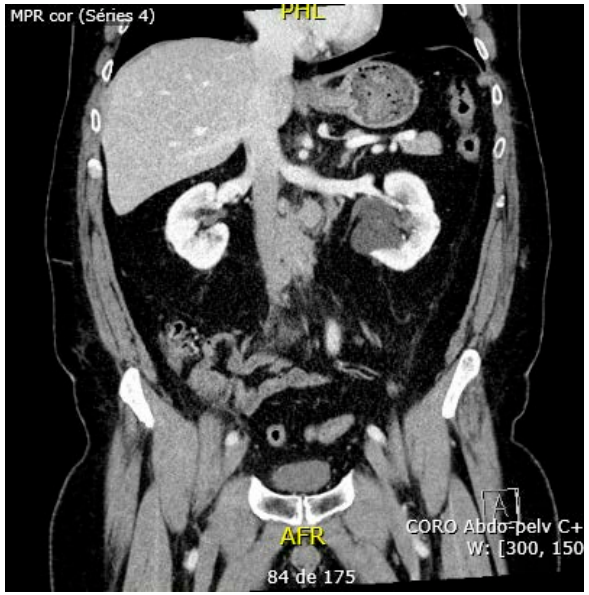
- 68-year-old patient treated for cT3, Gleason 4+3 prostate cancer, PSA 18
- Received radiation therapy + 6 months of ADT 4 years ago
- PSA nadir 0.8 6 months after radiation
- PSA rises to 3.5 2 years later
- Bone scan and CT abdomen and chest within normal limits
- Patient sexually active and declines ADT
- Patient travels 6 months to Florida
- Upon returning PSA is 23

CHUM

# Case Presentation – Dr Saad: 68-year-old man with mHSPC



- Bone scan reveals multiple new lesions suspicious of mets
- CT abdomen shows multiple retroperitoneal nodes
- Patient started on ADT and enzalutamide 160 mg/day
- PSA declines to 0.4 after 3 months
- Patient complains of fatigue and difficulty in concentrating that interferes with his work
- Enza dose reduced to 120 mg per day and patient feels much better
- PSA continues to decline to 0.2 and remains stable 18 months after starting ADT + Enza




CHUM

# HERO Phase III Trial: Results Comparing Relugolix, an Oral GnRH Receptor Antagonist, versus Leuprolide Acetate for Advanced Prostate Cancer[1]

# Oral Relugolix for Androgen-Deprivation Therapy in Advanced Prostate Cancer[2]


[1] Shore N et al.
ASCO 2020;Abstract 5602.

[2] Shore ND et al.
*N Engl J Med* 2020;382(23):2187-96.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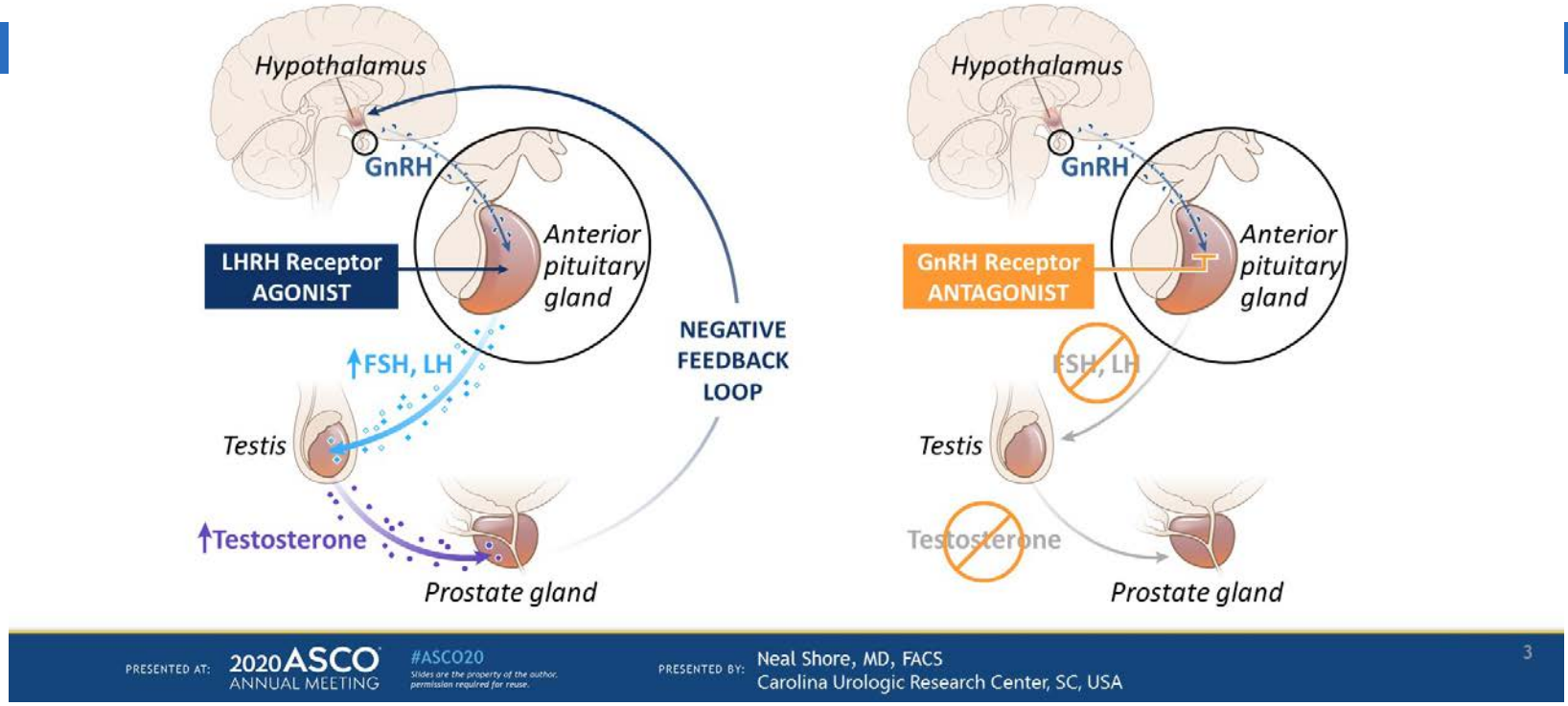
# LHRH agonist vs antagonist MOA and side effect profile




PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20 Slides are the property of the author. permission required for reuse.

PRESENTED BY: Neal Shore, MD, FACS
Carolina Urologic Research Center, SC, USA

3

| | Relugolix (N = 622) | Leuprolide (N = 308) |
|---|---|---|
| Hot flush | 54.3% | 51.6% |
| Fatigue | 21.5% | 18.5% |
| Constipation | 12.2% | 9.7% |
| Diarrhea* | 12.2% | 6.8% |
| Arthralgia | 12.1% | 9.1% |
| Hypertension | 7.9% | 11.7% |

Courtesy of Tanya B Dorff, MD

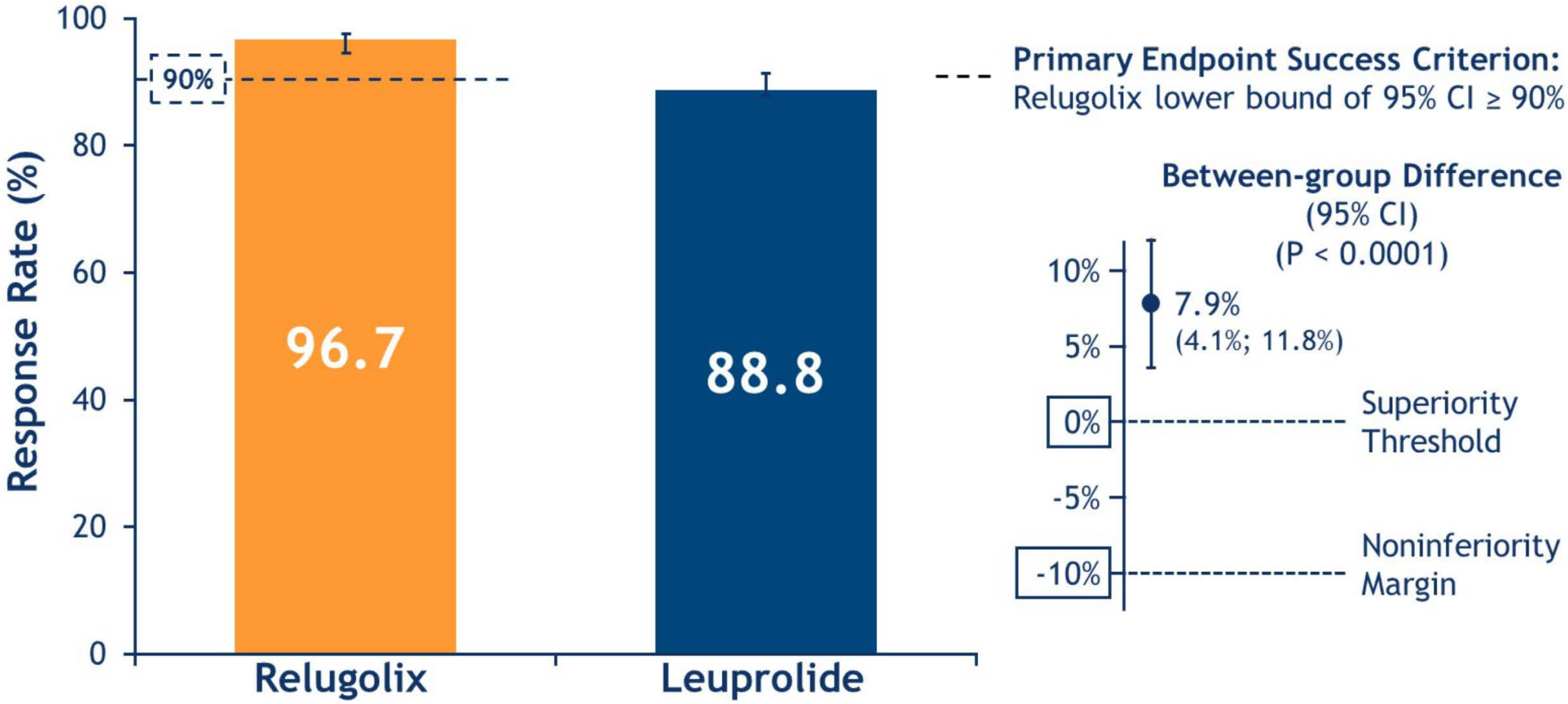
# HERO trial: relugolix vs leuprolide - Endpoints

| | Relugolix | Leuprolide | |
|---|---|---|---|
| Sustained T <50 (1○ endpoint) | 96.7% | 88.8% | P <0.001 |
| Confirmed PSA response d15 | 79.4% | 19.8% | P < 0.001 |
| Mean FSH level | 1.72 | 5.95 | P <0.001 |
| T recovery >280 at d90 post d/c | 54% | 3% | P = 0.002 |

City of Hope

Courtesy of Tanya B Dorff, MD

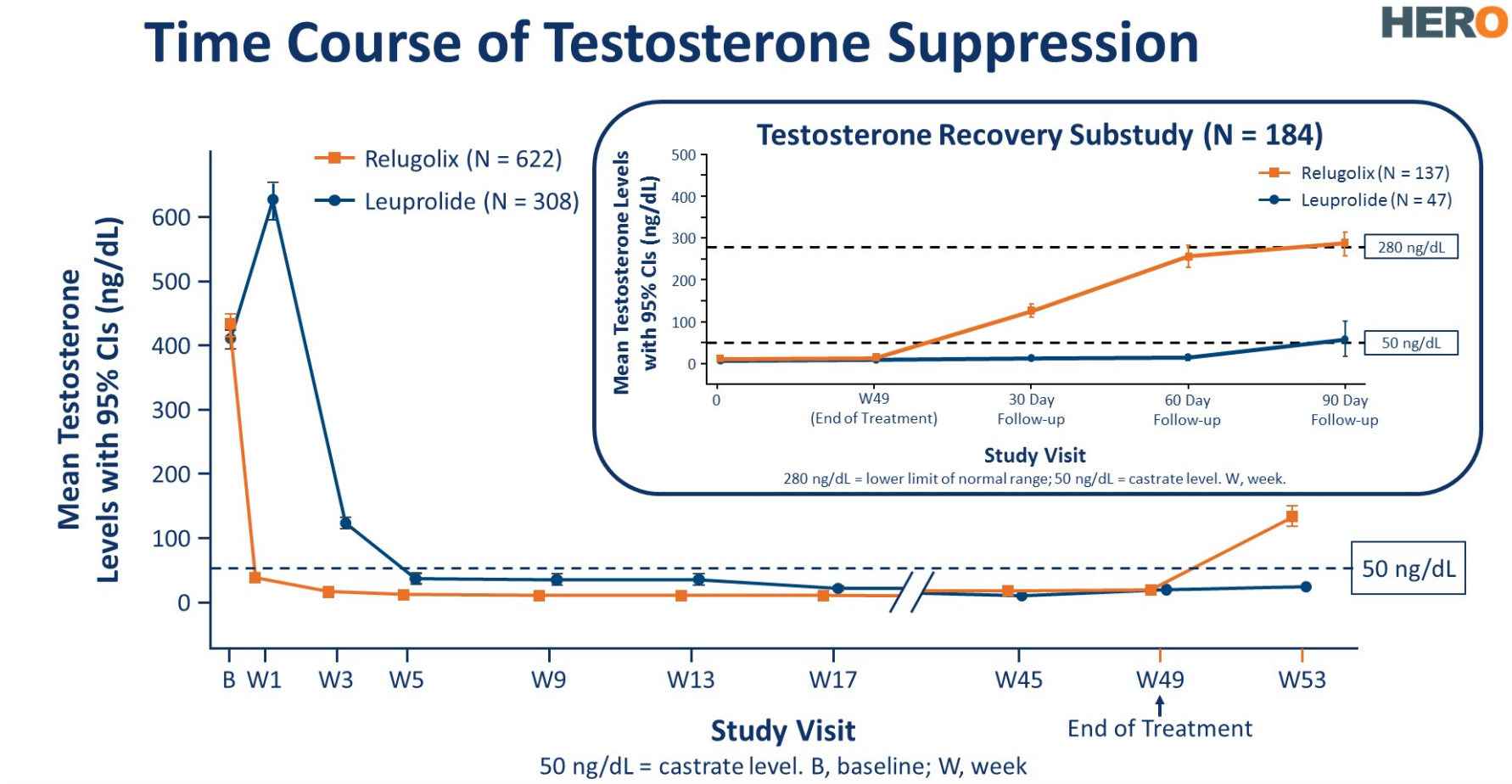
# HERO: Primary Endpoint – Sustained Castration
# Key Secondary Endpoint – Noninferiority to Leuprolide




Shore N et al. ASCO 2020;Abstract 5602; Shore ND et al. *N Engl J Med* 2020;382(23):2187-96.

RTP RESEARCH TO PRACTICE

# Quicker T recovery






City of Hope

Courtesy of Tanya B Dorff, MD

# Relugolix showed a better cardiovascular safety profile compared to leuprolide

| Event | Relugolix (N=622) | | Leuprolide (N=308) | |
|---|---|---|---|---|
| | Any Grade | Grade 3 or 4 | Any Grade | Grade 3 or 4 |
| Any adverse event — no. (%) | 578 (92.9) | 112 (18.0) | 288 (93.5) | 63 (20.5) |
| Serious adverse event — no. (%) | 76 (12.2) | 61 (9.8) | 47 (15.3) | 35 (11.4) |
| Fatal adverse event — no. (%) | 7 (1.1) | — | 9 (2.9) | — |
| MACE — no. (%)† | 18 (2.9) | 8 (1.3) | 19 (6.2) | 4 (1.3) |
| Without a history of MACE — no./total no. (%) | 15/538 (2.8) | — | 11/263 (4.2) | — |
| With a history of MACE — no./total no. (%) | 3/84 (3.6) | — | 8/45 (17.8) | — |

2/3 of patients had cardiovascular risk factors;
<15% had prior MACE

City of Hope

Courtesy of Tanya B Dorff, MD

# Impact of Concomitant Prostate Cancer Therapy on Efficacy and Safety of Relugolix versus Leuprolide in Men with Advanced Prostate Cancer: Subgroup Analysis from the Phase III HERO Study

George DJ et al.

Genitourinary Cancers Symposium 2021;Abstract 106.

# FDA Approves Relugolix for Advanced Prostate Cancer

## Press Release: December 18, 2020

"On December 18, 2020, the U.S. Food and Drug Administration approved the first oral gonadotropin-releasing hormone (GnRH) receptor antagonist, relugolix, for adult patients with advanced prostate cancer.

Efficacy was evaluated in HERO (NCT03085095), a randomized, open label trial in men requiring at least one year of androgen deprivation therapy with either prostate cancer recurrence following radiation or surgery or newly diagnosed castration-sensitive advanced prostate cancer.

Patients (N=934) were randomized (2:1) to receive relugolix 360 mg oral loading dose on the first day, followed by daily oral doses of 120 mg, or leuprolide acetate 22.5 mg injection subcutaneously every 3 months for 48 weeks."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-relugolix-advanced-prostate-cancer

RTP RESEARCH TO PRACTICE

# Practical Points: LHRH agonists and antagonists

Agonist preferred

- With abiraterone, enzalutamide, apalutamide, etc
- Without prescription drug coverage AND unable to come in for monthly injection

Antagonist preferred

- History of significant cardiovascular disease
- Side effects not well tolerated (rapid reversal)
- Inadequate T suppression with agonist

City of Hope

Courtesy of Tanya B Dorff, MD

# Adverse events reported with the 4 agents

| | CHAARTED |
|---|---|
| | Docetaxel (n = 390) |
| Any grade 3–5 AE | 29.6% |
| Completion of 6 cycles | 86% |
| Allergic reaction | 2.1% |
| Fatigue | 4.1% |
| Neutropenia | 12.1% |
| Febrile neutropenia | 6.1% |
| Infection with neutropenia | 2.3% |
| Anemia | 1.3% |
| Neuropathy | 0.5% |

| | ARCHES | |
|---|---|---|
| | Enzalutamide (N = 572) | Placebo (N = 574) |
| Any grade 3–5 AE | 24.3% | 25.6% |
| Any AE leading to discontinuation | 7.2% | 5.2% |
| Hypertension | 3.3% | 1.7% |
| Neutropenia | 0.3% | 0.3% |
| Hot flashes | 0.3% | 0% |
| Fatigue | 0.9% | 1% |
| Convulsion/seizure | 0.3% | 0.3% |
| Cognitive/memory impairment or delirium | 0.7% | 0% |

| | LATITUDE | |
|---|---|---|
| | Abiraterone (N = 597) | Placebo (N = 602) |
| Any grade 3–5 AE | 63% | 48% |
| Any AE leading to discontinuation | 12% | 10% |
| Hypertension | 20% | ~10% |
| Hypokalemia | 11% | ~1% |
| Fatigue | 2% | 2% |
| Cardiac disorder (any) | ~4% | ~1% |
| Hyperglycemia | ~4% | 3% |
| Endocrine disorders | NR | NR |
| ALT increased | ~5% | 1% |
| AST increased | ~4% | 1% |

| | Apalutamide (N = 524) | Placebo (N = 527) |
|---|---|---|
| Any grade 3–4 AE | 42.2% | 40.8% |
| Any AE leading to discontinuation | 8% | 5.3% |
| Fatigue | 8.4% | 9.1% |
| Rash | 6.3% | 0.6% |
| Bone pain | 1.1% | 1.7% |
| Anemia | 1.7% | 3.2% |
| Back pain | 2.3% | 2.7% |
| Anemia | 1.1% | 1.9% |

Kinsey, Emily N. MD*; Zhang, Tian MD, MHS†; Armstrong, Andrew J. MD, ScM, FACP†
Cancer Journal: 1/2 2020 - Volume 26 - Issue 1 - p 64-75

Courtesy of Fred Saad, MD

CHUM

Abstract #11

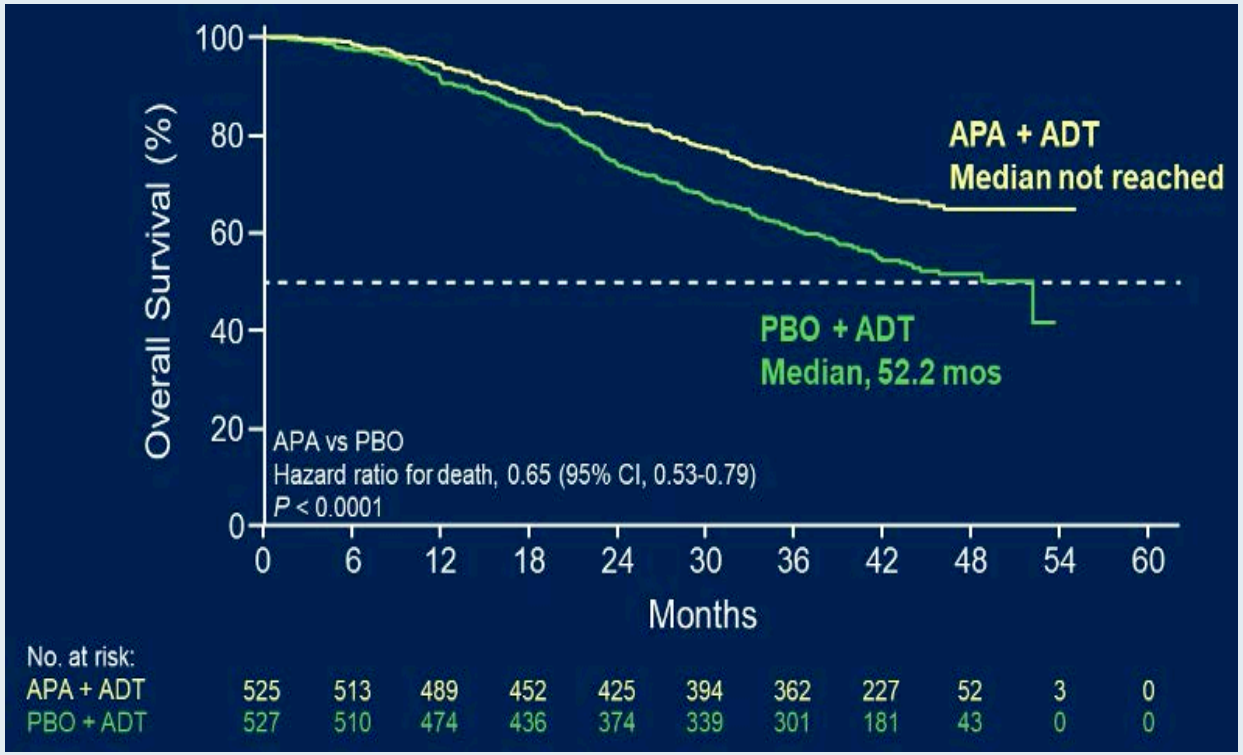
# Final Analysis Results From TITAN: A Phase 3 Study of Apalutamide vs Placebo in Patients With Metastatic Castration-Sensitive Prostate Cancer Receiving Androgen Deprivation Therapy

