Breakfast with the Investigators: Prostate Cancer

A CME Hybrid Symposium Held in Conjunction with the 2022 ASCO Annual Meeting

Saturday, June 4, 2022

6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty

Andrew J Armstrong, MD, ScM

Alan H Bryce, MD

Alicia K Morgans, MD, MPH

Moderator

Neil Love, MD

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Faculty

Andrew J Armstrong, MD, ScM
Professor of Medicine, Surgery, Pharmacology and Cancer Biology
Director of Research
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Divisions of Medical Oncology and Urology
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Durham, North Carolina

Alicia K Morgans, MD, MPH
Genitourinary Medical Oncologist
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Dana-Farber Cancer Institute
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Alan H Bryce, MD
Chair, Division of Hematology and Medical Oncology
Chair, Genitourinary Disease Group
Mayo Clinic
Phoenix, Arizona

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

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Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.

Answer Survey Questions: Complete the premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

Complete Your Evaluation: Tap the CME Evaluation button to complete your evaluation electronically to receive credit for your participation.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.

Answer Survey Questions: Complete the premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A CME credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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Friday June 3	**Acute Myeloid Leukemia and Myelodysplastic Syndromes** 11:45 AM – 12:45 PM CT (12:45 PM – 1:45 PM ET)
	Lung Cancer 6:30 PM – 9:00 PM CT (7:30 PM – 10:00 PM ET)
Saturday June 4	**Prostate Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Gastrointestinal Cancers 7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)
Sunday June 5	**Ovarian Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma 7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)
Monday June 6	**Urothelial Bladder Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Breast Cancer 7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)
Tuesday June 7	**Multiple Myeloma** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

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Exciting CME Events in Chicago You Do Not Want to Miss

A CME Hybrid Symposium Series Held in Conjunction with the 2022 ASCO Annual Meeting

Prostate Cancer

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Alan H Bryce, MD
Alicia K Morgans, MD, MPH

Ovarian Cancer

Sunday, June 5, 2022
6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty
Antonio González-Martín, MD, PhD
Joyce F Liu, MD, MPH
Kathleen N Moore, MD, MS

Gastrointestinal Cancers

Saturday, June 4, 2022
7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)

Faculty
Tanios Bekaii-Saab, MD
Kristen K Ciombor, MD, MSCI
Eileen M O'Reilly, MD
Philip A Philip, MD, PhD, FRCP
John Strickler, MD
Eric Van Cutsem, MD, PhD

Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma

Sunday, June 5, 2022
7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)

Faculty
Ian W Flinn, MD, PhD
Brian T Hill, MD, PhD
John P Leonard, MD
Matthew Lunning, DO
Laurie H Sehn, MD, MPH
Mitchell R Smith, MD, PhD

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Urothelial Bladder Cancer

Monday, June 6, 2022
6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty
Yohann Loriot, MD, PhD
Elizabeth R Plimack, MD, MS
Jonathan E Rosenberg, MD

Multiple Myeloma

Tuesday, June 7, 2022
6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty
Ajai Chari, MD
Elizabeth O'Donnell, MD
Robert Z Orlowski, MD, PhD

Breast Cancer

Monday, June 6, 2022
7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)

Faculty
Javier Cortés, MD, PhD
Matthew P Goetz, MD
Erika Hamilton, MD
Ian E Krop, MD, PhD
Hope S Rugo, MD
Sara M Tolaney, MD, MPH

Spencer H Bachow, MD
Lynn Cancer Institute
Boca Raton, Florida

Philip L Brooks, MD
Northern Light Eastern Maine Medical Center and Lafayette Family Cancer Institute
Brewer, Maine

Shams Bufalino, MD
Advocate Aurora Health
Park Ridge, Illinois

Lionel A Kankeu Fonkoua, MD
Mayo Clinic
Rochester, Minnesota

Shaachi Gupta, MD, MPH
Florida Cancer Specialists
Lake Worth, Florida

Zanetta S Lamar, MD
Florida Cancer Specialists
Naples, Florida

Neil Morganstein, MD
Atlantic Health System
Summit, New Jersey

Vignesh Narayanan, MD
Colorado Permanente Medical Group (CPMG)
Lone Tree, Colorado

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Namrata I Peswani, MD
Harold C Simmons
Comprehensive Cancer Center
Richardson, Texas

Matthew R Strickland, MD
Massachusetts General Hospital
Cancer Center
Boston, Massachusetts

Erik Rupard, MD
The Reading Hospital
West Reading, Pennsylvania

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Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Exelixis Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Merck, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, and Sanofi Genzyme.

Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

Dr Love — Disclosures

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Dr Armstrong — Disclosures

Advisory Committee	Advanced Accelerator Applications, Exelixis Inc, Merck, Myovant Sciences, Novartis, Pfizer Inc
Consulting Agreements	Advanced Accelerator Applications, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Dendreon Pharmaceuticals Inc, FORMA Therapeutics, Janssen Biotech Inc, Merck, Myovant Sciences, Novartis, Pfizer Inc
Contracted Research (to Institution)	Advanced Accelerator Applications, Amgen Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Bristol-Myers Squibb Company, Constellation Pharmaceuticals, Dendreon Pharmaceuticals Inc, Endocyte Inc, FORMA Therapeutics, Janssen Biotech Inc, Merck, Novartis, Pfizer Inc

Dr Bryce — Disclosures

No relevant conflicts of interest to disclose

Dr Morgans — Disclosures

Advisory Committee	Bayer HealthCare Pharmaceuticals, Gilead Sciences Inc, Myovant Sciences
Consulting Agreements	Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Exelixis Inc, Janssen Biotech Inc, Lantheus, Merck, Myovant Sciences, Novartis, Pfizer Inc, Sanofi Genzyme, Telix Pharmaceuticals
Contracted Research	Astellas, Bayer HealthCare Pharmaceuticals, Dendreon Pharmaceuticals Inc, Myovant Sciences, Pfizer Inc, Seagen Inc
Data and Safety Monitoring Board/Committee	Gilead Sciences Inc

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Agenda

Module 1 – Optimal Application of Hormonal Therapy in Prostate Cancer Management

Module 2 – Selection and Sequencing of Therapy for Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC); Novel Investigational Strategies

Module 3 – Current and Potential Role of PARP Inhibitors in the Management of Prostate Cancer

Agenda

Module 1 – Optimal Application of Hormonal Therapy in Prostate Cancer Management

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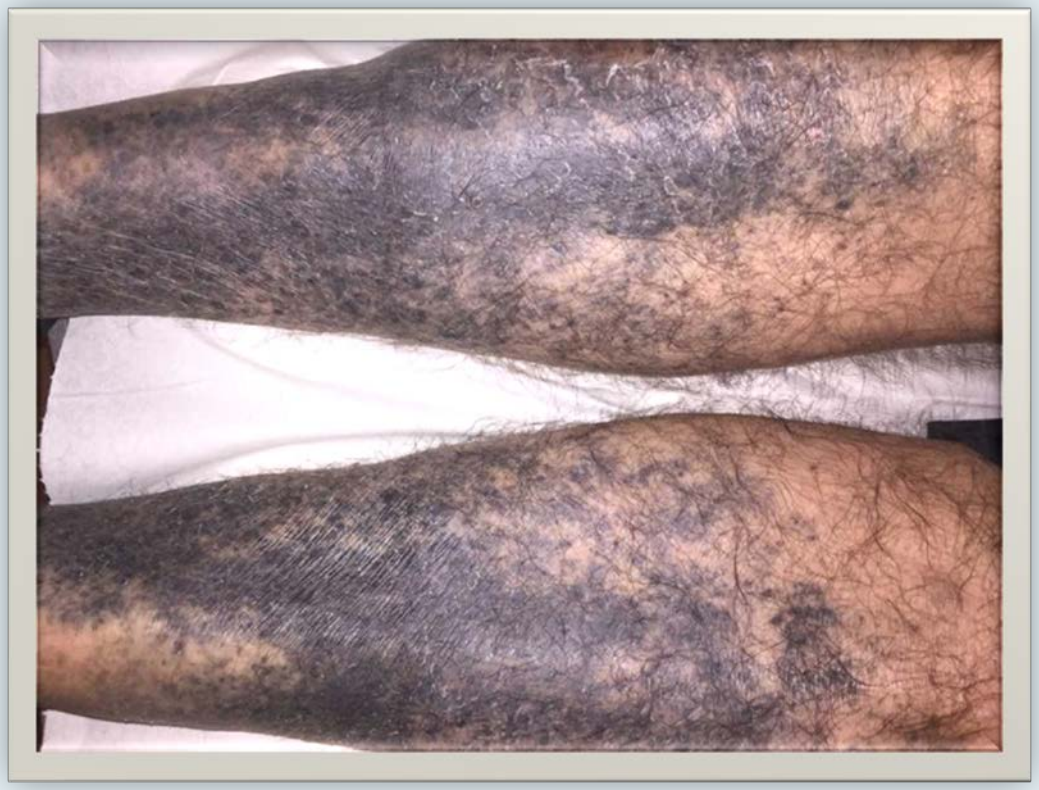
Module 3 – Current and Potential Role of PARP Inhibitors in the Management of Prostate Cancer

Case 1 — Andrew J Armstrong, MD, ScM

- **67-year-old AAM presented as a referral from his PCP for an elevated PSA of 6.7, and TRUS biopsy reveals GG4 adenocarcinoma, normal CT/bone scan c/w high risk localized prostate cancer**
- **Despite IMRT and 2 years of ADT, PSA starts to rise 2 years later in the face of castrate levels of testosterone (20), and imaging is normal**
- **Despite bicalutamide, PSA continues to rise and PSMA-PET CT shows only pelvic uptake in lymph nodes, which are not pathologically enlarged. PSA is now 10.2 and has doubled from 5 over 4 months**
- **Apalutamide is started with ongoing ADT for his rapid PSA rise (PSADT 4 mo), nmCRPC**

Case — Andrew J Armstrong, MD, ScM

- About 2-3 months into therapy, a hyperpigmented rash develops in his lower extremities, sparing palms/soles and rest of his body
- Rash is a little bit itchy, painless, somewhat nodular/bumpy and is largely covered by his socks
- He continues to be active, otherwise tolerating ADT/apalutamide well with only mild fatigue, hot flushes, and is active working
- PSA has dropped to undetectable



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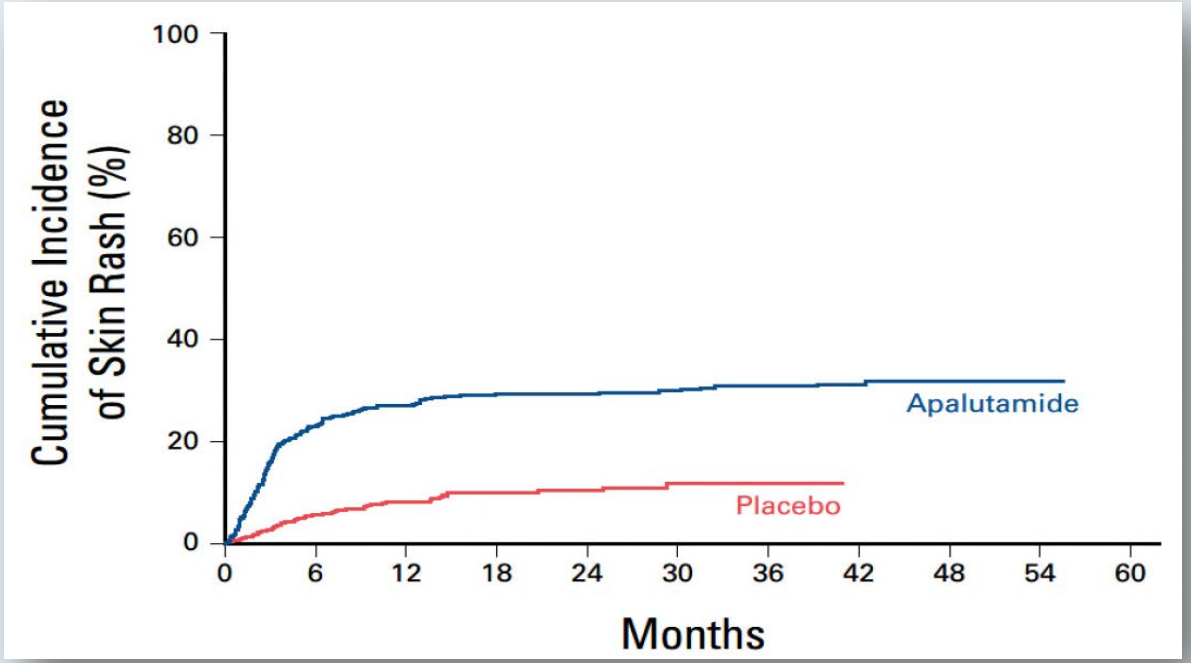
Case — Andrew J Armstrong, MD, ScM

Discussion

- **Rash is observed occasionally with novel AR inhibitor use in the nmCRPC setting ranging from 2-30%, particularly with apalutamide (24% risk, grade 3-4 in 5%), 2-3% of whom had to stop therapy due to rash, 6-7% required dose holds or reductions due to rash**
- **Similar results recently reported in TITAN (mHSPC setting) with apalutamide**



Chi K et al JCO 2021

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Case — Andrew J Armstrong, MD, ScM

Skin Rash with Apalutamide

- **Most commonly macular or maculo-papular**
- **Grade 3 rash by definition covers >30% of body surface area and is reported in 5.5% of men treated with apalutamide, vs 0.3% with placebo**
- **Therapies used in the trial with success included topical steroids, oral anti-histamines, oral steroids, drug holds, and dose reductions**
- **Median time to onset is 82 days, and 80% of patients with rash saw resolution within 2 months**
- **This patient was having a great response, and thus we dose reduced the apalutamide after a 3-week hold. Rash stabilized, regressed, and did not further progress with resumption of apalutamide at 180 mg daily**
- **Hyperpigmentation remained under his socks but did not cause any symptoms**

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Case — Alan H Bryce, MD

- **February Year 1: 71 yo otherwise healthy male with a rising PSA to 5.0. Biopsy shows G 4 + 3 prostate cancer**
- **April Year 1: RARP. G 4 + 3, T3 N0 M0. Nadir PSA <0.1**
- **February Year 2: PSA 0.6, begin ADT x 12 months**
- **July Year 2: Complete salvage radiation therapy**

Case — Alan H Bryce, MD

- **January Year 3: PSA 0.5. Testosterone <7.0.**
- **April Year 3: PSA 1.2. Choline PET-CT with uptake in a left iliac node, 1.7cm. Begin Apalutamide**
- **June Year 3: PSA 0.8. Patient intolerant of Apalutamide due to fatigue**
- **July Year 3: Begin Darolutamide**
- **May Year 5: PSA <0.1, ECOG 0. Continue on Darolutamide**

Overall Survival: Darolutamide, Enzalutamide, Apalutamide

	ARAMIS[1]	PROSPER[2]	SPARTAN[3]
Antiandrogen	Darolutamide	Enzalutamide	Apalutamide
Median follow-up	49 mo	47 mo	52 mo
Median OS	Not estimated	57 vs 56 mo	74 vs 60 mo
OS hazard ratio	0.69 (p = 0.003)	0.73 (p = 0.001)	0.78 (p = 0.0161)

[1] Fizazi K et al; ARAMIS Investigators. *N Engl J Med* 2020;383:1040-9.
[2] Sternberg CN et al; PROSPER Investigators. *N Engl J Med* 2020;382(23):2197-206.
[3] Smith MR et al; SPARTAN Investigators. *Eur Urol* 2021;79(1):150-158.

Comparison of Toxicities: Darolutamide, Enzalutamide or Apalutamide for Nonmetastatic CRPC

Toxicity	ARAMIS		PROSPER		SPARTAN	
	Darolutamide	Placebo	Enzalutamide	Placebo	Apalutamide	Placebo
Fatigue/asthenia	16%	11%	33%	14%	30%	21%
Falling	4%	5%	11%	4%	16%	9%
Dizziness	5%	4%	10%	4%	9%	6%
Mental impairment	1%	2%	5%	2%	5%	3%

Sternberg CN et al; PROSPER Investigators. *N Engl J Med* 2020;382(23):2197-206.
Fizazi K et al; ARAMIS Investigators. *N Engl J Med* 2020;383:1040-9.
Small EJ et al; SPARTAN Investigators. ASCO 2020;Abstract 5516.

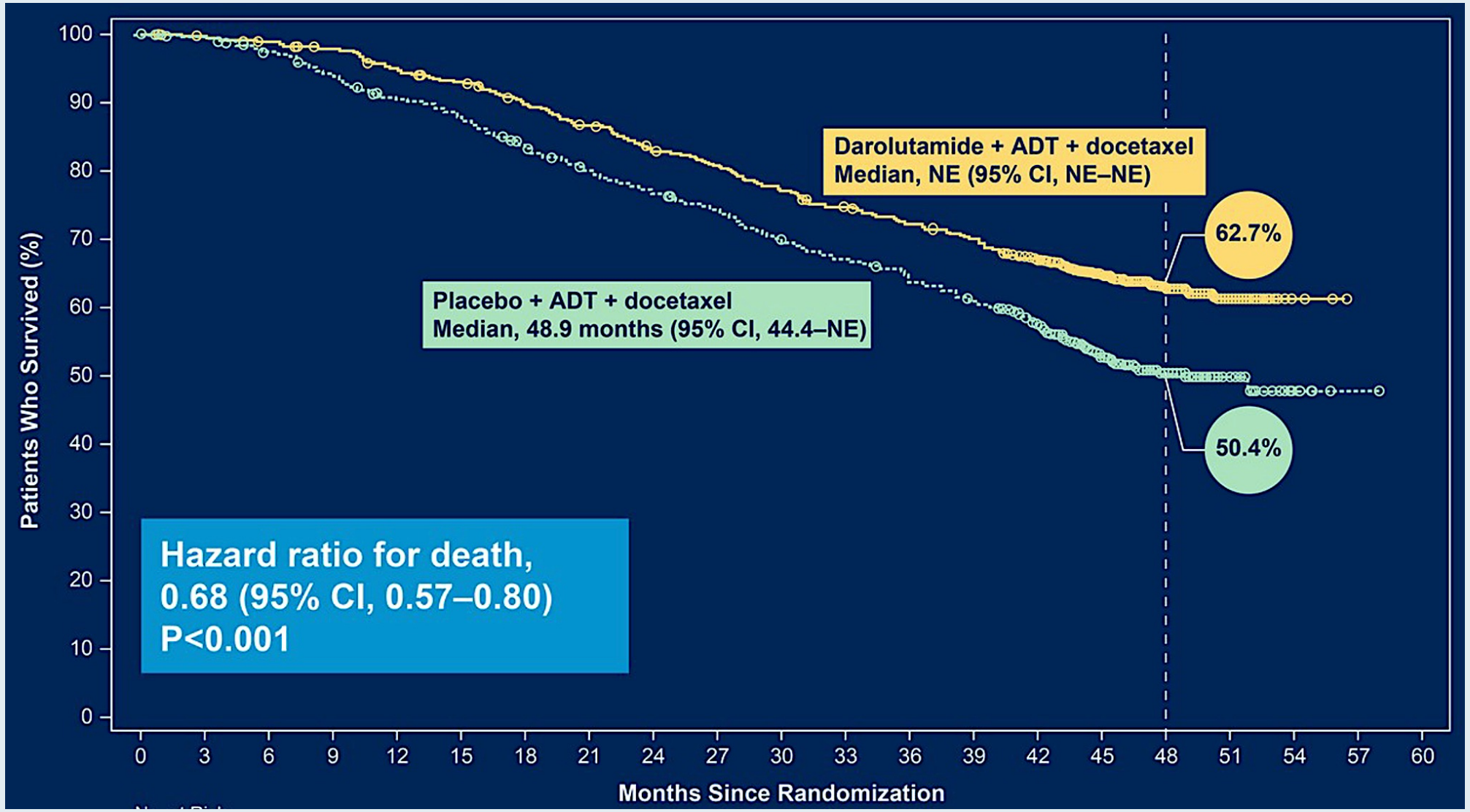
ASCO Genitourinary Cancers Symposium 2022;Abstract 13

Overall survival with darolutamide versus placebo in combination with androgen-deprivation therapy and docetaxel for metastatic hormone-sensitive prostate cancer in the phase 3 ARASENS trial

Matthew R. Smith, MD, PhD,[1] Maha Hussain, MD,[2] Fred Saad, MD,[3] Karim Fizazi, MD, PhD,[4] Cora N. Sternberg, MD,[5] E. David Crawford, MD,[6] Evgeny Kopyltsov, MD,[7] Chandler H. Park, MD,[8] Boris Alekseev, MD,[9] Álvaro Montesa Pino, MD,[10] Dingwei Ye, MD,[11] Francis Parnis, MB, BS,[12] Felipe Melo Cruz, MD,[13] Teuvo L.J. Tammela, MD, PhD,[14] Hiroyoshi Suzuki, MD, PhD,[15] Heikki Joensuu, MD,[16] Silke Thiele, MD,[17] Rui Li, MS,[18] Iris Kuss, MD,[17] Bertrand Tombal, MD, PhD[19]

[1]Massachusetts General Hospital Cancer Center, Boston, MA; [2]Northwestern University, Feinberg School of Medicine, Chicago, IL; [3]University of Montreal Hospital Center, Montreal, Quebec, Canada; [4]Institut Gustave Roussy, University of Paris-Saclay, Villejuif, France; [5]Englander Institute for Precision Medicine, Weill Cornell Department of Medicine, Meyer Cancer Center, New York-Presbyterian Hospital, New York, NY; [6]UC San Diego School of Medicine, San Diego, CA; [7]Clinical Oncological Dispensary of Omsk Region, Omsk, Russian Federation; [8]Norton Cancer Institute, Louisville, KY; [9]P. Hertsen Moscow Oncology Research Institute, Moscow, Russian Federation; [10]UGC Intercentros de Oncología Médica, Hospitales Universitarios Regional y Virgen Victoria, IBIMA, Málaga, Spain; [11]Fudan University Shanghai Cancer Center, Xuhui District, Shanghai, China; [12]Ashford Cancer Centre Research, Kurralta Park, SA, Australia; [13]Núcleo de Pesquisa e Ensino da Rede São Camilo, São Paulo, Brazil; [14]Tampere University Hospital, Tampere, Finland; [15]Toho University Sakura Medical Center, Chiba, Japan; [16]Orion Corporation Orion Pharma, Espoo, Finland; [17]Bayer AG, Berlin, Germany; [18]Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA; [19]Division of Urology, IREC, Cliniques Universitaires Saint Luc, UCLouvain, Brussels, Belgium

ARASENS: Primary Endpoint — Overall Survival



Smith MR et al. Genitourinary Cancers Symposium 2022;Abstract 13.

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Lancet 2022;399:1695-07.

Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design

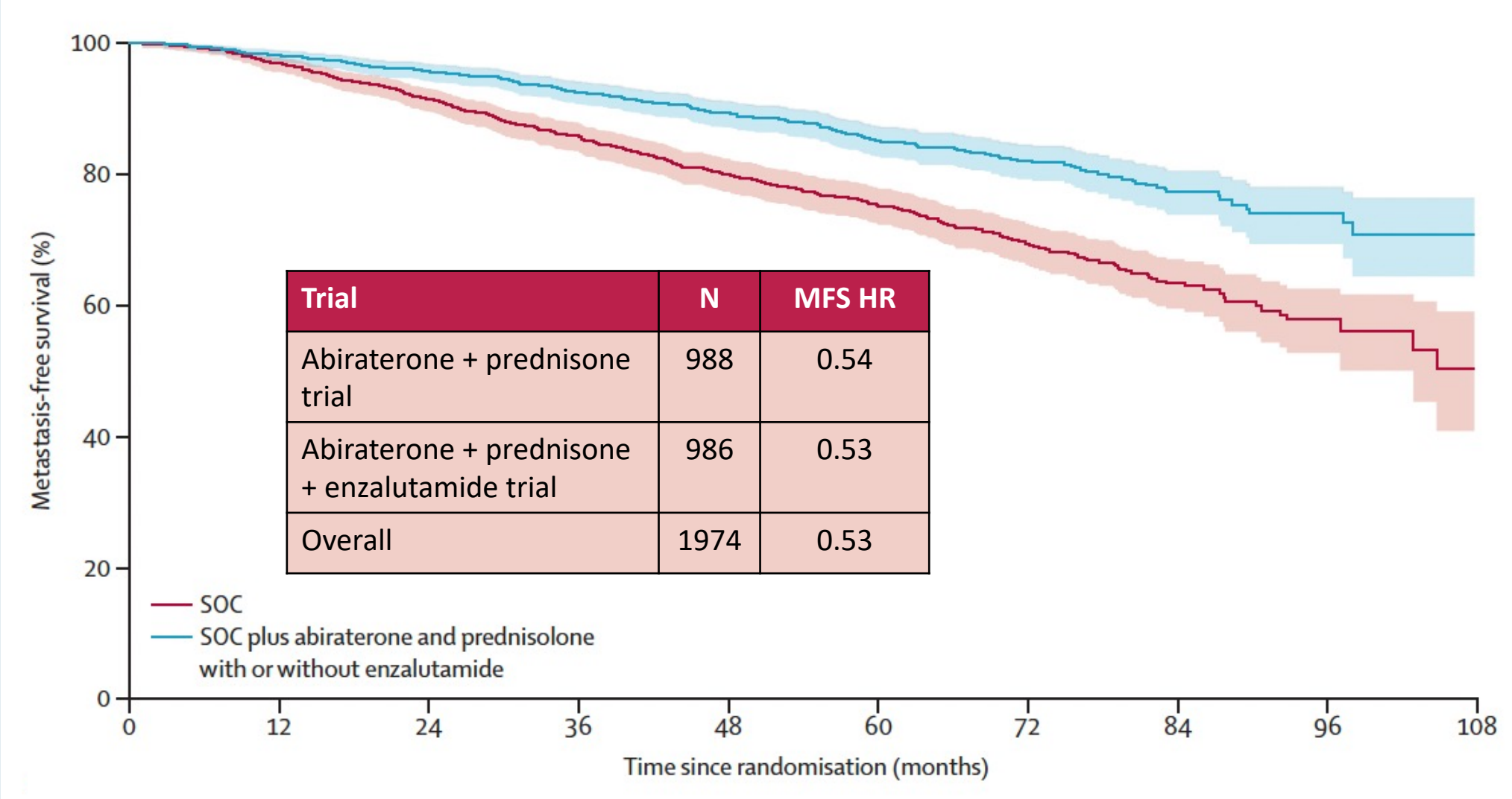
*Karim Fizazi, Stéphanie Foulon, Joan Carles, Guilhem Roubaud, Ray McDermott, Aude Fléchon, Bertrand Tombal, Stéphane Supiot, Dominik Berthold, Philippe Ronchin, Gabriel Kacso, Gwenaëlle Gravis, Fabio Calabro, Jean-François Berdah, Ali Hasbini, Marlon Silva, Antoine Thiery-Vuillemin, Igor Latorzeff, Loïc Mourey, Brigitte Laguerre, Sophie Abadie-Lacourtoisie, Etienne Martin, Claude El Kouri, Anne Escande, Alvar Rosello, Nicolas Magne, Friederike Schlurmann, Frank Priou, Marie-Eve Chand-Fouche, Salvador Villà Freixa, Muhammad Jamaluddin, Isabelle Rieger, Alberto Bossi, on behalf of the PEACE-1 investigators**

Lancet 2022;399(10323):447-60

Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol

Gerhardt Attard, Laura Murphy, Noel W Clarke, William Cross, Robert J Jones, Christopher C Parker, Silke Gillessen, Adrian Cook, Chris Brawley, Claire L Amos, Nafisah Atako, Cheryl Pugh, Michelle Buckner, Simon Chowdhury, Zafar Malik, J Martin Russell, Clare Gilson, Hannah Rush, Jo Bowen, Anna Lydon, Ian Pedley, Joe M O'Sullivan, Alison Birtle, Joanna Gale, Narayanan Srihari, Carys Thomas, Jacob Tanguay, John Wagstaff, Prantik Das, Emma Gray, Mymoona Alzoueb, Omi Parikh, Angus Robinson, Isabel Syndikus, James Wylie, Anjali Zarkar, George Thalmann, Johann S de Bono, David P Dearnaley, Malcolm D Mason*, Duncan Gilbert, Ruth E Langley, Robin Millman, David Matheson, Matthew R Sydes†, Louise C Brown†, Mahesh K B Parmar†, Nicholas D James†, on behalf of the Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) investigators‡*

STAMPEDE Primary Endpoint: Metastasis-Free Survival (Pooled Analysis)



Trial	N	MFS HR
Abiraterone + prednisone trial	988	0.54
Abiraterone + prednisone + enzalutamide trial	986	0.53
Overall	1974	0.53

Attard G et al. *Lancet* 2022;399(10323):447-60.