Kim N. Chi,[1] Simon Chowdhury,[2] Anders Bjartell,[3] Byung Ha Chung,[4] Andrea J. Pereira de Santana Gomes,[5] Robert Given,[6] Álvaro Juárez Soto,[7] Axel S. Merseburger,[8] Mustafa Özgüroğlu,[9] Hirotsugu Uemura,[10] Dingwei Ye,[11] Spyros Triantos,[12] Sabine Brookman-May,[12,13] Suneel Mundle,[14] Sharon A. McCarthy,[14] Julie S. Larsen,[15] Weili Sun,[15] Katherine Bevans,[16] Ke Zhang,[17] Nibedita Bandyopadhyay,[14] Neeraj Agarwal,[18] for the TITAN Investigators

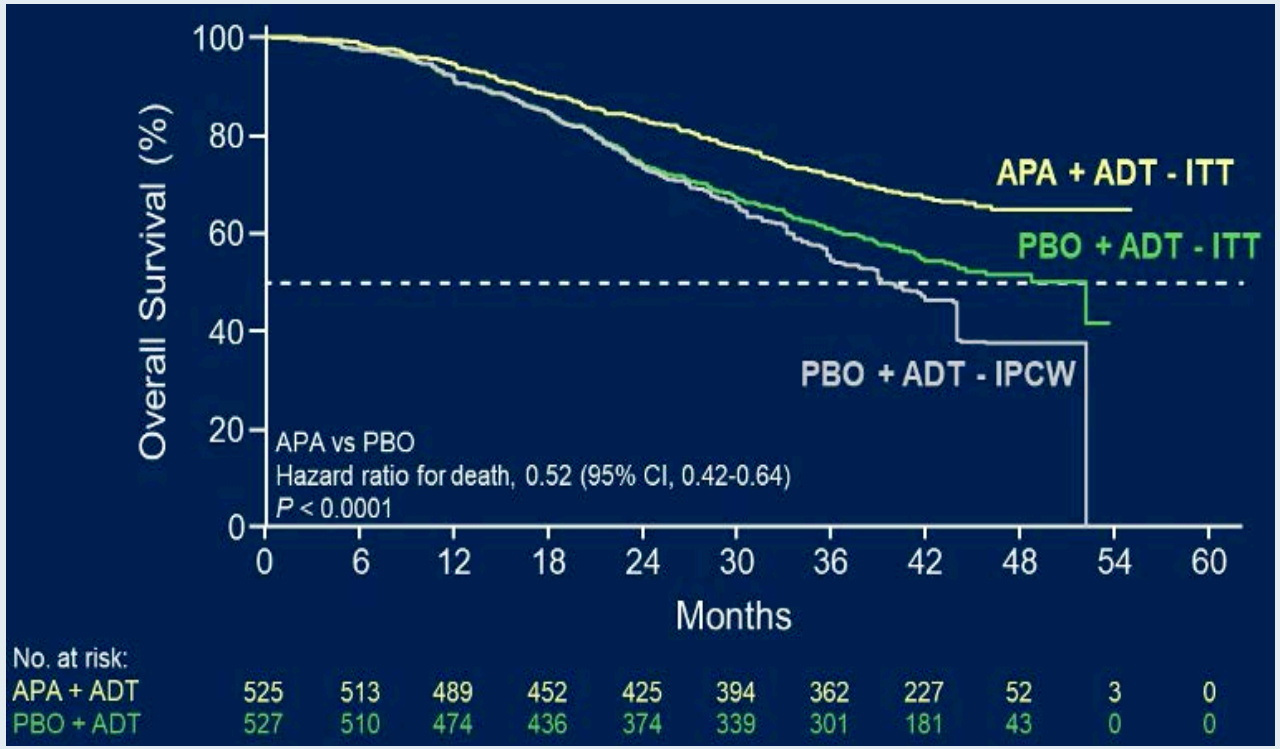
[1]BC Cancer and Vancouver Prostate Centre, Vancouver, BC, Canada; [2]Guy's, King's, and St. Thomas' Hospitals, and Sarah Cannon Research Institute, London, UK; [3]Skåne University Hospital, Lund University, Malmö, Sweden; [4]Yonsei University College of Medicine and Gangnam Severance Hospital, Seoul, South Korea; [5]Liga Norte Riograndense Contra O Cancer, Natal, Brazil; [6]Urology of Virginia, Eastern Virginia Medical School, Norfolk, VA; [7]Hospital Universitario de Jerez de la Frontera, Cadiz, Spain; [8]University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck, Germany; [9]Istanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine, Istanbul, Turkey; [10]Kindai University Faculty of Medicine, Osaka, Japan; [11]Fudan University Shanghai Cancer Center, Shanghai, China; [12]Janssen Research & Development, Spring House, PA; [13]Ludwig-Maximilians-University (LMU), Munich, Germany; [14]Janssen Research & Development, Raritan, NJ; [15]Janssen Research & Development, Los Angeles, CA; [16]Janssen Research & Development, Horsham, PA; [17]Janssen Research & Development, San Diego, CA; [18]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT

# TITAN – Final Analysis: Overall Survival

## OS (Co-primary endpoint)
## Median follow-up: 44.0 months




## OS with adjustment for ~40% crossover from PBO




Chi KN et al. Genitourinary Cancers Symposium 2021;Abstract 11.

RTP RESEARCH TO PRACTICE

# TITAN – Final Analysis: Conclusions

- The final analysis of TITAN, after a median follow-up of approximately 4 years, confirmed that APA + ADT consistently improved OS, with a reduced risk of death by 35% (HR, 0.65 [95% CI, 0.53-0.79]) compared with PBO + ADT in a broad population of patients with mCSPC
- After adjustment for almost 40% of PBO patients who crossed over to receive APA, the risk of death was reduced by 48% (HR, 0.52 [95% CI, 0.42-0.64])
- APA provided a consistent benefit in other end points, including delayed castration resistance and maintained health-related quality of life, with an acceptable safety profile and no new safety signals

Chi KN et al. Genitourinary Cancers Symposium 2021;Abstract 11.

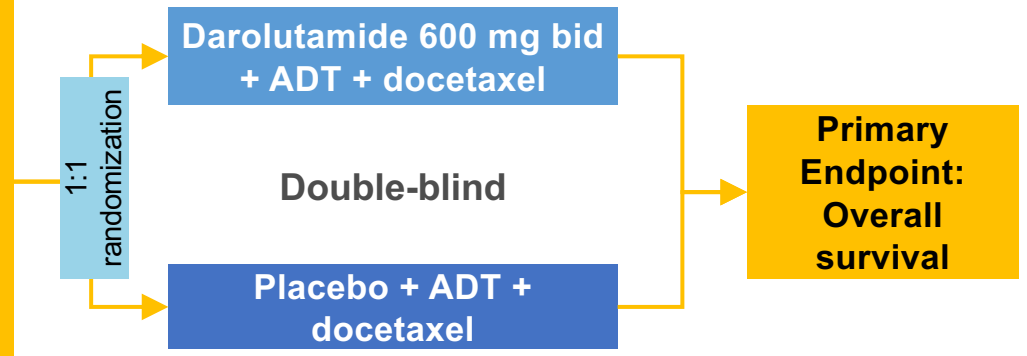
RTP RESEARCH TO PRACTICE

# Maximizing therapy for mHSPC

# ARASENS Phase III Trial Design

**Patients (N=1303)**
- mHSPC*
- Histologically or cytologically confirmed adenocarcinoma of the prostate
- ECOG PS ≤1
- Candidates for ADT and docetaxel†

**Stratification**
- Extent of disease
- Alkaline phosphatase levels



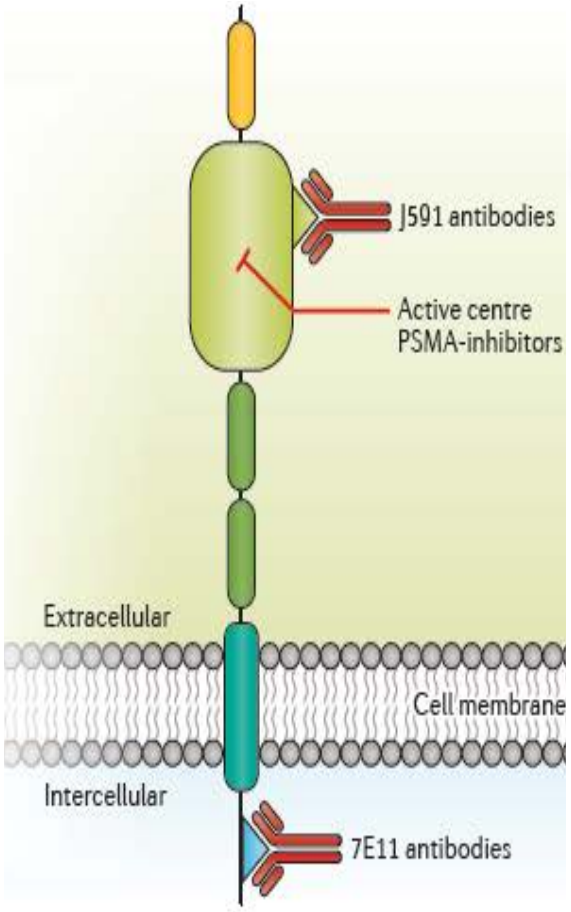

**Secondary and additional objectives**
- Time to castration-resistant prostate cancer
- Time to initiation of subsequent antineoplastic therapy
- Symptomatic skeletal event–free survival (SSE-FS)
- Time to first symptomatic skeletal event (SSE)
- Time to initiation of opioid use for ≥7 days
- Time to pain progression
- Time to worsening of physical symptoms of disease based on NCCN-FACT FPSI-17
- Safety

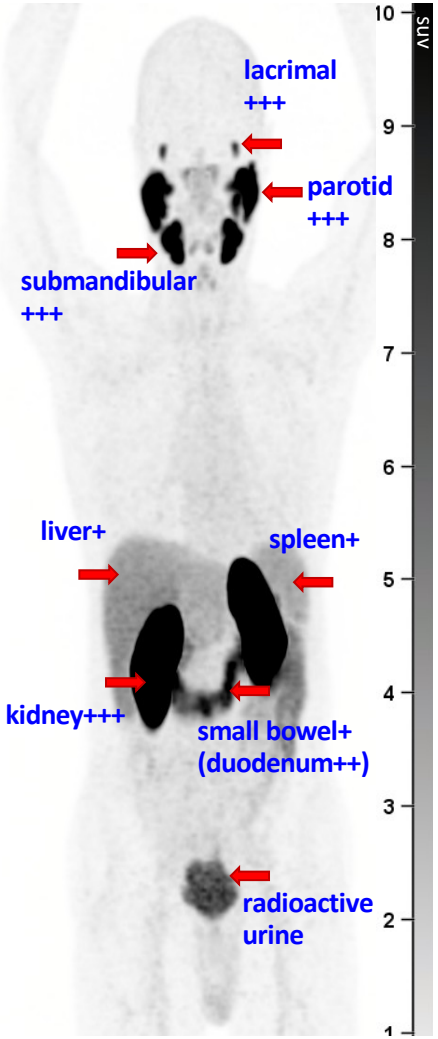
**Background treatments:**
- ADT at investigators' choice (including orchiectomy)
- Docetaxel: 6 cycles (in combination with prednisone/prednisolone at the discretion of the investigator) to be administered after randomization

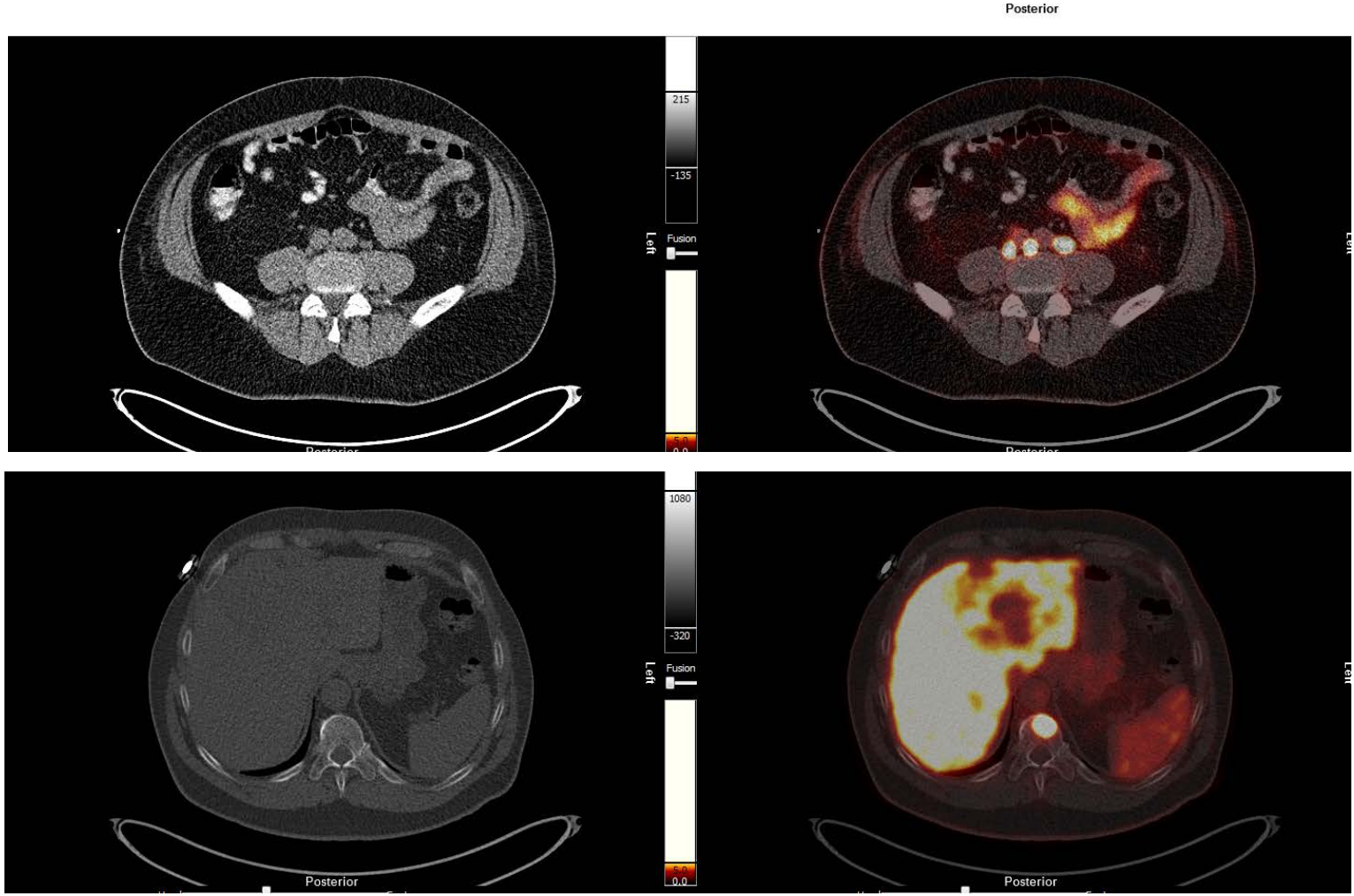
**Enrolment completed in June 2018**

Courtesy of Fred Saad, MD CHUM

# Diagnosing metastases earlier and more precisely
# Prostate specific membrane antigen (PSMA)




Courtesy of Fred Saad, MD

CHUM

# FDA Approves First PSMA-Targeted PET Imaging Drug for Men with Prostate Cancer

## Press Release: December 1, 2020

"The U.S. Food and Drug Administration approved Gallium 68 PSMA-11 (Ga 68 PSMA-11) – the first drug for positron emission tomography (PET) imaging of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer.

Ga 68 PSMA-11 is indicated for patients with suspected prostate cancer metastasis (when cancer cells spread from the place where they first formed to another part of the body) who are potentially curable by surgery or radiation therapy. Ga 68 PSMA-11 is also indicated for patients with suspected prostate cancer recurrence based on elevated serum prostate-specific antigen (PSA) levels. Ga 68 PSMA-11 is a radioactive diagnostic agent that is administered in the form of an intravenous injection.

Once administered via injection, Ga 68 PSMA-11 binds to PSMA, which is an important pharmacologic target for prostate cancer imaging because prostate cancer cells usually contain elevated levels of the antigen. As a radioactive drug that emits positrons, Ga 68 PSMA-11 can be imaged by PET to indicate the presence of PSMA-positive prostate cancer lesions in the tissues of the body."

https://www.fda.gov/news-events/press-announcements/fda-approves-first-psma-targeted-pet-imaging-drug-men-prostate-cancer#:~:text=Today%2C%20the%20U.S.%20Food%20and,in%20men%20with%20prostate%20cancer

RTP RESEARCH TO PRACTICE

# Head-to-head comparison of $^{68}$Ga-PSMA-11 PET/CT and mpMRI in the detection, intra-prostatic localization and local extension of primary prostate cancer: a single-center imaging study with histopathology gold-standard

**Ida Sonni**[1], Ely R. Felker[2], Andrew Lenis[3], Anthony E. Sisk[4], Shadfar Bahri[1], Martin Allen-Auerbach[1], Wesley Armstrong[1], Voraparee Suvannarerg[2], Teeravut Tubtawee[2], Tristan Grogan[5], David Elashoff[5], Johannes Czernin[1], Steven S. Raman[2], Robert E. Reiter[3] and Jeremie Calais[1]

1. Ahmanson Translational Theranostics Division, Department of Molecular and Medical Pharmacology, UCLA
2. Department of Radiology, UCLA
3. Department of Urology, UCLA
4. Department of Pathology, UCLA
5. Department of Medicine Statistics Core, UCLA



**Abstract 193**

# Comparison of 68Ga-PSMA-11 PET/CT and mpMRI: Conclusions

- PSMA PET/CT and mpMRI have **similar accuracy** in the detection and intra-prostatic localization of prostate cancer foci.
- mpMRI outperforms PSMA PET/CT in identifying ECE and SVI.
- **PSMA PET/CT+mpMRI** significantly **improves tumor extent delineation**, but **not prostate cancer detection rates**.
- **PSMA PET/CT and mpMRI have complimentary roles in the local staging of intermediate- to high-risk prostate cancer.**

Sonni I et al. Genitourinary Cancers Symposium 2021;Abstract 193.

# Prospective randomized trial of gene expression classifier utility following radical prostatectomy (G-MINOR)

**Todd Morgan**, Linda Okoth, Daniel Spratt, Rodney Dunn, Felix Feng, Anna Johnson, Brian Lane, Susan Linsell, Khurshid Ghani, James Montie, Rohit Mehra, Stephanie Daignault-Newton, Brent Hollenbeck, Huei-Chung Huang, Tamara Todorovic, Elai Davicioni, Thomas Maatman, Kirk Wojno, Frank Burks, Paul Rodriguez, Eduardo Kleer, Richard Sarle, David Miller, Michael Cher

**Abstract 15**

RTP RESEARCH TO PRACTICE

# G-MINOR: Conclusions

- First prospective, randomized assessment of molecular classifier utility in prostate cancer
- Primary analysis demonstrates that the Decipher genomic classifier impacts adjuvant RT use following RP
- Prospective serial patient reported outcome collection (MUSIC-PRO) will provide key quality of life data
- Long term oncologic outcome assessment will inform clinical impact of Decipher in this context

Morgan TM et al. Genitourinary Cancers Symposium 2021;Abstract 15.

# Association of the clinical cell-cycle risk score with metastasis after radiation therapy and identification of men with prostate cancer who can forgo combined androgen deprivation therapy.


Presented by: Jonathan D. Tward, M.D., Ph.D
Rudolph P. and Edna S. Reese Endowed Research Professor
Professor of Radiation Oncology
Leader, HCI Genitourinary Cancers Center
Huntsman Cancer Institute at the University of Utah

UNIVERSITY OF UTAH HUNTSMAN CANCER INSTITUTE
GENITOURINARY CANCERS CENTER

Jonathan David Tward, Constantine Mantz, Neal D. Shore, Paul Nguyen, Isla Garraway, Carl A Olsson, Steve Pai-hsun Lee, Arthur Hung, R Jonathan Henderson, Stanley L. Liauw, David Raben, Michael D. Fabrizio, Daniel R. Saltzstein, Paul Yonover, Hiram Alberto Gay, Daniel Joseph Albertson, Tatjana Antic, Lauren Lenz, Michael K Brawer, Steven Stone, Todd Cohen


OHSU · UROLOGY SAN ANTONIO · Urology of Virginia · AT THE FOREFRONT UChicagoMedicine · U.S. Department of Veterans Affairs · MUSC Medical University of South Carolina · CURC Carolina Urologic Research Center · Washington University School of Medicine in St. Louis · BE 21st Century Oncology · University of Colorado Anschutz Medical Campus · ARC Advanced Radiation Centers of New York · Dana-Farber Cancer Institute · Arizona Oncology · UroPartners · myriad · Regional Urology

**Abstract 195**

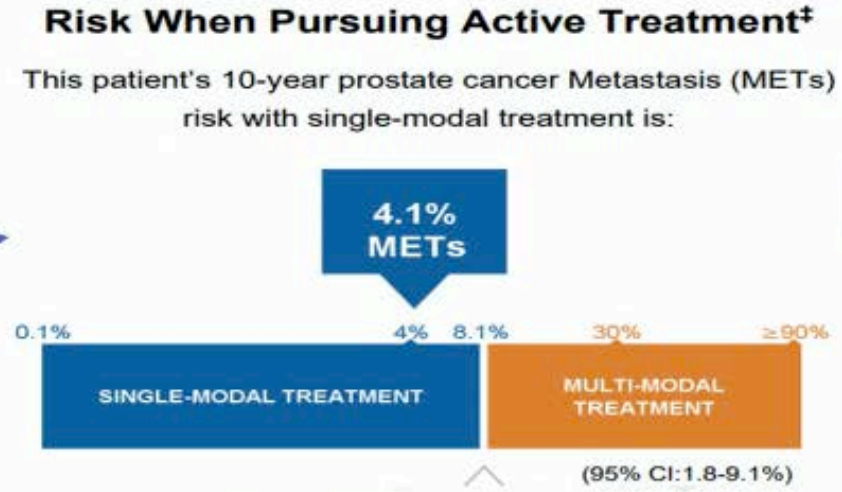
RTP RESEARCH TO PRACTICE

# Conclusion: The Prolaris® test provides useful and actionable information for shared-decision making between the patient and radiation oncologist

## VARIABLES USED FOR RISK ASSESSMENT

| | |
|---|---|
| Prolaris Molecular Score: | 3.4 → CCP Score (3.4) |
| Patient Age at Biopsy: | 63 |
| PSA Prior to This Biopsy: | 7.0 |
| Clinical T Stage: | T1c → CAPRA (5) |
| % Positive Cores: | < 34% |
| Gleason Score: | 4+3=7 (Group 3 ISUP[1]) |
| NCCN Risk[2]: | Unfavorable Intermediate |

CCR= 0.39*(5)+0.57*(-0.6) =1.6




Assuming a HR of 0.5 for adding ADT (best case from RCT, the Absolute risk Reduction would be ~ 2%.
Is a number needed to treat of 50 worth it?
**Communicate and let the patient decide !**

**CCR = (0.39 * CAPRA Score) + (0.57 * (CCP Score – 4))**

Tward JD et al. Genitourinary Cancers Symposium 2021;Abstract 195.

RTP RESEARCH TO PRACTICE

# Agenda

***Case Presentations***

- Dr Glynn: An 88-year-old man with metastatic hormone-sensitive prostate cancer (mHSPC)
- Dr Ma: Comments and questions – LHRH agonists vs antagonists; injections vs oral agents
- Dr Brooks: A 69-year-old man with mHSPC

***GU Cancers Journal Club – Part 1***

***Case Presentations***

- Dr Ma: An 87-year-old man with hormone-sensitive M0 prostate cancer

***GU Cancers Journal Club – Part 2***

***Case Presentations***

- Dr Shehadeh: A 60-year-old man with mCRPC – gBRCA2 mutation
- Dr Zafar: A 77-year-old man with mCRPC – Somatic BRCA2 mutation
- Dr Brooks: A 72-year-old man with mCRPC – gBRCA2 mutation

***GU Cancers Journal Club – Part 3***

***Case Presentations***

- Dr Glynn: A 72-year-old man with mHSPC
- Dr Brooks: A 69-year-old man with mHSPC – MSS, TMB 1, PTEN mutation
- Dr Ma: An 86-year-old man with mCRPC

***GU Cancers Journal Club – Part 4***

RTP RESEARCH TO PRACTICE

# Case Presentation – Dr Ma: An 87-year-old retired physician with hormone-sensitive M0 prostate cancer – Part 1

**Dr Yanjun Ma**

- 12/2017: Adenocarcinoma of the prostate, Gleason 4 + 5 = 9 involving all 4 cores with extraprostatic extension, PSA: 44 ng/mL
  - No other imaging studies done
- Leuprolide q6 months
- 1/2019: PSA: 1.05 ng/mL
- 2/2019: Proton therapy → Early 2020: PSA: 0.07 ng/mL

# Case Presentation – Dr Ma: An 87-year-old retired physician with hormone-sensitive M0 prostate cancer – Part 2

**Dr Yanjun Ma**

- 12/2017: Adenocarcinoma of the prostate, Gleason 4 + 5 = 9 involving all 4 cores with extraprostatic extension, PSA: 44 ng/mL
  - No other imaging studies done
- Leuprolide q6 months
- 1/2019: PSA: 1.05 ng/mL
- 2/2019: Proton therapy → Early 2020: PSA: 0.07 ng/mL
- 1/2020: Slow rise in PSA to 1.38 ng/mL, with PSADT: 4 months → Added darolutamide to leuprolide, due to reduced CNS sedation
  - No radiographic evidence of metastases
- 6/2020: Aortic valve repair for critical stenosis and simultaneous thoracic aortic aneurysm repair
  - PS: 0, exercising and jogging

**Question**

- Do you agree with the treatment choice of darolutamide plus leuprolide, or would you use a different antiandrogen?

RTP RESEARCH TO PRACTICE

# In general, which is your preferred antiandrogen agent to add to ADT for patients with castration-resistant M0 prostate cancer?

1. I don’t have a preferred antiandrogen agent in this setting
2. Enzalutamide
3. Darolutamide
4. Apalutamide

# Agenda

***Case Presentations***

- Dr Glynn: An 88-year-old man with metastatic hormone-sensitive prostate cancer (mHSPC)
- Dr Ma: Comments and questions – LHRH agonists vs antagonists; injections vs oral agents
- Dr Brooks: A 69-year-old man with mHSPC

***GU Cancers Journal Club – Part 1***

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- Dr Brooks: A 69-year-old man with mHSPC – MSS, TMB 1, PTEN mutation
- Dr Ma: An 86-year-old man with mCRPC

***GU Cancers Journal Club – Part 4***

# Case Presentation – Dr Dorff: A 68-Year-Old Man with M0 Prostate Cancer

- A retired police officer, with prostate cancer diagnosed at age 68 due to abnormal DRE although PSA was only 2.
- Biopsy revealed Gleason 4+5 adenocarcinoma, and radical prostatectomy confirmed T3bN1 Gleason 5+4.
- PSA failed to nadir, measured 0.77 at 2 months post op. Imaging revealed no evidence of metastatic disease.
- He was treated with ADT (Degarelix – has CAD) and PSA decreased to 0.08 after 3 months but then he developed early castration resistance with PSA rising to 0.539, 1.49 and then 2.16. PSA doubling time was <3 months.
- He was started on darolutamide, and PSA nadired to undetectable but then rose 6 months later. After 20 months, he developed metastatic disease.

# Recent FDA Approvals of Next-Generation Antiandrogens for Nonmetastatic Castration-Resistant Prostate Cancer

| Agent | Approval date | Pivotal study |
|---|---|---|
| Darolutamide | July 30, 2020 | ARAMIS |
| Enzalutamide | July 12, 2018 | PROSPER |
| Apalutamide | February 14, 2018 | SPARTAN |

https://www.fda.gov/drugs/resources-information-approved-drugs/

RTP RESEARCH TO PRACTICE

# Registrational trials of AR antagonists in nmCRPC

| Agent | Apalutamide 240 mg daily | Darolutamide 600 mg BID | Enzalutamide 160 mg daily |
|---|---|---|---|
| Study name | SPARTAN[1] | ARAMIS[2] | PROSPER[3] |
| Design | 2:1 apa/placebo | 2:1 daro/placebo | 2:1 enza/placebo |
| Number of pts | 1207 | 1509 | 1401 |
| Inclusion: | PSA DT <10 mo<br>Pelvic LN <2 cm OK | PSA DT ≤10 mo<br>Pelvic LN <2cm OK<br>bPSA ≥2 | PSA DT ≤10 mo<br>--<br>bPSA ≥2 |

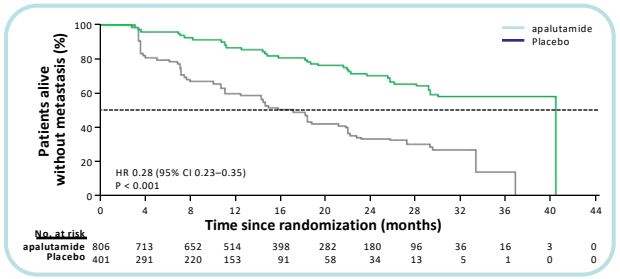

1. Chi KN et al. NEJM 2019; 381:13-24
2. Fizazi K et al. NEJM 2019; 380:1235-46
3. Hussain M et al. NEJM 2018; 378:2465-74


City of Hope

Courtesy of Tanya B Dorff, MD

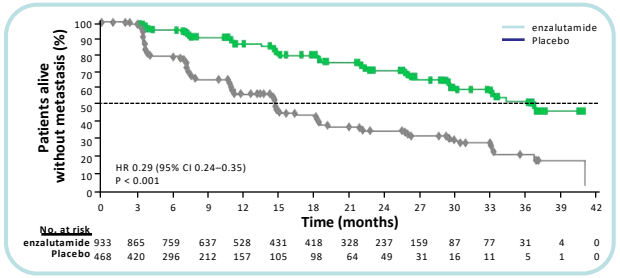
# Primary Endpoint: Metastasis-Free Survival

**SPARTAN[1]**
**apalutamide**



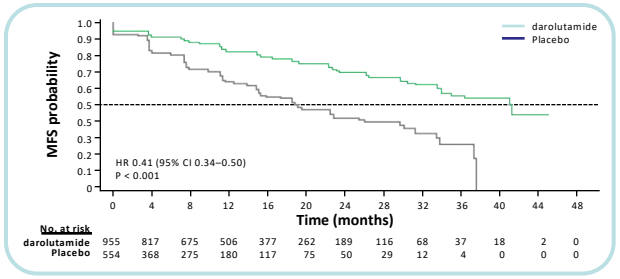

- 72% reduction of distant progression or death
- Median MFS: APA 40.5 vs PBO 16.2 months
- 24-month MFS benefit

**PROSPER[2]**
**enzalutamide**




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

**ARAMIS[3]**
**darolutamide**




- 59% reduction of distant progression or death
- Median MFS: DARO 40.4 vs PBO 18.4 months
- 22-month MFS benefit

APA, apalutamide; CI, confidence interval; DARO, darolutamide; ENZA, enzalutamide; HR, hazard ratio; MFS, metastasis-free survival; PBO, placebo

1. Smith MR, et al. N Engl J Med. 2018;378:1408-18; 2. Hussain M, et al. N Engl J Med. 2018;378:2465-74; 3. Fizazi K, et al. N Engl J Med. 2019;380:1235-46

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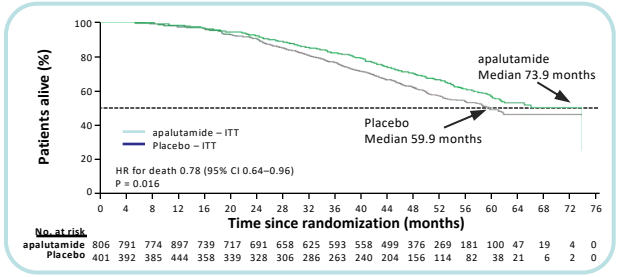
Courtesy of Tanya B Dorff, MD

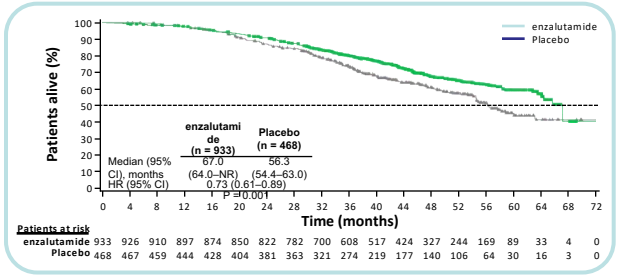
# Secondary Endpoint: Final Overall Survival

**SPARTAN[1]**
**apalutamide**



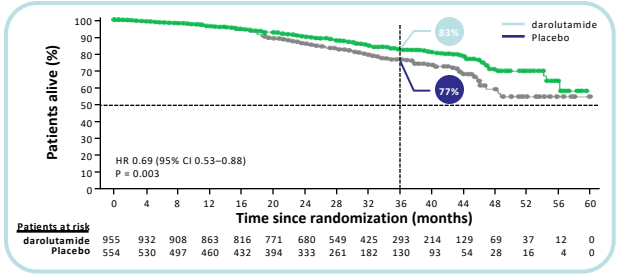

- 22% reduction in risk of death
  HR 0.78 (95% CI 0.64–0.96); P = 0.0161
- 71% of placebo patients received subsequent life-prolonging therapy

**PROSPER[2]**
**enzalutamide**




- 27% reduction in risk of death
  HR 0.73 (95% CI 0.61–0.89); P = 0.001
- 65% of placebo patients received subsequent antineoplastic therapy

**ARAMIS[3]**
**darolutamide**




- 31% reduction in risk of death
  HR 0.69 (95% CI 0.53–0.88); P = 0.003
- 55% of placebo patients received subsequent life-prolonging therapy

CI, confidence interval; HR, hazard ratio; ITT, intention to treat; NR, not reached

1. Smith MR, et al. Eur Urol. 2020; https://doi.org/10.1016/j.eururo.2020.08.011; 2. Sternberg CN, et al. N Engl J Med. 2020;382: 2197-206; 3. Fizazi K, et al. N Engl J Med. 2020; 383: 1040-1049

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Courtesy of Tanya B Dorff, MD

# Adverse Events of Interest: falls/fractures and cognitive impairment less different between darolutamide and placebo

| Safety | SPARTAN[1,2,3] | | PROSPER[4] | | ARAMIS[5] | |
|---|---|---|---|---|---|---|
| | APA (n = 803) | PBO (n = 398) | ENZA (n = 930) | PBO (n = 465) | DARO (n = 954) | PBO (n = 554) |
| Any AE, n (%) | 781 (97) | 373 (94) | 876 (94) | 380 (82) | 818 (85.7) | 439 (79.2) |
| Any serious AE, n (%) | 290 (36) | 99 (25) | 372 (40) | 100 (22) | 249 (26.1) | 121 (21.8) |
| AE leading to discontinuation, % | 15.0 | 7.3 | 17.0 | 9.0 | 8.9 | 8.7 |
| AE leading to death, n (%) | 24 (3.0) | 2 (0.5) | 51 (5.0) | 3 (1.0) | 38 (4.0) | 19 (3.4) |
| **AE (all grades), %** | | | | | | |
| Fatigue | 31.9† | 21.4† | 37 | 16 | 13.2 | 8.3 |
| Hypertension | 27.6† | 20.9† | 18.0 | 6.0 | 7.8 | 6.5 |
| Rash | 26.0 | 6.3 | 4 | 3 | 3.1 | 1.1 |
| Falls | 22.0 | 9.5 | 18.0 | 5.0 | 5.2 | 4.9 |
| Fractures | 18.0 | 7.5 | 18 | 6 | 5.5 | 3.6 |
| Mental impairment disorder# | 5.1§ | 3.0§ | 8.0 | 2.0 | 2.0 | 1.8 |

#SPARTAN: disturbance in attention, memory impairment, cognitive disorder and amnesia; PROSPER: as per SPARTAN trial with the addition of Alzheimer's disease, mental impairment, vascular dementia and senile dementia; ARAMIS trial: cognitive disorder, memory impairment and change in mental status; § Data taken from first interim analysis as placebo group not reported in final analysis[1] ; † Data taken from second interim analysis as placebo group not reported in final analysis[2]

AE, adverse event; APA, apalutamide; DARO, darolutamide; ENZA, enzalutamide; NA, not available; PBO, placebo

1. Smith MR, et al. N Engl J Med. 2018;378:1408-18; 2. Small EJ, et al. Annals of Oncology 2019; 30: 1813-1820; 3. Smith MR, et al. Eur Urol. 2020; https://doi.org/10.1016/j.eururo.2020.08.011; 4. Sternberg CN, et al. N Engl J Med. 2020;382: 2197-206; 5. Fizazi K, et al. N Engl J Med. 2020; 383: 1040-1049

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Courtesy of Tanya B Dorff, MD

# Adverse Events of Interest: rash fairly unique to apalutamide. Also need to monitor thyroid with this agent

| Safety | SPARTAN[1,2,3] | | PROSPER[4] | | ARAMIS[5] | |
|---|---|---|---|---|---|---|
| | APA (n = 803) | PBO (n = 398) | ENZA (n = 930) | PBO (n = 465) | DARO (n = 954) | PBO (n = 554) |
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City of Hope

Courtesy of Tanya B Dorff, MD

# Molecular Determinants Associated With Long-Term Response to Apalutamide in Nonmetastatic Castration-Resistant Prostate Cancer

Felix Y. Feng,[1] Clemente Aguilar-Bonavides,[2] Justin Lucas,[3] Shibu Thomas,[2] Michael Gormley,[2] Sharon A. McCarthy,[4] Sabine D. Brookman-May,[5,6] Spyros Triantos,[2] Suneel Mundle,[4] Matthew R. Smith,[7] Eric J. Small[1]

[1]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA; [2]Janssen Research & Development, Spring House, PA; [3]Janssen Research & Development, Bridgewater, NJ; [4]Janssen Research & Development, Raritan, NJ; [5]Ludwig Maximilians University, Munich, Germany; [6]Janssen Research & Development, Los Angeles, CA; [7]Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA

**Abstract 8**

# SPARTAN Biomarker Cohort Analysis: Molecular Determinants of Long-Term Responders (LTR) or Early Progressors (EP)

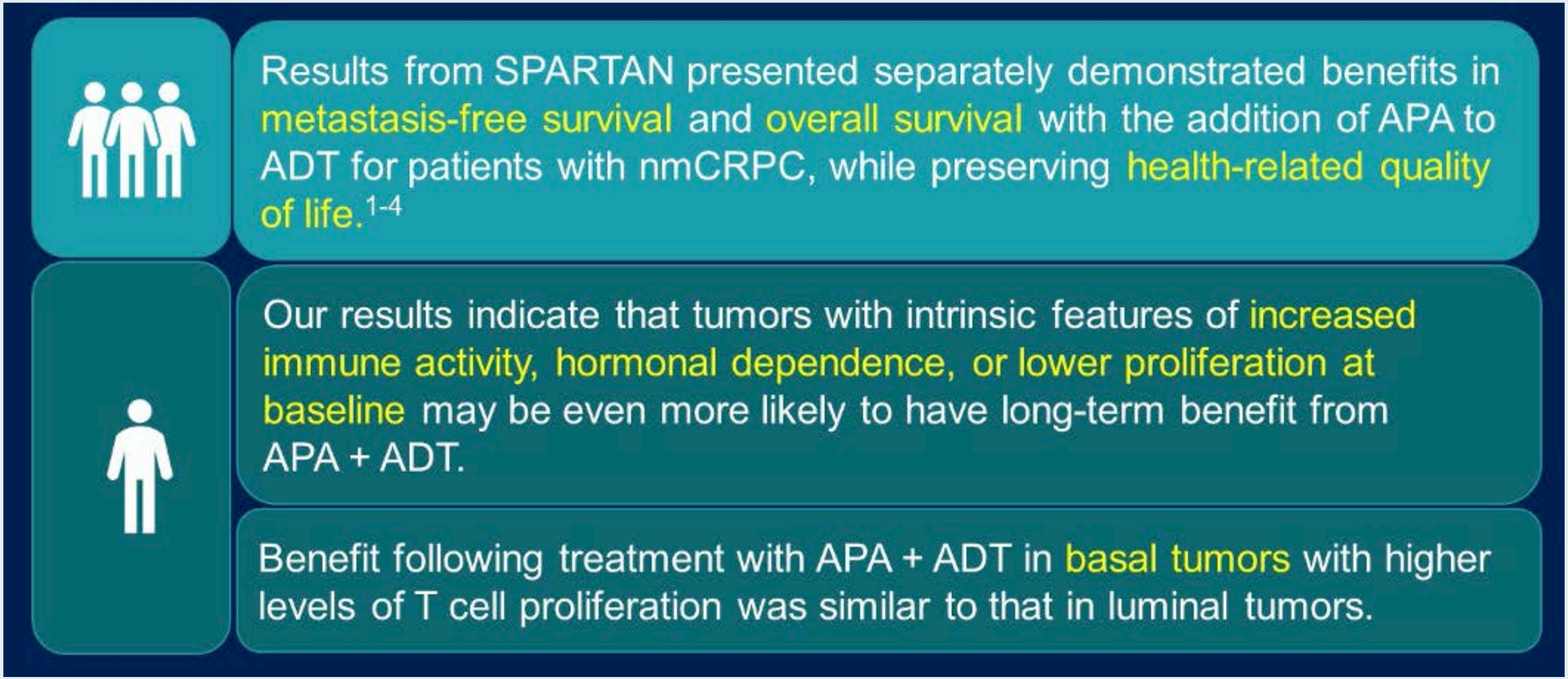
## APA + ADT Group: Increased Immune Activity, or Decreased Vascularization or Proliferative Capacity at Baseline, Were Associated With LTR

| Signature Classification | Transcriptional Signatures | Differential Expression | Nominal *P* Value[a] LTR vs EP |
|---|---|---|---|
| Immune activity | T cell stimulation: ICOS | ↑ LTR | **0.003** |
| | T cell proliferation: IL-2 signaling | ↑ LTR | 0.072[b] |
| | Antigen presentation: TAP2 | ↑ LTR | **0.025** |
| Tumor vascularization | Tumor hypoxia | ↓ LTR | 0.061[b] |
| | Angiogenesis | ↓ LTR | **0.038** |
| Proliferative capacity | Prostate Tumor Proliferation Score 1 | ↓ LTR | 0.053[b] |
| | Prostate Tumor Proliferation Score 2 | ↓ LTR | 0.053[b] |

- In contrast, the inverse was true for patients with EP
- None of these signatures was associated with LTR in the PBO group
- In the PBO group, increased hormonal independence or metastatic capacity at baseline was associated with EP

Feng FY et al. Genitourinary Cancers Symposium 2021;Abstract 8.

# SPARTAN Biomarker Cohort Analysis: Conclusions




Feng FY et al. Genitourinary Cancers Symposium 2021;Abstract 8.

# Agenda

***Case Presentations***

- Dr Glynn: An 88-year-old man with metastatic hormone-sensitive prostate cancer (mHSPC)
- Dr Ma: Comments and questions – LHRH agonists vs antagonists; injections vs oral agents
- Dr Brooks: A 69-year-old man with mHSPC

***GU Cancers Journal Club – Part 1***

***Case Presentations***

- Dr Ma: An 87-year-old man with hormone-sensitive M0 prostate cancer

***GU Cancers Journal Club – Part 2***

***Case Presentations***

- Dr Shehadeh: A 60-year-old man with mCRPC – gBRCA2 mutation
- Dr Zafar: A 77-year-old man with mCRPC – Somatic BRCA2 mutation
- Dr Brooks: A 72-year-old man with mCRPC – gBRCA2 mutation

***GU Cancers Journal Club – Part 3***

***Case Presentations***

- Dr Glynn: A 72-year-old man with mHSPC
- Dr Brooks: A 69-year-old man with mHSPC – MSS, TMB 1, PTEN mutation
- Dr Ma: An 86-year-old man with mCRPC

***GU Cancers Journal Club – Part 4***

RTP RESEARCH TO PRACTICE

# Case Presentation – Dr Shehadeh: A 60-year-old man with metastatic CRPC – Germline BRCA2 mutation

**Dr Nasfat Shehadeh**

- 2010: PSA 270 ng/mL, de novo metastatic prostate cancer
- Leuprolide and bicalutamide at an academic center
- 12/2012: PD → Abiraterone/prednisone → 3/2016: Enzalutamide, discontinued due to fatigue
- 9/2016: Radium-223
- 1/2018: Sipuleucel-T
- 7/2018 Testing: Germline BRCA2 mutation
- 8/2018: Docetaxel x 4 → PD, with new back pain and bone metastases (PSA 136)
- 12/2018: Olaparib 150 mg BID (PSA: 130s → 29 in 1/2020), pain improved → PSA gradually rising
  - Patient has CKD with Cr: 5-6, requiring few sessions of dialysis in 2018
- 9/2020: PSA: 162, Bone scan: T11 new lesion, other lesions stable
- 10/2020: Increased olaparib dose to 300 mg BID (Cr: 6, producing good urine output)

**Question**

- Is it possible now to add darolutamide or apalutamide to a PARP inhibitor, because I don't think he will be eligible for any chemotherapy?

# Case Presentation – Dr Zafar: A 77-year-old man with metastatic CRPC – Somatic BRCA2 mutation

**Dr Syed Zafar**

- PMH: CAD, HTN, dementia, RA
- 2006-7: Gleason 4 + 4 Prostate cancer (PSA: 20s per patient) s/p EBRT and CAB x 3 years
- 2015: Biochemical recurrence + osseous metastases→ ADT
- 2016: PSA progression → Added enzalutamide to ADT
- 2018: Disease and PSA progression (all osseous) → switched to Abiraterone/prednisone + zoledronic acid
- 2019: More symptomatic → Radium-223
- Early 2020: PSA and now visceral/osseous progression → Docetaxel x 3 → PD → Cabazitaxel
- Now with PD, both PSA and Imaging
- NGS not performed on tissue (too old), patient refused new biopsy
- Olaparib x 4 months → PD

**Question**

- Does it make sense to add a platinum while he's on olaparib, or to switch to platinum chemotherapy completely?