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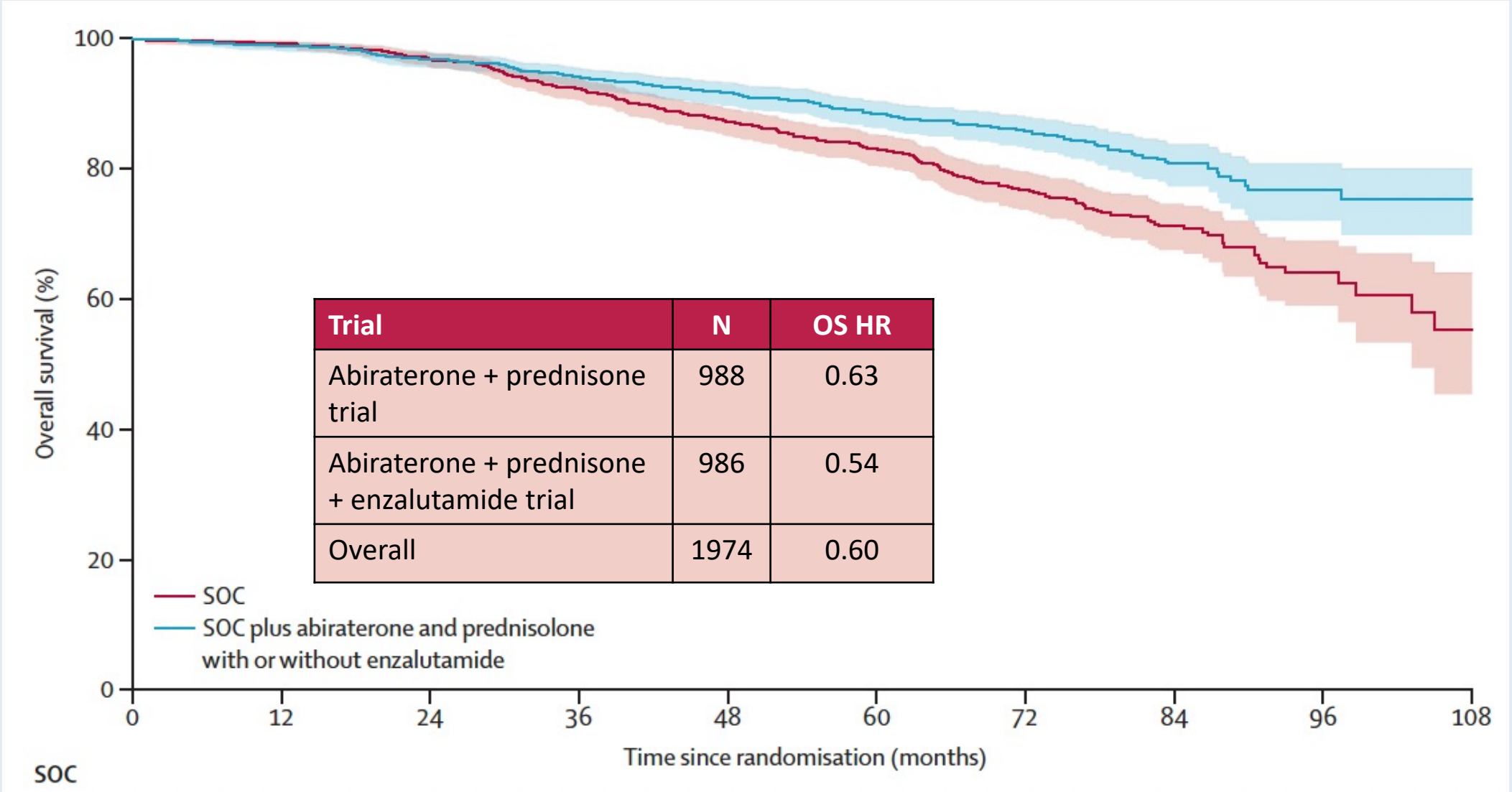
STAMPEDE: Overall Survival (Pooled Analysis)



Trial	N	OS HR
Abiraterone + prednisone trial	988	0.63
Abiraterone + prednisone + enzalutamide trial	986	0.54
Overall	1974	0.60

Attard G et al. *Lancet* 2022;399(10323):447-60.

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Case — Alicia K Morgans, MD, MPH

- **This patient is a 71 yo man with a history of CAD with prior MI and advanced prostate cancer diagnosed 8 years ago.**
- **Diagnosed after PSA 9.7 ng/mL at annual physical, and underwent prostatectomy.**
  - **Gleason 4 + 4 (GG 4) prostate adenocarcinoma, pT3aN0, post-op PSA undetectable**
- **In 18 months, PSA increased to 4.7 ng/mL (testosterone level WNL).**
  - **Conventional imaging with bone metastases in multiple vertebral bodies, left 7th rib**
- **Started ADT + abiraterone acetate for mHSPC, PSA nadir 0.05 ng/mL.**
- **11 months later, PSA 6.8 ng/mL. Repeat imaging with bone scan and CT performed.**

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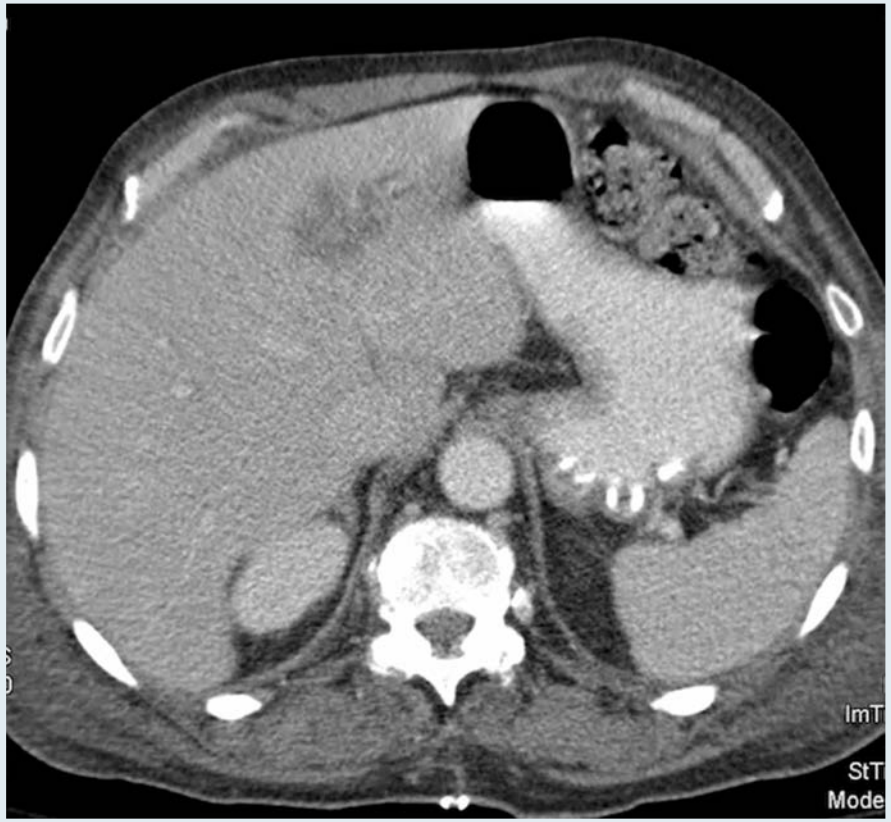
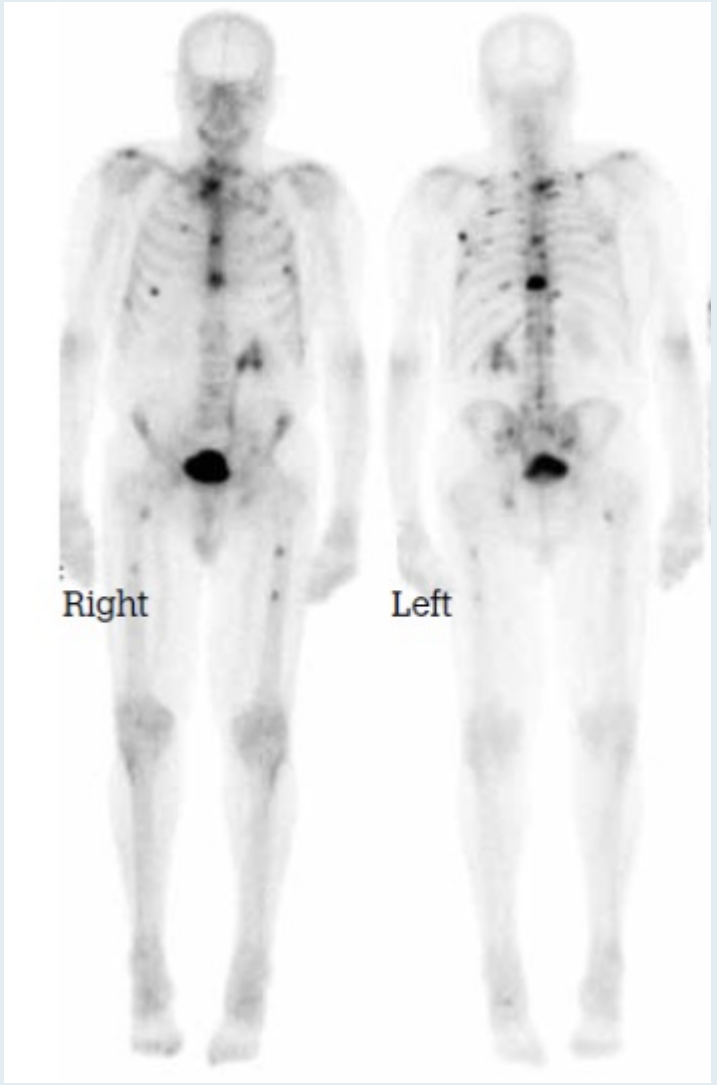
Case — Alicia K Morgans, MD, MPH

Imaging

- **New liver lesions and progression of bone metastases**





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Case — Alicia K Morgans, MD, MPH

- **This patient was treated with 10 cycles of docetaxel, and had improvement of mid-back pain and decrease in PSA (nadir 1.8 ng/mL).**
- **Tolerated well with mild fatigue and mild neuropathy in fingers.**
- **CBC after completing treatment with mild anemia (Hgb 11.2), otherwise no cytopenias.**
- **3 months after completing docetaxel, he presents with fatigue but otherwise remains active.**
  - **Labs demonstrate PSA 37.3 ng/mL**
  - **CT and bone scan were performed**

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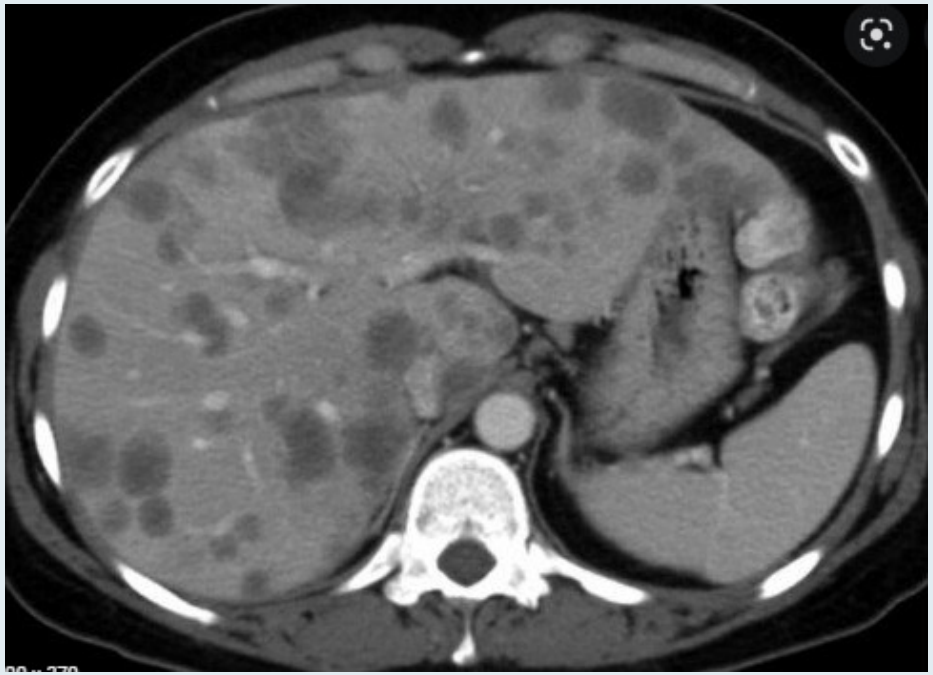
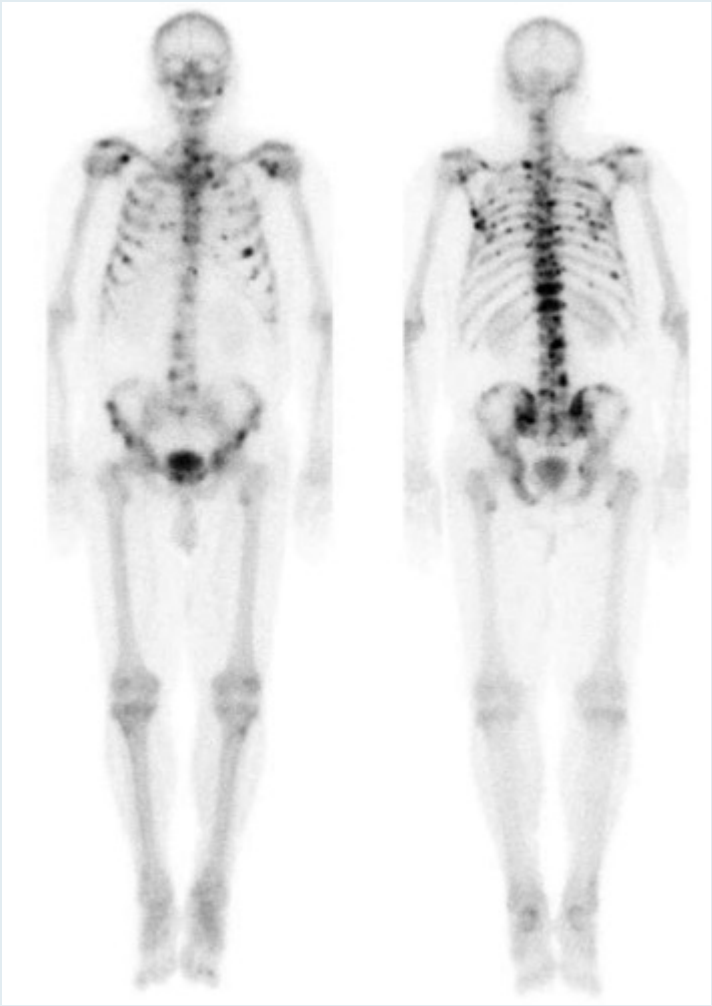
Case — Alicia K Morgans, MD, MPH

Imaging

- **Increased liver lesions and progression of bone metastases**





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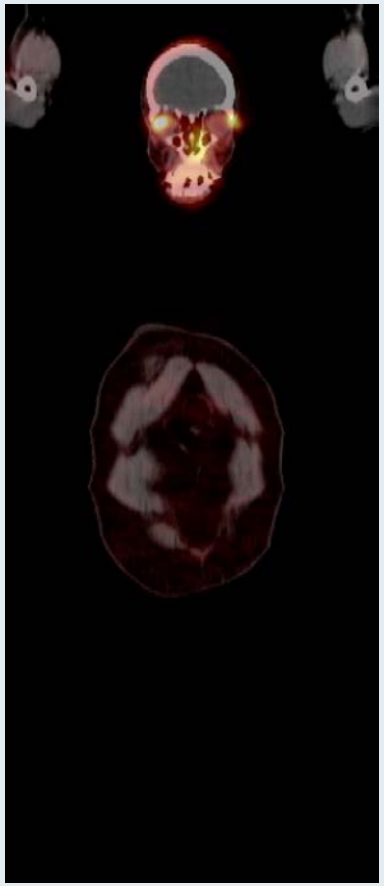
Case — Alicia K Morgans, MD, MPH

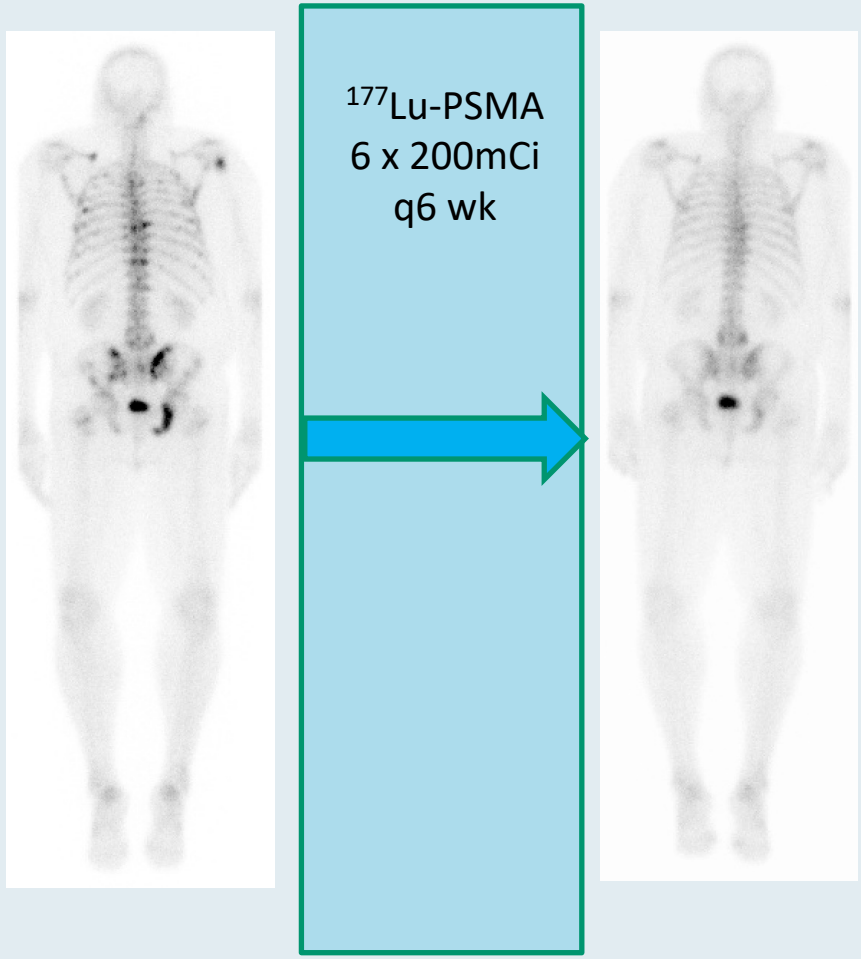
- **What options for treatment could be considered at this point?**

Case — Andrew J Armstrong, MD, ScM

- **68 yo AAM with high volume mCRPC, no soft tissue metastases.**
- **Progressed despite prior docetaxel/ADT for mHSPC and enzalutamide for mCRPC.**
- **PSADT is rapid, with bone only metastases.**



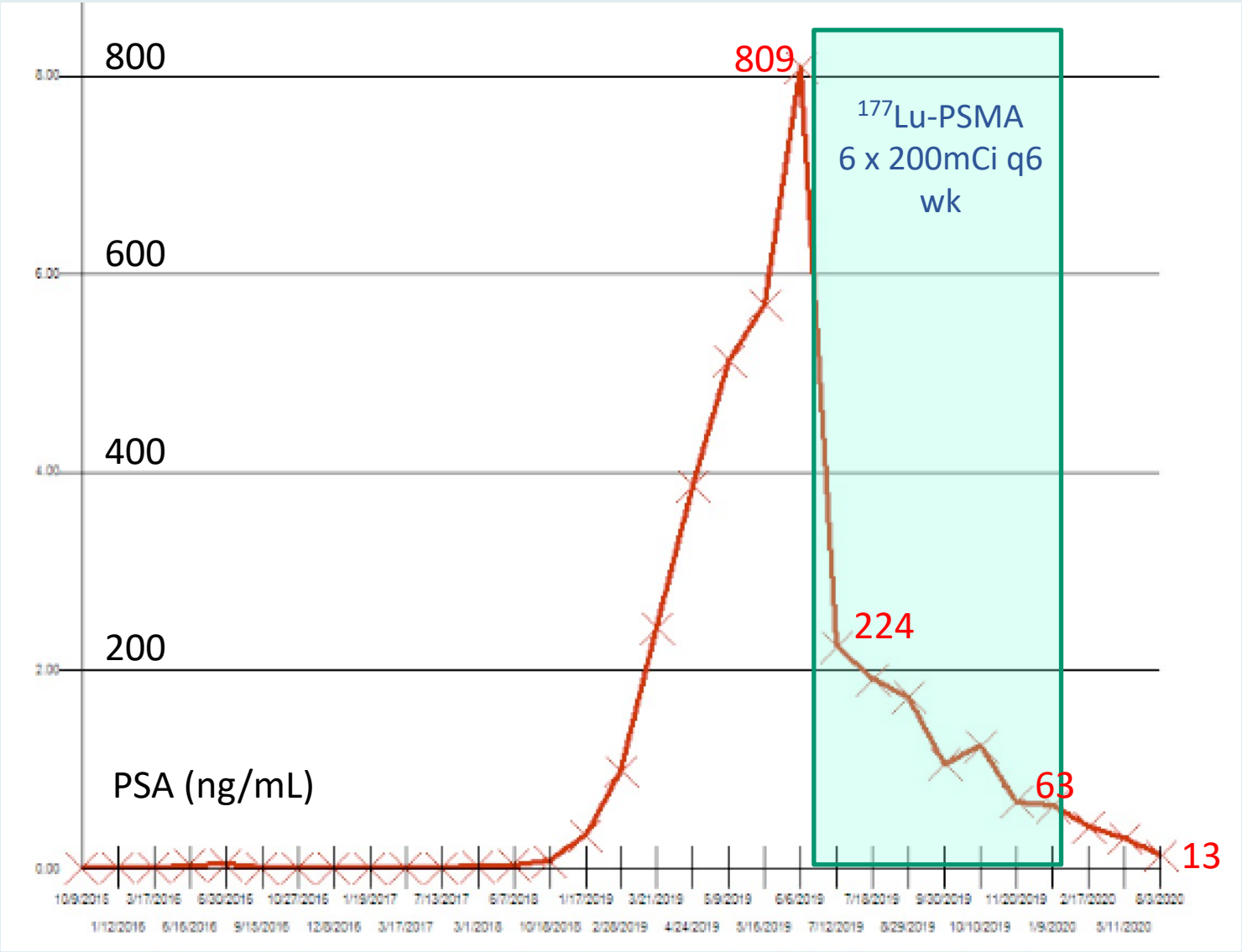
PSMA-PET/CT



Treatment included ADT and a short course of abiraterone but abi stopped due to intolerance and PSA rise prior to ^{177}Lu-PSMA-617 initiation. Anemia due to bone metastases improved after 2-3 doses.

RTP RESEARCH TO PRACTICE

Case — Andrew J Armstrong, MD, ScM



Patient remains active and working, asymptomatic from his prostate cancer, with a high QOL, now off therapy other than ADT for 8 months

CT/BS show ongoing response without progression

RTP RESEARCH TO PRACTICE

Case — Andrew J Armstrong, MD, ScM

- **After 3 cycles of ^{177}Lu-PSMA-617, the patient's bone pain and anemia resolved. He did experience mild fatigue but was able to return full time to work in the legal profession**
- **Bone scan and CT revealed a complete remission by imaging that lasted for 12 months**
- **PSA rose subsequently with reappearance of high volume bone metastases and recurrence of fatigue, weight loss, and bone pain**
- **He was subsequently treated with cabazitaxel and responded well to therapy with an ongoing PSA decline and improvement in symptoms**

Case — Andrew J Armstrong, MD, ScM

- **What predisposes to extraordinary responses to ^{177}Lu-PSMA-617?**
  - **PSMA uptake, lack of PSMA heterogeneity**
  - **Lack of genomic alterations associated with lineage plasticity and NEPC (TP53, RB1, PTEN)?**
- **Patient's PSA is now back up to 600 with new bone metastases. PSMA PET is brightly positive still about 18 months after completing 6 doses of ^{177}Lu-PSMA-617 which he tolerated well and he had returned to work full time**
- **How would you treat him now?**
  - **Cabazitaxel vs repeat ^{177}Lu-PSMA-617?**

RTP RESEARCH TO PRACTICE

CARD Study Design

- Multicenter, randomized, open-label study
- Enrollment: Nov 2015 – Nov 2018
- Median follow-up: 9.2 months

Patients with mCRPC who progressed ≤ 12 months on prior AR-targeted agent (before or after docetaxel)[a]

N = 255

RANDOMIZE

1:1

Cabazitaxel (25 mg/m² Q3W) + prednisone + G-CSF[b]
n = 129

Abiraterone (1000 mg QD) + prednisone
OR
Enzalutamide (160 mg QD)
n = 126

Endpoints

Primary: rPFS

Key secondary: OS, PFS, PSA response, tumor response

Other secondary: Pain response, time to SSE, safety, FACT-P, EQ-5D-5L, biomarkers

Stratification factors:

- ECOG PS (0/1 vs 2)
- time to disease progression (≤ 6 vs > 6–12 months)
- timing of previous alternative AR-targeted agent (before vs after docetaxel)

Tombal B et al. ASCO 2020;Abstract 5569.

FDA Approves ^{177}Lu-PSMA-617 for mCRPC

Press Release: March 23, 2022

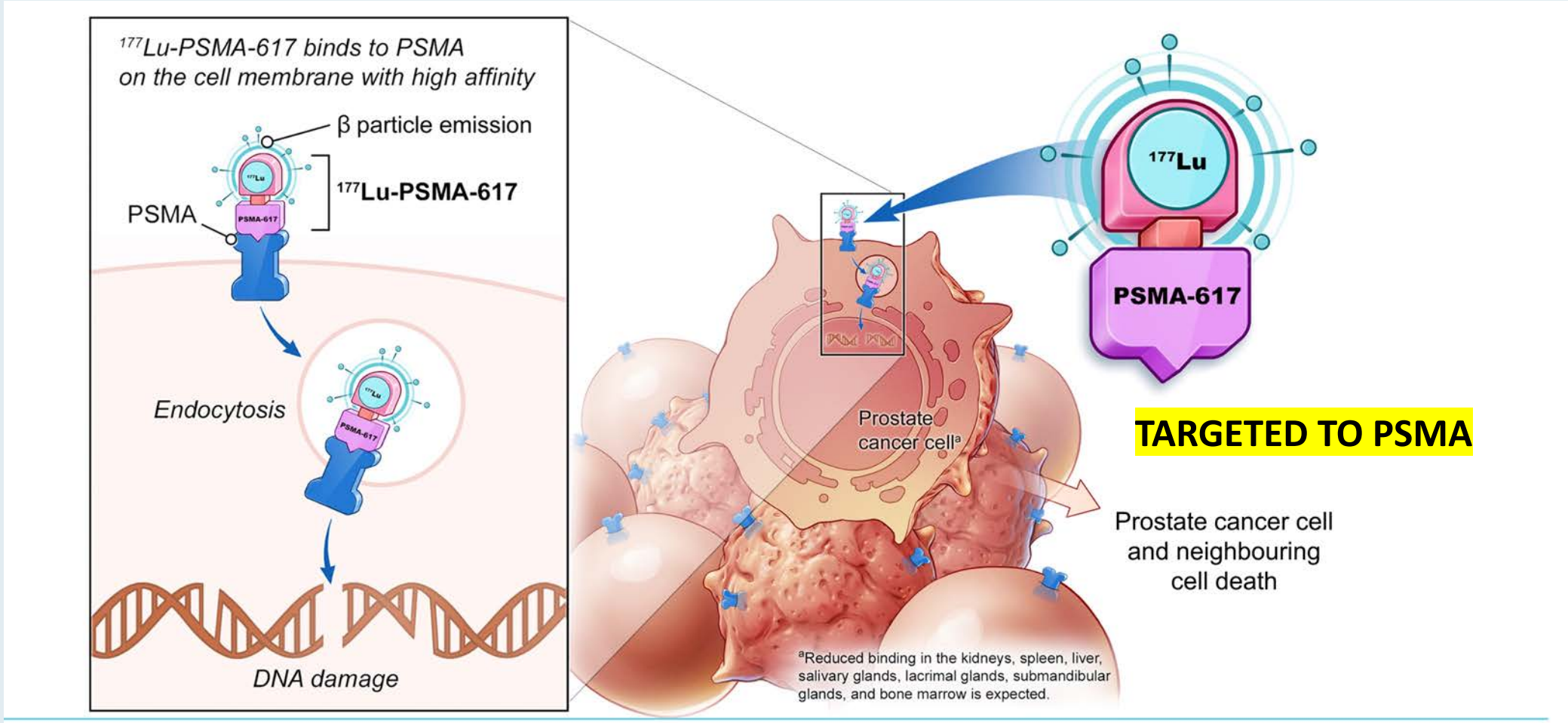
On March 23, 2022, the Food and Drug Administration approved the radioligand therapy ^{177}Lu-PSMA-617 for the treatment of prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) in adult patients who have received treatment with androgen receptor pathway inhibition and taxane-based chemotherapy.