# Case Presentation – Dr Zafar: A 77-year-old man with metastatic CRPC – Somatic BRCA2 mutation

Dr Syed Zafar

## Liquid Biopsy Testing

### Summary of Somatic Alterations & Associated Treatment Options

KEY ✓ Approved in indication ✓ Approved in other indication ⊗ Lack of response

| Alteration | % cfDNA or Amplification | Associated FDA-approv therapies |
|---|---|---|
| *BRCA2* T3033fs | 26.7% | ✓ Olaparib, Rucaparib<br>✓ Niraparib, Talazoparib |
| *TP53* R156C | 0.1% | None |
| *APC* V2706fs | 0.3% | None |

Synonymous Alterations

*FGFR1* L769L (11.9%), *MET* N1353N (0.1%)

This sequence change does not alter the amino acid at this position and is unlikely to be a therapeutic

# Case Presentation – Dr Zafar: A 77-year-old man with metastatic CRPC – Somatic BRCA2 mutation

Dr Syed Zafar

## Germline Testing

final and comprehensive interpretation of this patient's genetic testing by the healthcare provider should include the results from the additional testing as well as the results included in this report.

**GENETIC RESULT: NEGATIVE - NO CLINICALLY SIGNIFICANT MUTATION IDENTIFIED**

Note: "CLINICALLY SIGNIFICANT," as defined in this report, is a genetic change that is associated with the potential to alter medical intervention.

**ADDITIONAL FINDINGS: NO VARIANT(S) OF UNCERTAIN SIGNIFICANCE (VUS) IDENTIFIED**

**Details About Non-Clinically Significant Variants:** All individuals carry DNA changes (i.e., variants), and most variants do not increase an individual's risk of cancer or other diseases. When identified, variants of uncertain significance (VUS) are reported. Likely benign variants (Favor Polymorphisms) and benign variants (Polymorphisms) are not reported and available data indicate that these variants most likely do not cause increased cancer risk. Present evidence does not suggest that non-clinically significant variant findings be used to modify patient medical management beyond what is indicated by the personal and family history and any other clinically significant findings.

**Variant Classification:** Myriad's myVision™ Variant Classification Program performs ongoing evaluations of variant classifications. In certain cases, healthcare providers may be contacted for more clinical information or to arrange family testing to aid in variant classification. When new evidence about a variant is identified and determined to result in clinical significance and management change, that information will automatically be made available to the healthcare provider through an amended report.

RTP RESEARCH TO PRACTICE

# Case Presentation – Dr Brooks: A 72-year-old man with metastatic CRPC – Germline BRCA2 mutation

**Dr Philip Brooks**

- Metastatic prostate cancer s/p progression on conventional hormonal therapy
- Testing: Germline BRCA2 mutation
- Olaparib x 6 months

**Questions**

- Which PARP inhibitors do you use and how do you dose them to increase tolerability?
- Do we have evidence of PARP inhibitors being effective in patients with other indicators of defects in DNA repair pathways, such as LOH?

RTP RESEARCH TO PRACTICE

**A 65-year-old man with a germline BRCA mutation presents with minimally symptomatic prostate cancer metastatic to the bone and receives enzalutamide and ADT with response followed by progression. What would you recommend?**

a. Abiraterone
b. Docetaxel
c. Olaparib
d. Rucaparib
e. Other
f. I don't know

RTP RESEARCH TO PRACTICE

**A 65-year-old man with an ATM mutation presents with minimally symptomatic prostate cancer metastatic to the bone and receives enzalutamide and ADT with response followed by progression. What would you recommend?**

a. Abiraterone
b. Docetaxel
c. Olaparib
d. Rucaparib
e. Other
f. I don't know

RTP RESEARCH TO PRACTICE

# Agenda

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***GU Cancers Journal Club – Part 1***

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- Dr Ma: An 86-year-old man with mCRPC

***GU Cancers Journal Club – Part 4***

RTP RESEARCH TO PRACTICE

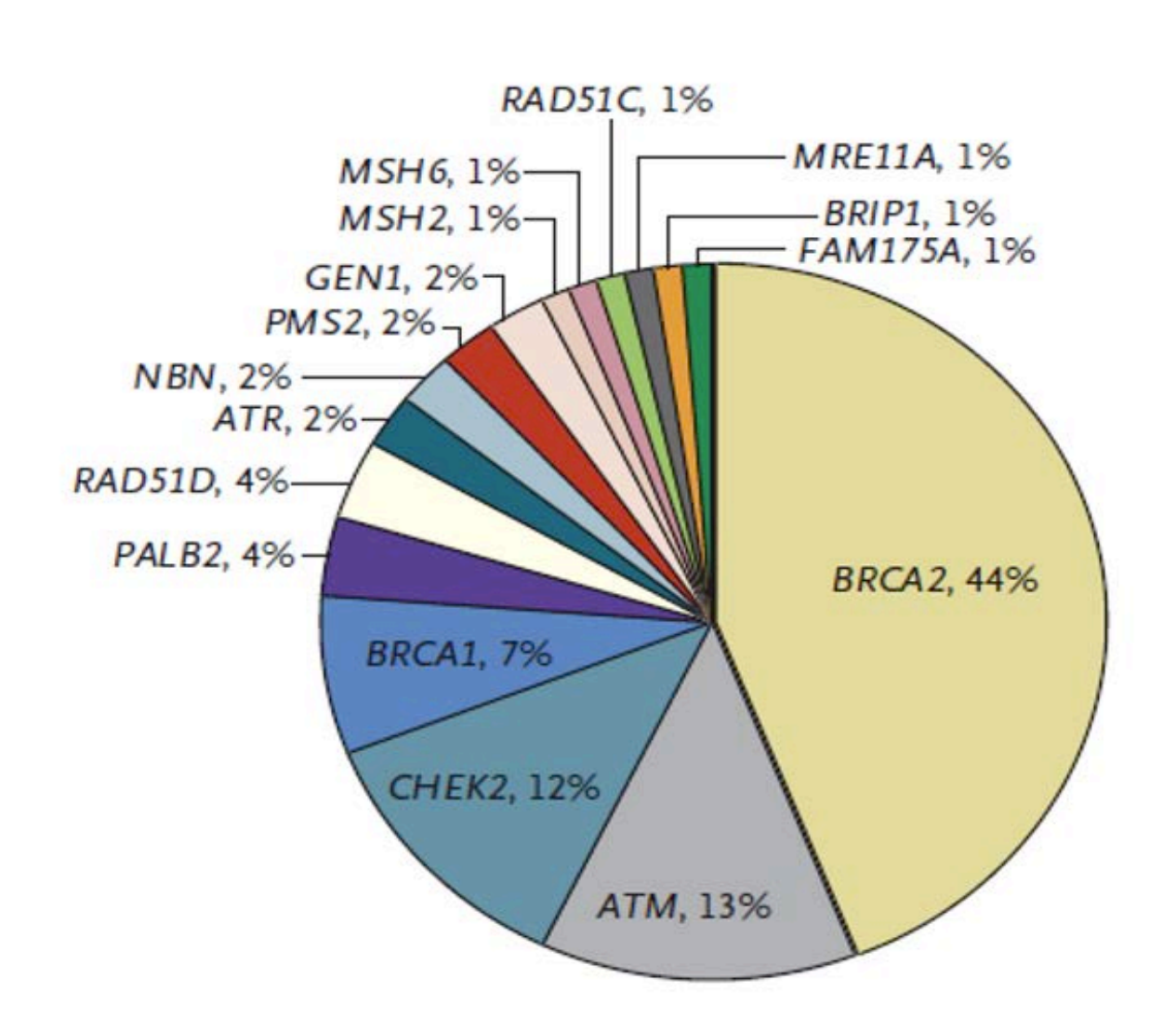
# Case Presentation – Dr Smith: A man in his early 60s with mCRPC and a BRCA2 mutation

- In 2015, patient was diagnosed with prostate cancer at age 57 after presenting with back pain and anemia
- PSA >1,000, MRI with extensive bone metastases
- 10/2015 started continuous ADT
- 11/2015-3/2016 docetaxel x 6 cycles of mHSPC
- 11/2016 radiation to skull base after presenting with diplopia
- 2/2017-6/2017 retreated with docetaxel; discontinued for progression
- 8/2017-4/2018 abiraterone acetate plus prednisone; best response was progressive disease
- 4/2018 PSA 290. Restaging with extensive bone metastases

# Case Presentation – Dr Smith: A man in his early 60s with mCRPC and a BRCA2 mutation – continued

- Family History
  - Father died from prostate cancer at age 91
  - Mother died from breast cancer at age 61
- Germline genetic testing with pathogenic BRCA2 mutation c.3847_3848delGT (p.Val1283Lysfs*2)
- 4/2018-1/2019 Olaparib
  - He had treatment interruptions and dose reductions for hematologic toxicity (low ANC, anemia)
  - Prompt improvement in pain
  - PSA declined from 290 to nadir of 90
  - Discontinued for clinical disease progression

# Inherited DNA Repair Gene Mutations in Men with Metastatic Prostate Cancer




- Multicenter study of 692 men
- Deleterious mutations were found in 82 men (11.8%) in 16 genes
- Observed rate exceeded that associated with localized prostate cancer (4.6%) and general population without cancer (2.7%)

Courtesy of Matthew Smith, MD, PhD.

RTP RESEARCH TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

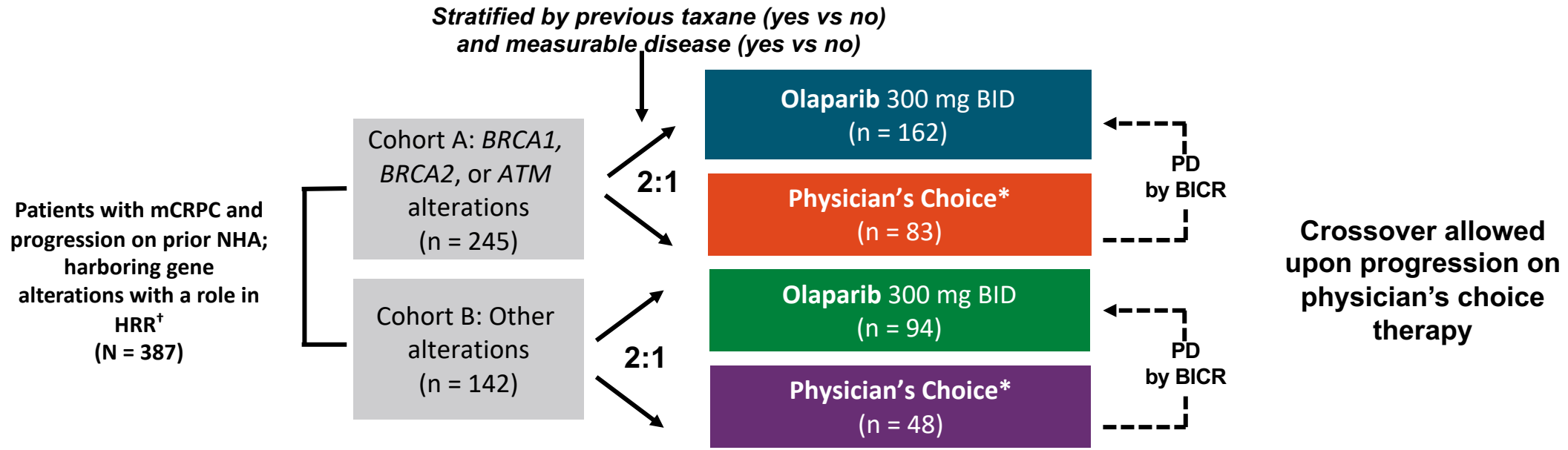
# Olaparib for Metastatic Castration-Resistant Prostate Cancer

J. de Bono, J. Mateo, K. Fizazi, F. Saad, N. Shore, S. Sandhu, K.N. Chi, O. Sartor, N. Agarwal, D. Olmos, A. Thiery-Vuillemin, P. Twardowski, N. Mehra, C. Goessl, J. Kang, J. Burgents, W. Wu, A. Kohlmann, C.A. Adelman, and M. Hussain

***N Engl J Med* 2020;382:2091-102**

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

# PROfound: Olaparib vs Physician's Choice in mCRPC




*Enzalutamide 160 mg QD or abiraterone acetate 1000 mg QD plus prednisone 5 mg BID.
†***BRCA1/2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RA51D, or RAD54L***.

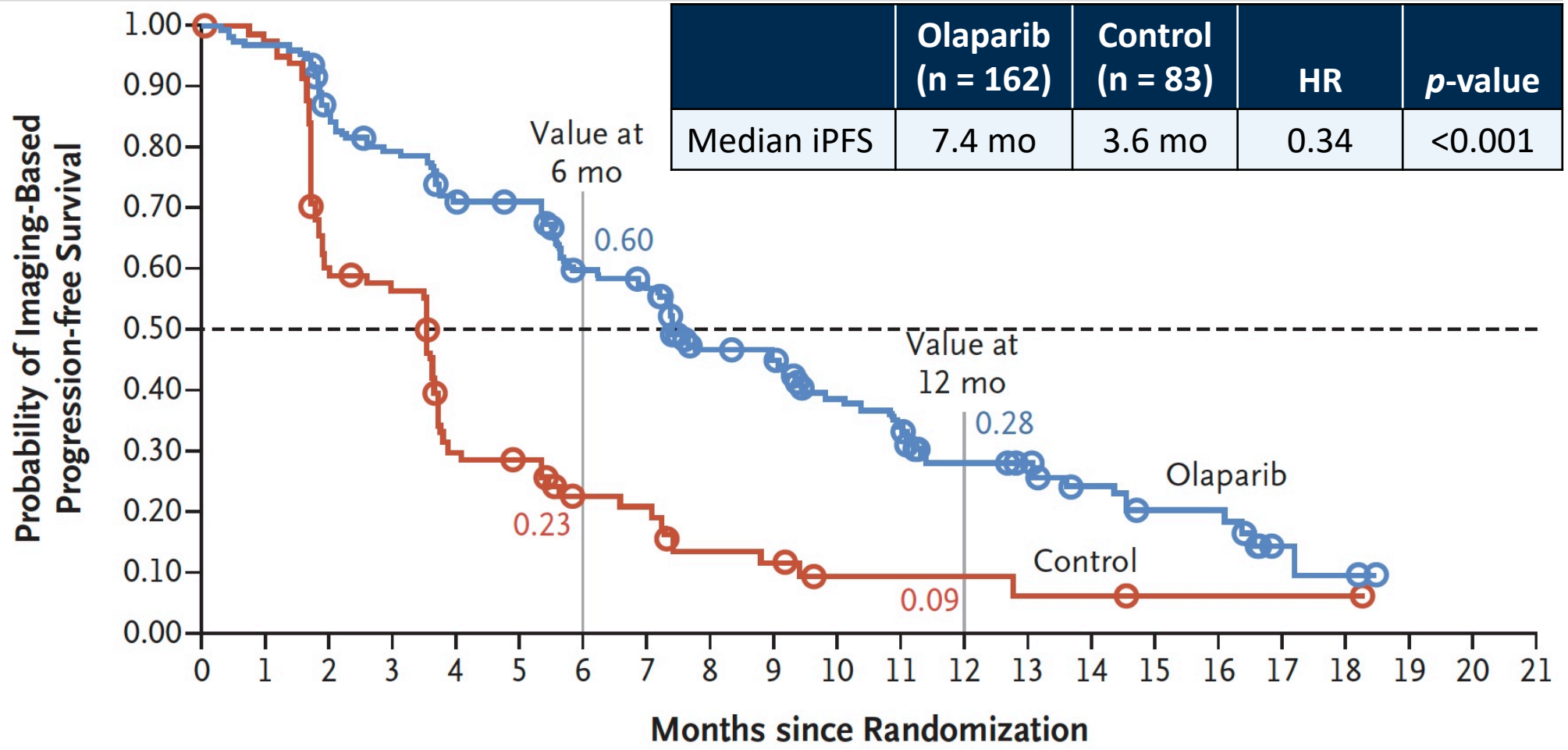
- Primary endpoint: radiographic PFS in cohort A by BICR using RECIST 1.1 and PCWG3
- Secondary endpoints: radiographic PFS in both cohorts, confirmed radiographic ORR in cohort A, time to pain progression in cohort A, OS in cohort A

de Bono et al. *N Engl J Med.* 2020;382:2091.

Courtesy of Matthew Smith, MD, PhD.

# PROfound Primary Endpoint: Imaging-Based PFS with Olaparib in Patients with mCRPC Who Had at Least 1 Alteration in BRCA1, BRCA2 or ATM (Cohort A)

| | Olaparib (n = 162) | Control (n = 83) | HR | *p*-value |
|---|---|---|---|---|
| Median iPFS | 7.4 mo | 3.6 mo | 0.34 | <0.001 |




de Bono J et al; PROfound investigators. *N Engl J Med* 2020;382(22):2091-102.

RTP RESEARCH TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

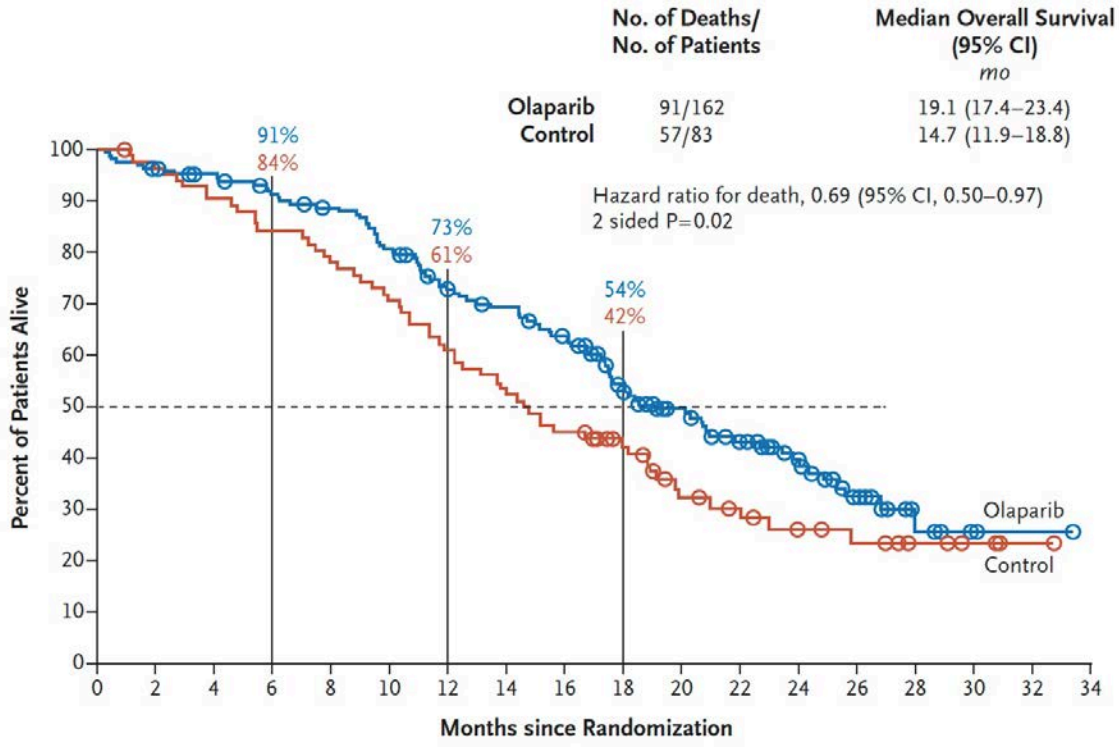
# Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer

M. Hussain, J. Mateo, K. Fizazi, F. Saad, N. Shore, S. Sandhu, K.N. Chi, O. Sartor, N. Agarwal, D. Olmos, A. Thiery-Vuillemin, P. Twardowski, G. Roubaud, M. Özgüroğlu, J. Kang, J. Burgents, C. Gresty, C. Corcoran, C.A. Adelman, and J. de Bono, for the PROfound Trial Investigators*

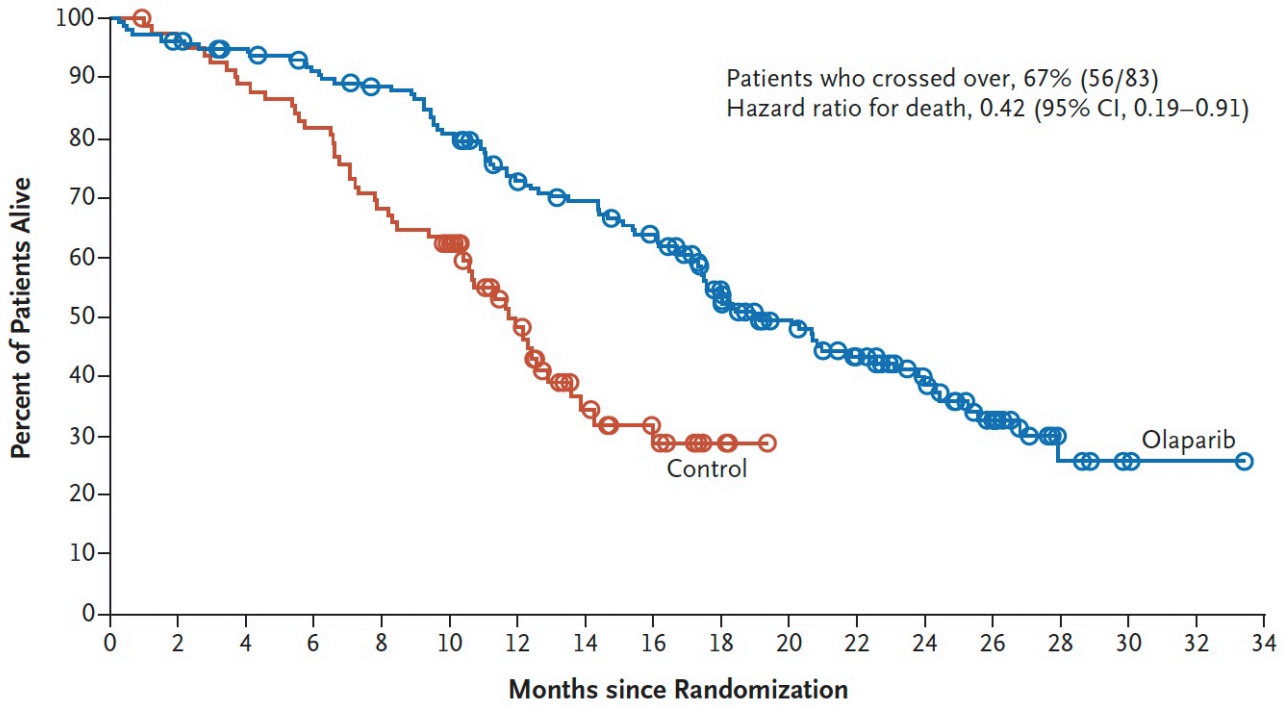
***N Engl J Med* 2020;383(24):2345-57.**

# PROfound: Overall Survival with Olaparib in Patients with mCRPC Who Had at Least 1 Alteration in BRCA1, BRCA2 or ATM (Cohort A)

## Overall survival




## Cross-over adjusted overall survival




Hussain M et al; PROfound investigators. *N Engl J Med* 2020;383(24):2345-57.

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

# PROfound: Safety Summary

**Median treatment duration: Olaparib 7.4 months; Physician's choice 3.9 months**

| | Olaparib (N=256) | Physician's choice (N=130) |
|---|---|---|
| Any AE, n (%) | 244 (95.3) | 114 (87.7) |
| Any AE of CTCAE grade 3 or higher, n (%) | 130 (50.8) | 49 (37.7) |
| Dose reduction due to AE, n (%) | 57 (22.3) | 5 (3.8) |
| Discontinuation due to AE, n (%) | 42 (16.4) | 11 (8.5) |
| Death due to AE, n (%) | 10 (3.9) | 5 (3.8) |
| Reported to be related to study treatment | 1 (0.4) | 1 (0.8) |

**AEs are reported irrespective of attribution, unless otherwise stated**

Hussain M, et al. 2019 ESMO. Abstract LBA12.

Courtesy of Matthew Smith, MD, PhD.

# Exploratory gene-by-gene analysis of olaparib efficacy in patients with metastatic castration-resistant prostate cancer: PROfound

Johann de Bono,[1] Nobuaki Matsubara,[2] Nicolas Penel,[3] Niven Mehra,[4] Michael Kolinsky,[5] Emmanuelle Bompas,[6] Susan Feyerabend,[7] Gwenaelle Gravis,[8] Jae Young Joung,[9] Kazuo Nishimura,[10] Craig Gedye,[11] Joaquin Mateo,[12] Fred Saad,[13] Karim Fizazi,[14] Neal Shore,[15] Jinyu Kang,[16] Chintu Desai,[17] Joseph Burgents,[18] Elizabeth A. Harrington,[19] Maha Hussain[20]

Genitourinary Cancers Symposium 2021;Abstract 126.

# Olaparib efficacy in patients with metastatic castration-resistant prostate cancer carrying circulating tumor DNA alterations in *BRCA1*, *BRCA2* or *ATM*: results from the PROfound study

Nobuaki Matsubara,[1] Johann de Bono,[2] David Olmos,[3] Giuseppe Procopio,[4] Satoru Kawakami,[5] Yuksel Urun,[6] Robbert van Alphen,[7] Aude Flechon,[8] Michael A. Carducci,[9] Young Deuk Choi,[10] Sebastien J. Hotte,[11] Ernesto Korbenfeld,[12] Gero Kramer,[13] Neeraj Agarwal,[14] Simon Dearden,[15] Chris Gresty,[16] Jinyu Kang,[17] Christian Poehlein,[18] Elizabeth A. Harrington,[19] Maha Hussain[20]

Genitourinary Cancers Symposium 2021;Abstract 27.

# FDA Approves Olaparib for HRR Gene-Mutated mCRPC

## Press Release: May 19, 2020

"On May 19, 2020, the U.S. Food and Drug Administration approved 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.

The FDA also approved FoundationOne CDx for selection of patients with mCRPC carrying HRR gene alterations and BRACAnalysis CDx test for selection of patients with mCRPC carrying germline *BRCA1/2* alterations as companion diagnostic devices for treatment with olaparib.

Efficacy was investigated in PROfound (NCT02987543), an open-label, multicenter trial randomizing (2:1) 256 patients to olaparib 300 mg twice daily and 131 patients to investigator's choice of enzalutamide or abiraterone acetate. All patients received a GnRH analog or had prior bilateral orchiectomy."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-olaparib-hrr-gene-mutated-metastatic-castration-resistant-prostate-cancer

RTP RESEARCH TO PRACTICE

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

# TRITON2: Rucaparib in Metastatic CRPC With HRR Gene Alterations

- International, multicenter, open-label phase II study

Patients with mCRPC and deleterious somatic or germline alteration in HRR genes*; progression on AR-directed tx† for PC and 1 prior line of taxane-based CT for CRPC; no prior PARPi, mitoxantrone, cyclophosphamide, or platinum-based CT; ECOG PS 0/1
(N = 190‡)

**Rucaparib** 600 mg BID in 28-d cycles §

***Until radiographic progression or discontinuation for other reason***

*Local or central testing of blood or tumor samples for alterations in HRR genes: ***BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD54L***. †Abiraterone, enzalutamide, or apalutamide. ‡Enrollment cutoff: February 28, 2019.
§ Assessments: tumor Q8W for 24 wks, then Q12W; PSA Q4W.

- Primary endpoints
  - *Among patients with measurable disease at BL:* centrally assessed, confirmed ORR per modified RECIST¶/PCWG3
  - *Among patients without measurable disease at BL:* locally assessed, confirmed PSA response (≥50% decrease) rate

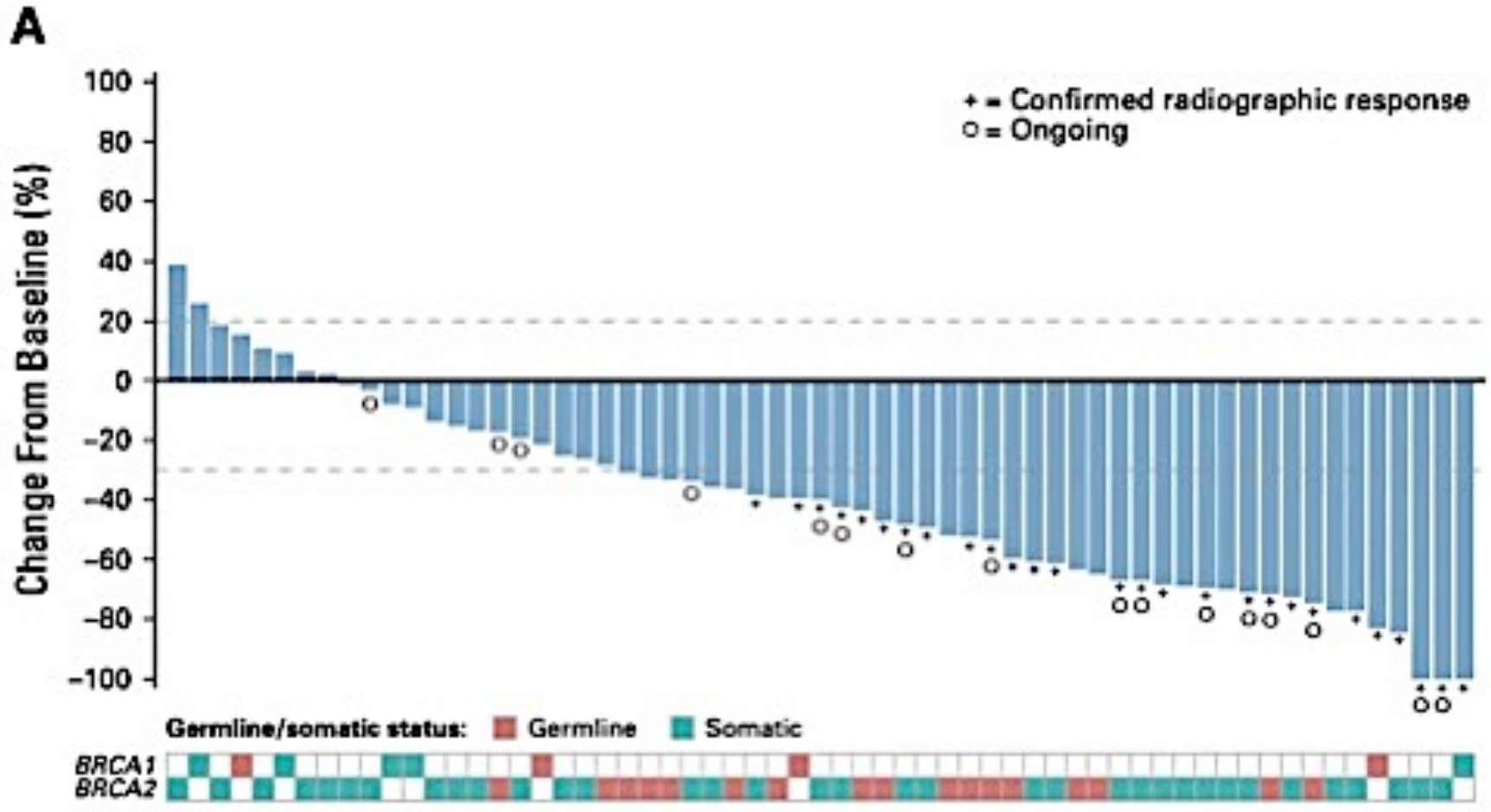
¶RECIST modified to include up to 10 target lesions (maximum 5 per site), excluding prostatic bed or bone lesions; MRI permitted.

Abida et al. ESMO 2018. Abstract 793PD; Abida et al. *J Clin Oncol* 2020;38(32):3763-72.

Courtesy of Matthew Smith, MD, PhD.

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

# TRITON2: Tumor Response in *BRCA1*/*BRCA2* Cohort




Abida et al. *J Clin Oncol* 2020;38(32):3763-72.

Courtesy of Matthew Smith, MD, PhD.

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# TRITON2: Adverse Event Profile

**TABLE 3.** Most Commonly Reported TEAEs (N = 115)

| Individual TEAE (preferred terms) Occurring in ≥ 15% of Patients | Any Grade | Grade ≥ 3 |
|---|---|---|
| Asthenia/fatigue | 71 (61.7) | 10 (8.7) |
| Nausea | 60 (52.2) | 3 (2.6) |
| Anemia/decreased hemoglobin | 50 (43.5) | 29 (25.2) |
| ALT/AST increased | 38 (33.0) | 6 (5.2) |
| Decreased appetite | 32 (27.8) | 2 (1.7) |
| Constipation | 31 (27.0) | 1 (0.9) |
| Thrombocytopenia/decreased platelets | 29 (25.2) | 11 (9.6) |
| Vomiting | 25 (21.7) | 1 (0.9) |
| Diarrhea | 23 (20.0) | 0 |
| Dizziness | 21 (18.3) | 0 |
| Blood creatinine increased | 18 (15.7) | 1 (0.9) |

NOTE. Data presented as No. (%). Visit cutoff date: September 13, 2019. TEAEs were graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.03. There were no TEAEs of myelodysplastic syndrome or acute myeloid leukemia reported.

Abbreviation: TEAE, treatment-emergent adverse event.

Abida et al. *J Clin Oncol* 2020;38(32):3763-72.

Courtesy of Matthew Smith, MD, PhD.

# FDA Approves Rucaparib for mCRPC with BRCA Mutation

**Press Release: August 26, 2020**
**Press Release: May 15, 2020**

"On August 26, 2020, the Food and Drug Administration approved the liquid biopsy next-generation sequencing-based Liquid CDx test as a companion diagnostic to identify mutations in *BRCA1* and *BRCA2* genes in cell free-DNA isolated from plasma specimens from patients with mCRPC eligible for treatment with rucaparib."

"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.

Efficacy was investigated in TRITON2 (NCT02952534), an ongoing, multi-center, single arm clinical trial in 115 patients with *BRCA*-mutated (germline and/or somatic) mCRPC who had been treated with androgen receptor-directed therapy and taxane-based chemotherapy. Patients received rucaparib 600 mg orally twice daily and concomitant GnRH analog or had prior bilateral orchiectomy."

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-liquid-biopsy-next-generation-sequencing-companion-diagnostic-test
https://www.fda.gov/drugs/fda-grants-accelerated-approval-rucaparib-brca-mutated-metastatic-castration-resistant-prostate

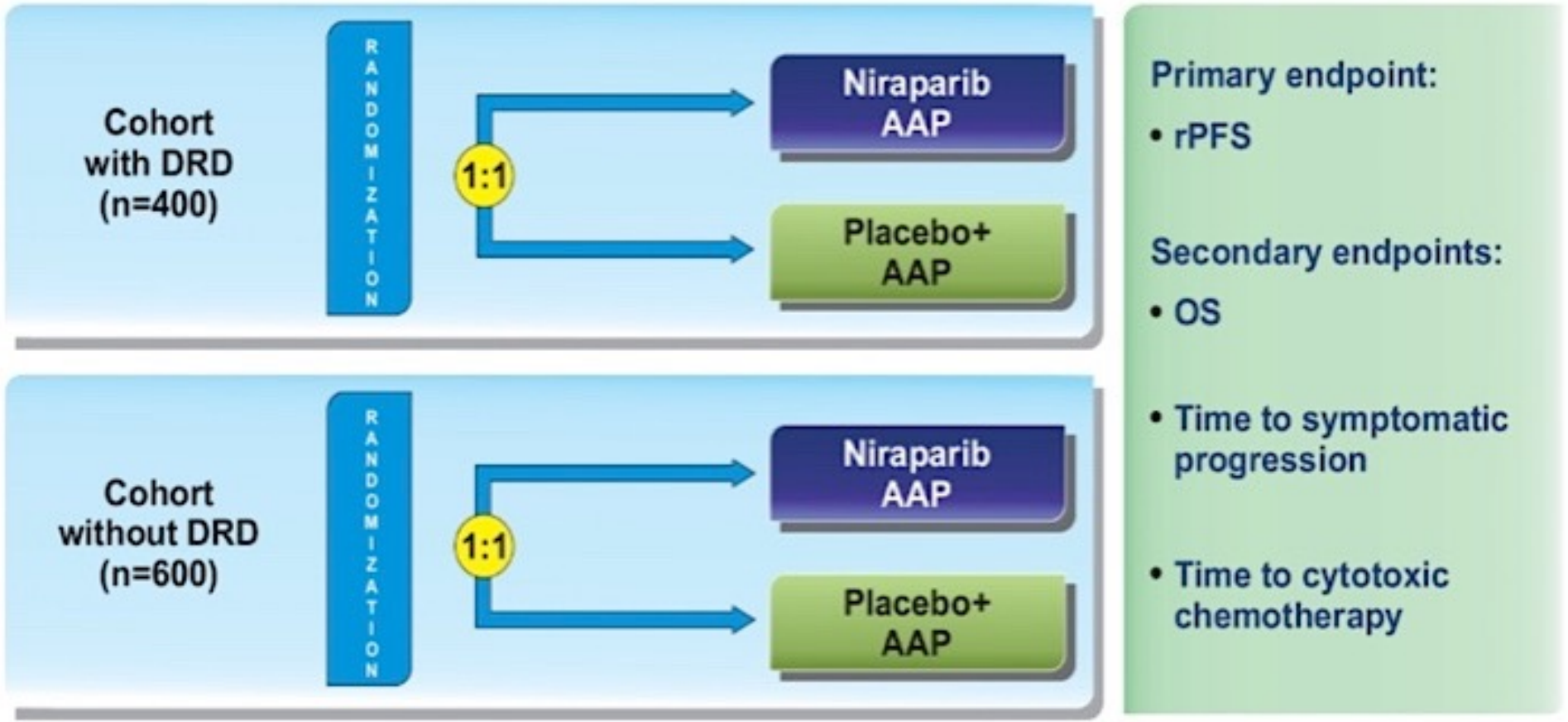
RTP RESEARCH TO PRACTICE

# CASPAR (Alliance A031902): A Randomized, Phase III Trial of Enzalutamide (ENZ) with Rucaparib (RUCA)/Placebo (PBO) as a Novel Therapy in First-Line Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Rao A et al.

Genitourinary Cancers Symposium 2021;Abstract TPS181.

# MAGNITUDE: Phase 3 Study of Abiraterone +/- Niraparib




ClinicalTrials.gov Identifier: NCT03748641

Courtesy of Matthew Smith, MD, PhD.

# AMPLITUDE: A Study of Niraparib in Combination with Abiraterone Acetate plus Prednisone (AAP) versus AAP for the Treatment of Patients with Deleterious Germline or Somatic Homologous Recombination Repair (HRR) Gene-Altered Metastatic Castration-Sensitive Prostate Cancer (mCSPC)

Rathkopf DE et al.

Genitourinary Cancers Symposium 2021;Abstract TPS176.

# Differential Activity of PARP Inhibitors in BRCA1- versus BRCA2-Altered Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Taza F et al.
Genitourinary Cancers Symposium 2021;Abstract 100.

# TALAPRO-1: Phase II Study of Talazoparib (TALA) in Patients (pts) with DNA Damage Repair Alterations (DDRm) and Metastatic Castration-Resistant Prostate Cancer (mCRPC)

de Bono JS et al.

Genitourinary Cancers Symposium 2021;Abstract 93.

# Agenda

***Case Presentations***

- Dr Glynn: An 88-year-old man with metastatic hormone-sensitive prostate cancer (mHSPC)
- Dr Ma: Comments and questions – LHRH agonists vs antagonists; injections vs oral agents
- Dr Brooks: A 69-year-old man with mHSPC

***GU Cancers Journal Club – Part 1***

***Case Presentations***

- Dr Ma: An 87-year-old man with hormone-sensitive M0 prostate cancer

***GU Cancers Journal Club – Part 2***

***Case Presentations***

- Dr Shehadeh: A 60-year-old man with mCRPC – gBRCA2 mutation
- Dr Zafar: A 77-year-old man with mCRPC – Somatic BRCA2 mutation
- Dr Brooks: A 72-year-old man with mCRPC – gBRCA2 mutation

***GU Cancers Journal Club – Part 3***

***Case Presentations***

- Dr Glynn: A 72-year-old man with mHSPC
- Dr Brooks: A 69-year-old man with mHSPC – MSS, TMB 1, PTEN mutation
- Dr Ma: An 86-year-old man with mCRPC

***GU Cancers Journal Club – Part 4***

RTP RESEARCH TO PRACTICE

# Case Presentation – Dr Glynn: A 72-year-old man with hormone-sensitive metastatic prostate cancer

**Dr Philip Glynn**

- 2009: Prostatic intraepithelial neoplasia (PIN) followed clinically
- 6/2011: PSA: 5.8 ng/mL → Biopsies: Gleason 3 + 3 = 6, in 1/12 biopsies
- Active surveillance
- 6/2013: PSA: 14.8 ng/ml → Biopsy: Gleason 4 + 4 = 8 → ADT x 18 months + RT
- 10/2020: PSA: 2.2 ng/mL
- 1/2021: PSA: 2.5 ng/mL → Fluciclovine F18 PET CT scan: 3-subcentimeter pelvic nodes, 0.7-cm iliac lesion

**Questions**

- How do people go about selecting apalutamide versus abiraterone versus enzalutamide?
- What would be the appropriate length of ADT in the setting of radiation therapy? In patients who decided to hold off on therapy, at what point would you strongly recommend transition to treatment?
- Suppose he had a PSA relapse a few years after radiation therapy and 18 months of ADT, what would you have done?
- What would be the threshold PSADT for selection of the patient who is going on therapy for M0?
- What is your selection in their primary agent and then what's the subsequent criteria for selection of treatment when they progress to M1?

RTP RESEARCH TO PRACTICE

# Case Presentation – Dr Brooks: A 69-year-old man with metastatic hormone-sensitive prostate cancer – MSS, TMB 1, PTEN mutation

**Dr Philip Brooks**

- PMH: H&N cancer treated with RT; BPH s/p green light laser in 2018, with subsequent discomfort treated with gabapentin
- More recently, new pelvic pain, increasing problems with urination
  - CT: Diffuse hepatic mets, small pulmonary mets, stable lytic lesions
  - PSA: 12/2019 to 11/2020: 1 → 23 ng/mL
  - Liver biopsy: Positive for poorly differentiated carcinoma with findings most suggestive of metastasis from a prostatic primary
- Degarelix and apalutamide
- 1/2021 after 4 weeks of treatment: Liver enzymes: Normal, pain resolved, PSA: 0.95 ng/mL
- Foundation One assay: MSS, TMB: 1, PTEN mutation

**Questions**

- With his liver metastases, would you have been comfortable treating him with degarelix and apalutamide, or would you absolutely have started docetaxel?
- If you were going to use endocrine therapy, how would you choose among all the available agents?

# Case Presentation – Dr Ma: An 86-year-old man with metastatic CRPC – Part 1

**Dr Yanjun Ma**

- Patient lives alone and travels to remote medical clinic, PS 0-1
- 12/2018: De novo metastatic prostate cancer, with multiple bone metastases, including the right parietal skull, ribs and spine
  - Gleason 4 + 5 = 9
- 1/2019: Leuprolide q4 months + enzalutamide + denosumab
- 2/2020: Sipuleucel-T x 3
- 2/2021: Radiographic disease progression of bone-only disease

# Case Presentation – Dr Ma: An 86-year-old man with metastatic CRPC – Part 2

**Dr Yanjun Ma**

- Patient lives alone and travels to remote medical clinic, PS 0-1
- 12/2018: De novo metastatic prostate cancer, with multiple bone metastases, including the right parietal skull, ribs and spine
  - Gleason 4 + 5 = 9
- 1/2019: Leuprolide q4 months + enzalutamide + denosumab
- 2/2020: Sipuleucel-T x 3
- 2/2021: Radiographic disease progression of bone-only disease

**Questions**

- What is your suggestion about his next line of treatment? Would you stay with the alternative antiandrogen treatment like abiraterone? What about radium-223?
- This patient is elderly but is still living independently with a performance status between 0 and 1. What are your thoughts about docetaxel for him?

RTP RESEARCH TO PRACTICE

**A 75-year-old man presents with prostate cancer (BRCA wild type) metastatic to the bone and receives ADT + docetaxel with disease progression 1 year later. He responds to enzalutamide for 9 months, then has symptomatic progression in the bone along with new lung lesions. What is your most likely treatment?**

1. Abiraterone
2. Apalutamide
3. Docetaxel
4. Cabazitaxel
5. Other

**A 75-year-old man presents with prostate cancer (BRCA wild type) metastatic to the bone and receives ADT + docetaxel with disease progression 18 months later. He responds to enzalutamide for 9 months, then has symptomatic progression in the bone along with new lung lesions. What is your most likely treatment?**

1. Abiraterone
2. Apalutamide
3. Docetaxel
4. Cabazitaxel
5. Other

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## At what point, if any, do you generally recommend radium-223 to a patient with bone-only metastatic castration-resistant prostate cancer?