On the same day, the FDA approved gallium Ga 68 gozetotide, a radioactive diagnostic agent for positron emission tomography (PET) of PSMA-positive lesions, including selection of patients with metastatic prostate cancer for whom ^{177}Lu-PSMA-617 PSMA-directed therapy is indicated. Gallium Ga 68 gozetotide is the first radioactive diagnostic agent approved for patient selection for a radioligand therapeutic agent.

Efficacy was evaluated in the Phase III VISION trial, which demonstrated a statistically significant improvement in the primary endpoints OS and radiographic progression-free survival. Hazard ratio (HR) for OS was 0.62 (95% CI: 0.52-0.74; $p < 0.001$) for the comparison of ^{177}Lu-PSMA-617 with best standard care (BSoC) to BSoC. Median OS was 15.3 months (95% CI: 14.2-16.9) on the ^{177}Lu-PSMA-617 with BSoC arm and 11.3 months (95% CI: 9.8, 13.5) on the BSoC arm.

https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pluvicto-metastatic-castration-resistant-prostate-cancer

^{177}Lu-PSMA-617: Mechanism of Action



Morris MJ et al. ASCO 2021;Abstract LBA4.

N Engl J Med 2021;385:1091-103

The NEW ENGLAND JOURNAL of MEDICINE

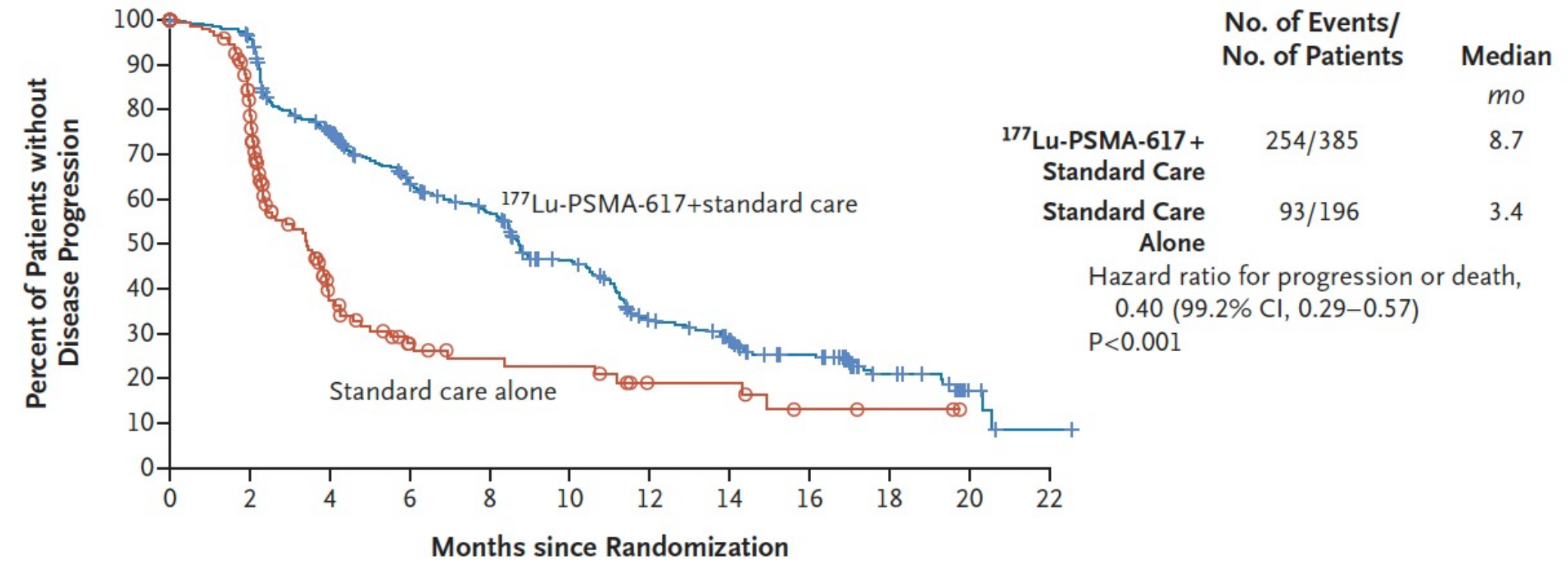
ORIGINAL ARTICLE

Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

O. Sartor, J. de Bono, K.N. Chi, K. Fizazi, K. Herrmann, K. Rahbar, S.T. Tagawa, L.T. Nordquist, N. Vaishampayan, G. El-Haddad, C.H. Park, T.M. Beer, A. Armour, W.J. Pérez-Contreras, M. DeSilvio, E. Kpamegan, G. Gericke, R.A. Messmann, M.J. Morris, and B.J. Krause, for the VISION Investigators*

VISION: Efficacy Summary

Imaging–based progression-free survival



- Median OS (^{177}Lu-PSMA-617 vs standard therapy): 15.3 mo vs 11.3 mo (HR 0.62, $p < 0.001$)
- Time to first symptomatic skeletal event (^{177}Lu-PSMA-617 vs standard therapy): 11.5 mo vs 6.8 mo (HR 0.50, $p < 0.001$)

Sartor O et al. *N Engl J Med* 2021;385:1091-103.

RTP RESEARCH TO PRACTICE

VISION: Selected Adverse Events

Event	^{177}Lu-PSMA-617 plus Standard Care (N = 529)		Standard Care Alone (N = 205)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Any adverse event	519 (98.1)	279 (52.7)	170 (82.9)	78 (38.0)
Adverse event that occurred in >12% of patients				
Fatigue	228 (43.1)	31 (5.9)	47 (22.9)	3 (1.5)
Dry mouth	205 (38.8)	0	1 (0.5)	0
Thrombocytopenia	91 (17.2)	42 (7.9)	9 (4.4)	2 (1.0)
Lymphopenia	75 (14.2)	41 (7.8)	8 (3.9)	1 (0.5)
Leukopenia	66 (12.5)	13 (2.5)	4 (2.0)	1 (0.5)
Adverse event that led to reduction in ^{177}Lu-PSMA-617 dose	30 (5.7)	10 (1.9)	NA	NA
Adverse event that led to interruption of ^{177}Lu-PSMA-617†	85 (16.1)	42 (7.9)	NA	NA
Adverse event that led to discontinuation of ^{177}Lu-PSMA-617†	63 (11.9)	37 (7.0)	NA	NA
Adverse event that led to death‡	19 (3.6)	19 (3.6)	6 (2.9)	6 (2.9)

Sartor O et al. *N Engl J Med* 2021;385:1091-103.

RTP RESEARCH TO PRACTICE

Lancet 2021;397:797-804.

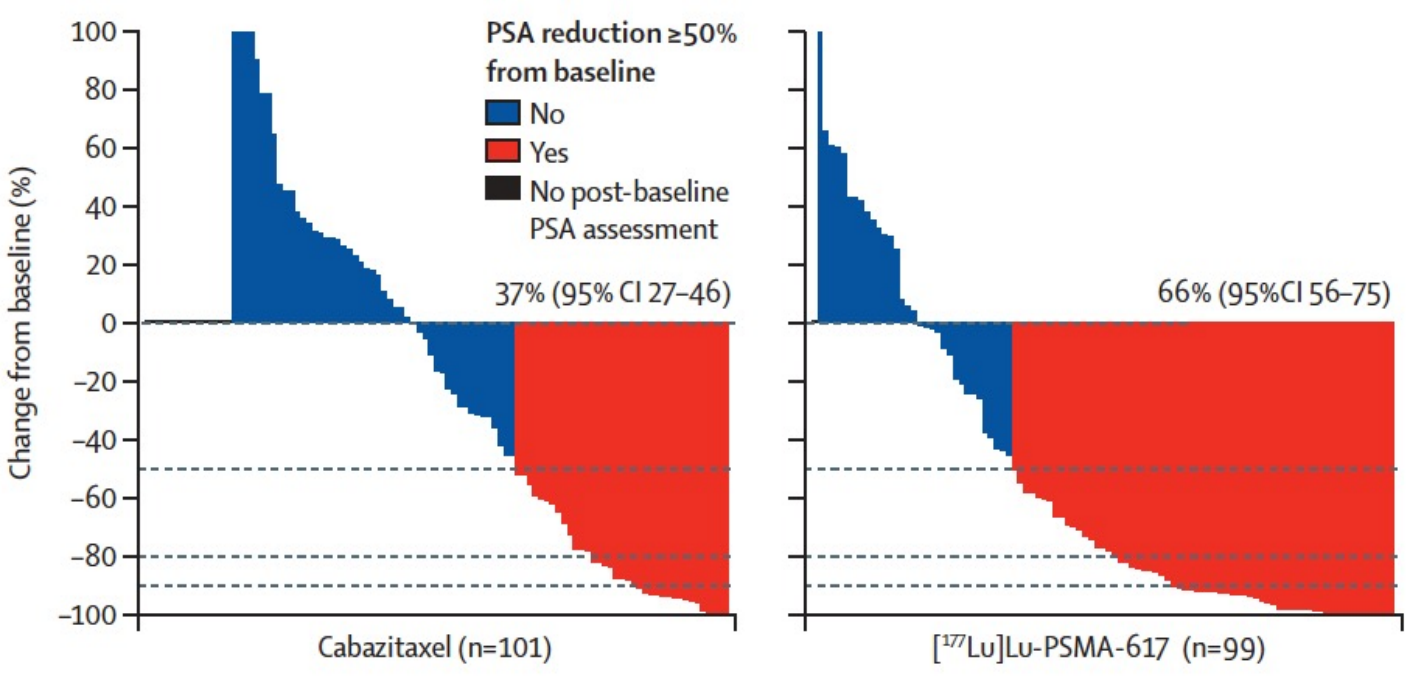
[^{177}Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial

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†*

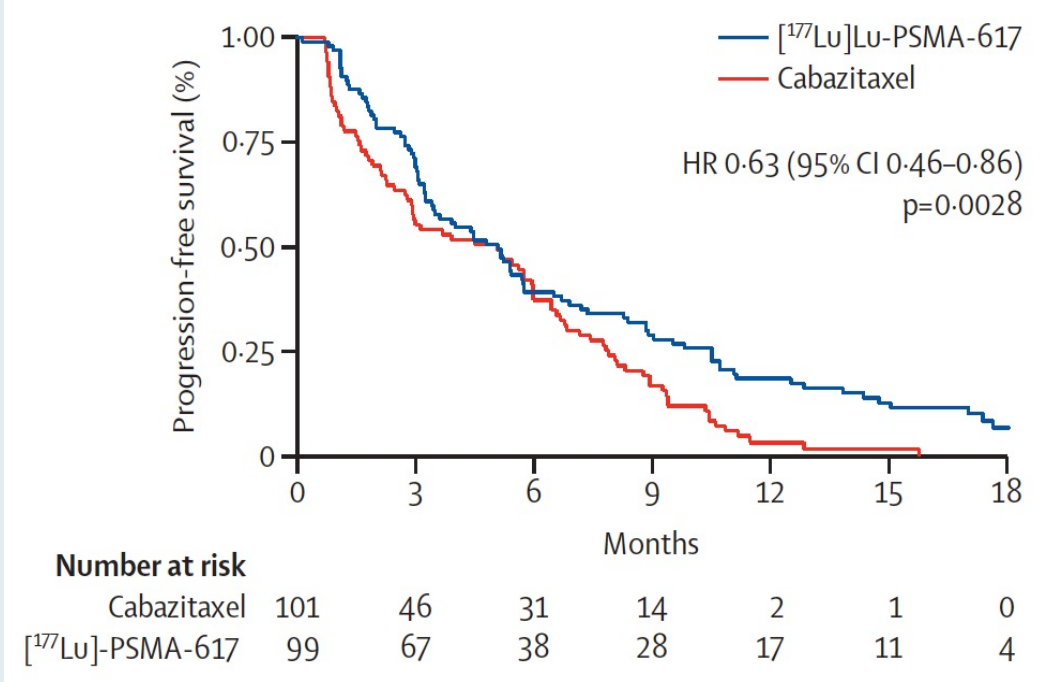
TheraP ANZUP 1603: ^{177}Lu-PSMA-617 versus Cabazitaxel for mCRPC

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;397(10276):797-804.

RTP RESEARCH TO PRACTICE

TheraP: ^{177}Lu-PSMA-617 (LuPSMA) versus Cabazitaxel in Metastatic Castration-Resistant Prostate Cancer (mCRPC) Progressing After Docetaxel—Overall Survival After Median Follow-Up of 3 Years (ANZUP 1603)

Hofman MS et al.

ASCO 2022;Abstract 5000.

Track: Genitourinary Cancer – Prostate, Testicular, and Penile
June 5, 2022, 9:00 AM

[^{177}Lu]Lu-PSMA-617 in PSMA-Positive Metastatic Castration-Resistant Prostate Cancer: Prior and Concomitant Treatment Subgroup Analyses of the VISION Trial

Vaishampayan N et al.

ASCO 2022;Abstract 5001.

Track: Genitourinary Cancer – Prostate, Testicular, and Penile
June 5, 2022, 9:00 AM

[^{68}Ga]Ga-PSMA-11 PET Baseline Imaging as a Prognostic Tool for Clinical Outcomes to [^{177}Lu]Lu-PSMA-617 in Patients with mCRPC: A VISION Substudy

Kuo P et al.

ASCO 2022;Abstract 5002.

Track: Genitourinary Cancer – Prostate, Testicular, and Penile
June 5, 2022, 9:00 AM

2021 ESMO congress

Abstract LBA24

Cabozantinib in combination with atezolizumab in patients with metastatic castration-resistant prostate cancer (mCRPC): results of expanded cohort 6 of the COSMIC-021 Study

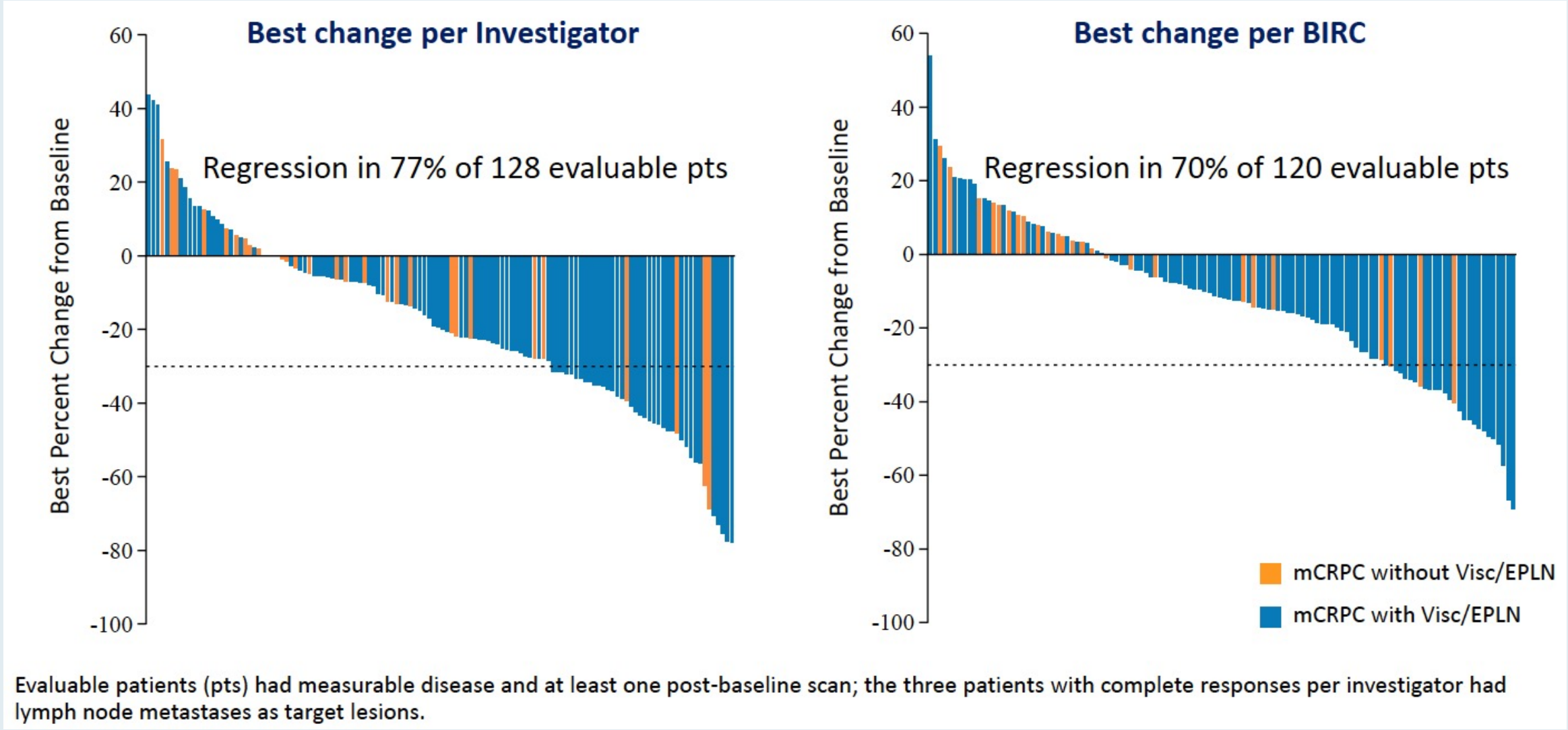
Neeraj Agarwal,[1] Bradley McGregor,[2] Benjamin L. Maughan,[1] Tanya B. Dorff,[3] William Kelly,[4] Bruno Fang,[5] Rana R. McKay,[6] Parminder Singh,[7] Lance Pagliaro,[8] Robert Dreicer,[9] Sandy Srinivas,[10] Yohann Loriot,[11] Ulka Vaishampayan,[12] Sanjay Goel,[13] Dominic Curran,[14] Ashok Panneerselvam,[14] Li-Fen Liu,[14] Toni K. Choueiri,[2*] Sumanta Pal[3*]

[1]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [2]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [3]City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [4]Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA, USA; [5]Regional Cancer Care Associates, East Brunswick, NJ, USA; [6]University of California San Diego, San Diego, CA, USA; [7]Department of Oncology, Mayo Clinic, Scottsdale, AZ, USA; [8]Department of Oncology, Mayo Clinic, Rochester, MN, USA; [9]University of Virginia Cancer Center, Charlottesville, VA, USA; [10]Division of Medical Oncology, Stanford University Medical Center, Stanford, CA, USA; [11]Department of Cancer Medicine, Gustave Roussy Institute, INSERM 981, University Paris-Saclay, Villejuif, France; [12]Karmanos Cancer Center, Wayne State University, Detroit, MI, USA (Current affiliation: Division of Hematology/Oncology, University of Michigan, Ann Arbor, MI, USA); [13]Department of Medical Oncology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA; [14]Exelixis, Inc., Alameda, CA, USA

*Co-senior authors

COSMIC-021: Cabozantinib/Atezolizumab for mCRPC

Best Change from Baseline in Sum of Target Lesions



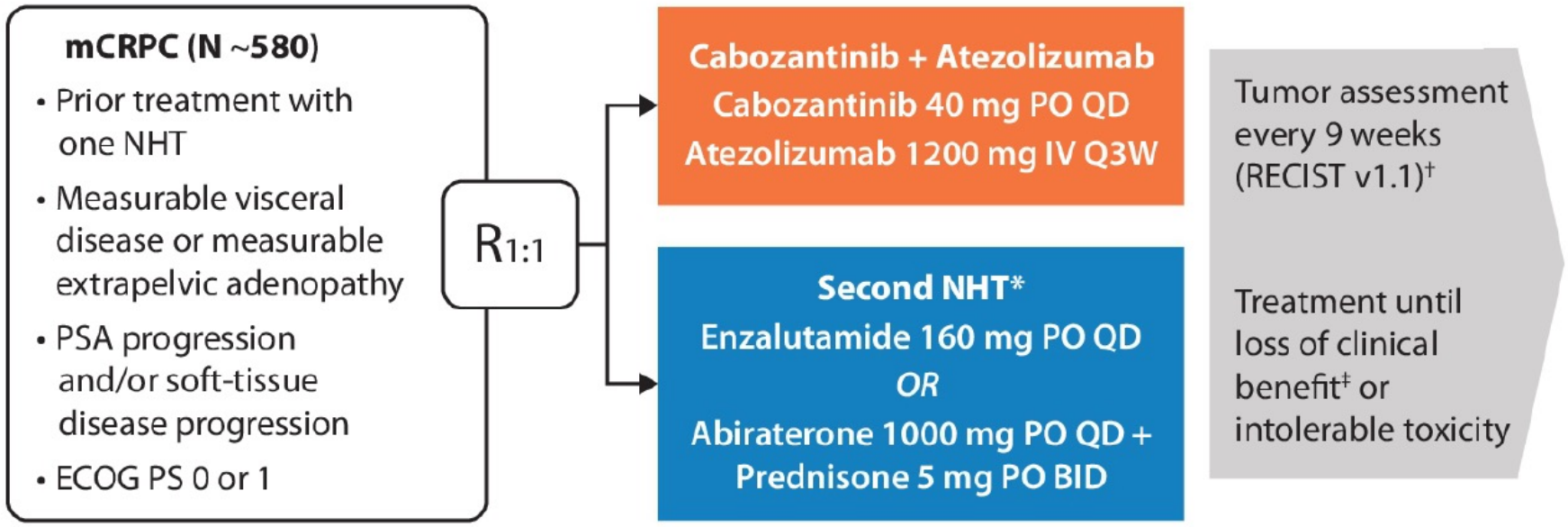
Evaluable patients (pts) had measurable disease and at least one post-baseline scan; the three patients with complete responses per investigator had lymph node metastases as target lesions.

BIRC = blinded independent review committee; EPLN = extrapelvic lymph nodes

Agarwal N et al. ESMO 2021;Abstract LBA24.

RTP RESEARCH TO PRACTICE

CONTACT-02: Phase III Trial Schema



Stratification

- Liver metastasis (yes, no)
- Prior docetaxel treatment for mCSPC (yes, no)
- Disease stage for which the first NHT was given (mCSPC, M0 CRPC, mCRPC)

*Second NHT must differ from previous NHT taken
†Tumor assessment (RECIST v1.1) every 9 weeks for the first 28 weeks then every 12 weeks thereafter
‡Patients may be treated beyond progression if there is a clinical benefit in the opinion of the investigator

Primary Endpoints

- PFS per RECIST v1.1 by BIRC
- OS

Secondary Endpoint

- ORR per RECIST v1.1 by BIRC

NHT = novel hormone therapy

Agarwal N et al. Genitourinary Cancers Symposium 2021;Abstract TPS190.

Agenda

Module 1 – Optimal Application of Hormonal Therapy in Prostate Cancer Management

Module 2 – Selection and Sequencing of Therapy for Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC); Novel Investigational Strategies

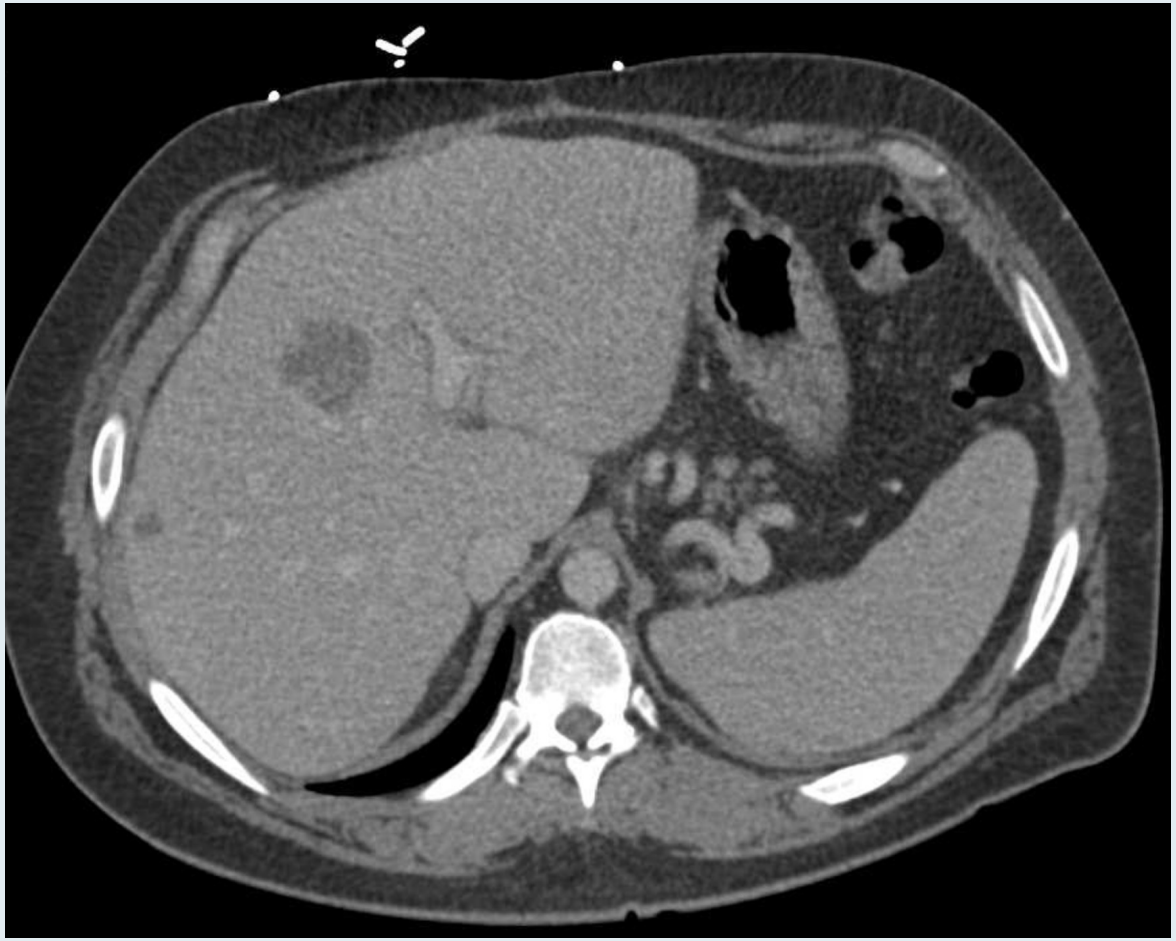
Module 3 – Current and Potential Role of PARP Inhibitors in the Management of Prostate Cancer

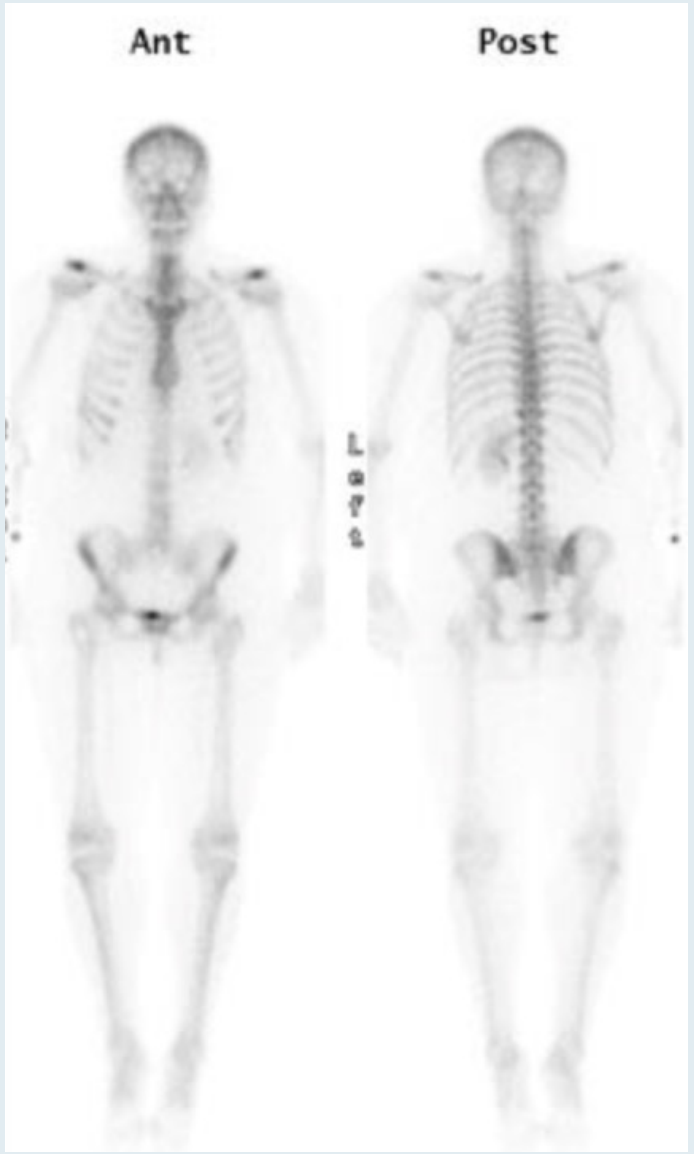
RTP RESEARCH TO PRACTICE

Case — Alicia K Morgans, MD, MPH

- **This patient is a 69-year-old gentleman with a history of HTN, and localized prostate cancer diagnosed in 6/2013**
  - **Underwent radical prostatectomy in 9/2015, with PSA 11.3 ng/mL at diagnosis**
  - **Pathology was pT3aN0M0, Gleason 5 + 5 (Grade Group 5) prostate adenocarcinoma**
- **8/2019 presents with 6-month history of progressive fatigue, new and worsening lower back pain, decreased appetite and a 22 lb weight loss**
- **PSA 23.5 ng/mL. CT/bone scan obtained**

Case — Alicia K Morgans, MD, MPH





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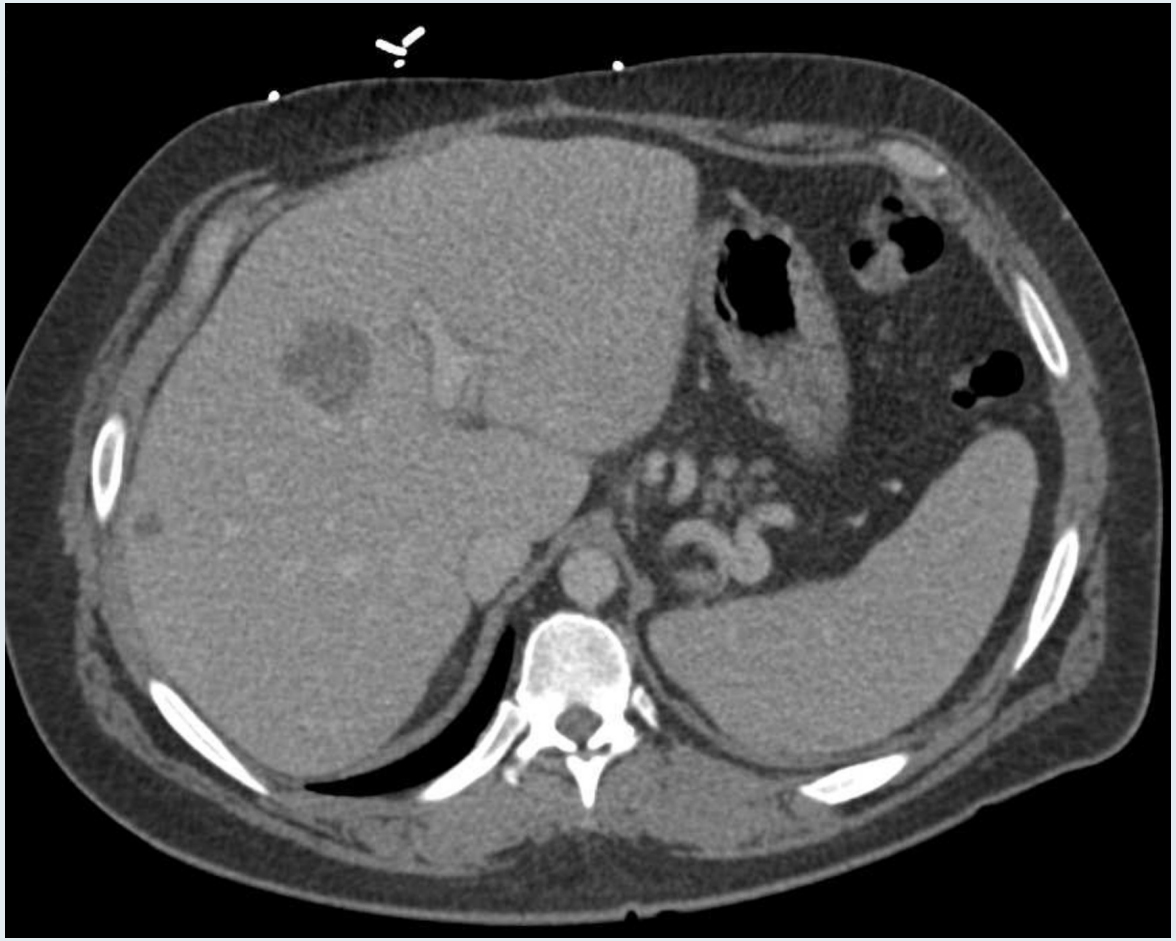
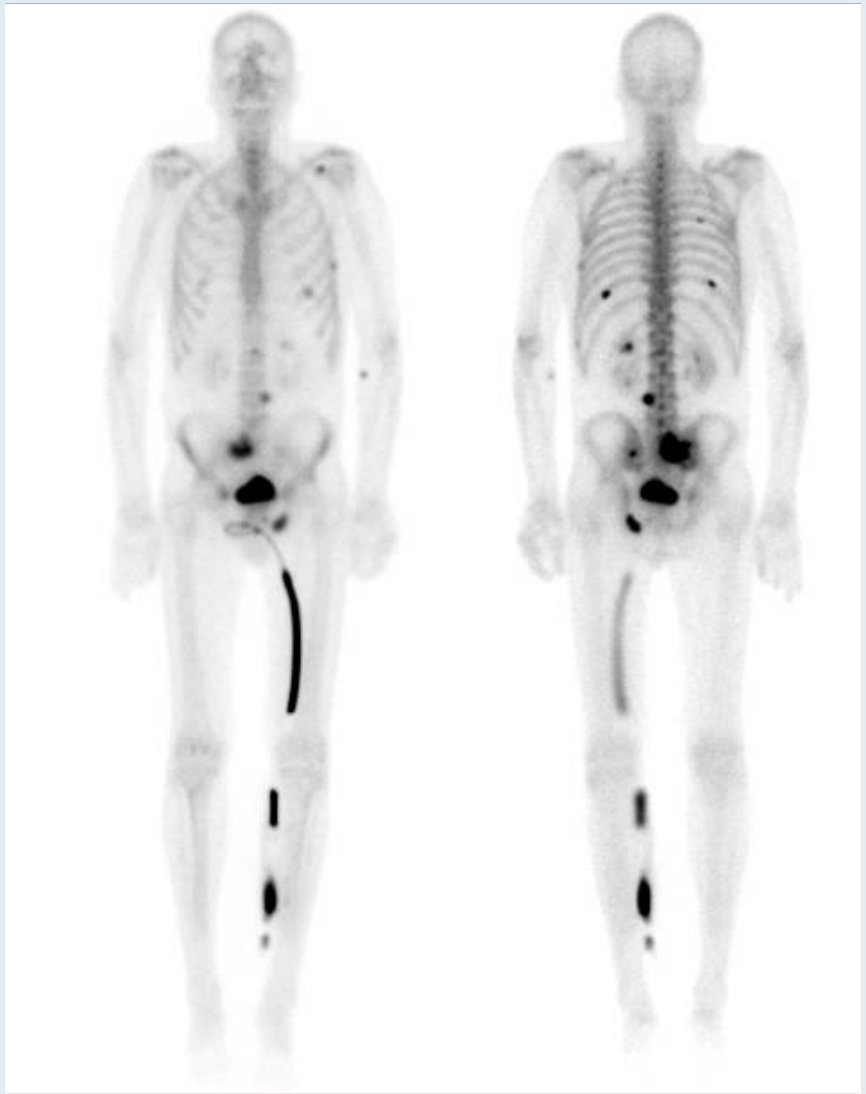
Case — Alicia K Morgans, MD, MPH

- **Diagnosed with mHSPC in liver and with retroperitoneal adenopathy.**
- **Initiated treatment with docetaxel x 6 cycles.**
- **Tolerated treatment well with disease response for 9 months (PSA nadir 1.7 ng/mL), then PSA increased to 4.3 ng/mL in 6/2020. Patient noted increase in lower back pain.**
- **CT abd/pelvis and bone scan repeated.**

Case — Alicia K Morgans, MD, MPH





Case — Alicia K Morgans, MD, MPH

- **Liver lesions stable, progression of disease retroperitoneal lymph nodes and bone.**

What do you consider next in terms of workup and potential treatment?

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Case — Alicia K Morgans, MD, MPH

Patient undergoes germline DNA testing that identifies an ATM mutation.

GENERAL GUIDELINES

POSITIVE RESULTS GUIDE: ATM

What is a positive ATM result?

A positive test result means that a genetic change (variant) called c.7271T>G (p.Val2424Gly) was found in the ATM gene. This variant is considered "pathogenic" because it may increase the risk for certain types of cancer.

RTP RESEARCH TO PRACTICE

Case — Alicia K Morgans, MD, MPH

ATM and CHIP

JAMA Oncology | Brief Report

Association of Clonal Hematopoiesis in DNA Repair Genes With Prostate Cancer Plasma Cell-free DNA Testing Interference

Kendal Jensen, MD, PhD; Eric Q. Konnick, MD; Michael T. Schweizer, MD; Alexandra O. Sokolova, MD; Petros Grivas, MD, PhD; Heather H. Cheng, MD, PhD; Nola M. Klemfuss, MHA; Mallory Beightol, BS, MB; Evan Y. Yu, MD; Peter S. Nelson, MD; Bruce Montgomery, MD; Colin C. Pritchard, MD, PhD

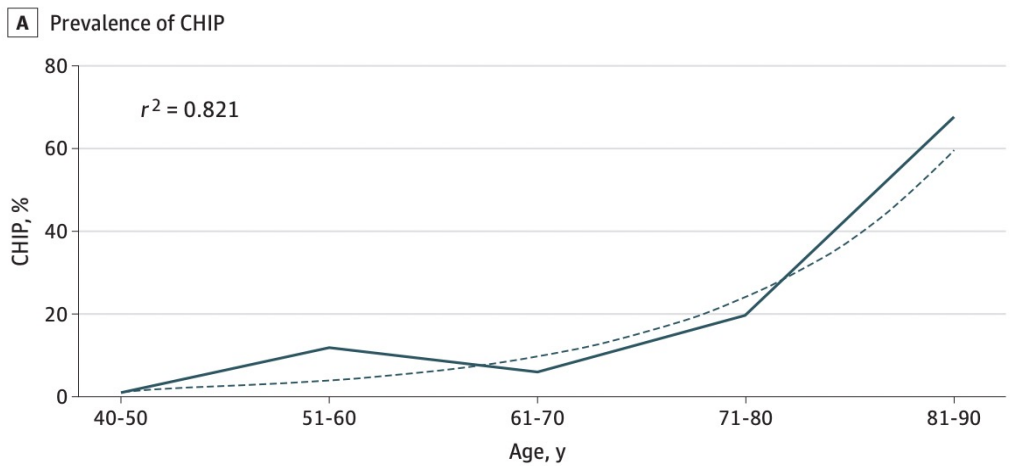

Table. CHIP Clones Detected in DNA Repair Genes Used for PARPi Eligibility

Age, y	Gene[a]	CHIP Variant(s)	VAF cfDNA	VAF blood control	Notes
81	*ATM*	p.R3008C, p.E3007D	16%; 5%	16%; 5%	CHIP hotspot, reported by outside lab in bone marrow
54	ATM	p.S305*	2%	3%	
82	*ATM*	p.G2891D	12%	13%	Kinase domain
81	*ATM*	c.2921 + 1G>A	78%	65%	Not germline based on tumor testing
87	*ATM*	p.L2492R	7%	9%	CHIP hotspot
76	*BRCA2*	p.T3310Nfs*17	3%	3%	Reported by outside lab, recommending PARPi
74	*CHEK2*	p.P426H	19%	18%	Kinase domain

- Prostate cancer mutations are identified in plasma only.
- CHIP can be detected in plasma and whole blood.
- Use of a whole blood control can distinguish between these.

Jensen K, et al. JAMA Oncol, 2021.

RTP RESEARCH TO PRACTICE

Case — Alicia K Morgans, MD, MPH

Patient initiates therapy with
Olaparib 300 mg PO BID + abiraterone acetate 1000 mg PO daily + prednisone 5 mg PO daily.

He tolerated treatment well after experiencing Grade 1 anorexia/nausea in the first week of treatment. He had inadequately controlled HTN prior to treatment, and his BP meds were adjusted, and his BP improved to the normal range. CBC was monitored closely, and he had a stable anemia (Hgb 10.9).

Case — Alicia K Morgans, MD, MPH

Managing Side Effects with PARP Inhibitor Combinations

Considerations for patient counseling

- Counsel patients prior to treatment specifically on risk of hematologic and GI AEs, as well as fatigue
- Explain the necessity of regular blood tests for AE monitoring for cytopenias and liver function tests
- Prepare the patient for the possibility of blood transfusions
- Ensure that the patient has first recovered from hematologic toxicity caused by prior anticancer therapies before initiating treatment (if possible)

Considerations for clinical evaluation

- Other causes of AEs should be identified, including androgen deprivation therapy
- Common causes of fatigue include ADT, depression, sleep disturbances
- Common causes of anemia include low iron levels in blood, stomach ulcer bleeding, CKD
- Workup should include iron studies, vitamin B12, and folic acid levels to determine whether supplementation is needed

Adverse events appear additive, not synergistic.

RTP RESEARCH TO PRACTICE

Case — Alan H Bryce, MD

1. January Year 1: 67 yo man, screening PSA 6.5. Biopsy demonstrates Gleason 3 + 4 adenocarcinoma

2. April Year 3: PSA 10.3. RARP. Gleason 4 + 3, 2/27 lymph nodes positive. T3a N1 MX. Post-op PSA <0.1. Begin ADT

3. May Year 5: PSA recurrence 0.6. Imaging study showed no evidence of metastatic disease

4. August Year 5: Complete salvage radiation therapy to the prostate bed with 7425 cGy in 30 total fractions

Germline- No pathogenic variants

Somatic- 1) Prostatectomy tissue- KMT2D p.G4603fs, TMB 0.8 m/MB, MSI-S

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Case — Alan H Bryce, MD

5. March Year 6: PSA 23. F18 PET-CT showed enlarging retroperitoneal lymphadenopathy

6. May Year 6: Begin sipuleucel T

7. August Year 6: Begin abiraterone acetate PSA 66

8. January Year 8: PSA 24 over nadir of 2.6. Imaging shows new small volume bone metastases. Discontinue abiraterone

Case — Alan H Bryce, MD

9. May Year 8: Begin docetaxel

10. October Year 8: Chemotherapy discontinued after 8 cycles with stable disease. PSA 95.3. Imaging with equivocal progression of bone metastases. Obtain cfDNA

Germline- No pathogenic variants

Somatic- 1) Prostatectomy tissue- KMT2D p.G4603fs, TMB 0.8 m/MB, MSI-S

2) cfDNA testing BRCA2 T3033fs

11. December Year 8: Progression of bone and LN metastases. PSA 163. Begin rucaparib

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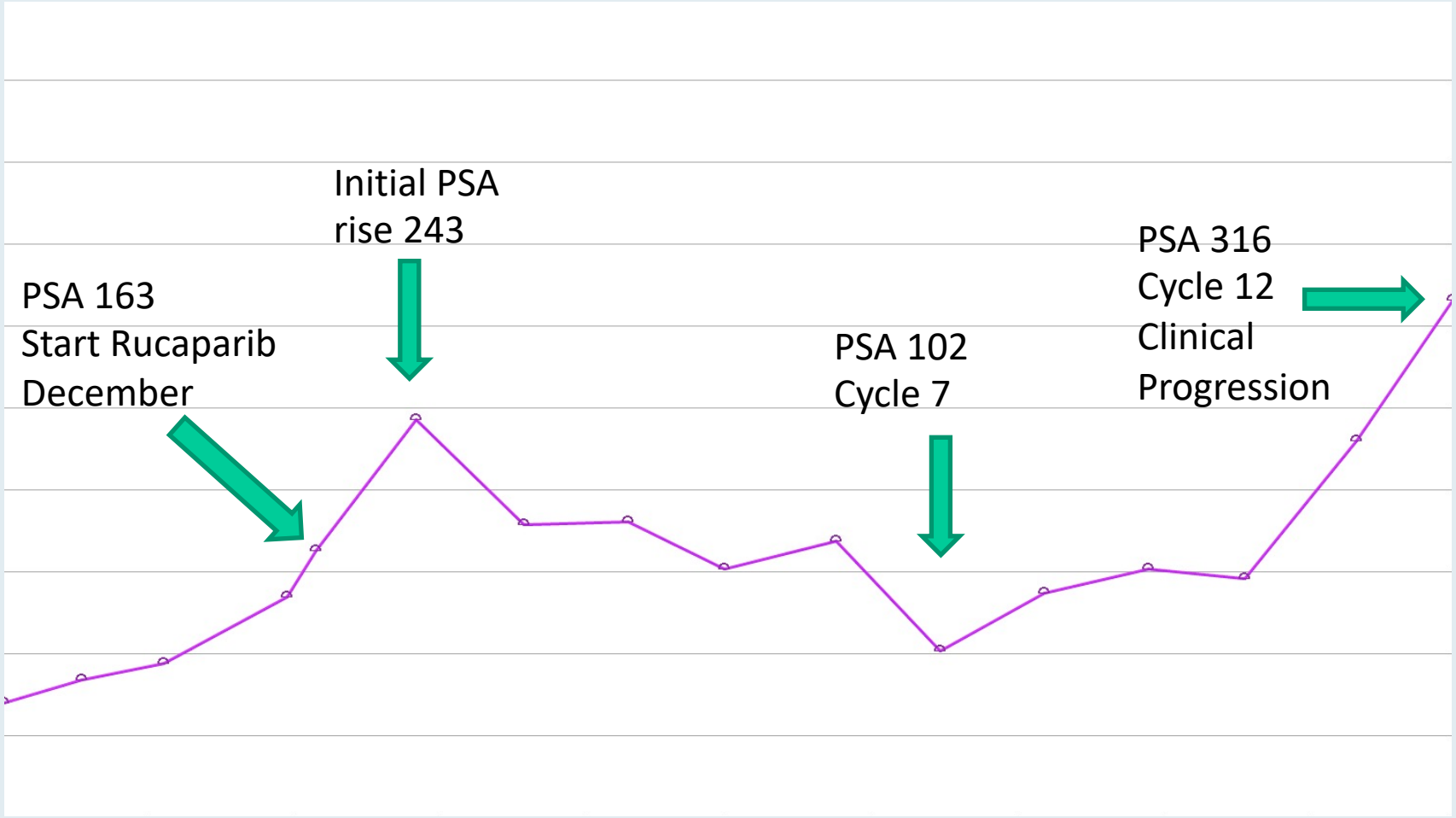
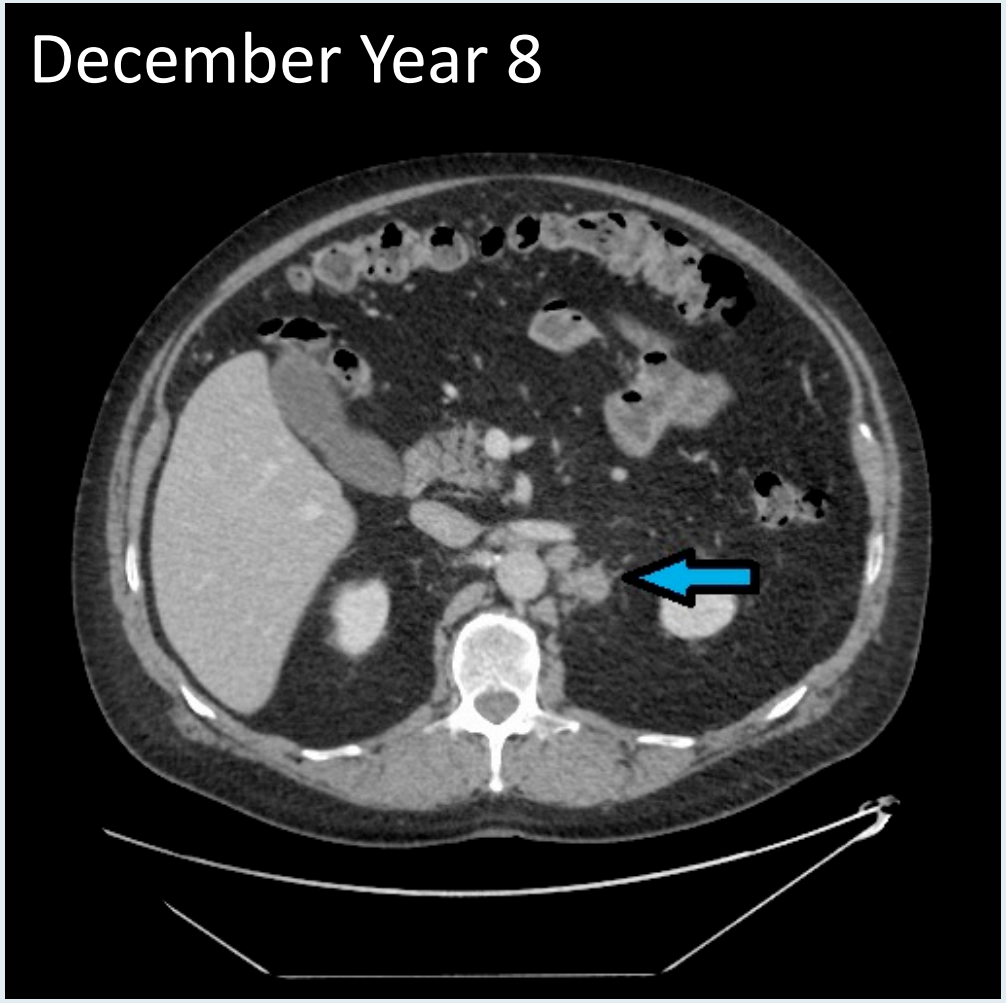
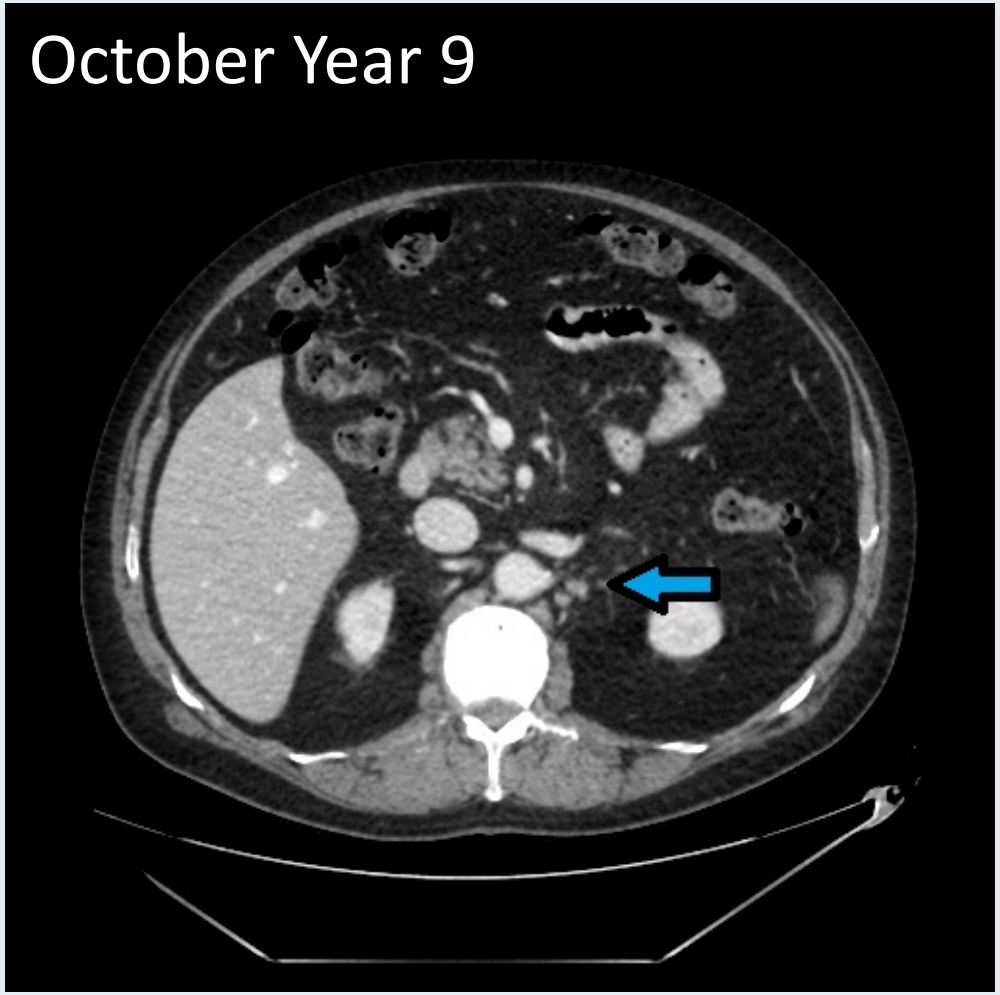
Case — Alan H Bryce, MD



11. December Year 8: Progression of bone and LN metastases. PSA 163, initiate rucaparib

Case — Alan H Bryce, MD





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TO PRACTICE

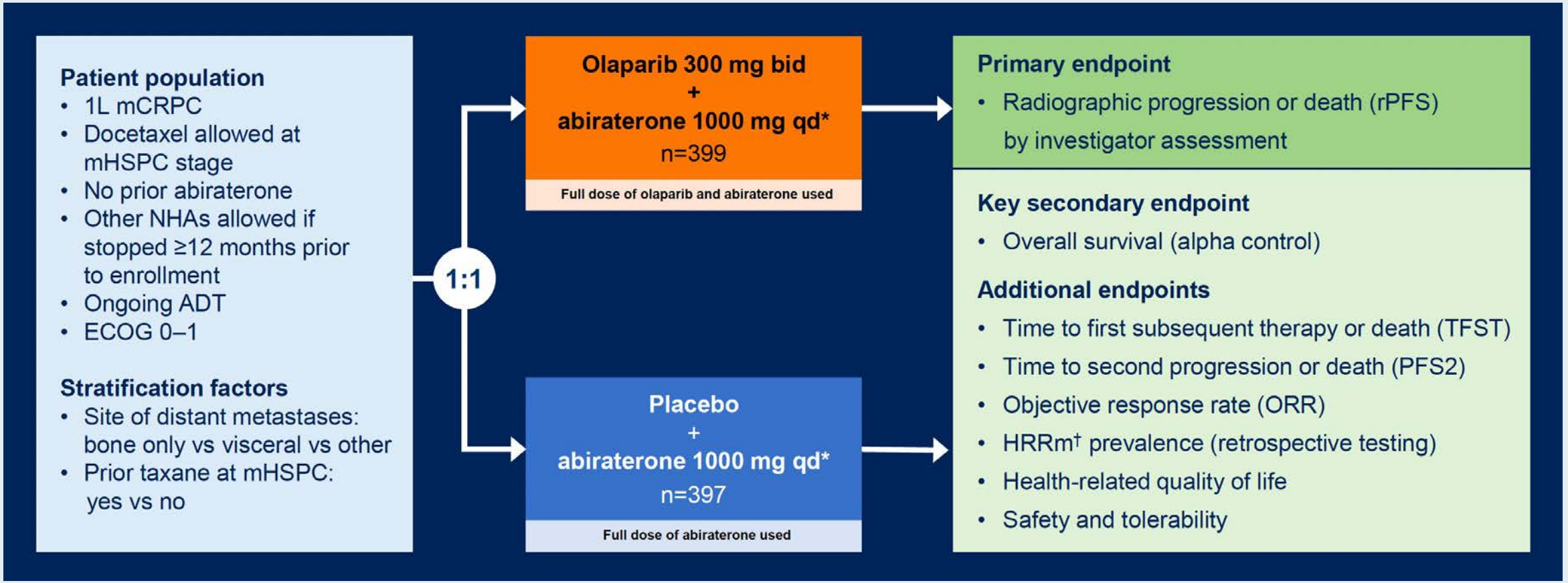
ASCO Genitourinary Cancers Symposium 2022;Abstract 11

PROpel: phase III trial of olaparib and abiraterone versus placebo and abiraterone as first-line therapy for patients with metastatic castration-resistant prostate cancer

Fred Saad, Andrew J. Armstrong, Antoine Thiery-Vuillemin, Mototsugu Oya, Eugenia Loredo, Giuseppe Procopio, Juliana de Menezes, Gustavo Girotto, Cagatay Arslan, Niven Mehra, Francis Parnis, Emma Brown, Friederike Schlürmann, Jae Young Joung, Mikio Sugimoto, Christian Poehlein, Elizabeth A. Harrington, Chintu Desai, Jinyu Kang, and Noel Clarke

ClinicalTrials.gov identifier: NCT03732820.