1. After 1 line of hormonal therapy
2. After 1 line of chemotherapy
3. After at least 1 line of both hormonal therapy and chemotherapy
4. Other
5. I generally would not administer radium-223

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TO PRACTICE

# Agenda

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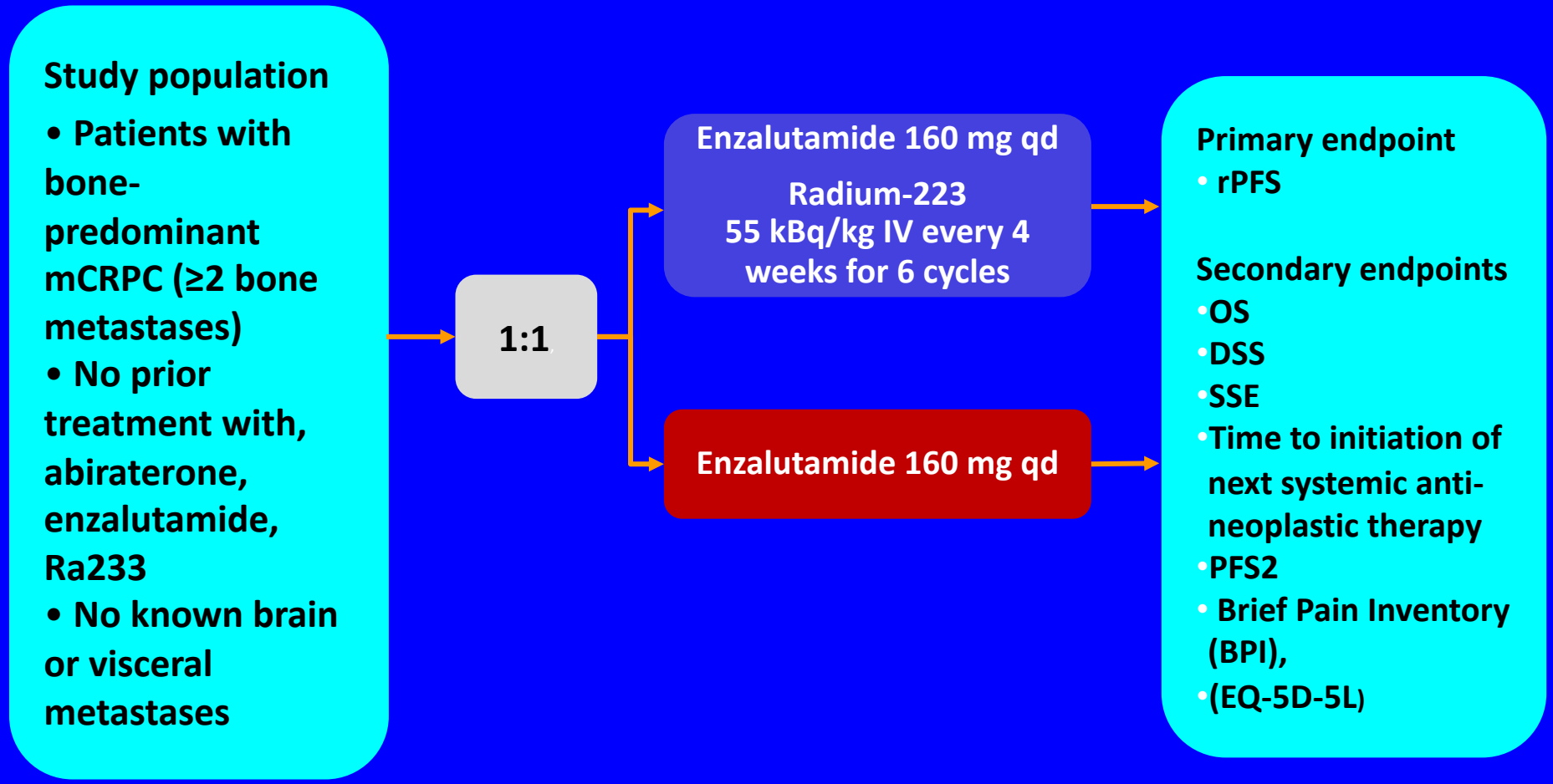
- Dr Ma: An 86-year-old man with mCRPC

***GU Cancers Journal Club – Part 4***

# Case Presentation – Dr Sartor: A 90-year-old man with castration-resistant prostate cancer

- Treated with ADT and abiraterone for an extended period
  - Feeble, confined to bed
- Just began treatment with high-dose testosterone
  - Family noted increased energy levels and vigor
- Slight PSA rise as of 3rd dose of testosterone
  - Monitoring and will re-evaluate patient in 4 weeks

# EORTC-1333-GUCG (PEACE III) is ongoing




Courtesy of A Oliver Sartor, MD

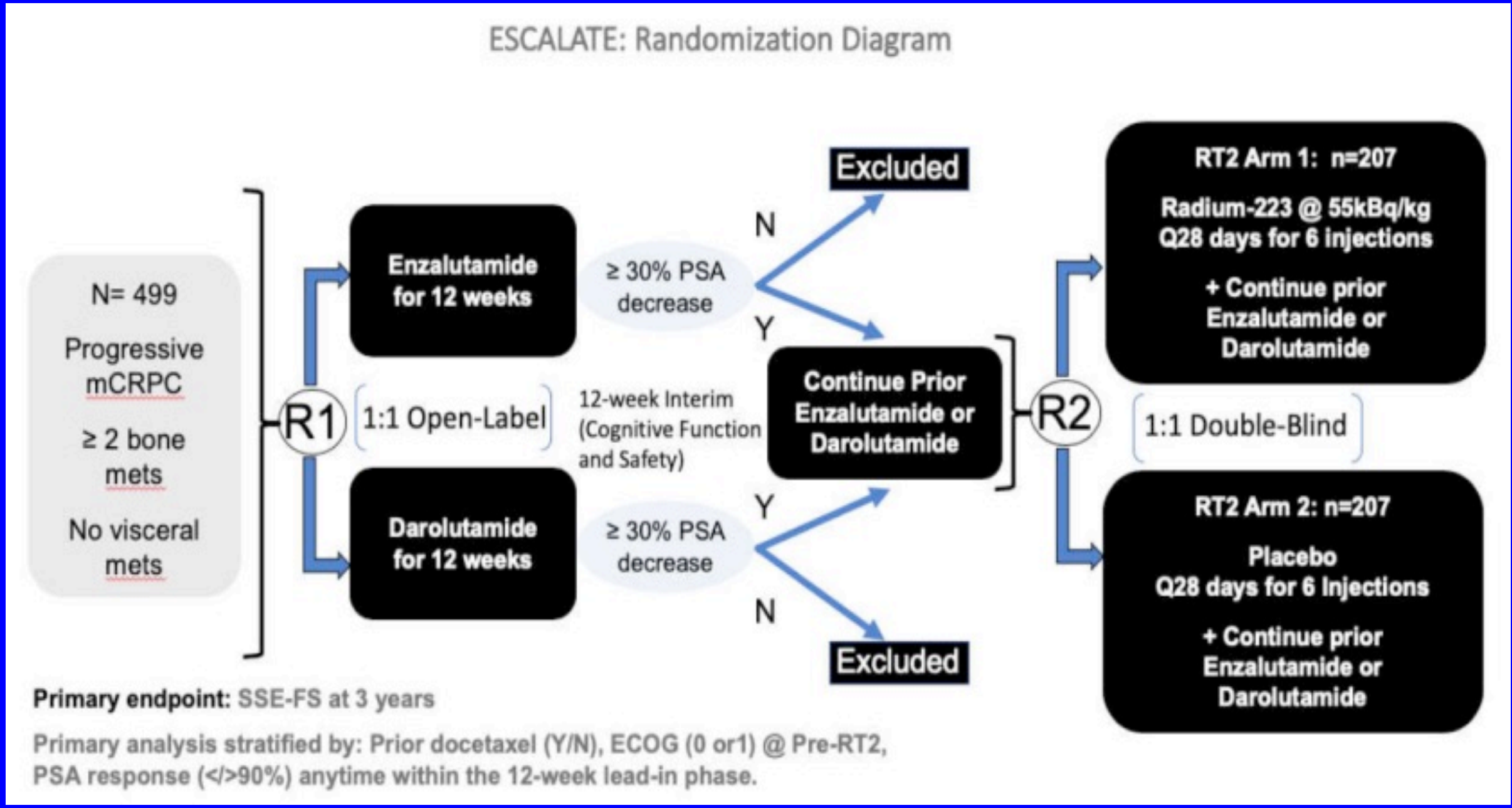
# Bone fractures and cumulative incidence safety population of PEACE III:

## Huge differences with bone protective agents

Tombal, ASCO 2019, #5007

| Time point | Treatment and use of bone protecting agents | | | |
|---|---|---|---|---|
| | With exposure to BPA | | Without exposure to BPA | |
| | Enza+Rad (N=39) | Enza (N=49) | Enza+Rad (N=37) | Enza (N=35) |
| | Cum Incidence (95% CI)* | Cum Incidence (95% CI) | Cum Incidence (95% CI) | Cum Incidence (95% CI) |
| 3 months | 0 (-) | 0 (-) | 0 (-) | 5.7 (1.0-16.7) |
| 6 months | 0 (-) | 0 (-) | 5.6 (1.0-16.3) | 8.8 (2.2-21.0) |
| 9 months | 0 (-) | 0 (-) | 22.6 (10.6-37.3) | 8.8 (2.2-21.0) |
| **12 months** | **0 (-)** | **0 (-)** | **37.4 (21.8-53.1)** | **12.4 (3.9-26.2)** |
| 15 months | 0 (-) | 0 (-) | 43.6 (26.8-59.3) | 16.6 (5.9-32.0) |
| 18 months | 0 (-) | 0 (-) | 43.6 (26.8-59.3) | 16.6 (5.9-32.0) |

Courtesy of A Oliver Sartor, MD




Courtesy of A Oliver Sartor, MD

# Real-World Clinical Outcomes Study of Sequential Novel Antihormonal Therapy (NAH) or Radium-223 (Ra-223) Treatment of Metastatic Castration-Resistant Prostate Cancer (mCRPC) That Progressed After First-Line NAH

Sartor AO et al.

Genitourinary Cancers Symposium 2021;Abstract 48.

# Clinical Outcomes of Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC) Receiving Radium-223 (Ra-223) Early versus Late in the Treatment Sequence

Mbuagbaw L et al.

Genitourinary Cancers Symposium 2021;Abstract 136.

# Fractionated Docetaxel and Radium-223 (Ra223) in Metastatic Castration-Resistant Prostate Cancer (CRPC): A Phase I Trial

Connell BJ et al.

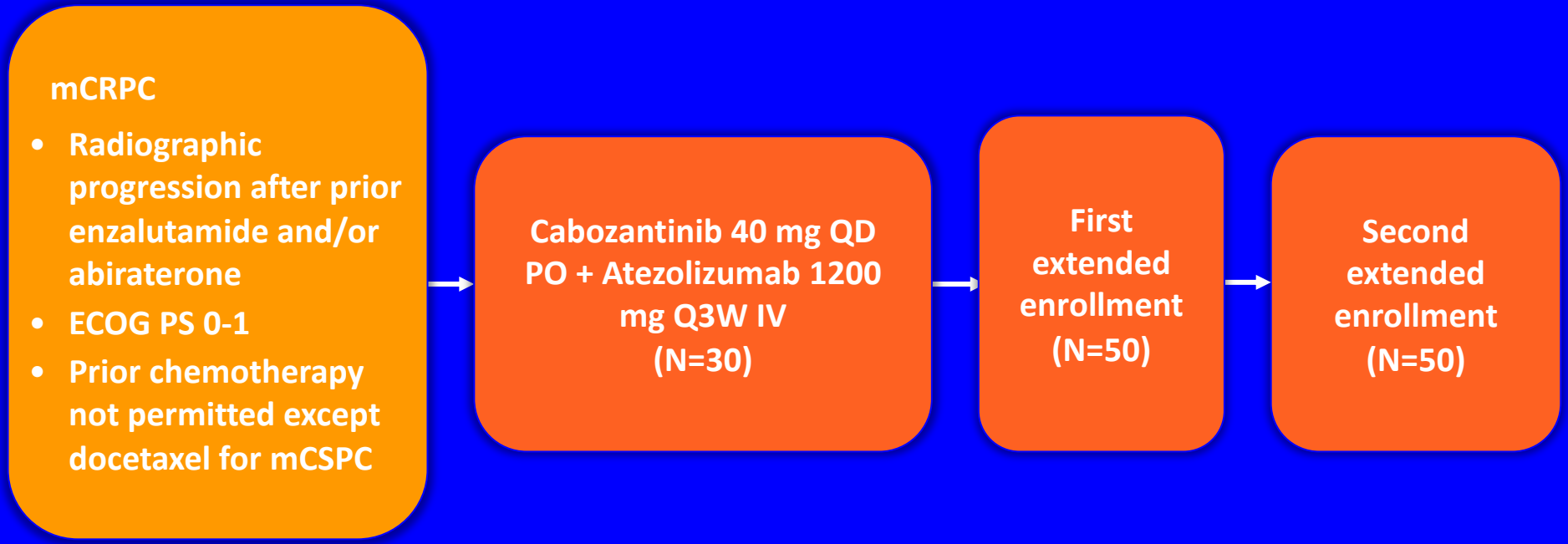
Genitourinary Cancers Symposium 2021;Abstract TPS175.

# A Phase I/II Study of Combination Olaparib and Radium-223 in Men with Metastatic Castration-Resistant Prostate Cancer with Bone Metastases (COMRADE): A Trial in Progress

Shaya J et al.

Genitourinary Cancers Symposium 2021;Abstract TPS182.

# COSMIC-021: Study Design of the Expansion for CRPC Cohort 6




Patients receive study treatment as long as they continue to experience clinical benefit as assessed by the investigator or until unacceptable toxicity

Agarwal N, et al. ASCO GU. 2020 (abstr 139)

Courtesy of A Oliver Sartor, MD

CONTACT-02 is a global, multicenter, randomized, phase 3, open-label study that plans to enroll approximately 580 patients at 250 sites.

Patients will be randomized 1:1 to the experimental arm of cabozantinib in combination with atezolizumab and the control arm of a second novel hormonal therapy (either abiraterone/prednisone or enzalutamide).

The co-primary endpoints of the trial are PFS and OS. Additional endpoints include objective response rate, PSA response, and duration of response.

Courtesy of A Oliver Sartor, MD

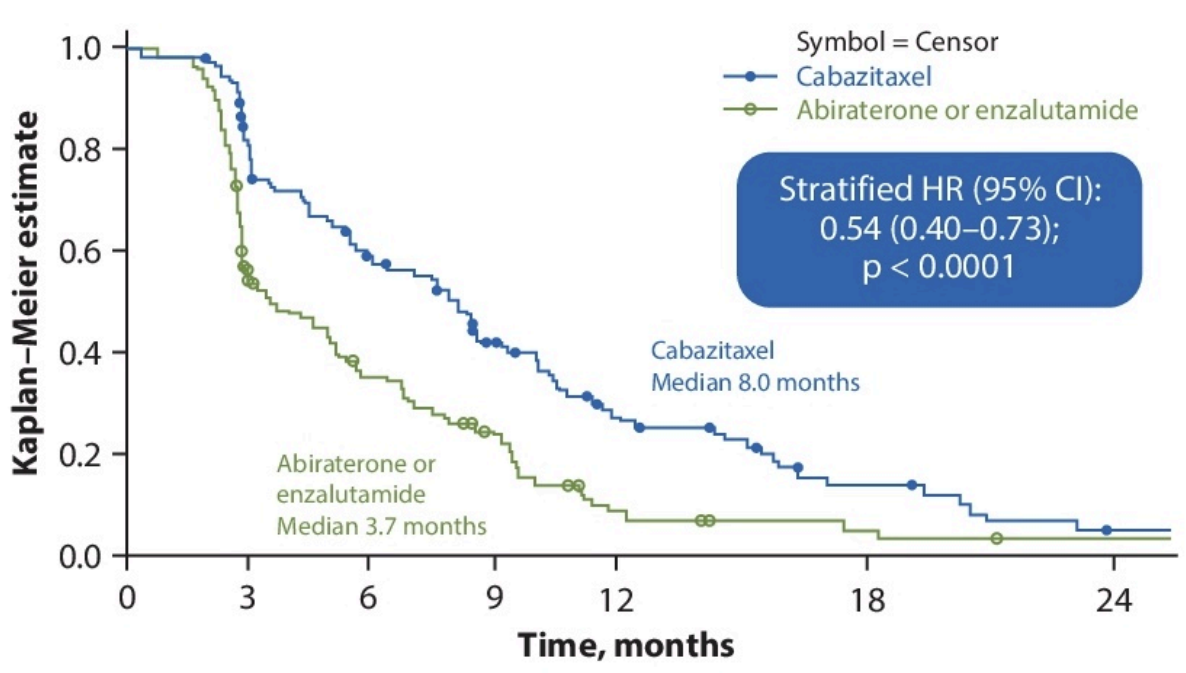
# CARD: Overall Survival Analysis of Patients with Metastatic Castration-Resistant Prostate Cancer Receiving Cabazitaxel vs Abiraterone or Enzalutamide

Tombal B et al.

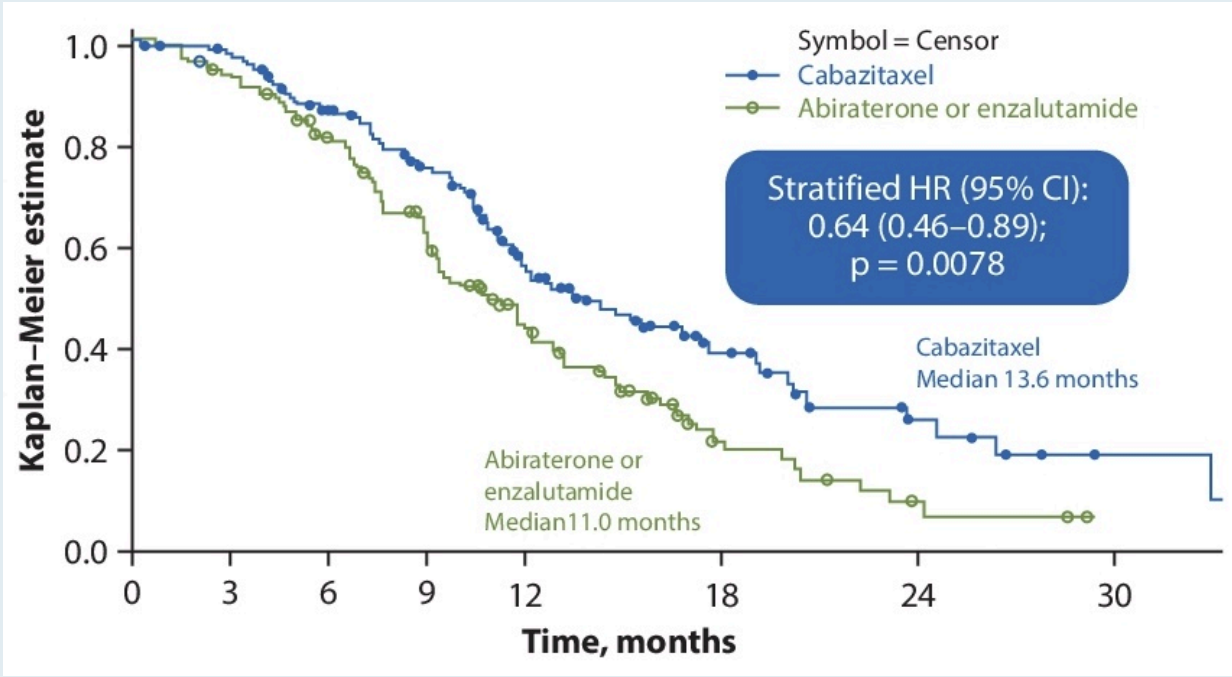
ASCO 2020;Abstract 5569.

# CARD Study of Cabazitaxel: Survival Analyses

## rPFS (primary endpoint)




## OS (key secondary endpoint)




Tombal B et al. ASCO 2020;Abstract 5569.

RTP RESEARCH TO PRACTICE

# Phase II TheraP Trial of 177Lu-PSMA-617 (LuPSMA) Theranostic vs Cabazitaxel for mCRPC Progressing After Docetaxel

- 200 of 291 PET screened men randomized to LuPSMA (n = 99) or cabazitaxel (n = 101).
- 17 patients withdrew or died before receiving study treatment (1 LuPSMA vs 16 cabazitaxel).
- The PSA50-RR was higher in those assigned to LuPSMA than cabazitaxel ($p<0.001$).
- At a median follow-up of 11.3 months, LuPSMA significantly improved PSA-PFS ($p = 0.007$).
- Efficacy results were similar when analyses were restricted to per-protocol treated men.
- OS data remain immature (57 deaths).
- Grade III-IV AEs occurred in 31/98 (32%) LuPSMA-treated men vs 42/85 (49%) in cabazitaxel-treated men.
- Discontinuations for toxicity occurred in 1/98 (1%) LuPSMA vs 3/85 (4%) cabazitaxel-treated.
- There were no treatment-related deaths.

Hofman MS et al. ASCO 2020;Abstract 5500.

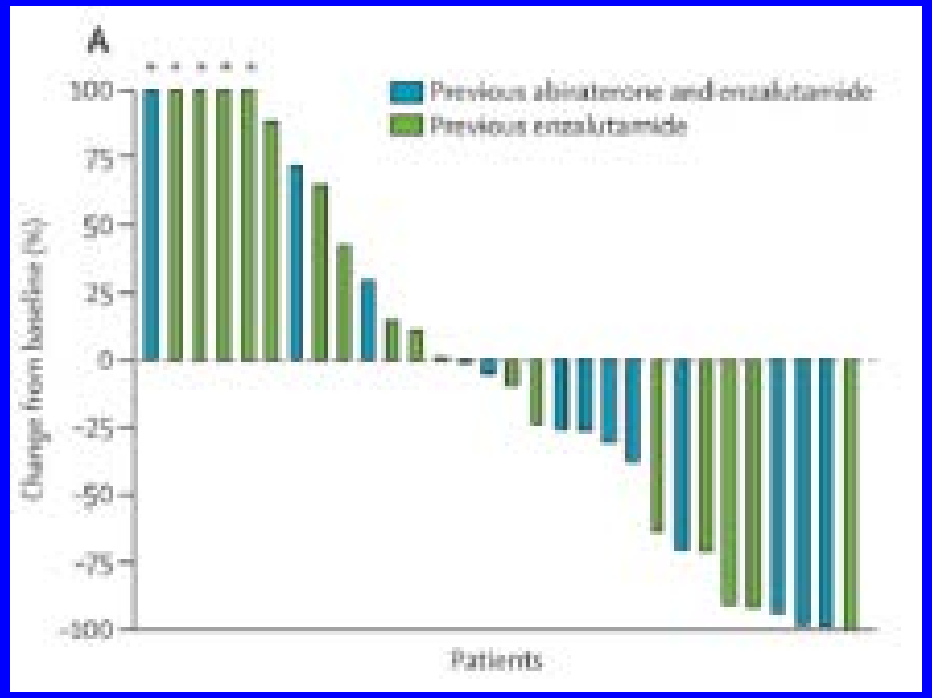
# Cabazitaxel Multiple Rechallenge in Metastatic Castration-Resistant Prostate Cancer: A Therapeutic Option to Increase Overall Survival?

Pobel C et al.
Genitourinary Cancers Symposium 2021;Abstract 97.

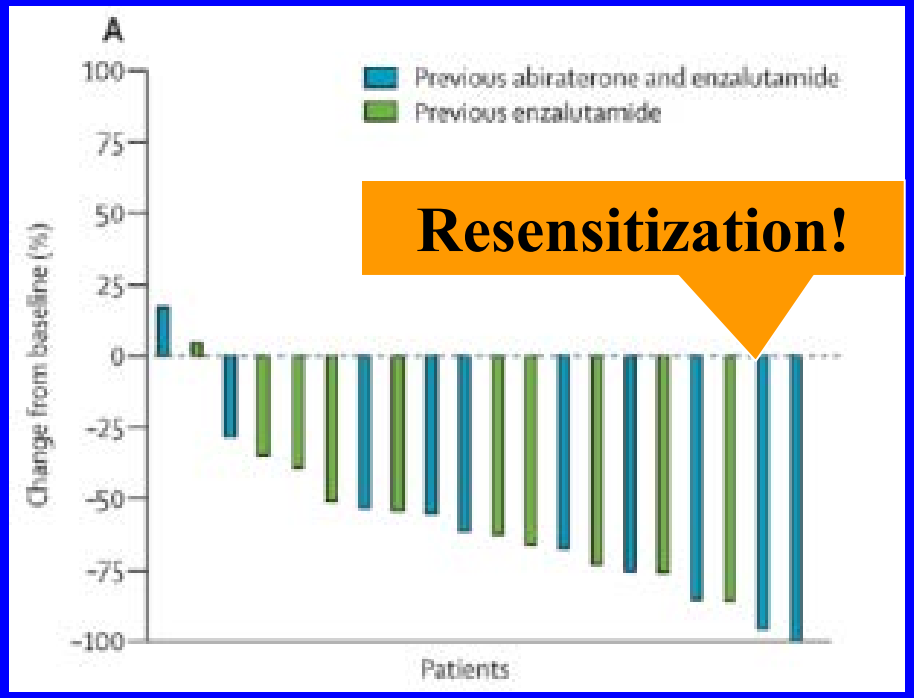
**Bipolar androgen therapy in men with metastatic castration-resistant prostate cancer after progression on enzalutamide: an open-label, phase 2, multicohort study**

Benjamin A Teply, MD, Hao Wang, PhD, Brandon Luber, MS, Rana Sullivan, RN, Irina Rifkind, RN, Ashley Bruns, RN, Avery Spitz, RN, Morgan DeCarli, BS, Victoria Sinibaldi, CRNP, Caroline F Pratz, CRNP, Changxue Lu, PhD, John L Silberstein, MHS, Jun Luo, PhD, Michael T Schweizer, MD, Prof Charles G Drake, MD, Prof Michael A Carducci, MD, Channing J Paller, MD, Emmanuel S Antonarakis, MD, Prof Mario A Eisenberger, MD, and Prof Samuel R Denmeade, MD

*Lancet Oncol.* 2018 January ; 19(1): 76–86.