PROpel Phase III Study Design

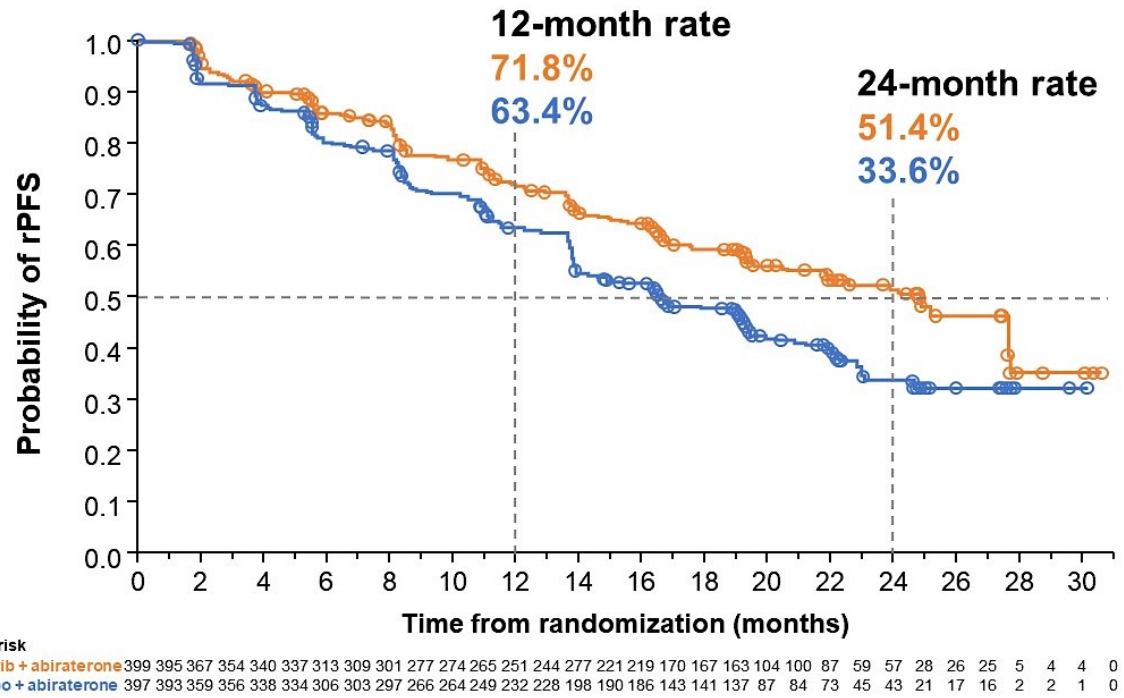


Saad F et al. Genitourinary Cancers Symposium 2022;Abstract 11.

PROpel: Olaparib and Abiraterone versus Placebo and Abiraterone as First-Line Therapy for mCRPC

Primary Endpoint: Investigator-Assessed Radiographic Progression-Free Survival (rPFS)

34% risk reduction of progression or death with olaparib + abiraterone



	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Events, n (%)	168 (42.1)	226 (56.9)
Median rPFS (months)	24.8	16.6
HR (95% CI)	0.66 (0.54–0.81); *P*<0.0001	

Pre-specified 2-sided alpha: 0.0324

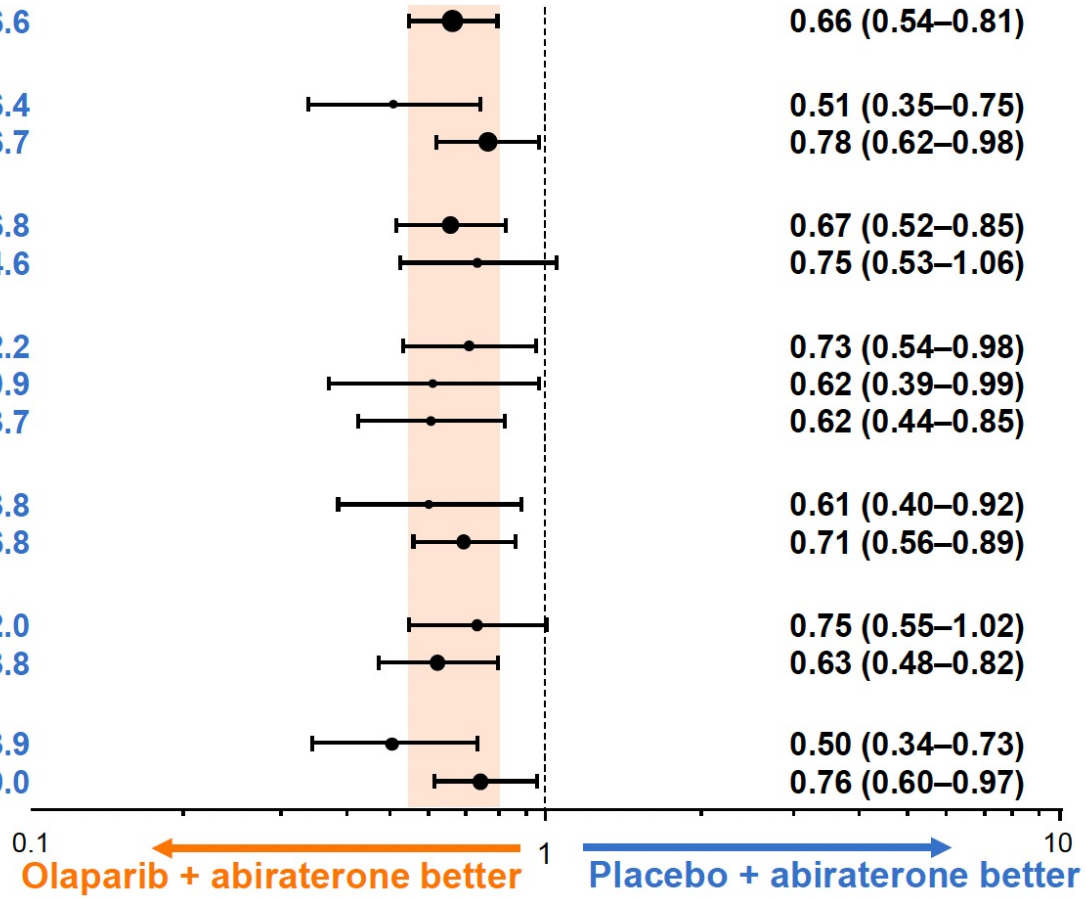
Median rPFS improvement of 8.2 months favors olaparib + abiraterone*

Events: 394; Maturity 49.5%
*In combination with prednisone or prednisolone
CI, confidence interval; HR, hazard ratio.

Saad F et al. Genitourinary Cancers Symposium 2022;Abstract 11.

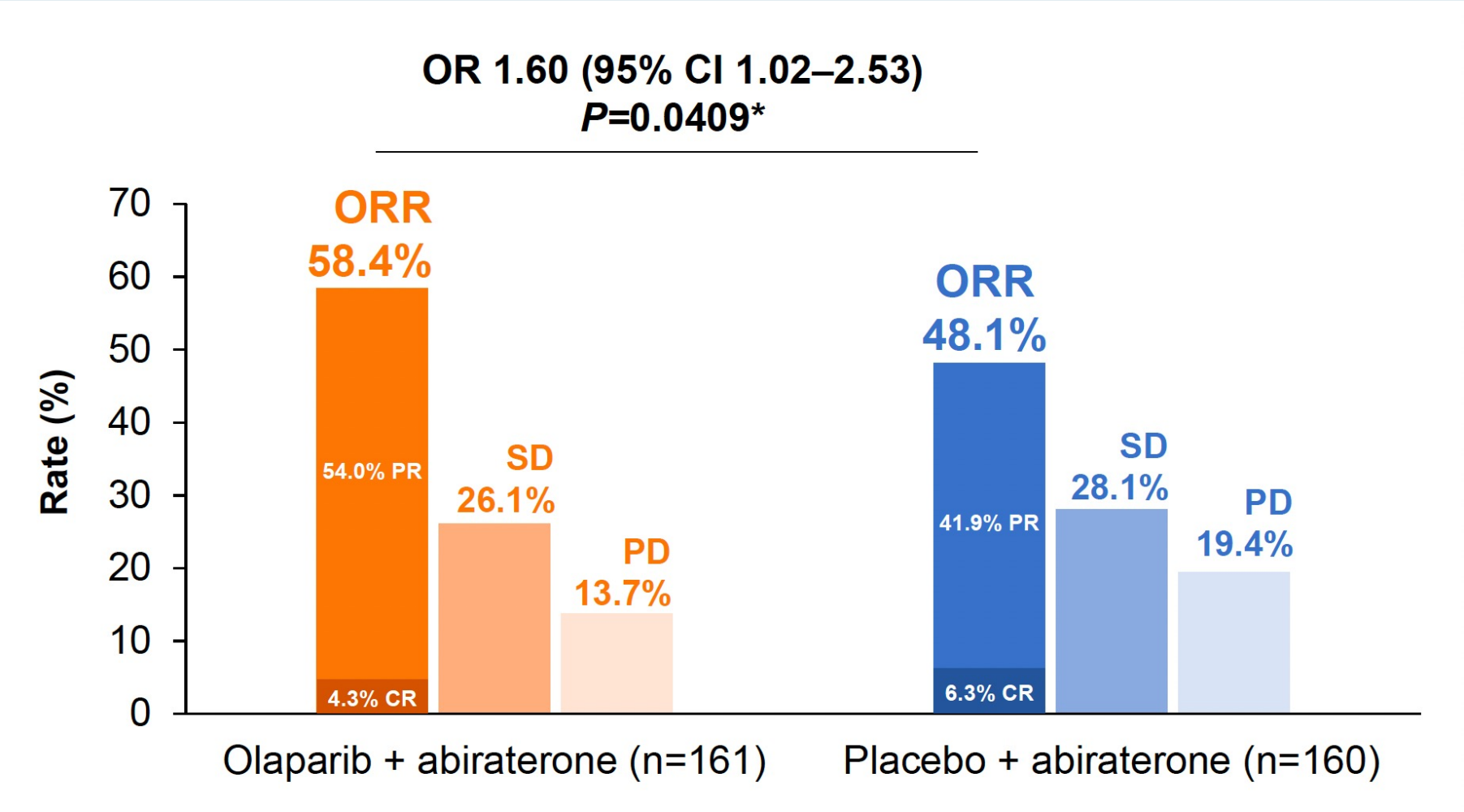
PROpel: Subgroup Analysis of rPFS

	Number of patients, n	Median rPFS, months		HR (95% CI)
All patients	796	24.8	16.6	**0.66 (0.54–0.81)**
Age at randomization				
<65	227	NR	16.4	**0.51 (0.35–0.75)**
≥65	569	22.0	16.7	**0.78 (0.62–0.98)**
ECOG performance status at baseline				
0	558	24.9	16.8	**0.67 (0.52–0.85)**
1	236	17.5	14.6	**0.75 (0.53–1.06)**
Site of distant metastases				
Bone only	434	27.6	22.2	**0.73 (0.54–0.98)**
Visceral	105	13.7	10.9	**0.62 (0.39–0.99)**
Other	257	20.5	13.7	**0.62 (0.44–0.85)**
Docetaxel treatment at mHSPC stage				
Yes	189	27.6	13.8	**0.61 (0.40–0.92)**
No	607	24.8	16.8	**0.71 (0.56–0.89)**
Baseline PSA				
Below median baseline PSA	396	25.2	22.0	**0.75 (0.55–1.02)**
Above or equal to median baseline PSA	397	18.5	13.8	**0.63 (0.48–0.82)**
HRRm status*				
HRRm	226	NR	13.9	**0.50 (0.34–0.73)**
Non-HRRm	552	24.1	19.0	**0.76 (0.60–0.97)**



Saad F et al. Genitourinary Cancers Symposium 2022;Abstract 11.

PROpel: Overall Response Rate (Patients with Measurable Disease)



Saad F et al. Genitourinary Cancers Symposium 2022;Abstract 11.

PROpel: Overall Safety Profile

n (%)	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Any AE	387 (97.2)	376 (94.9)
Any AE CTCAE Grade ≥3	188 (47.2)	152 (38.4)
Death due to an AE	**16 (4.0)**	**17 (4.3)**
Any AE leading to:		
Dose interruption of **olaparib/placebo**	178 (44.7)	100 (25.3)
Dose reduction of **olaparib/placebo**	80 (20.1)	22 (5.6)
Discontinuation of olaparib/placebo	**55 (13.8)**	**31 (7.8)**
Discontinuation of abiraterone	**34 (8.5)**	**35 (8.8)**

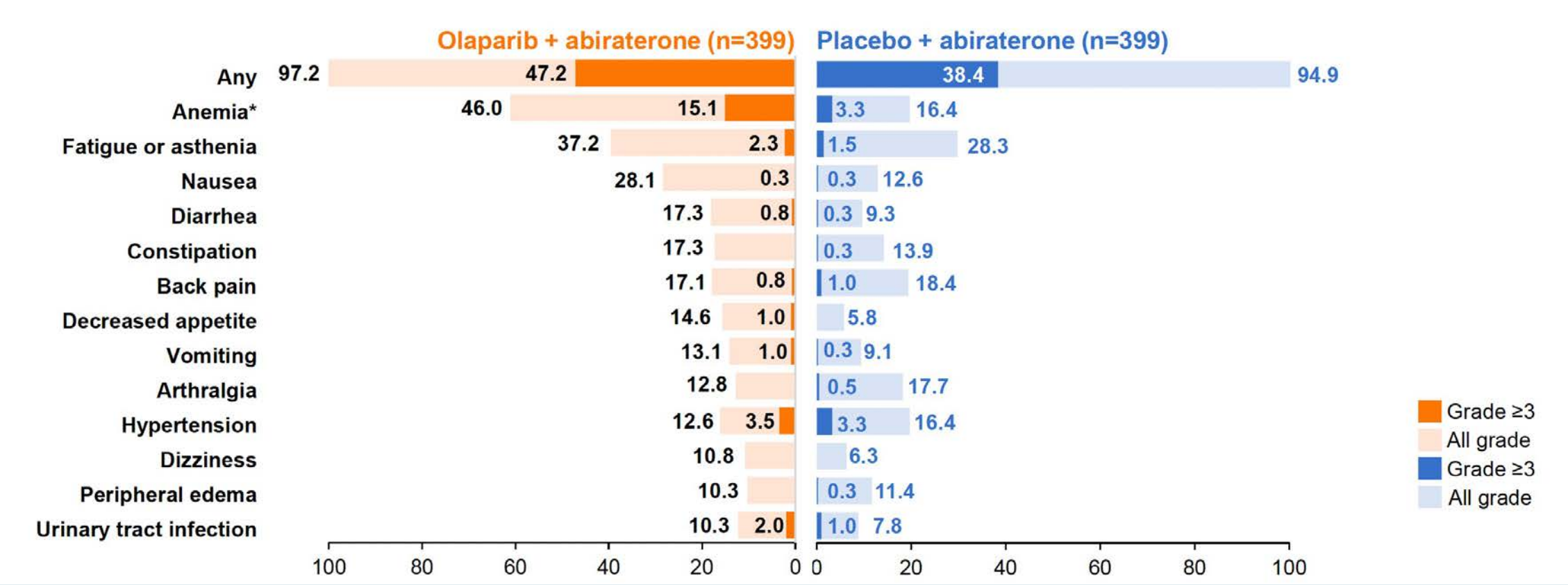
AEs of special interest for olaparib

- No MDS/AML reported
- Incidence of new primary malignancies and pneumonitis were balanced between treatment arms

CTCAE = Common Terminology Criteria for Adverse Events

Saad F et al. Genitourinary Cancers Symposium 2022;Abstract 11.

PROpel: Most Common Adverse Events



Saad F et al. Genitourinary Cancers Symposium 2022;Abstract 11.

PROpel: Cardiac and Thromboembolic Adverse Events

- Cardiac failure and arterial thromboembolic events were balanced between the two arms
- Numerically higher venous thromboembolic events were reported for olaparib + abiraterone
  - Pulmonary embolism was the most commonly reported venous thromboembolic event
  - Pulmonary embolism events were mostly incidental finding by CT scans and did not lead to discontinuation of olaparib or abiraterone

n (%)	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Cardiac failure SMQ	6 (1.5)	5 (1.3)
Embolic and thrombotic events, arterial SMQ	8 (2.0)	10 (2.5)
Embolic and thrombotic events, venous SMQ	29 (7.3)	13 (3.3)
Pulmonary embolism	26 (6.5)	7 (1.8)

Saad F et al. Genitourinary Cancers Symposium 2022;Abstract 11.

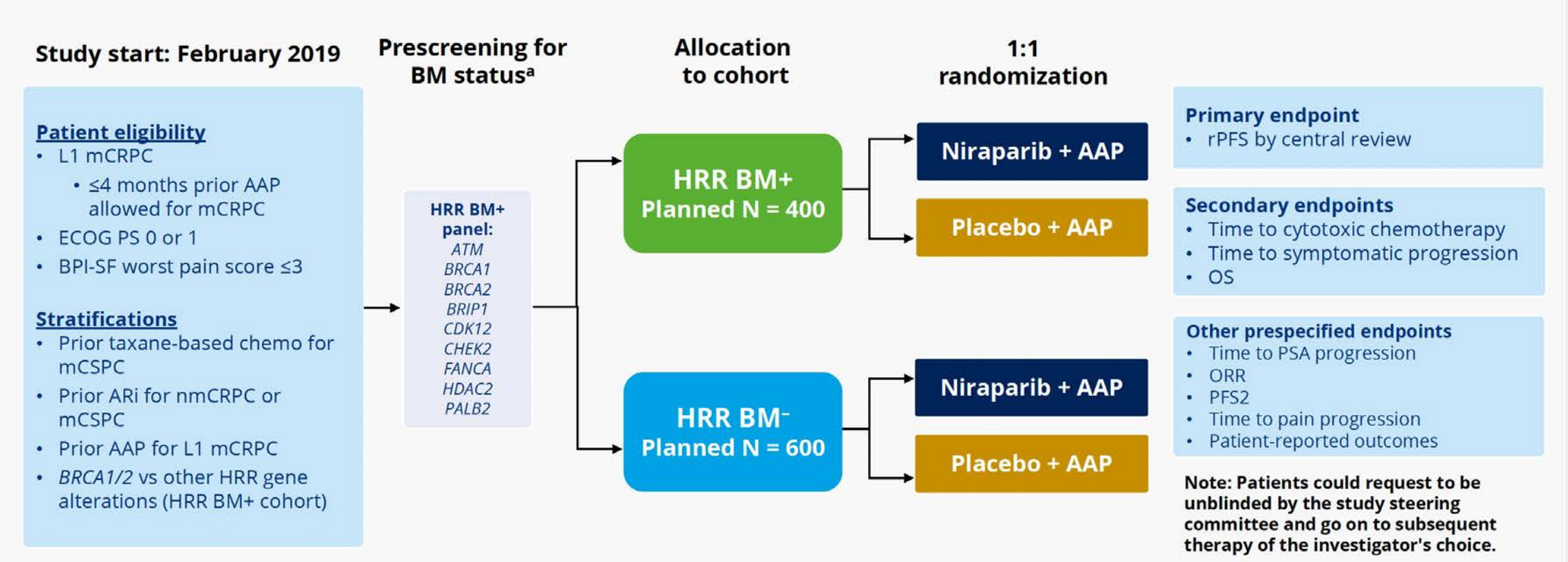
ASCO Genitourinary Cancers Symposium 2022;Abstract 12

Phase 3 MAGNITUDE study: First results of niraparib (NIRA) with abiraterone acetate and prednisone (AAP) as first-line therapy in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) with and without homologous recombination repair (HRR) gene alterations

Kim N. Chi,[1] Dana E. Rathkopf,[2] Matthew R. Smith,[3] Eleni Efstathiou,[4] Gerhardt Attard,[5] David Olmos,[6] Ji Youl Lee,[7] Eric J. Small,[8] Andrea J. Pereira de Santana Gomes,[9] Guilhem Roubaud,[10] Marniza Saad,[11] Bogdan Zurawski,[12] Valerii Sakalo,[13] Gary E. Mason,[14] Adam del Corral,[15] George Wang,[14] Daphne Wu,[16] Brooke Diorio,[17] Angela Lopez-Gitlitz,[16] Shahneen Sandhu[18]

[1]University of British Columbia, BC Cancer – Vancouver Center, Vancouver, BC, Canada; [2]Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine, New York, NY, USA; [3]Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA; [4]Houston Methodist Cancer Center, Houston, TX, USA; [5]University College London, London, UK; [6]Department of Medical Oncology, Hospital Universitario 12 de Octubre, Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Madrid, Spain; [7]Department of Urology Cancer Center, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea; [8]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA; [9]Liga Norte Riograndense Contra o Câncer, Natal, Brazil; [10]Department of Medical Oncology, Institut Bergonié, Bordeaux, France; [11]Department of Clinical Oncology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; [12]Department of Outpatient Chemotherapy, Professor Franciszek Lukaszczyk Oncology Center, Bydgoszcz, Poland; [13]Institute of Urology named after Academician OF Vozianov of NAMS of Ukraine, Kyiv, Ukraine; [14]Janssen Research & Development, Spring House, PA, USA; [15]Janssen Research & Development, Bridgewater, NJ, USA; [16]Janssen Research & Development, Los Angeles, CA, USA; [17]Janssen Research & Development, Titusville, NJ, USA; [18]Peter MacCallum Cancer Center and the University of Melbourne, Melbourne, Australia

MAGNITUDE Phase III Study Design

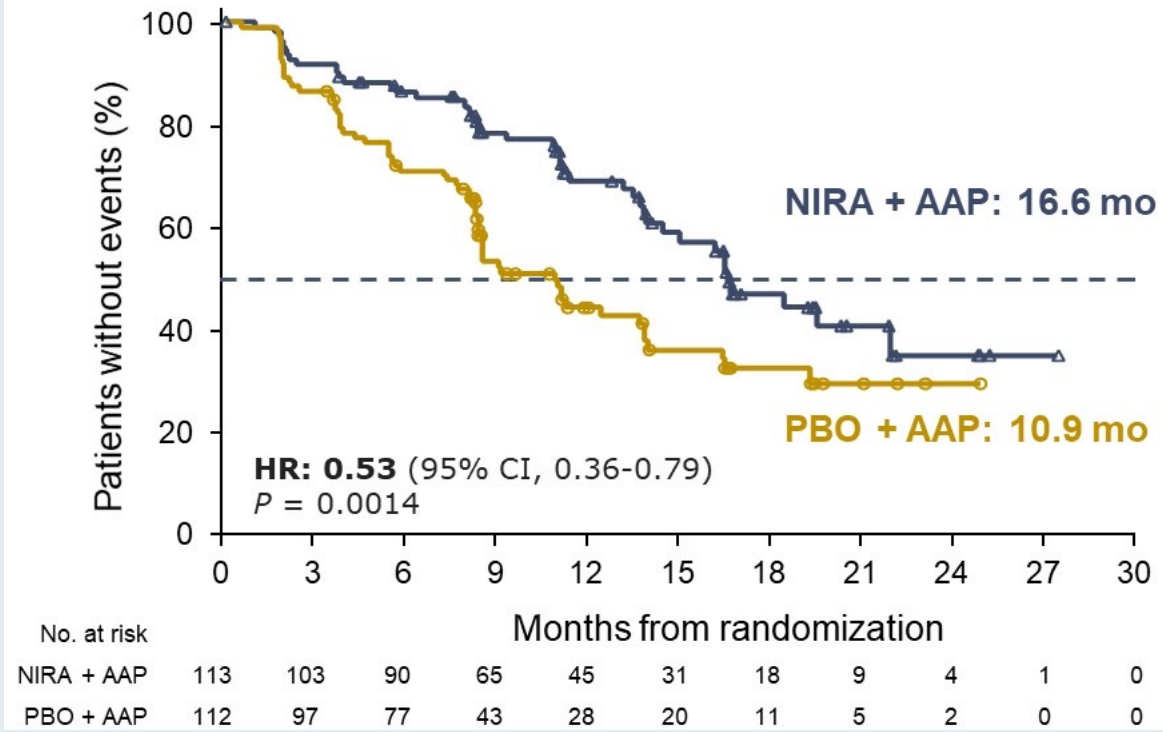


Chi KN et al. Genitourinary Cancers Symposium 2022;Abstract 12.

MAGNITUDE: BRCA1/2 Mutations — Primary Endpoint

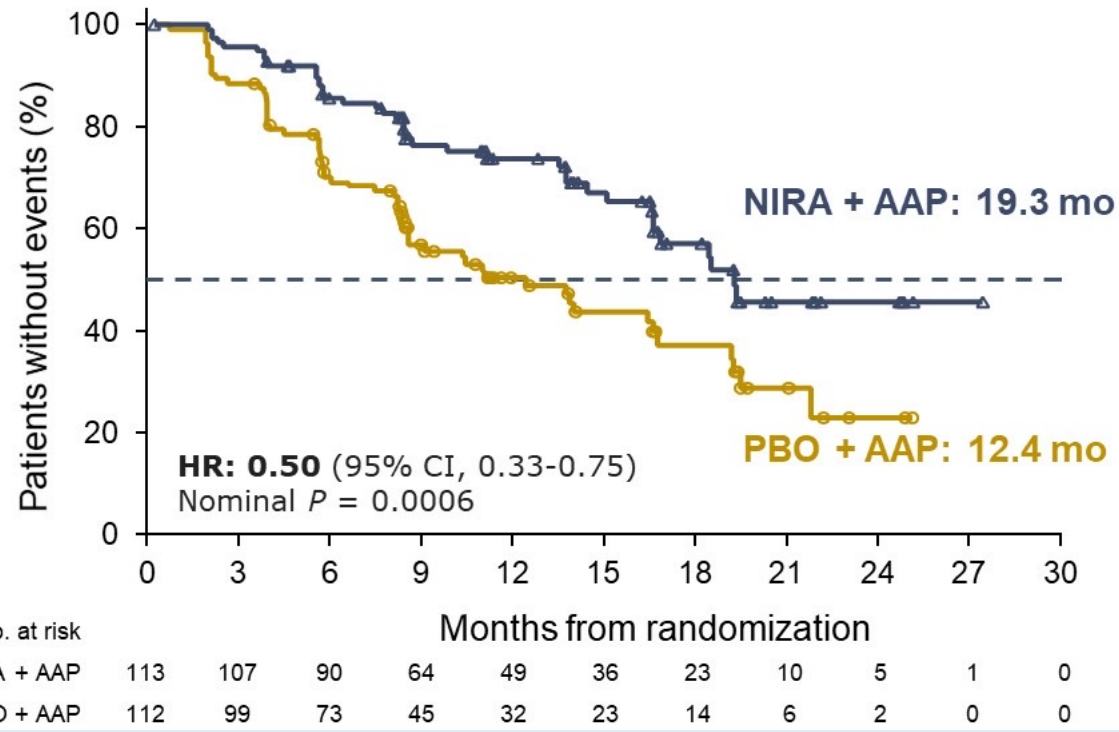
Niraparib with Abiraterone Acetate Significantly Reduced the Risk of Disease Progression or Death by 47% in mCRPC

rPFS assessed by central review



No. at risk											
NIRA + AAP	113	103	90	65	45	31	18	9	4	1	0
PBO + AAP	112	97	77	43	28	20	11	5	2	0	0

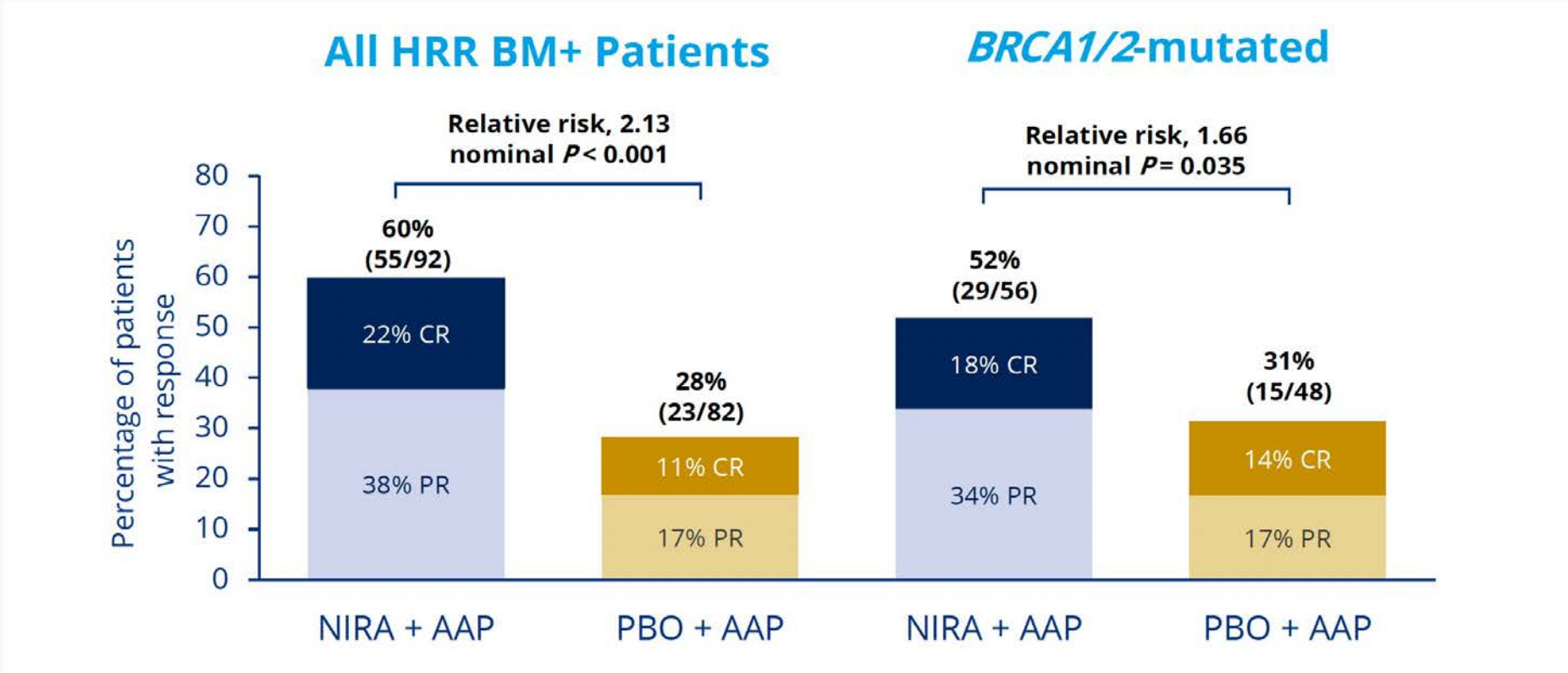
rPFS assessed by investigator



No. at risk											
NIRA + AAP	113	107	90	64	49	36	23	10	5	1	0
PBO + AAP	112	99	73	45	32	23	14	6	2	0	0

Chi KN et al. Genitourinary Cancers Symposium 2022;Abstract 12.

MAGNITUDE: Overall Response Rate



NIRA + AAP nearly doubles ORR rate and provides deeper response in patients with measurable disease

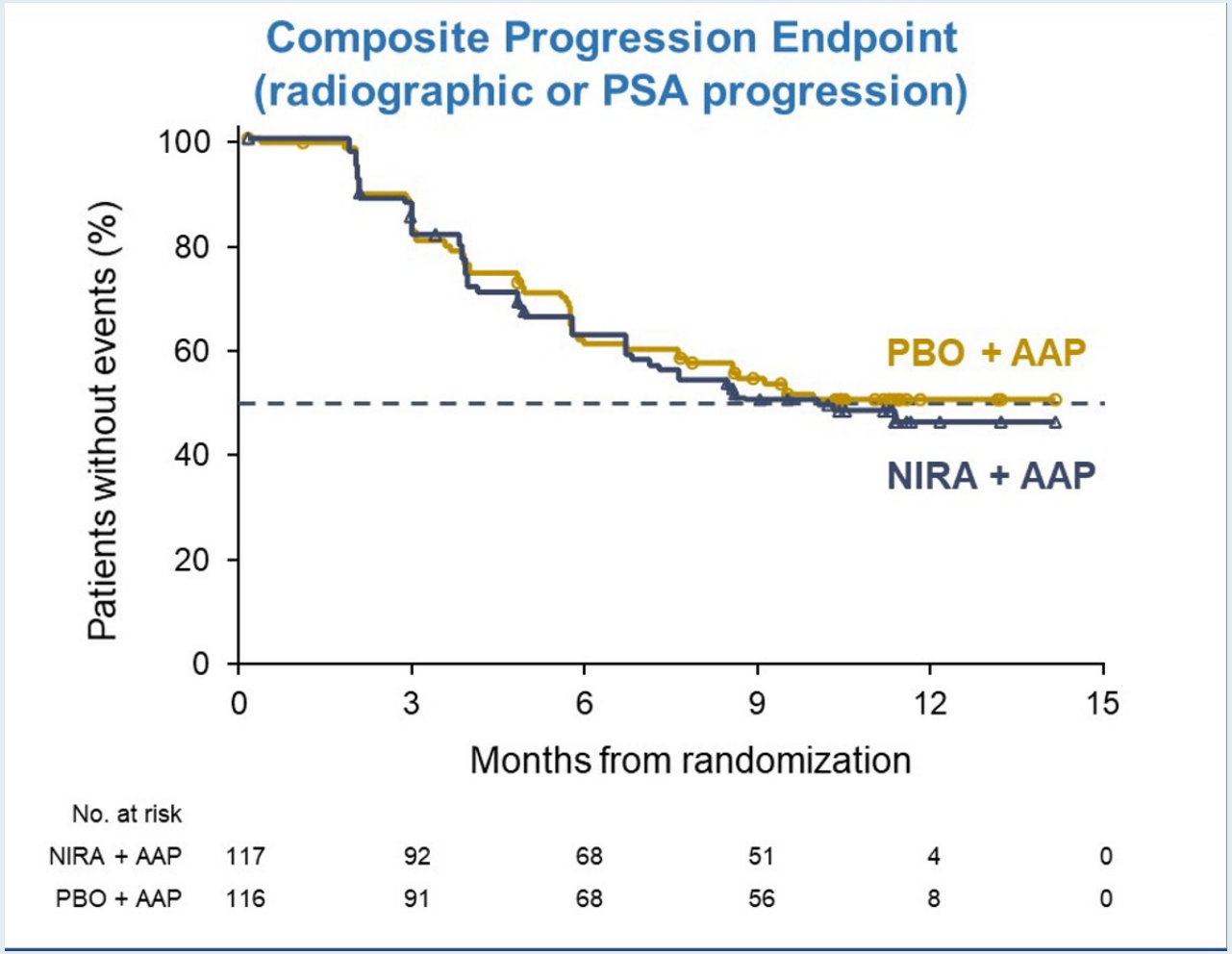
Chi KN et al. Genitourinary Cancers Symposium 2022;Abstract 12.

MAGNITUDE HRR Biomarker-Positive: Treatment-Emergent Adverse Events

Treatment-emergent adverse events occurring at >20% in the NIRA arm or otherwise of clinical interest, n (%)		NIRA + AAP, n = 212		PBO + AAP, n = 211	
		All grades	Grade ≥3	All grades	Grade ≥3
Hematologic	Anemia	98 (46.2)	63 (29.7)	43 (20.4)	16 (7.6)
	Thrombocytopenia	45 (21.2)	14 (6.6)	18 (8.5)	5 (2.4)
	Neutropenia	29 (13.7)	14 (6.6)	12 (5.7)	3 (1.4)
	Acute myeloid leukemia/ Myelodysplastic syndrome	0	0	1 (0.5)	1 (0.5)
Cardiovascular	Hypertension	67 (31.6)	33 (15.6)	47 (22.3)	30 (14.2)
	Arrhythmia	27 (12.7)	6 (2.8)[a]	12 (5.7)	3 (1.4)
	Cardiac failure	4 (1.9)	3 (1.4)[a]	4 (1.9)	1 (0.5)
	Ischemic heart disease	4 (1.9)	4 (1.9)	8 (3.8)	6 (2.8)[b]
General disorders	Fatigue	56 (26.4)	7 (3.3)	35 (16.6)	9 (4.3)
Gastrointestinal	Constipation	65 (30.7)	–	29 (13.7)	–
	Nausea	50 (23.6)	1 (0.5)	29 (13.7)	0
Hepatotoxicity		25 (11.8)	4 (1.9)	26 (12.3)	10 (4.7)
Cerebrovascular disorders		6 (2.8)	2 (0.9)	2 (0.9)	1 (0.5)[a]

Chi KN et al. Genitourinary Cancers Symposium 2022;Abstract 12.

MAGNITUDE HRR BM-: Prespecified Early Futility Analysis
No Benefit of NIRA + AAP in HRR BM- Patients



- Composite endpoint[a] (N= 222)
  HR = 1.09[b] (95% CI 0.75-1.59)
  [futility was defined as ≥1
- Additional grade 3/4 toxicity was observed using NIRA + AAP vs PBO + AAP
- With added toxicity and no added efficacy in patients with HRR BM- mCRPC, the IDMC recommend stopping enrollment in this cohort
- [b]Breakdown of composite events
  83 PSA events (HR = 1.03, 95% CI 0.67-1.59)
  65 rPFS events (HR = 1.03, 95% CI 0.63-1.67)

[a]rPFS or PSA progression, whichever occurred first

Select Ongoing Phase III Trials of PARP Inhibitor Combined with Secondary Hormonal Therapy

Study	No. of patients	Randomization	Est primary completion
Metastatic castration resistant prostate cancer (mCRPC)			
TALAPRO-2	1060	• Talazoparib + enzalutamide • Placebo + enzalutamide	Nov 2024
CASPAR	1002	• Rucaparib + enzalutamide +/- ADT • Placebo + enzalutamide +/- ADT	Sep 2026
Metastatic hormone-sensitive prostate cancer (mHSPC)			
TALAPRO-3	550	• Talazoparib + enzalutamide • Placebo + enzalutamide	Dec 2024
AMPLITUDE	788	• Niraparib + abiraterone • Placebo + abiraterone	Nov 2024

www.clinicaltrials.gov. Accessed May 2022.

Appendix of Key Data Sets

STAMPEDE: Noteworthy Adverse Event Differences

Event	Control: Abiraterone trial (n = 455)		Control: Abiraterone and enzalutamide trial (n = 533)		Combination: Abiraterone trial (n = 451)		Combination: Abiraterone and enzalutamide trial (n = 513)	
	All grades	Grade 3-4	All grades	Grade 3-4	All grades	Grade 3-4	All grades	Grade 3-4
Hypertension	15%	1%	16%	2%	29%	5%	51%	14%
ALT increased	11%	0	15%	1%	23%	5%	41%	13%
Grade 5 AEs	0		0		3*		4**	

*** Three Grade 5 AEs: rectal adenocarcinoma, pulmonary hemorrhage, respiratory disorder**

**** Four Grade 5 AEs: 2 septic shock, 2 sudden death**

Attard G et al. *Lancet* 2022;399(10323):447-60.

Select Ongoing Phase III Trials of Secondary Hormonal Therapy for High-Risk Localized or Locally Advanced Prostate Cancer

	No. of patients	Setting	Randomization
DASL-HiCaP	1,100	Localized, very high risk, undergoing definitive RT	• Darolutamide + LHRH analogue + EBRT • Placebo + LHRH analogue + EBRT
ATLAS	1,503	Localized, high risk, receiving primary RT	• Apalutamide + bicalutamide + GnRH agonist + RT • Placebo + bicalutamide + GnRH agonist + RT
PROTEUS	2,400	Localized, high risk, candidates for prostatectomy	• Apalutamide + ADT • Placebo + ADT
EMBARK	1,068	High-risk M0 after definitive therapy	• Enzalutamide + leuprolide • Enzalutamide • Placebo + leuprolide
ERADICATE	810	High-risk M0 after prostatectomy	• ADT • Darolutamide + ADT

RT = radiation therapy; EBRT = external beam RT

Clinicaltrials.gov. Accessed May 18, 2022

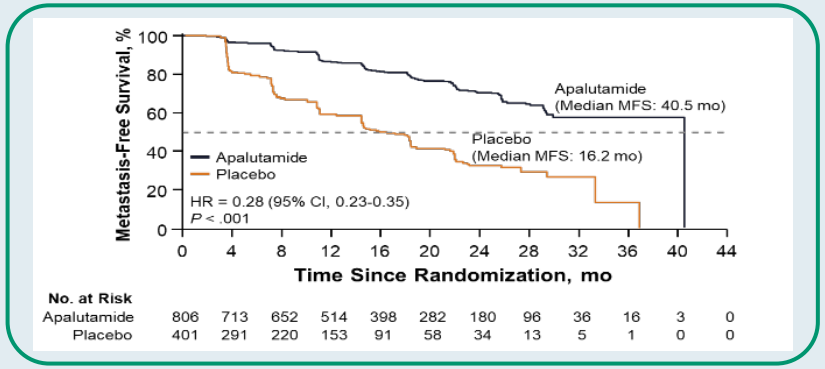
FDA Approvals of Next-Generation Antiandrogens for Nonmetastatic CRPC

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/

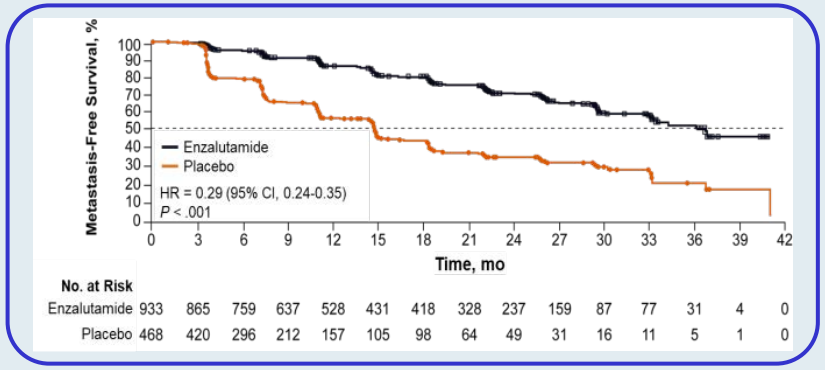
Primary Endpoint: Metastasis-Free Survival (MFS) in Nonmetastatic CRPC

SPARTAN[1]
Apalutamide



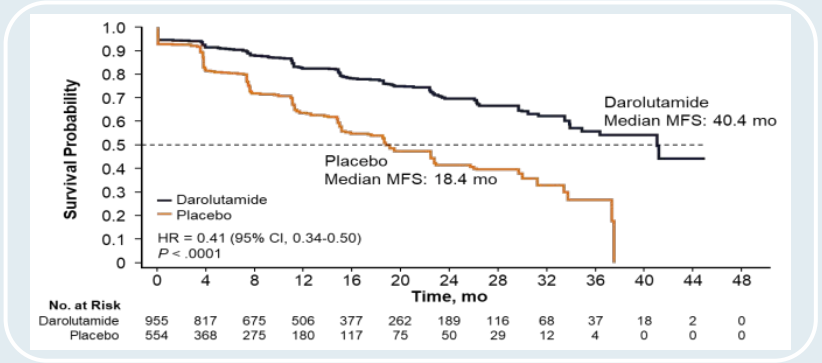
- 72% reduction of distant progression or death
- Median MFS: APA 40.5 vs PBO 16.2 months
- 24-month MFS benefit

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

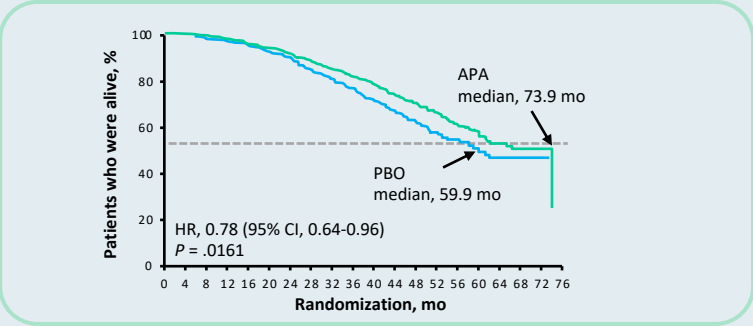
PBO = placebo

1. Smith MR et al. *NEJM* 2018;378:1408-18. 2. Hussain M et al. *NEJM* 2018;378:2465-74. 3. Fizazi K et al. *NEJM* 2019;380:1235-46.

RTP RESEARCH TO PRACTICE

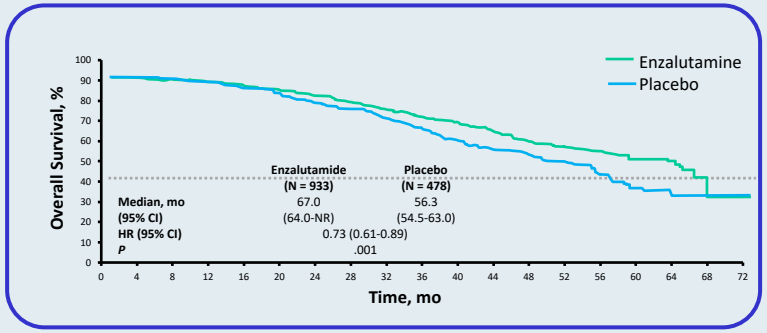
Secondary Endpoint: Overall Survival (OS) in Nonmetastatic CRPC

SPARTAN[1]
Apalutamide



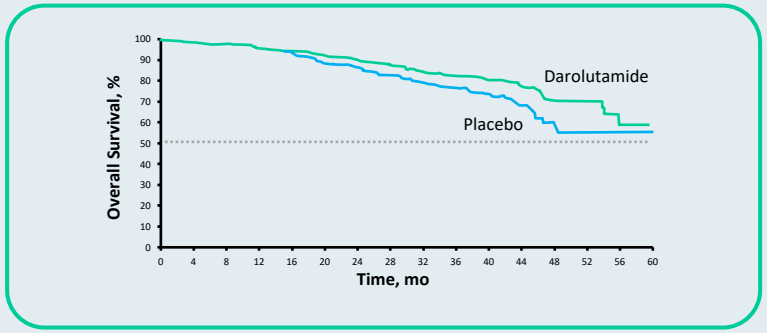
- 22% reduction in risk of death
- Median OS
  - 73.9 mo vs 59.9 mo
  - **HR = 0.78; *p* = 0.016**

PROSPER[2]
Enzalutamide



- 27% reduction in risk of death
- Median OS
  - 67.0 mo vs 56.3 mo
  - **HR = 0.73; *p* = 0.001**

ARAMIS[3]
Darolutamide



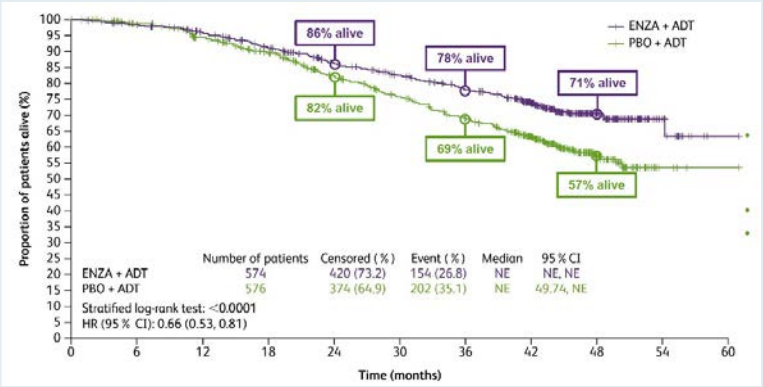
- 31% reduction in risk of death
- Median OS
  - **HR = 0.69; *p* = 0.003**

1. Smith MR et al. *Eur Urol* 2020;79:150-8. 2. Sternberg CN et al. *NEJM* 2020;382:2197-206. 3. Fizazi K et al. *NEJM* 2020;383:1040-9.

RTP RESEARCH TO PRACTICE

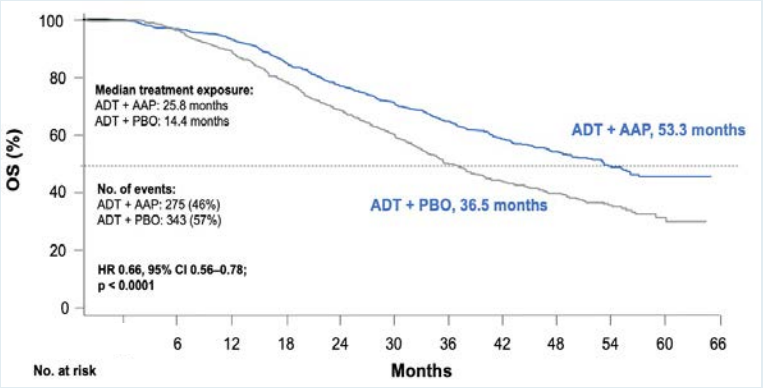
Final OS Analyses: Enzalutamide, Abiraterone and Apalutamide for mHSPC

ARCHES[1]
Enzalutamide + ADT



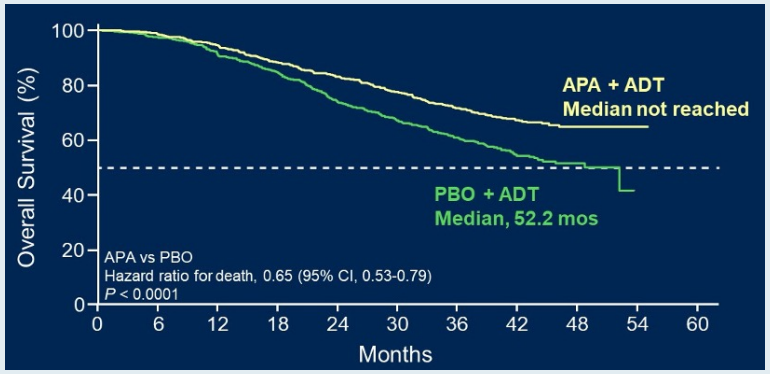
- 34% reduction in risk of death
- Median OS
  - **Not reached vs not reached**
  - **HR = 0.66; *p* < 0.001**

LATITUDE[2]
Abiraterone + ADT



- 34% reduction in risk of death
- Median OS
  - 53.3 mo vs 36.5 mo
  - **HR = 0.66; *p* < 0.0001**

TITAN[3]
Apalutamide + ADT



- 35% reduction in risk of death
- Median OS
  - Not reached vs 52.2 mo
  - **HR = 0.65; *p* < 0.0001**

1. Armstrong AJ et al. *J Clin Oncol* 2022;40(15):1616-22. 2. Fizazi K et al. GU Cancers Symposium 2019;Abstract 141. 3. Chi KN et al. GU Cancers Symposium 2021;Abstract 11.

ARASENS: Grade 3-4 Adverse Events

Grade 3–4 AEs in ≥2% of darolutamide-treated patients, n (%)	Darolutamide + ADT + docetaxel (n=652)	Placebo + ADT + docetaxel (n=650)
Any AE	431 (66.1)	413 (63.5)
Neutropenia*	220 (33.7)	222 (34.2)
Febrile neutropenia	51 (7.8)	48 (7.4)
Hypertension	42 (6.4)	21 (3.2)
Anemia	31 (4.8)	33 (5.1)
Pneumonia	21 (3.2)	20 (3.1)
Hyperglycemia	18 (2.8)	24 (3.7)
Increased alanine aminotransferase	18 (2.8)	11 (1.7)
Increased aspartate aminotransferase	17 (2.6)	7 (1.1)
Increased weight	14 (2.1)	8 (1.2)
Urinary tract infection	13 (2.0)	12 (1.8)

Smith MR et al. Genitourinary Cancers Symposium 2022;Abstract 13.

ARASENS: Adverse Events of Special Interest with Androgen Receptor (AR) Pathway Inhibitors

AEs associated with AR pathway inhibitor therapy	Darolutamide + ADT + docetaxel (n=652)		Placebo + ADT + docetaxel (n=650)	
	Patients, n (%)	EAIR/100 PY*	Patients, n (%)	EAIR/100 PY*
Fatigue	216 (33.1)	12.5	214 (32.9)	17.8
Bone fracture	49 (7.5)	2.8	33 (5.1)	2.7
Falls	43 (6.6)	2.5	30 (4.6)	2.5
Rash†	108 (16.6)	6.2	88 (13.5)	7.3
Diabetes mellitus and hyperglycemia‡	99 (15.2)	5.7	93 (14.3)	7.7
Weight decreased	22 (3.4)	1.3	35 (5.4)	2.9
Vasodilatation and flushing	133 (20.4)	7.7	141 (21.7)	11.7
Breast disorders/gynecomastia‡	21 (3.2)	1.2	10 (1.5)	0.8
Hypertension‡	89 (13.7)	5.1	60 (9.2)	5.0
Cardiac disorder‡	71 (10.9)	4.1	76 (11.7)	6.3
Cerebral ischemia	8 (1.2)	0.5	8 (1.2)	0.7
Mental impairment disorder‡	23 (3.5)	1.3	15 (2.3)	1.2
Depressed mood disorder‡	21 (3.2)	1.2	24 (3.7)	2.0
Seizure	4 (0.6)	0.2	1 (0.2)	0.1

Smith MR et al. Genitourinary Cancers Symposium 2022;Abstract 13.