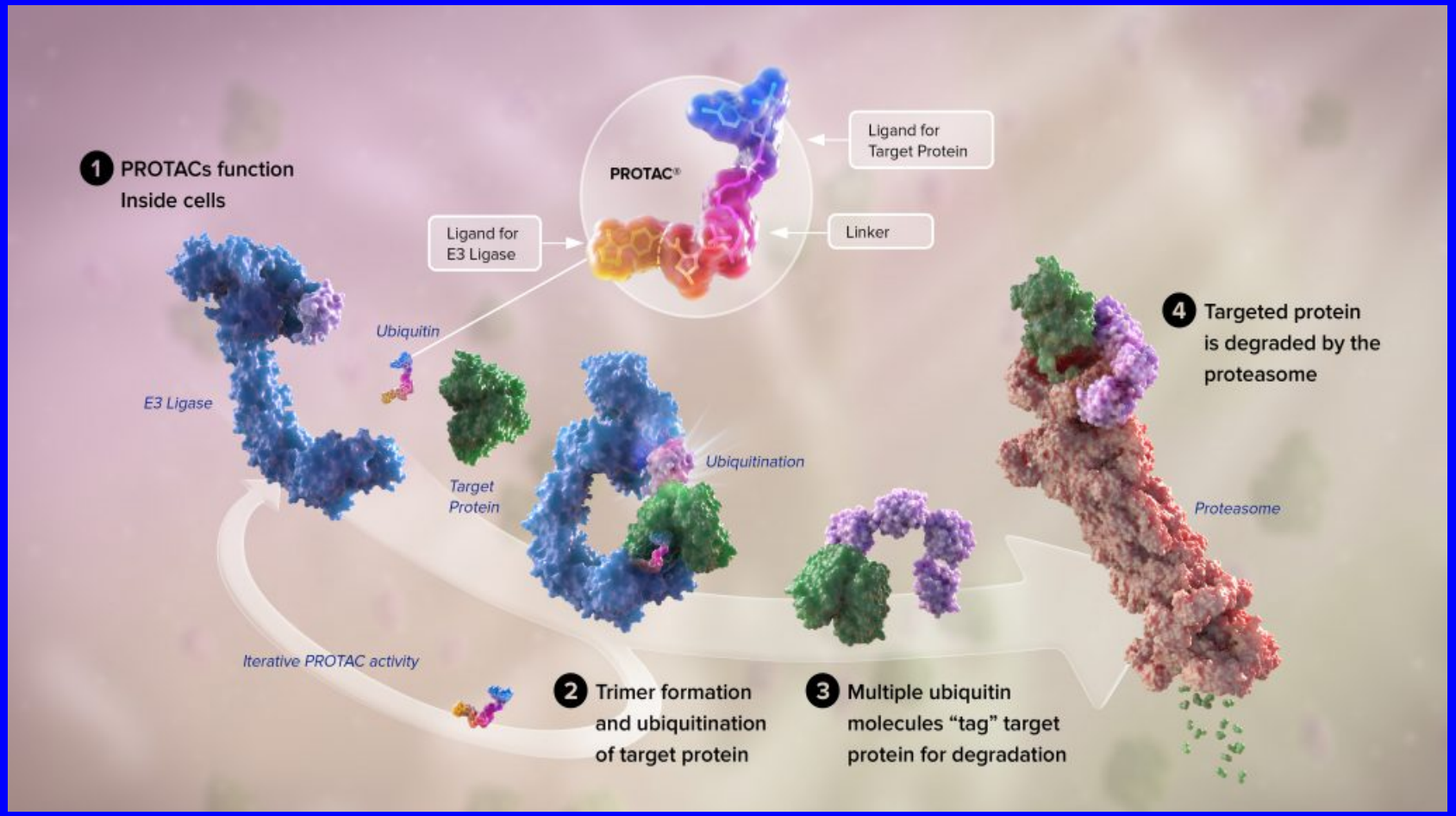

BAT




Enzalutamide post-BAT

Courtesy of A Oliver Sartor, MD

# Targeted AR Degradation…..PROTAC

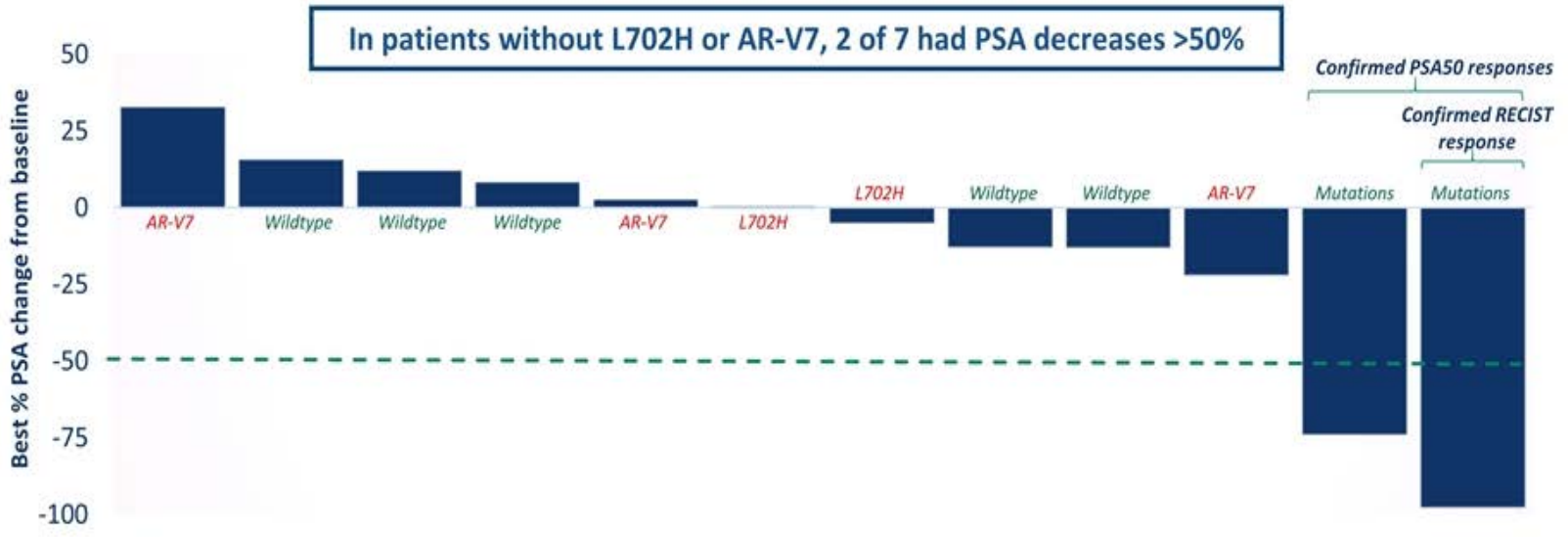



Courtesy of A Oliver Sartor, MD

# PROTAC: Selected biomarker data

**Petrylak et al. ASCO 2020 #3500**

## AR biomarker status and best % PSA change in patients at ≥140 mg (excludes DLT patient; N=12)[1]




| 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]One 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

ARVINAS

30

Courtesy of A Oliver Sartor, MD

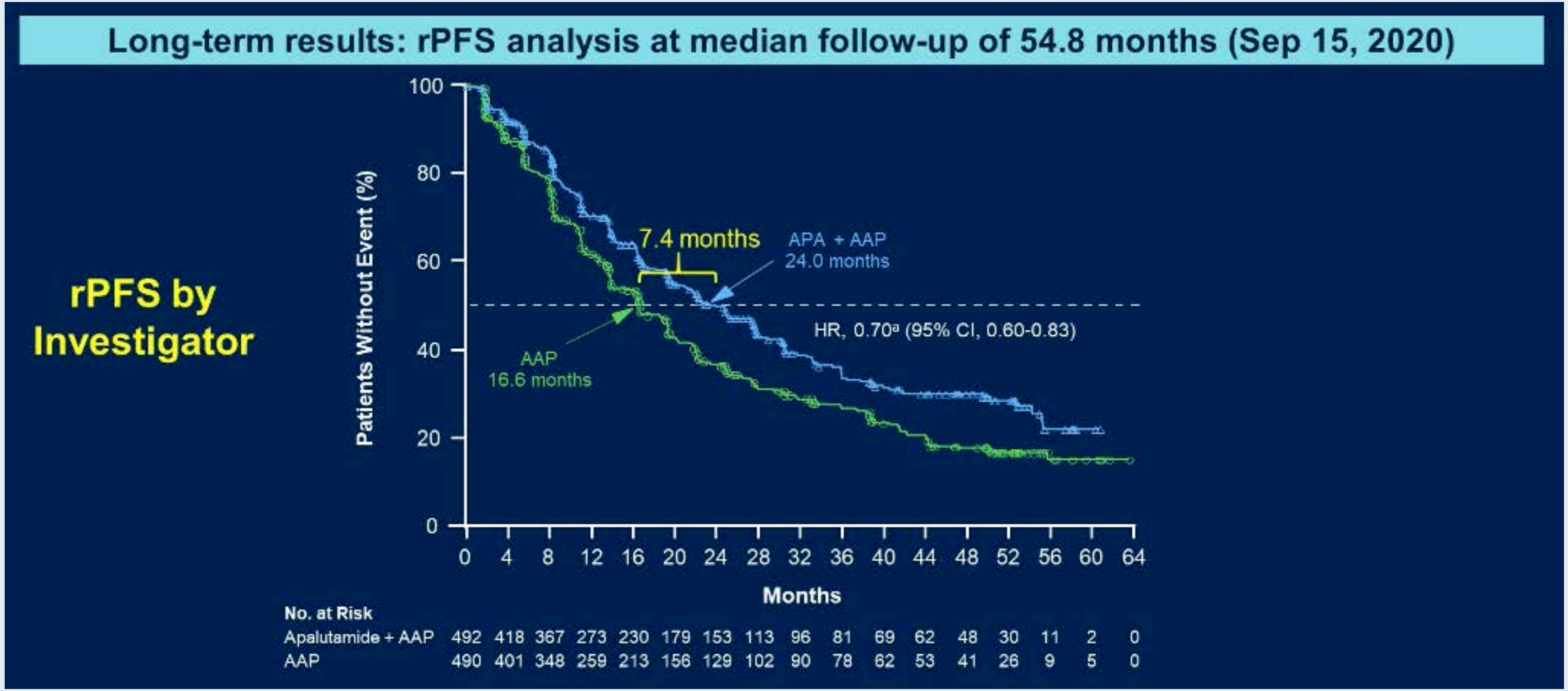
Abstract #9

# Results From ACIS, a Randomized, Placebo-Controlled Double-Blind Phase 3 Study of Apalutamide and Abiraterone Acetate Plus Prednisone Versus Abiraterone in Patients With Chemo-Naive Metastatic Castration-Resistant Prostate Cancer

Dana E. Rathkopf,[1] Eleni Efstathiou,[2] Gerhardt Attard,[3] Thomas W. Flaig,[4] Fabio Andre Franke,[5] Oscar B. Goodman Jr,[6] Stéphane Oudard,[7] Thomas Steuber,[8] Hiroyoshi Suzuki,[9] Daphne Wu,[10] Kesav Yeruva,[10] Peter De Porre,[11] Sabine Brookman-May,[10,12] Susan Li,[13] Jinhui Li,[14] Suneel Mundle,[15] Sharon A. McCarthy,[15] Fred Saad,[16] on behalf of the ACIS investigators

[1]Memorial Sloan Kettering Cancer Center , New York, NY; [2]The University of Texas MD Anderson Cancer Center, Houston, TX; [3]University College London, London, UK; [4]University of Colorado Cancer Center, Aurora, CO; [5]Oncosite Centro de Pesquisa Clínica de Ijuí, Brazil; [6]Comprehensive Cancer Centers of Nevada, Las Vegas, NV; [7]Georges Pompidou Hospital, University of Paris, Paris, France; [8]Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany; [9]Toho University Sakura Medical Center, Chiba, Japan; [10]Janssen Research & Development, Los Angeles, CA; [11]Janssen Research & Development, Beerse, Belgium; [12]Ludwig Maximilians University, Munich, Germany; [13]Janssen Research & Development, Spring House, PA; [14]Janssen Research & Development, San Diego, CA; [15]Janssen Research & Development, Raritan, NJ; [16]Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada

# ACIS: Radiographic Progression-Free Survival (Primary Endpoint)




Rathkopf DE et al. Genitourinary Cancers Symposium 2021;Abstract 9.

RTP RESEARCH TO PRACTICE

# ACIS: Survival and Response Analyses

| Endpoint | APA + AAP (n = 492) | AAP (n = 490) | HR | *p*-value |
|---|---|---|---|---|
| Median rPFS | 24.0 mo | 16.6 mo | 0.70 | <0.0001 |
| PSA response (≥50% decline) | 79.5% | 72.9% | 1.09 | 0.015 |
| Median OS | 36.2 mo | 33.7 mo | 0.95 | 0.498 |

Rathkopf DE et al. Genitourinary Cancers Symposium 2021;Abstract 9.

# ACIS: Adverse Events

| n (%) | APA + AAP (n = 490) | | AAP (n = 489) | |
|---|---|---|---|---|
| | Any grade | Grade 3 or 4 | Any grade | Grade 3 or 4 |
| **Any TEAE** | 484 (98.8) | 310 (63.3) | 473 (96.7) | 275 (56.2) |
| **SAE** | 192 (39.2) | 183 (37.3) | 165 (33.7) | 152 (31.1) |
| **TEAE leading to discontinuation** | 83 (16.9) | 46 (9.4) | 61 (12.5) | 31 (6.3) |
| **TEAE associated with death[a]** | 17 (3.5) | | 37 (7.6) | |
| **TEAEs of special interest[b]** | | | | |
| Fatigue | 213 (43.5) | 23 (4.7) | 183 (37.4) | 19 (3.9) |
| Hypertension | 158 (32.2) | 101 (20.6) | 130 (26.6) | 61 (12.5) |
| Fall | 107 (21.8) | 16 (3.3) | 93 (19.0) | 3 (0.6) |
| Skin rash | 101 (20.6) | 22 (4.5) | 49 (10.0) | 2 (0.4) |
| Cardiac disorders[c] | 93 (19.0) | 44 (9.0) | 94 (19.2) | 28 (5.7) |
| Hypokalemia | 79 (16.1) | 17 (3.5) | 74 (15.1) | 20 (4.1) |
| Peripheral edema | 92 (18.8) | 1 (0.2) | 93 (19.0) | 4 (0.8) |
| Fracture and osteoporosis | 74 (15.1) | 20 (4.1) | 59 (12.1) | 7 (1.4) |
| Ischemic cerebrovascular disorders | 9 (1.8) | 3 (0.6) | 14 (2.9) | 6 (1.2) |
| Seizures | 3 (0.6) | 1 (0.2) | 1 (0.2) | 0 |

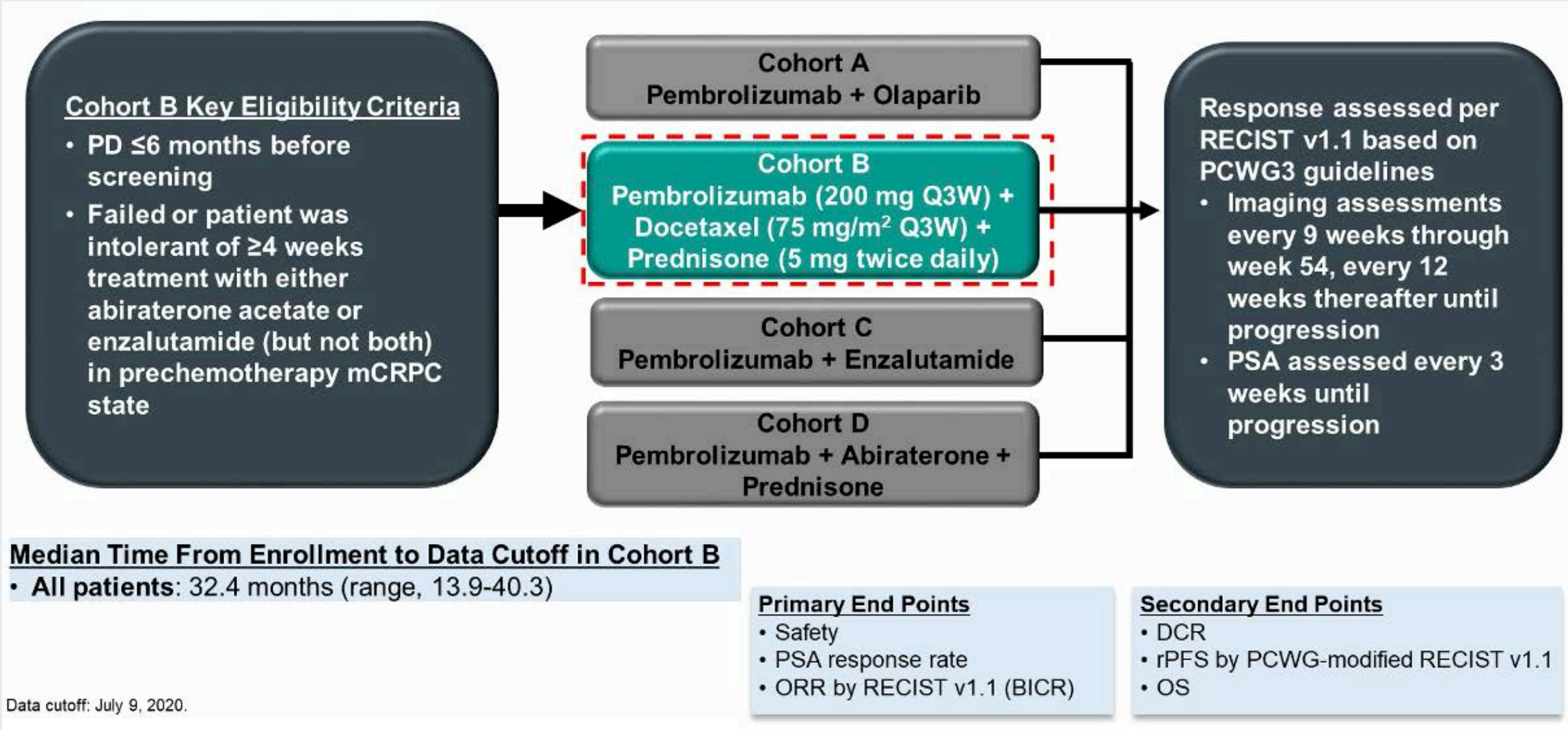
Rathkopf DE et al. Genitourinary Cancers Symposium 2021;Abstract 9.

# KEYNOTE-365 Cohort B: Pembrolizumab plus docetaxel and prednisone in abiraterone or enzalutamide-pretreated patients with metastatic castration-resistant prostate cancer: New data after an additional year of follow-up

Leonard Appleman[1]; Michael Kolinsky[2]; William Berry[3]; Margitta Retz[4]; Loic Mourey[5]; Josep M Piulats[6]; Emanuela Romano[7]; Gwenaelle Gravis[8]; Howard Gurney[9]; Johann de Bono[10]; Martin Boegemann[11]; Urban Emmenegger[12]; Anthony Joshua[13]; Christophe Massard[14]; Srikala Sridhar[15]; Henry Conter[16]; Xin Tong Li[17]; Charles Schloss[17]; Christian Poehlein[17]; Evan Y. Yu[18]

[1]University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [2]Cross Cancer Institute, Edmonton, AB, Canada; [3]Duke Cancer Center Cary, Cary, NC, USA; [4]Rechts der Isar University Hospital, Technical University of Munich, Munich Germany; [5]Institut Universitaire du Cancer-Oncopole, Toulouse, France; [6]Catalan Institute of Oncology, Barcelona, Spain; [7]Center of Cancer Immunotherapy, Institut Curie, Paris, France; [8]CLCC Institut Paoli Calmettes, Paris, France; [9]Macquarie University Hospital, Sydney, NSW, Australia; [10]The Royal Marsden NHS Foundation Trust, London, United Kingdom; [11]University Hospital Muenster, Munster, Germany; [12]Sunnybrook Research Institute, Toronto, ON, Canada; [13]Kinghorn Cancer Centre, St Vincent's Hospital, Sydney, NSW, Australia; [14]Gustave Roussy Cancer Campus and Paris-Sud University, Villejuif, France; [15]UHN Princess Margaret Cancer Centre, Toronto, ON, Canada; [16]University of Western Ontario, Brampton, ON, Canada; [17]Merck & Co., Inc., Kenilworth, NJ, USA; [18]University of Washington, Seattle, WA, USA

# KEYNOTE-365: Study Design




**Median Time From Enrollment to Data Cutoff in Cohort B**

- **All patients**: 32.4 months (range, 13.9-40.3)

Data cutoff: July 9, 2020.