PEACE-1: Study Design

Key Eligibility Criteria

De novo mCSPC

Distant metastatic disease by ≥ 1 lesion on bone scan and/or CT scan

ECOG PS 0 -2

On-Study Requirement

Continuous ADT

Permitted

ADT ≤ 3 months

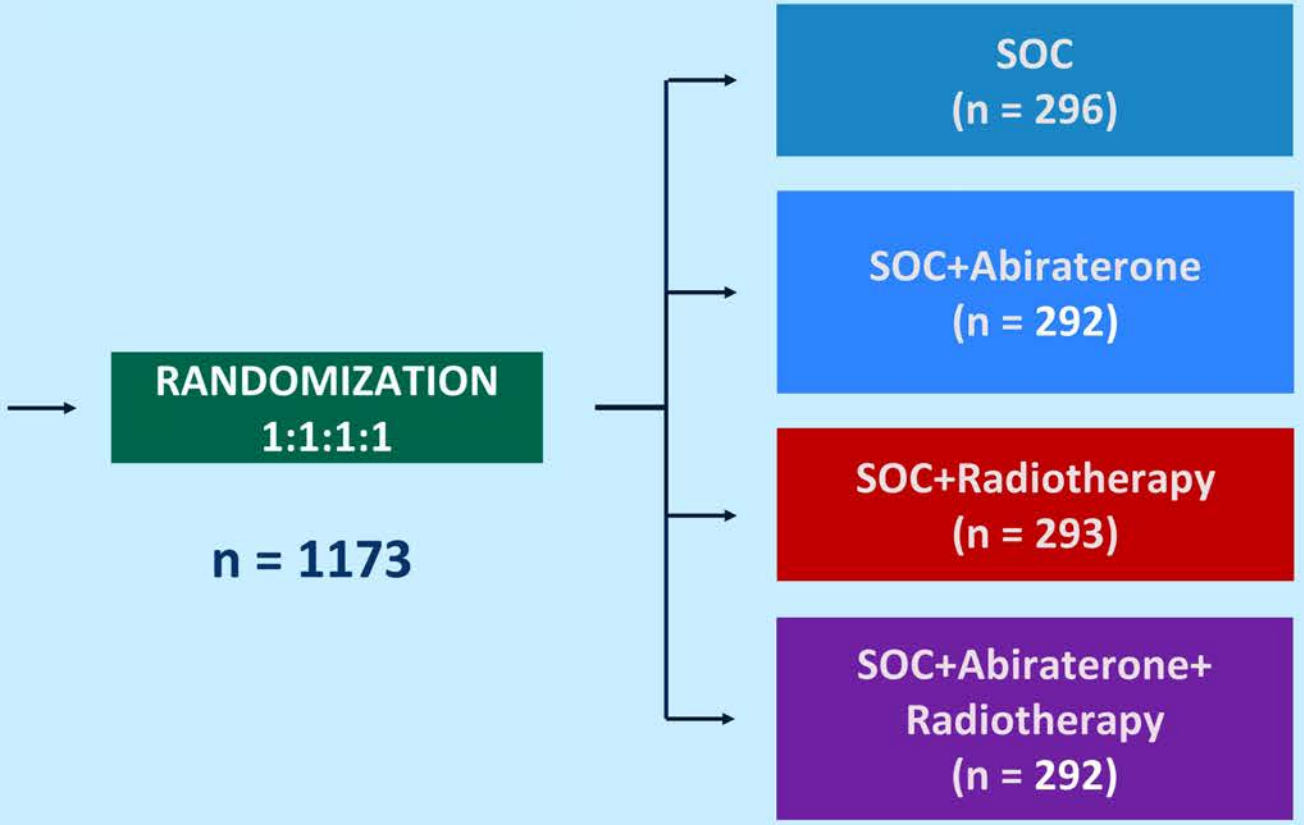
Stratification

ECOG PS (0 vs 1-2)

Metastatic sites (LN vs bone vs visceral)

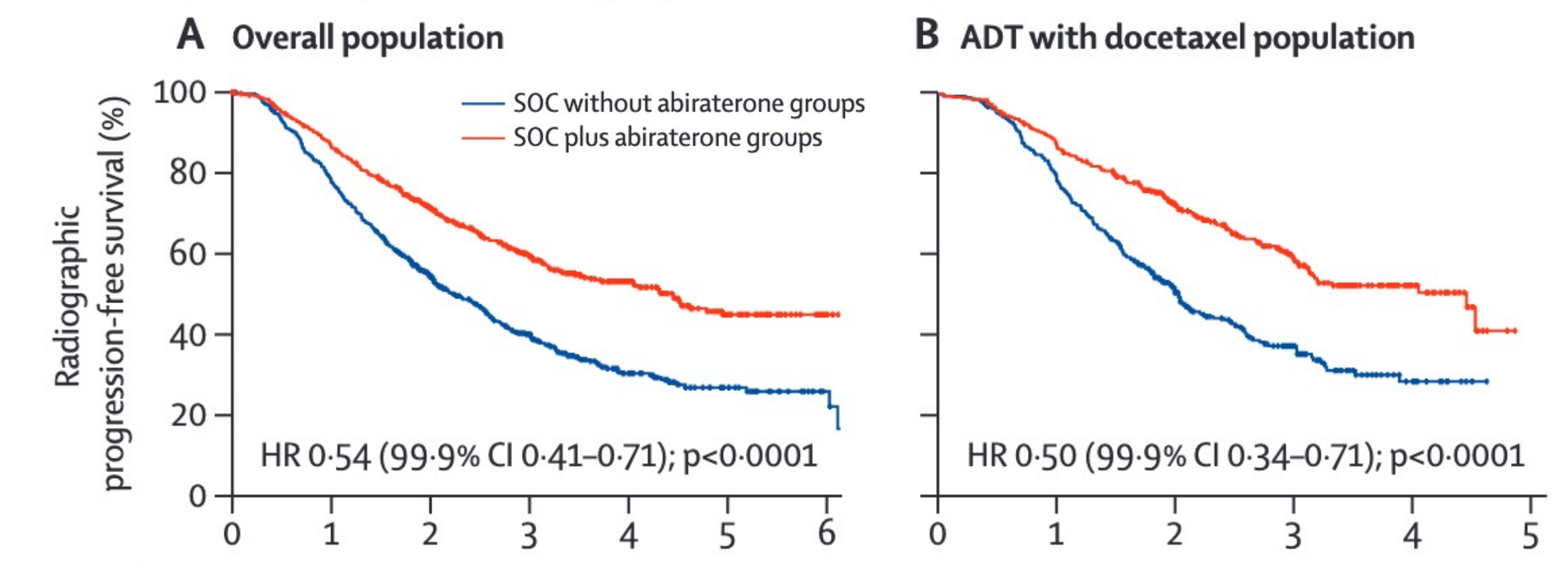
Type of castration (orchidectomy vs LHRH agonist vs LHRH antagonist)

Docetaxel (yes vs no)



Fizazi K et al. ASCO 2021;Abstract 5000.

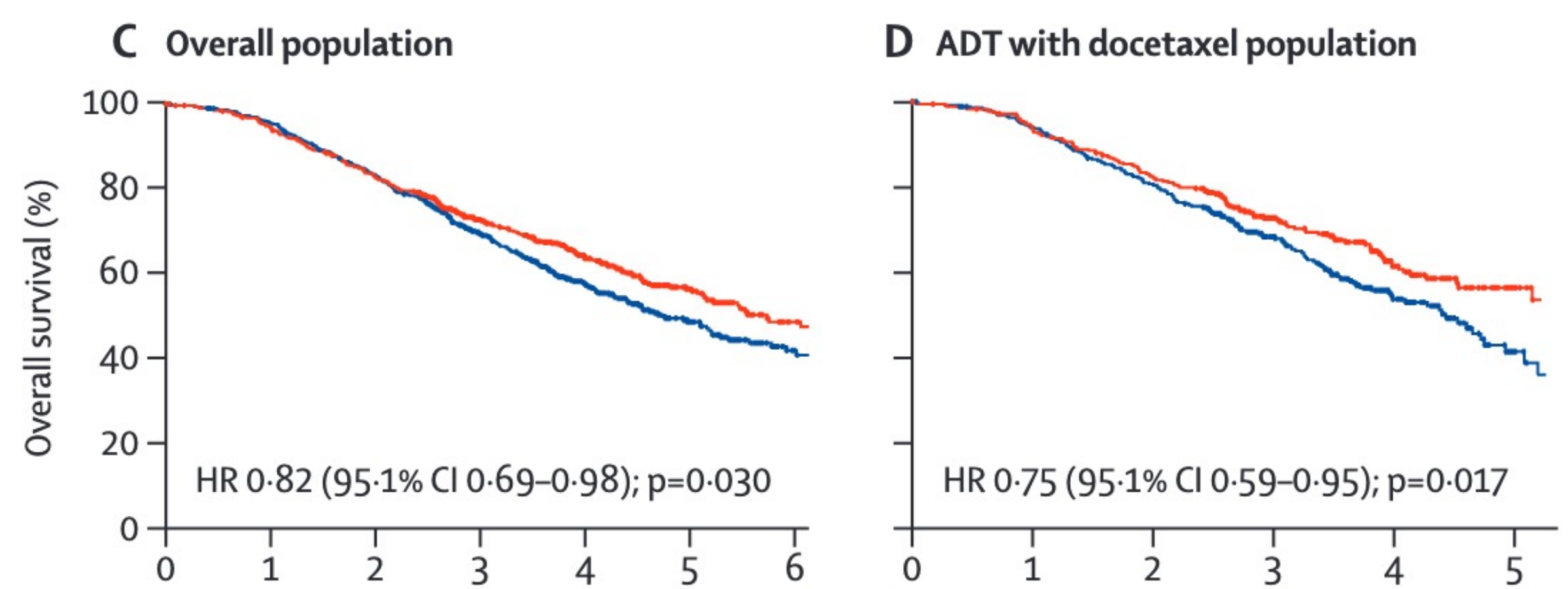
PEACE-1 Coprimary Endpoint: Radiographic Progression-Free Survival



Fizazi K et al. *Lancet* 2022;399:1695-07.

RTP RESEARCH TO PRACTICE

PEACE-1 Coprimary Endpoint: Overall Survival



Fizazi K et al. *Lancet* 2022;399:1695-07.

RTP RESEARCH TO PRACTICE

PEACE-1: Efficacy Outcomes in the ITT Population

	Patients assessed, n		Median, years		Median difference, years	Hazard ratio	p value
	SOC with abiraterone groups	SOC without abiraterone groups	SOC with abiraterone groups	SOC without abiraterone groups			
Primary outcomes in the overall population							
Overall survival	583	589	5·7	4·7	0·9 (95·1% CI 0·0–2·0)	0·82 (95·1% CI 0·69–0·98)	0·030
Radiographic progression-free survival	583	589	4·5	2·2	2·1 (99·9% CI 0·7–2·9)	0·54 (99·9% CI 0·41–0·71)	<0·0001
Secondary outcomes in the overall population							
CRPC-free survival	583	589	3·8	1·5	2·3 (95% CI 1·6–3·0)	0·40 (95% CI 0·35–0·47)	<0·0001
Prostate-cancer-specific survival	583	589	NR	5·8	NA	0·75 (95% CI 0·61–0·91)	0·0038
Primary outcomes in the ADT with docetaxel population							
Overall survival	355	355	NR	4·4	NA	0·75 (95·1% CI 0·59–0·95)	0·017
Radiographic progression-free survival	355	355	4·5	2·0	2·2 (99·9% CI 0·6–2·8)	0·50 (99·9% CI 0·34–0·71)	<0·0001
Secondary outcomes in the ADT with docetaxel population							
Overall survival in patients with low-volume metastatic burden	131	123	NR	NR	NA	0·83 (95·1% CI 0·50–1·39)	0·66
Overall survival in patients with high-volume metastatic burden	224	232	5·1	3·5	1·1 (95·1% CI 0·2–1·9)	0·72 (95·1% CI 0·55–0·95)	0·019

Fizazi K et al. *Lancet* 2022;399:1695-07.

PEACE-1: Adverse Events in the Safety Population

	ADT with docetaxel population		ADT without docetaxel population	
	SOC plus abiraterone groups (with or without radiotherapy; n=347)	SOC without abiraterone groups (with or without radiotherapy; n=350)	SOC plus abiraterone groups (with or without radiotherapy; n=226)	SOC without abiraterone groups (with or without radiotherapy; n=237)
Any adverse events	346 (100%)	349 (100%)	226 (100%)	233 (99%)
Severe (grade ≥3) adverse events	217 (63%)	181 (52%)	149 (66%)	97 (41%)
Fatal (grade 5) adverse events	7 (2%)	3 (1%)	8 (4%)	5 (2%)
Frequent severe adverse events				
Hypertension	76 (22%)	45 (13%)	66 (29%)	38 (16%)
Neutropenia	34 (10%)	32 (9%)	0	0
Hepatotoxicity	20 (6%)	2 (1%)	14 (6%)	3 (1%)
Febrile neutropenia	18 (5%)	19 (5%)	2 (1%)	1 (<1%)
Gamma-glutamyl transferase increase	17 (5%)	14 (4%)	6 (3%)	4 (2%)
Erectile dysfunction	7 (2%)	5 (1%)	12 (5%)	13 (5%)
Blood alkaline phosphatase increase	15 (4%)	12 (3%)	6 (3%)	13 (5%)
Other severe adverse events				
Fatigue	10 (3%)	15 (4%)	3 (1%)	0
Peripheral neuropathy	4 (1%)	6 (2%)	1 (<1%)	0

Fizazi K et al. *Lancet* 2022;399:1695-07.

RTP RESEARCH TO PRACTICE

Summary of Key Clinical Trials in mHSPC

Trial name	Experimental arm	Comparator arm	rPFS	OS
CHAARTED[1]	Docetaxel	ADT	32 vs 19 mo	HR: 0.72; 57.6 vs 47.2 mo
STAMPEDE-C[2]	Docetaxel	ADT	44 vs 34.8 mo, HR: 0.61	HR: 0.81; 81 vs 71 mo
LATITUDE[3]	Abiraterone	ADT	NR	HR: 0.66; 53.3 vs 36.5 mo
STAMPEDE-G[4]	Abiraterone	ADT	NR	HR: 0.6; 6.6 vs 3.8 y
ARCHES[5]	Enzalutamide	ADT	HR: 0.39 NR vs 19	HR: 0.66; NR vs NR
ENZAMET[6]	Enzalutamide	ADT + NSAA with docetaxel	HR: 0.34 HR: 0.48	HR: 0.53 HR: 90
TITAN[7]	Apalutamide	ADT	HR: 0.48	HR: 0.67; NR vs 52.2
PEACE-1[8]	Abiraterone	ADT + docetaxel	4.5 vs 2 y HR: 0.50	HR: 0.75
ARASENS[9]	Darolutamide	ADT + docetaxel	NR	HR: 0.68; NR vs 48.9 mo

ADT = androgen deprivation therapy; NSAA = nonsteroidal anti-antigen

1. Sweeney CJ et al. *NEJM* 2015; 2. James ND et al. *Eur Urol* 2015; 3. Fizazi K et al. *Lancet Oncol* 2019; 4. Clarke NW et al. *Ann Oncol* 2019; 5. Armstrong AJ et al. *J Clin Oncol* 2019; 6. Davis ID et al. *NEJM* 2019; 7. Chi KN et al. *NEJM* 2019; 8. Fizazi K et al. *Lancet* 2022; 9. Smith MR et al. *NEJM* 2022.

Updated Overall Survival Outcomes in ENZAMET (ANZUP 1304), an International, Cooperative Group Trial of Enzalutamide in Metastatic Hormone-Sensitive Prostate Cancer (mHSPC)

Davis ID et al.

ASCO 2022;Abstract LBA5004.

Track: Genitourinary Cancer – Prostate, Testicular, and Penile
June 5, 2022, 9:00 AM

N Engl J Med 2019 Dec 26;381(26):2506-2518
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer

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

EUROPEAN UROLOGY 80 (2021) 497–506

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

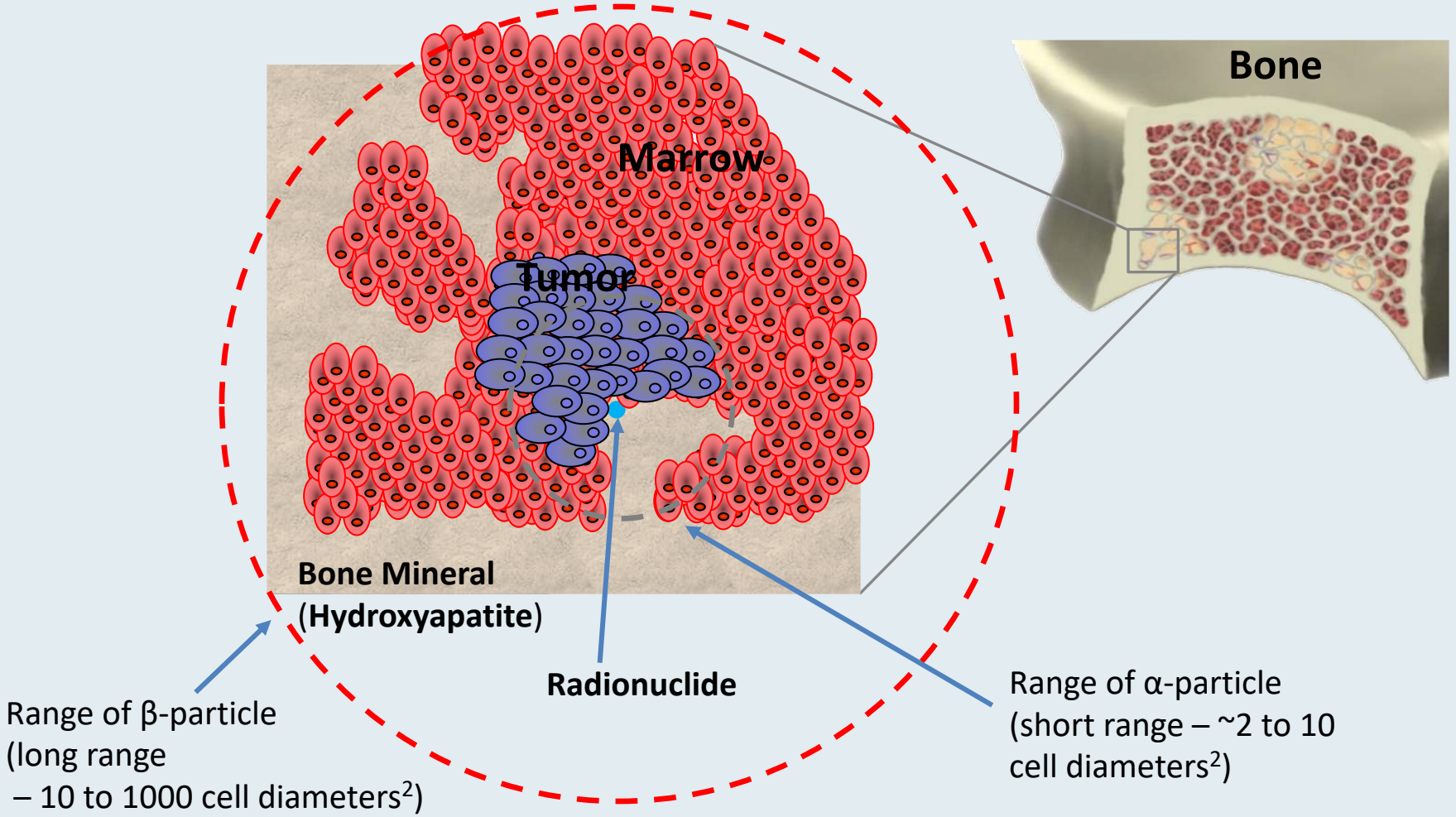
Prostate Cancer

Efficacy and Safety of Cabazitaxel Versus Abiraterone or Enzalutamide in Older Patients with Metastatic Castration-resistant Prostate Cancer in the CARD Study

Cora N. Sternberg[a,], Daniel Castellano[b], Johann de Bono[c], Karim Fizazi[d], Bertrand Tombal[e], Christian Wülfing[f], Gero Kramer[g], Jean-Christophe Eymard[h], Aristotelis Bamias[i], Joan Carles[j], Roberto Iacovelli[k,l], Bohuslav Melichar[m], Ásgerður Sverrisdóttir[n], Christine Theodore[o], Susan Feyerabend[p], Carole Helissey[q], Elizabeth M. Poole[r], Ayse Ozatilgan[r], Christine Geffriaud-Ricouard[s], Ronald de Wit[t]*

Range of an α-Emitting Radiopharmaceutical Compared to a β-Emitter

Short range of α-particles could reduce bone marrow exposure[1]



1. Henriksen G, et al. *Cancer Res* 2002;62:3120–5. **2.** Brechbiel MW. *Dalton Trans* 2007;43:4918-28.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 18, 2013 VOL. 369 NO. 3

Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

C. Parker, S. Nilsson, D. Heinrich, S.I. Helle, J.M. O'Sullivan, S.D. Fossâ, A. Chodacki, P. Wiechno, J. Logue, M. Seke, A. Widmark, D.C. Johannessen, P. Hoskin, D. Bottomley, N.D. James, A. Solberg, I. Syndikus, J. Kliment, S. Wedel, S. Boehmer, M. Dall'Oglio, L. Franzén, R. Coleman, N.J. Vogelzang, C.G. O'Bryan-Tear, K. Staudacher, J. Garcia-Vargas, M. Shan, Ø.S. Bruland, and O. Sartor, for the ALSYMPCA Investigators*

Lancet Oncol 2014;15:738-46

Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: results from a phase 3, double-blind, randomised trial

Oliver Sartor, Robert Coleman, Sten Nilsson, Daniel Heinrich, Svein I Helle, Joe M O'Sullivan, Sophie D Fossâ, Aleš Chodacki, Paweł Wiechno, John Logue, Anders Widmark, Dag Clement Johannessen, Peter Hoskin, Nicholas D James, Arne Solberg, Isabel Syndikus, Nicholas J Vogelzang, C Gillies O'Bryan-Tear, Minghua Shan, Øyvind S Bruland, Christopher Parker

Lancet Oncol 2019;20:408-19

Addition of radium-223 to abiraterone acetate and prednisone or prednisolone in patients with castration-resistant prostate cancer and bone metastases (ERA 223): a randomised, double-blind, placebo-controlled, phase 3 trial

Matthew Smith, Chris Parker, Fred Saad, Kurt Miller, Bertrand Tombal, Quan Sing Ng, Martin Boegemann, Vsevolod Matveev, Josep Maria Piulats, Luis Eduardo Zucca, Oleg Karyakin, Go Kimura, Nobuaki Matsubara, William Carlos Nahas, Franco Nolè, Eli Rosenbaum, Axel Heidenreich, Yoshiyuki Kakehi, Amily Zhang, Heiko Krissel, Michael Teufel, Junwu Shen, Volker Wagner, Celestia Higano

RTP RESEARCH TO PRACTICE

ALSYMPCA AND ERA 223: Summary of Key Outcomes with Radium-223 in mCRPC

	ALSYMPCA			ERA 223		
	R-223 + BSC (n = 614)	BSC (n = 307)	HR (*p*-value)	AAP + R-223 (n = 401)	AAP + placebo (n = 405)	HR (*p*-value)
Skeletal EFS, median	15.6 mo	9.8 mo	0.66 (0.0004)	22.3 mo	26.0 mo	1.12 (0.26)
OS, median	14.9 mo	11.3 mo	0.70 (<0.001)	30.7 mo	33.3 mo	1.2 (0.13)

BSC = best supportive care; AAP = abiraterone acetate with prednisone or prednisolone; EFS = event-free survival; OS = overall survival

Parker C et al. *N Engl J Med* 2013;369(3):213-23; Sartor O et al. *Lancet Oncol* 2014;15(7):738-46; Smith M et al. *Lancet Oncol* 2019;20(3):408-19.

2021 ASCO ANNUAL MEETING **Abstract 5002**

DECREASED FRACTURE RATE BY MANDATING BONE PROTECTING AGENTS IN THE EORTC 1333/PEACE-3 TRIAL COMBINING RA-223 WITH ENZALUTAMIDE VERSUS ENZALUTAMIDE ALONE: AN UPDATED SAFETY ANALYSIS

Silke GILLESSEN, Ananya CHOUDHURY, Alejo RODRIGUEZ-VIDA, Franco NOLE, Enrique GALLARDO, Thierry Andre ROUMEGUERE, Gedske DAUGAARD, Yohann LORIOT, Fred SAAD, Raymond S. McDERMOTT, Anouk NEVEN, Beatrice FOURNIER, Bertrand F. TOMBAL

For EORTC GUCG, CUOG, UNICANCER and Cancer Trials Ireland

EORTC Genito-Urinary Cancers Group
The future of cancer therapy

CUOG

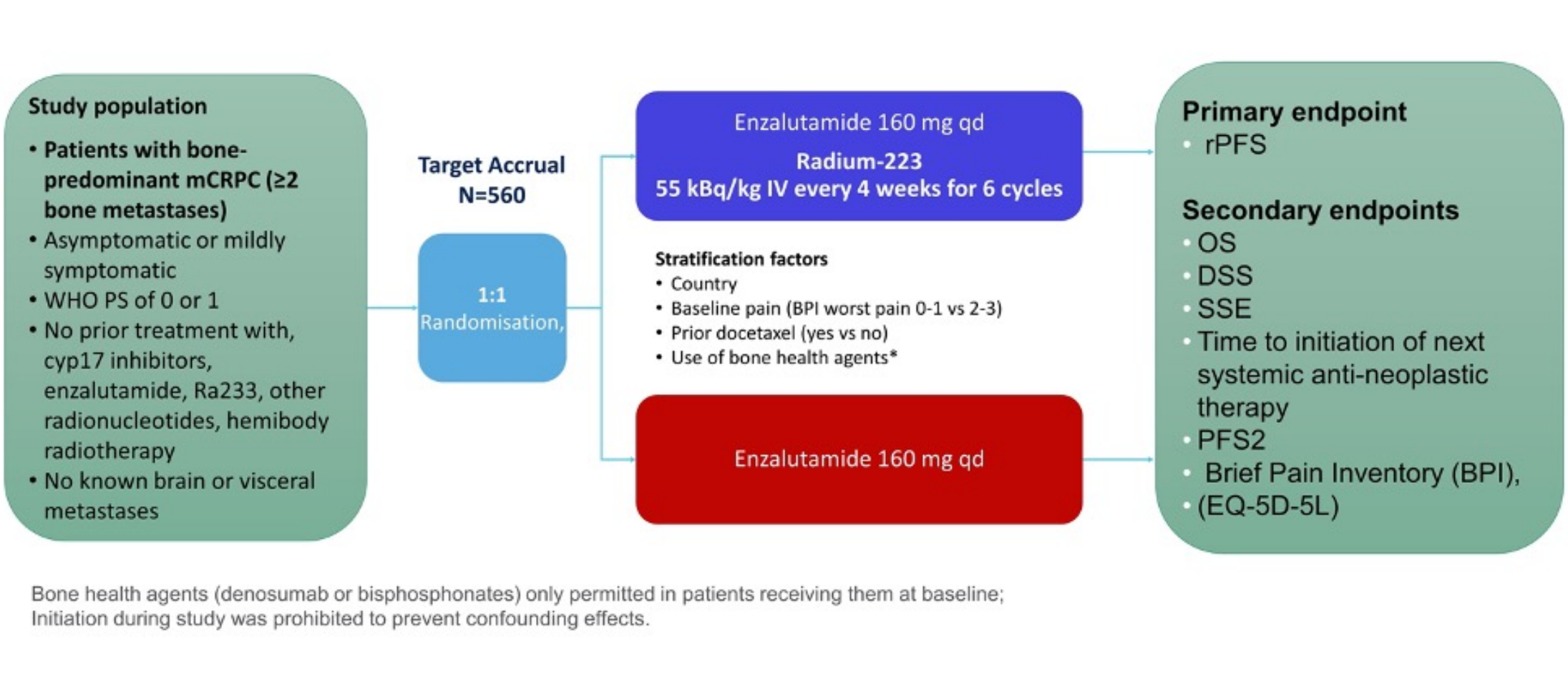
GETUG
unicancer

cancer trials ireland

RTP RESEARCH TO PRACTICE

Gillessen S et al. ASCO 2021;Abstract 5002.