**Primary End Points**

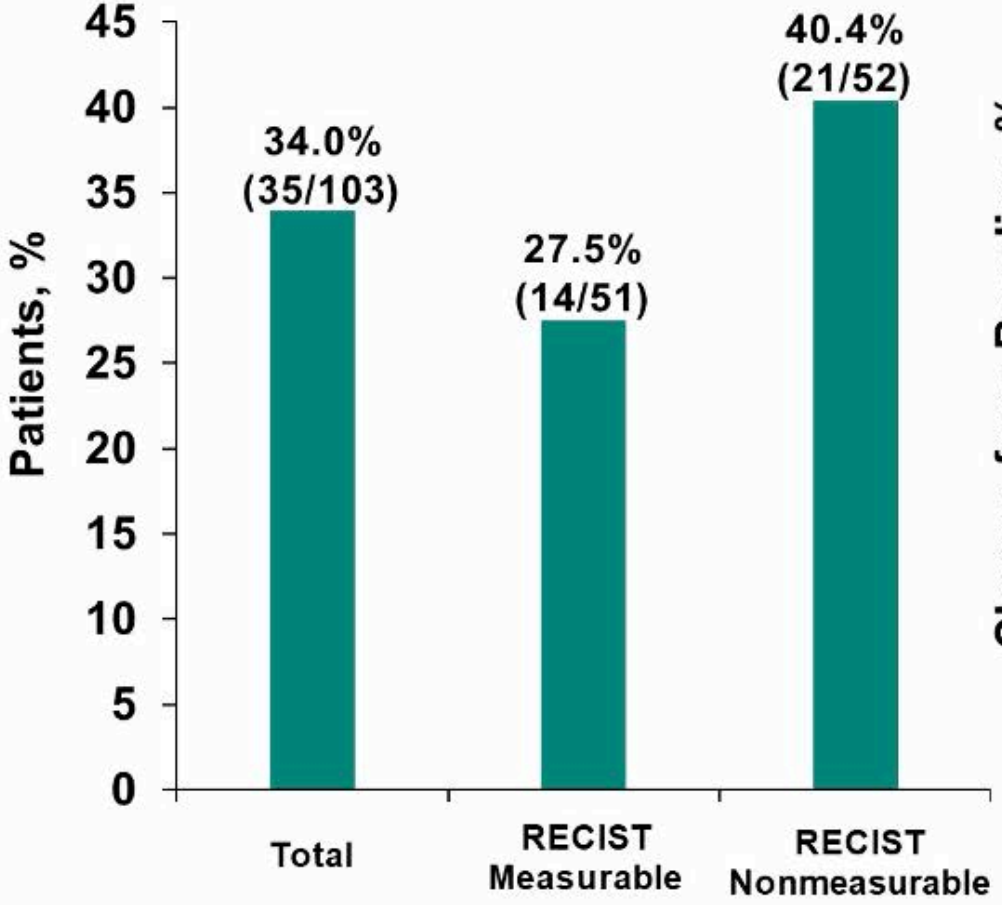
- Safety
- PSA response rate
- ORR by RECIST v1.1 (BICR)

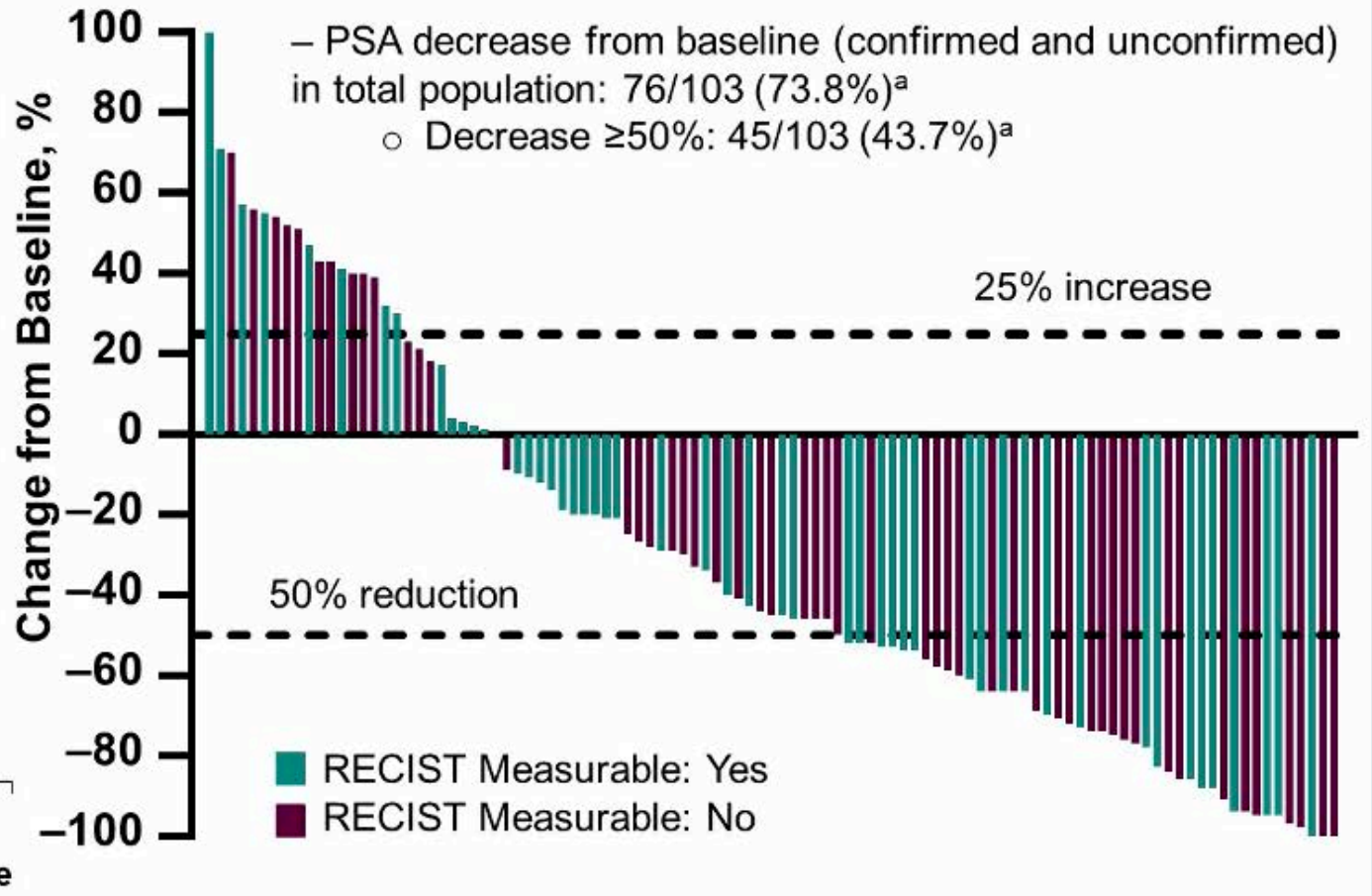
**Secondary End Points**

- DCR
- rPFS by PCWG-modified RECIST v1.1
- OS

Appleman L et al. Genitourinary Cancers Symposium 2021;Abstract 10.

# KEYNOTE-365 Cohort B: Confirmed PSA Response Rate and Percentage Change from Baseline




Appleman L et al. Genitourinary Cancers Symposium 2021;Abstract 10.

RTP RESEARCH TO PRACTICE

# KEYNOTE-365 Cohort B: Conclusions

- With 1 year of additional follow-up, encouraging antitumor activity was observed in patients who received combination therapy with pembrolizumab + docetaxel and prednisone
  - Confirmed PSA response rate: Total population, 34.0%
  - ORR in patients with RECIST-measurable disease, 23.1% (95% CI: 12.5%-36.8%)
  - In the total population
    - Median rPFS, 8.5 months (8.3-10.1)
    - Median OS, 20.2 months (16.9-24.2)
- The safety profile was generally consistent with individual profiles of each agent
- The promising rPFS and OS data from this study support further evaluation of pembrolizumab + docetaxel/prednisone in patients with mCRPC previously treated with abiraterone or enzalutamide
  - A randomized phase 3 study of docetaxel + prednisone with and without pembrolizumab in NHA-pretreated patients who have not received chemotherapy for mCRPC is currently enrolling (KEYNOTE-921, NCT03834506)

Appleman L et al. Genitourinary Cancers Symposium 2021;Abstract 10.

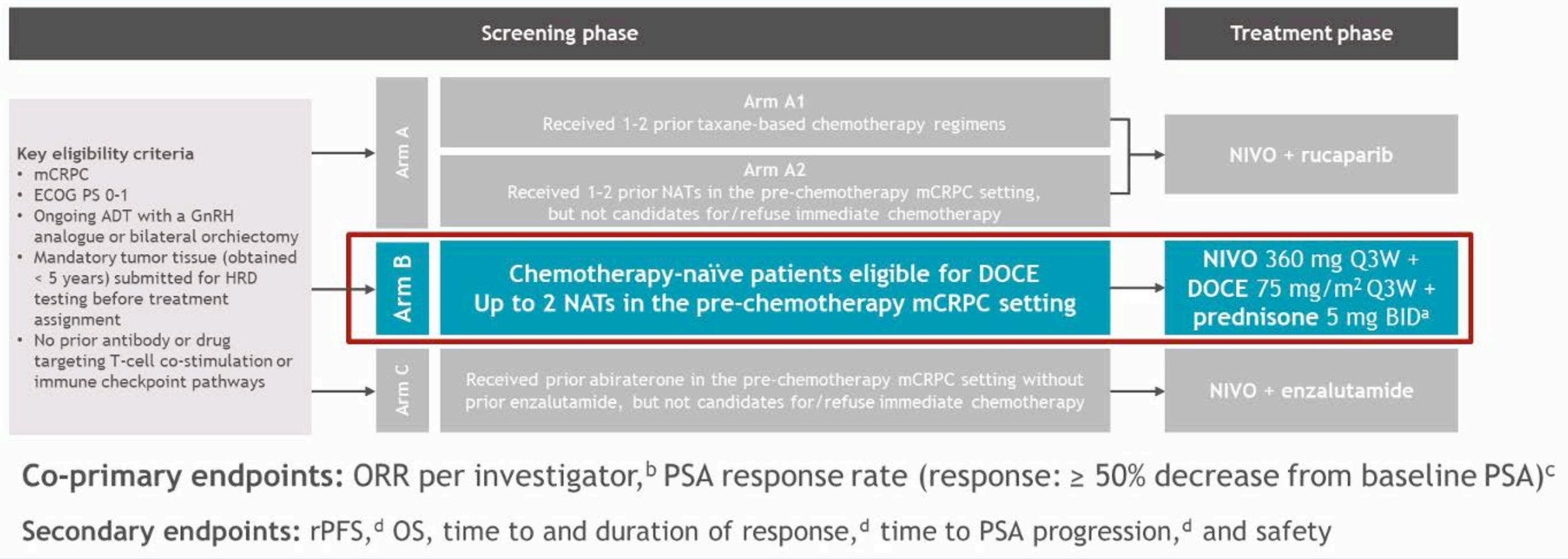
# CheckMate 9KD arm B final analysis: efficacy and safety of nivolumab plus docetaxel for chemotherapy-naïve metastatic castration-resistant prostate cancer

Karim Fizazi,[1] Pablo González Mella,[2] Daniel Castellano,[3] Jose N. Minatta,[4] Arash Rezazadeh Kalebasty,[5] David Shaffer,[6] Juan Carlos Vázquez Limón,[7] Héctor Manuel Sánchez López,[8] Andrew J. Armstrong,[9] Lisa Horvath,[10] Carlos Dzik,[11] Neha P. Amin,[12] Jia Li,[12] Keziban Unsal-Kacmaz,[12] Margitta Retz,[13] Fred Saad,[14] Daniel P. Petrylak,[15] Russell K. Pachynski[16]

[1]Gustave Roussy, University Paris Saclay, Villejuif, France; [2]Fundación Arturo López Pérez, Santiago, Chile; [3]Hospital Universitario 12 de Octubre, Madrid, Spain; [4]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; [5]Norton Cancer Institute, Louisville, KY; [6]New York Oncology Hematology, Albany, NY; [7]Instituto Jalisciense de Cancerología, Guadalajara, Mexico; [8]Hospital Regional de Alta Especialidad del Bajío, Guanajuato, Mexico; [9]Duke Cancer Institute Center for Prostate and Urologic Cancers, Duke University, Durham, NC; [10]Chris O'Brien Lifehouse, Camperdown, NSW, Australia; [11]Instituto de Cancer do Estado de São Paulo, São Paulo, Brazil; [12]Bristol Myers Squibb, Princeton, NJ; [13]Rechts der Isar Medical Center, Technical University Munich, Munich, Germany; [14]Centre Hospitalier de l'Université de Montréal/CHUM, Montreal, QC, Canada; [15]Smilow Cancer Center, Yale School of Medicine, New Haven, CT; [16]Washington University School of Medicine, St. Louis, MO

*Abstract Number 12*

# CheckMate 9KD: Study Design




**Co-primary endpoints:** ORR per investigator,[b] PSA response rate (response: ≥ 50% decrease from baseline PSA)[c]

**Secondary endpoints:** rPFS,[d] OS, time to and duration of response,[d] time to PSA progression,[d] and safety

Fizazi K et al. Genitourinary Cancers Symposium 2021;Abstract 12.

# CheckMate 9KD: ORR and PSA Response (Coprimary Endpoints)

| Objective response[a] | All patients (N = 45) | No prior NAT (n = 14) | Prior NAT (n = 31) |
|---|---|---|---|
| ORR, % (95% CI) | 40.0 (25.7-55.7) | 42.9 (17.7-71.1) | 38.7 (21.8-57.8) |
| **Best overall response, n (%)** | | | |
| Complete response | 1 (2.2) | 0 | 1 (3.2) |
| Partial response | 17 (37.8) | 6 (42.9) | 11 (35.5) |
| Stable disease | 24 (53.3) | 7 (50.0) | 17 (54.8) |
| Progressive disease | 3 (6.7) | 1 (7.1) | 2 (6.5) |
| **PSA response[b]** | **All patients (N = 81)** | **No prior NAT (n = 28)** | **Prior NAT (n = 53)** |
| **Confirmed PSA response rate, %** (95% CI) | 46.9 (35.7-58.3) | 60.7 (40.6-78.5) | 39.6 (26.5-54.0) |

- For the 18 objective responders
  - Median time to response (range) was 2.0 (1.6-7.3) months
  - Median duration of response (95% CI) was 7.0 (6.4-12.4) months
- Among 81 PSA-evaluable patients, median time to PSA progression (95% CI) was 8.7 (7.3-10.4) months

Fizazi K et al. Genitourinary Cancers Symposium 2021;Abstract 12.

# CheckMate 9KD Arm B Final Analysis: Conclusions

- With longer follow-up, the combination of NIVO+DOCE continued to show encouraging clinical activity in patients with mCRPC, with an ORR of 40% and confirmed PSA response rate of 47%
- Notably, the antitumor effects of NIVO+DOCE were apparent regardless of whether patients had received prior NAT
- Additional biomarker analyses are ongoing to investigate potential markers of response to the combination of NIVO+DOCE
- No new safety signals were reported with longer follow-up with NIVO+DOCE
  - Monitoring of immune-related adverse events will be important in future studies of this combination
- These results support further investigation of the combination of NIVO+DOCE for patients with mCRPC in the ongoing phase 3 CheckMate 7DX trial[1]

Fizazi K et al. Genitourinary Cancers Symposium 2021;Abstract 12.

RTP RESEARCH TO PRACTICE

# 177Lu-PSMA-617 (LuPSMA) versus Cabazitaxel in Metastatic Castration-Resistant Prostate Cancer (mCRPC) Progressing After Docetaxel: Updated Results Including Progression-Free Survival (PFS) and Patient-Reported Outcomes (PROs) (TheraP ANZUP 1603)[1]

## [$^{177}$Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial [2]

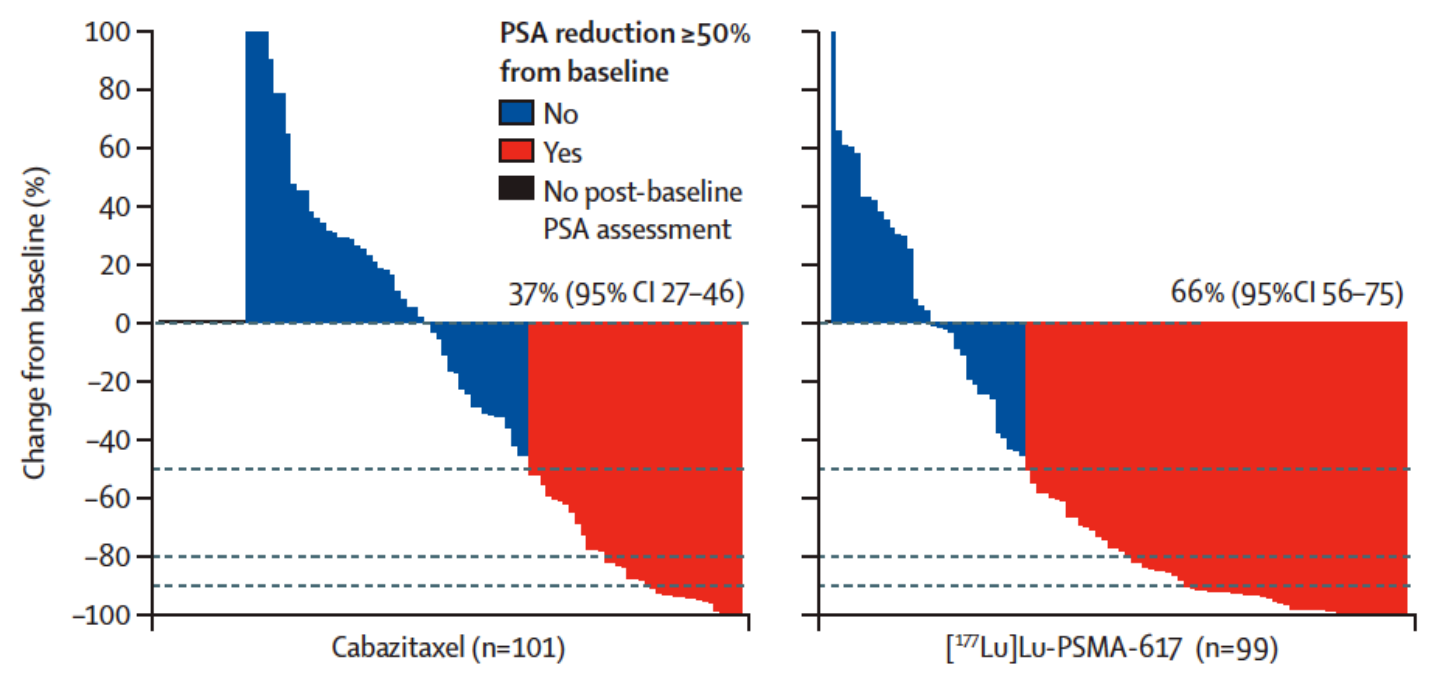
*Michael S Hofman, Louise Emmett, Shahneen Sandhu, Amir Iravani, Anthony M Joshua, Jeffrey C Goh, David A Pattison, Thean Hsiang Tan, Ian D Kirkwood, Siobhan Ng, Roslyn J Francis, Craig Gedye, Natalie K Rutherford, Andrew Weickhardt , Andrew M Scott, Sze-Ting Lee, Edmond M Kwan, Arun A Azad, Shakher Ramdave, Andrew D Redfern, William Macdonald, Alex Guminski, Edward Hsiao, Wei Chua, Peter Lin, Alison Y Zhang, Margaret M McJannett, Martin R Stockler, John A Violet*, Scott G Williams, Andrew J Martin, Ian D Davis, for the TheraP Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group†*

[1] Hofman MS et al. Genitourinary Cancers Symposium 2021;Abstract 6.
[2] Hofman MS et al. *Lancet* 2021;[Online ahead of print].

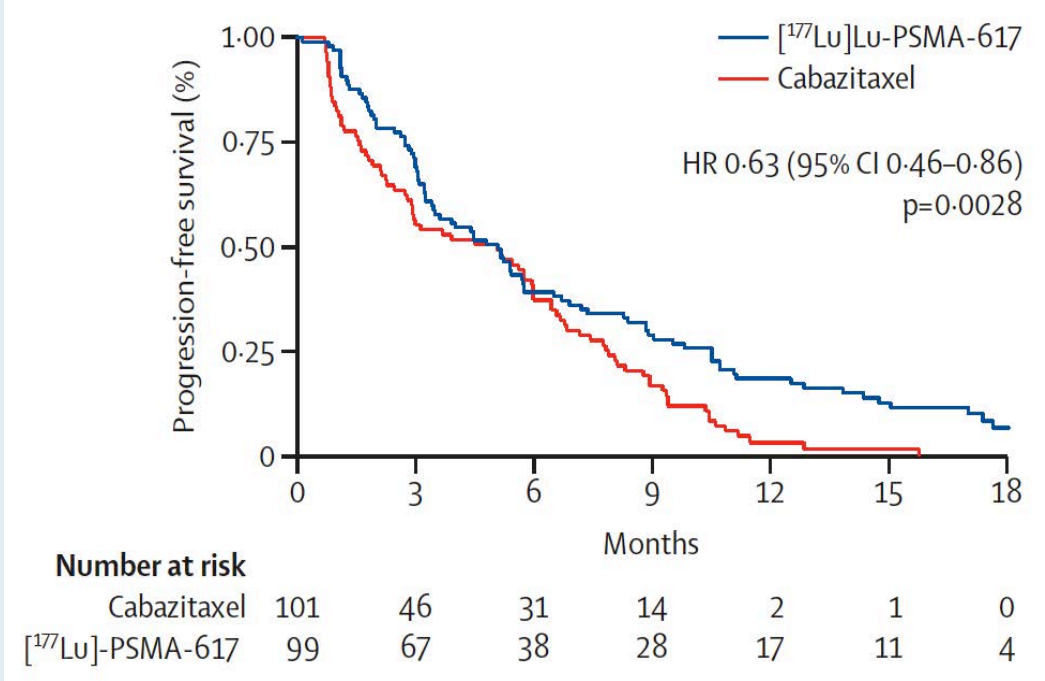
RTP RESEARCH TO PRACTICE

# TheraP ANZUP 1603: PSA Response and Progression-Free Survival

## PSA response




## Radiographic or PSA progression-free survival




Hofman MS et al. Genitourinary Cancers Symposium 2021;Abstract 6; Hofman MS et al. *Lancet* 2021;[Online ahead of print].

RTP RESEARCH TO PRACTICE

# TheraP ANZUP 1603: Adverse Events

| | [$^{177}$Lu]Lu-PSMA-617 (n=98) | | Cabazitaxel (n=85) | |
|---|---|---|---|---|
| | Grade 1–2 | Grade 3–4 | Grade 1–2 | Grade 3–4 |
| Fatigue | 69 (70%) | 5 (5%) | 61 (72%) | 3 (4%) |
| Pain* | 60 (61%) | 11 (11%) | 52 (61%) | 4 (5%) |
| Dry mouth | 59 (60%) | 0 | 18 (21%) | 0 |
| Diarrhoea | 18 (18%) | 1 (1%) | 44 (52%) | 4 (5%) |
| Nausea | 39 (40%) | 1 (1%) | 29 (34%) | 0 |
| Thrombocytopenia | 18 (18%) | 11 (11%) | 4 (5%) | 0 |
| Dry eyes | 29 (30%) | 0 | 3 (4%) | 0 |
| Anaemia | 19 (19%) | 8 (8%) | 11 (13%) | 7 (8%) |
| Neuropathy† | 10 (10%) | 0 | 22 (26%) | 1 (1%) |
| Dysgeusia | 12 (12%) | 0 | 23 (27%) | 0 |
| Haematuria | 3 (3%) | 1 (1%) | 12 (14%) | 5 (6%) |
| Neutropenia‡ | 7 (7%) | 4 (4%) | 4 (5%) | 11 (13%) |
| Insomnia | 9 (9%) | 0 | 12 (14%) | 1 (1%) |
| Vomiting | 12 (12%) | 1 (1%) | 10 (12%) | 2 (2%) |
| Dizziness | 4 (4%) | 0 | 11 (13%) | 0 |
| Leukopenia | 10 (10%) | 1 (1%) | 5 (6%) | 1 (1%) |
| Any adverse event | 53 (54%) | 32 (33%) | 34 (40%) | 45 (53%) |

Hofman MS et al. Genitourinary Cancers Symposium 2021;Abstract 6; Hofman MS et al. *Lancet* 2021;[Online ahead of print].

RTP RESEARCH TO PRACTICE

# Cases from the Community: Investigators Discuss Emerging Research and Actual Patients with Renal Cell Carcinoma (Part 2 of a 3-Part Series)

**Monday, March 1, 2021**
**5:00 PM – 6:00 PM ET**

## Faculty

**Thomas E Hutson, DO, PharmD**
**Thomas Powles, MBBS, MRCP, MD**

## Moderator

**Neil Love, MD**

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***Thank you for joining us!***

***CME credit information will be emailed to each participant within 3 business days.***