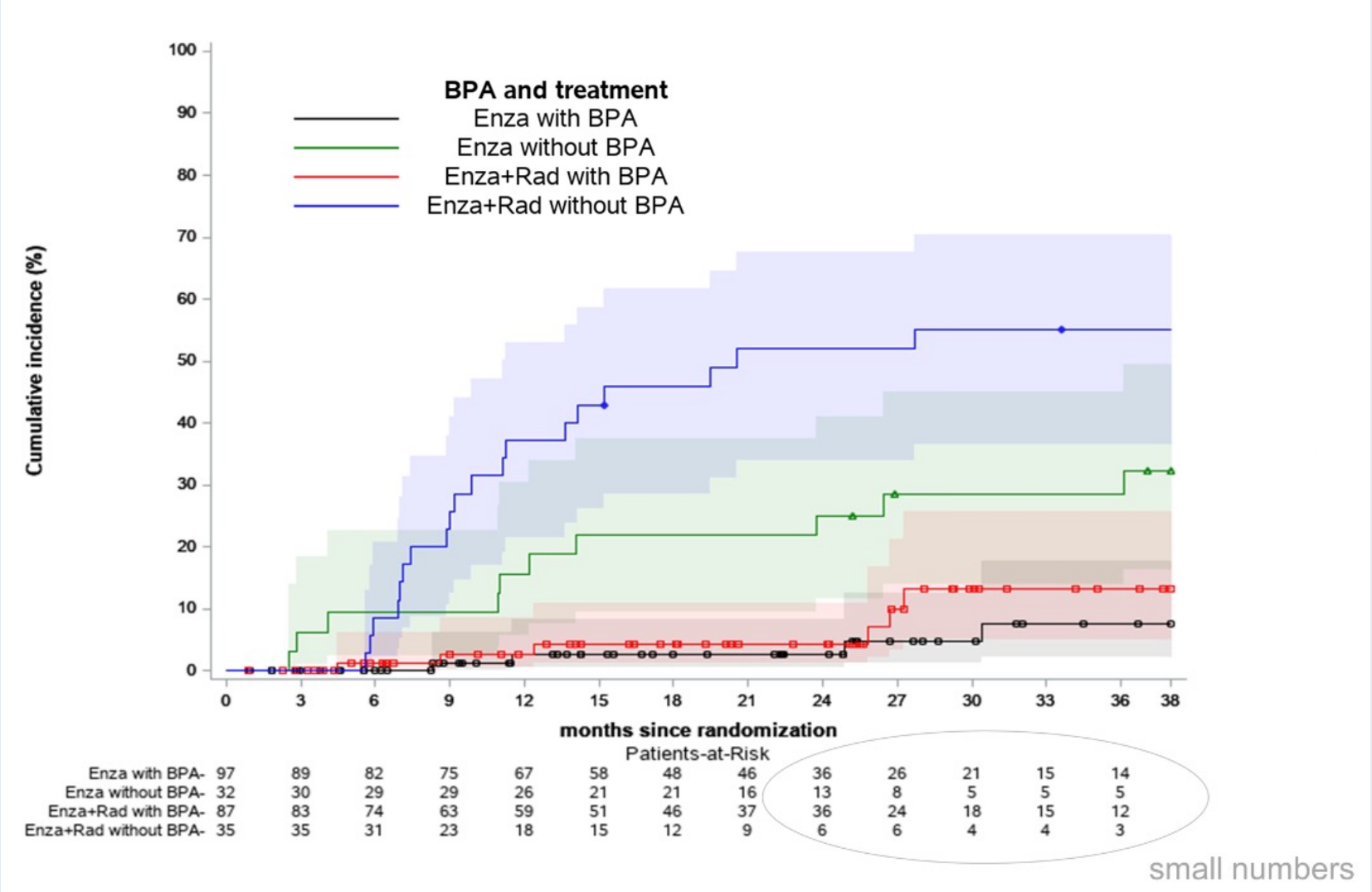
PEACE-3 Original Study Schema



Bone health agents (denosumab or bisphosphonates) only permitted in patients receiving them at baseline; Initiation during study was prohibited to prevent confounding effects.

Gillessen S et al. ASCO 2021;Abstract 5002.

PEACE-3: Cumulative Incidence of Fractures by Treatment Arm and Use of Bone Protecting Agents



Gillessen S et al. ASCO 2021;Abstract 5002.

RTP RESEARCH TO PRACTICE

PEACE-3: Bone Fractures and Cumulative Incidence — Safety Population

Time point	Without BPA		With BPA	
	Enza+Rad (N=35)	Enza (N=32)	Enza+Rad (N=87)	Enza (N=97)
	Cum Incidence (95% CI)	Cum Incidence (95% CI)	Cum Incidence (95% CI)	Cum Incidence (95% CI)
9 months	25.7 (12.6-41.0)	9.4 (2.3-22.5)	2.7 (0.5-8.5)	1.3 (0.1-6.1)
12 months	**37.1 (21.3-53.0)**	**15.6 (5.6-30.3)**	**2.7 (0.5-8.5)**	**2.6 (0.5-8.3)**
15 months	42.9 (26.1-58.6)	21.9 (9.5-37.5)	4.3 (1.1-10.9)	2.6 (0.5-8.3)
18 months	**45.9 (28.6-61.6)**	**21.9 (9.5-37.5)**	**4.3 (1.1-10.9)**	**2.6 (0.5-8.3)**
21 months	52.0 (33.8-67.5)	21.9 (9.5-37.5)	4.3 (1.1-10.9)	2.6 (0.5-8.3)

Gillessen S et al. ASCO 2021;Abstract 5002.

PRINCE: Interim Analysis of the Phase Ib Study of ^{177}Lu-PSMA-617 in Combination with Pembrolizumab for Metastatic Castration Resistant Prostate Cancer (mCRPC)

Shahneen Sandhu, Anthony M. Joshua, Louise Emmett, Lavinia Spain, Lisa G. Horvath, Megan Crumbaker, Arsha Anton, Roslyn Wallace, Anupama Pasam, Mathias Bressel, Erin Cassidy, Patricia Banks, Aravind Ravi Kumar, Ramin Alipour, Tim Akhurst, Grace Kong, Ian D. Davis, Scott Williams, Rod Hicks, Michael S. Hofman

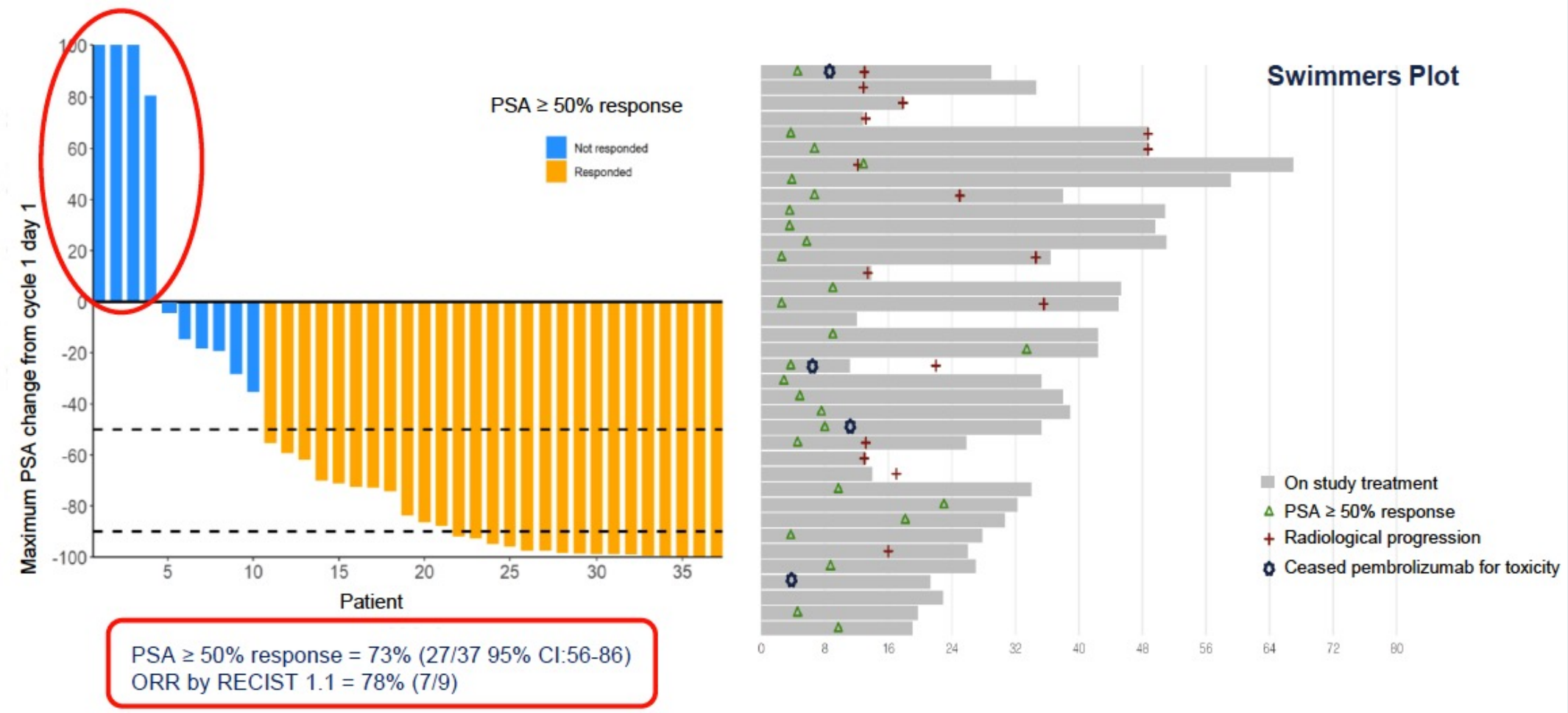
2021 ESMO congress

Abstract 577O

Presented by: Shahneen Sandhu

PRINCE: ^{177}Lu-PSMA-617 Combined with Pembrolizumab for mCRPC

PSA Response Rate (Primary Endpoint)



Sandhu S et al. ESMO 2021;Abstract 577O.

PRINCE: Treatment-Related Adverse Events (TRAEs)

TRAE term	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	N=37 (%)
Xerostomia	21 (57%)	7 (19%)	-	28 (76%)
Fatigue	11 (29 %)	3 (8%)	2 (5%)	16 (43%)
Rash	5 (14%)	4 (11%)		9 (25%)
Nausea	8 (21%)	1 (3%)	-	9 (24%)
Pruritus	6 (16%)	1 (3%)	-	7 (19%)
Anorexia	3 (8%)	3 (8%)	-	6 (16%)
Thrombocytopenia	4 (11%)	1(3%)	-	5 (14%)
Bone pain (flare)	4 (11%)	-	-	4 (11%)
Aspartate aminotransferase elevation	2 (5%)	2 (5%)	-	4 (11%)
Dry eye	3 (8%)	-	-	3 (8%)
Dysgeusia	2 (5%)	1 (3%)	-	3 (8%)
Weight loss	2 (5%)	1 (3%)		3 (8%)
Anemia	-	2 (5%)	1(3%)	3 (8%)
Alanine aminotransferase elevation	2 (5%)	1(3%)	-	3 (8%)
Amylase elevation	1 (3%)	1 (3%)	1 (3%)	3 (8%)
Arthralgia	3 (8%)	-	-	3 (8%)
Neutropenia	1 (3%)	-	-	1 (3%)

Pembrolizumab cycles: Median (range)	8 (1 - 22)
^{177}Lu-PSMA-617 cycles: Median (range)	4 (2 - 6)
Discontinuation for toxicity:	
Pembrolizumab, n (%)	4 (11%)
^{177}Lu-PSMA-617, n (%)	0 (0%)

- Treatment related adverse events (TRAEs) by worst grade affecting > 5% and all hematological toxicity
- There were no grade 4 TRAEs or treatment related deaths

Sandhu S et al. ESMO 2021;Abstract 577O.

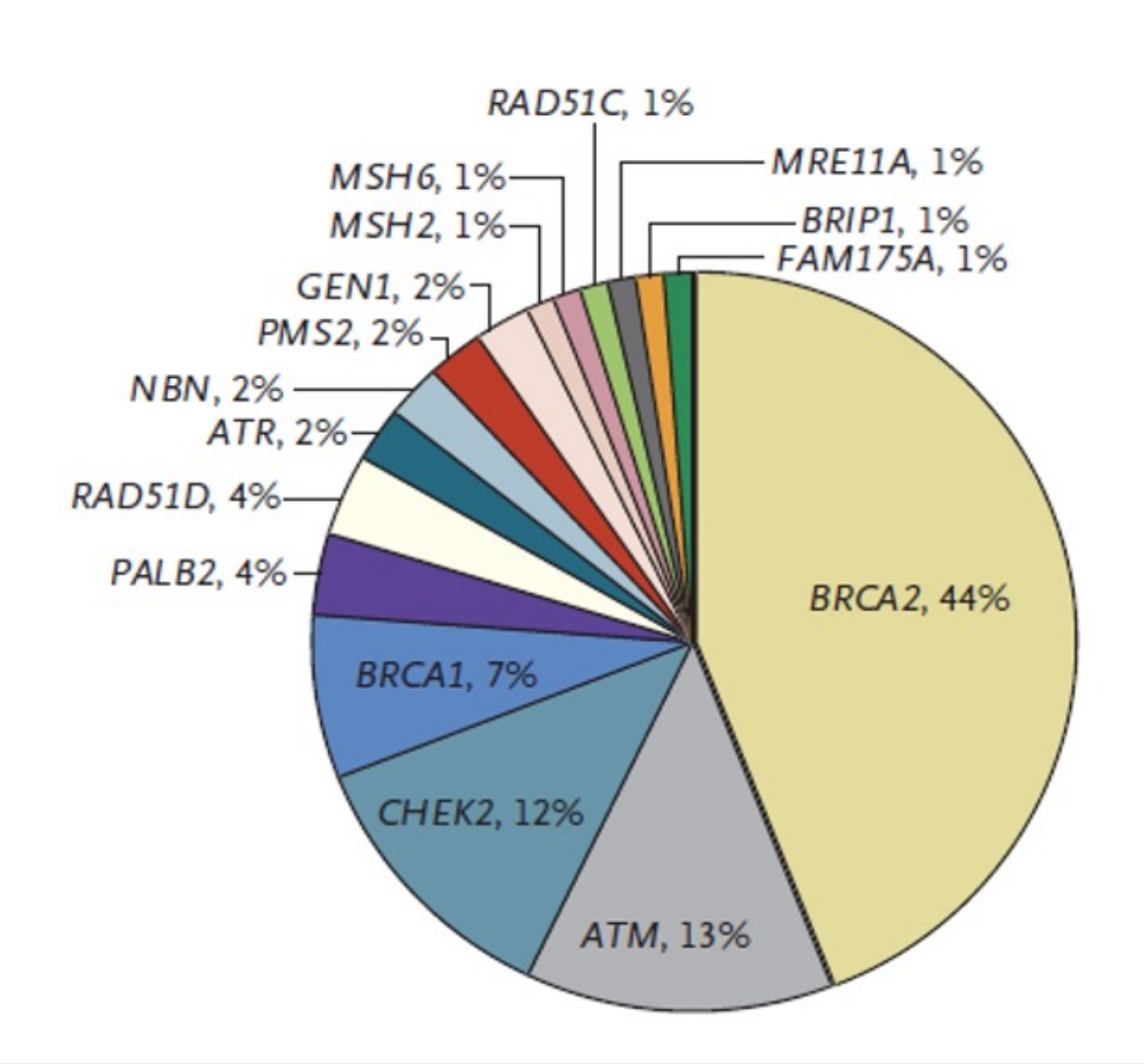
RTP RESEARCH TO PRACTICE

Immune Checkpoint Inhibitors in mCRPC

Therapy	Disease state	Disease response
Pembrolizumab monotherapy[a]	Postchemotherapy	ORR 9% PSA RR 14%
Pembrolizumab + enzalutamide[b]	Prechemotherapy, progressing on enzalutamide	ORR 12% PSA RR 14%
Atezolizumab + enzalutamide[c]	Pre- and postchemotherapy, s/p abiraterone	ORR 14% PSA RR 26%
Atezolizumab + cabozantinib[d]	Prechemotherapy, s/p enzalutamide or abiraterone	ORR 34% PSA RR 29%

[a] Antonarakis ES et al. *JCO* 2020:38(5):395-405. [b] Presented at the 2021 ASCO Annual Meeting – Virtual. [c] Sweeney C. AACR 2020; IMbassador250. [d] Agarwal ASCO 2020; COSMIC-021.

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

N Engl J Med 2020;383:2345-57.

The NEW ENGLAND JOURNAL of MEDICINE

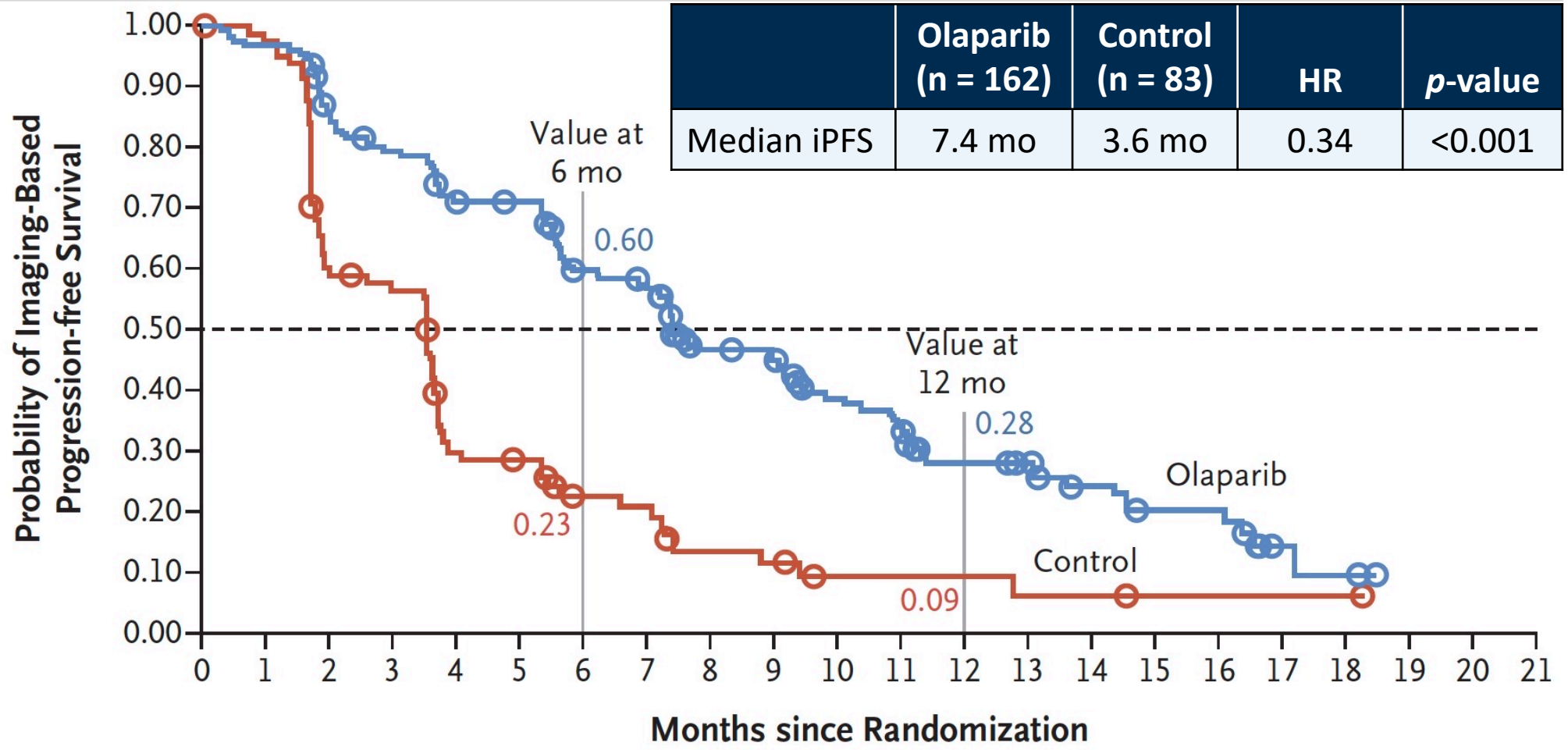
ORIGINAL ARTICLE

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*

PROfound Primary Endpoint: Imaging-Based PFS with Olaparib for Patients with mCRPC and 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

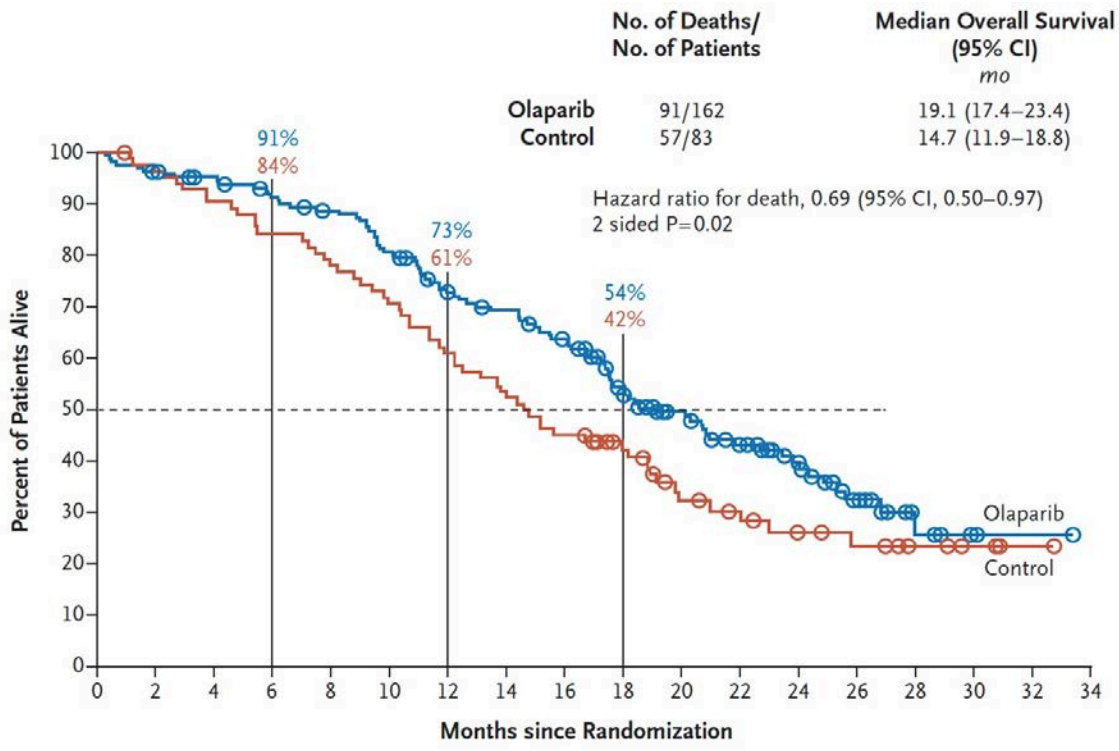


de Bono J et al; PROfound investigators. *N Engl J Med* 2020;382(22):2091-102.

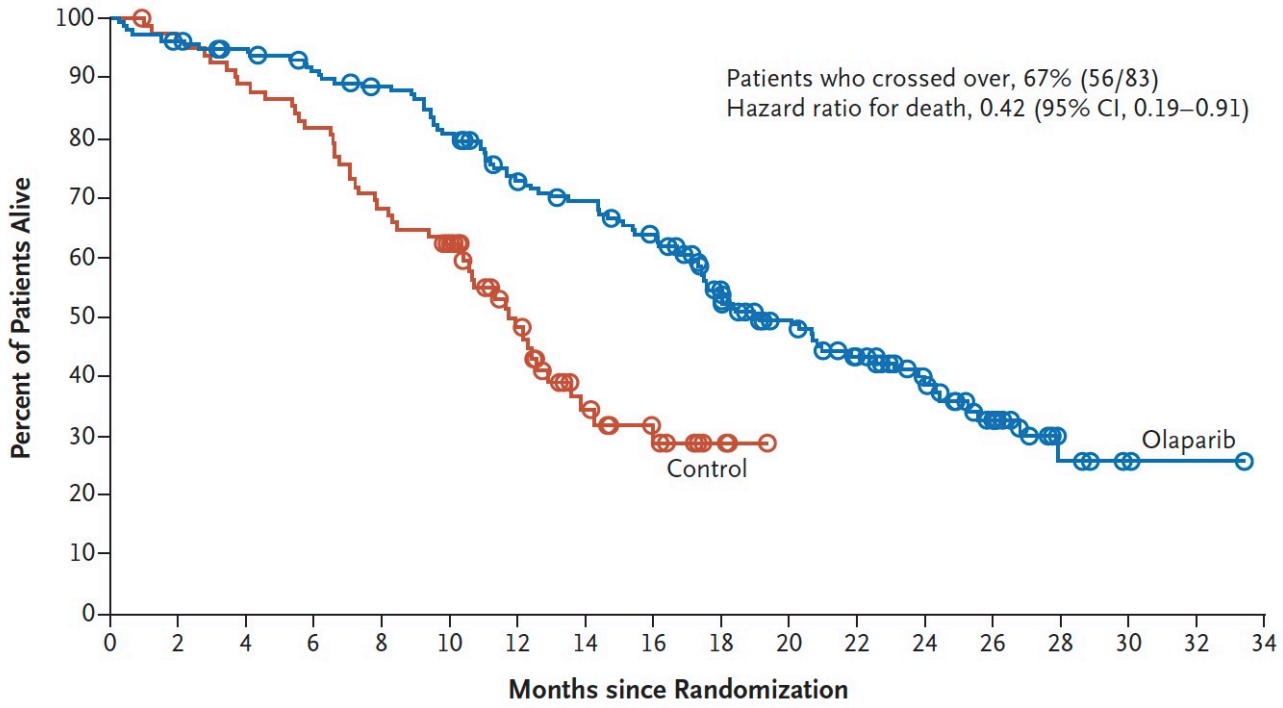
RTP RESEARCH TO PRACTICE

PROfound: OS with Olaparib for Patients with mCRPC and at Least 1 Alteration in BRCA1, BRCA2 or ATM (Cohort A)

Overall survival



Crossover-adjusted overall survival



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

rapid communications

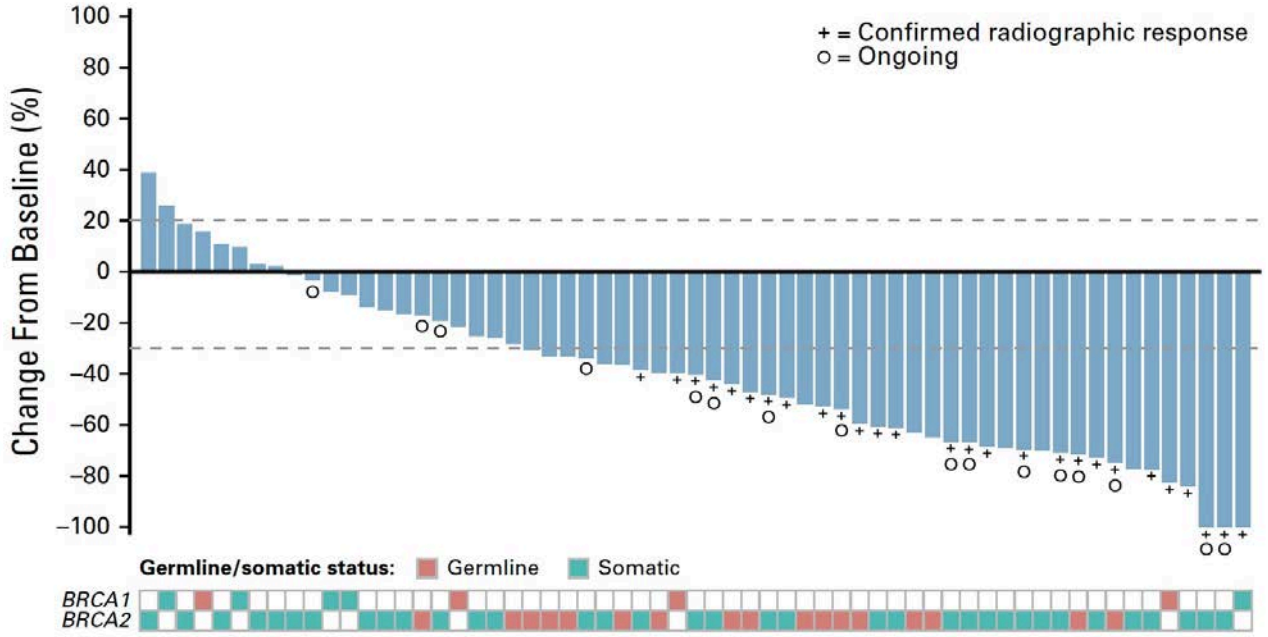
Rucaparib in Men With Metastatic Castration-Resistant Prostate Cancer Harboring a *BRCA1* or *BRCA2* Gene Alteration

Wassim Abida, MD, PhD[1]; Akash Patnaik, MD, PhD, MMSc[2]; David Campbell, MBBS[3]; Jeremy Shapiro, MBBS[4]; Alan H. Bryce, MD[5]; Ray McDermott, MD, PhD, MBA[6]; Brieuc Sautois, MD, PhD[7]; Nicholas J. Vogelzang, MD[8]; Richard M. Bambury, MD[9]; Eric Voog, MD[10]; Jingsong Zhang, MD, PhD[11]; Josep M. Piulats, MD[12]; Charles J. Ryan, MD[13]; Axel S. Merseburger, PhD[14]; Gedske Daugaard, DMSc[15]; Axel Heidenreich, MD[16]; Karim Fizazi, MD, PhD[17]; Celestia S. Higano, MD[18]; Laurence E. Krieger, MBChB[19]; Cora N. Sternberg, MD[20]; Simon P. Watkins, PhD[21]; Darrin Despain, MStat[22]; Andrew D. Simmons, PhD[23]; Andrea Loehr, PhD[23]; Melanie Dowson, BA[24]; Tony Golsorkhi, MD[25]; and Simon Chowdhury, MD, PhD[26,27]; on behalf of the TRITON2 investigators

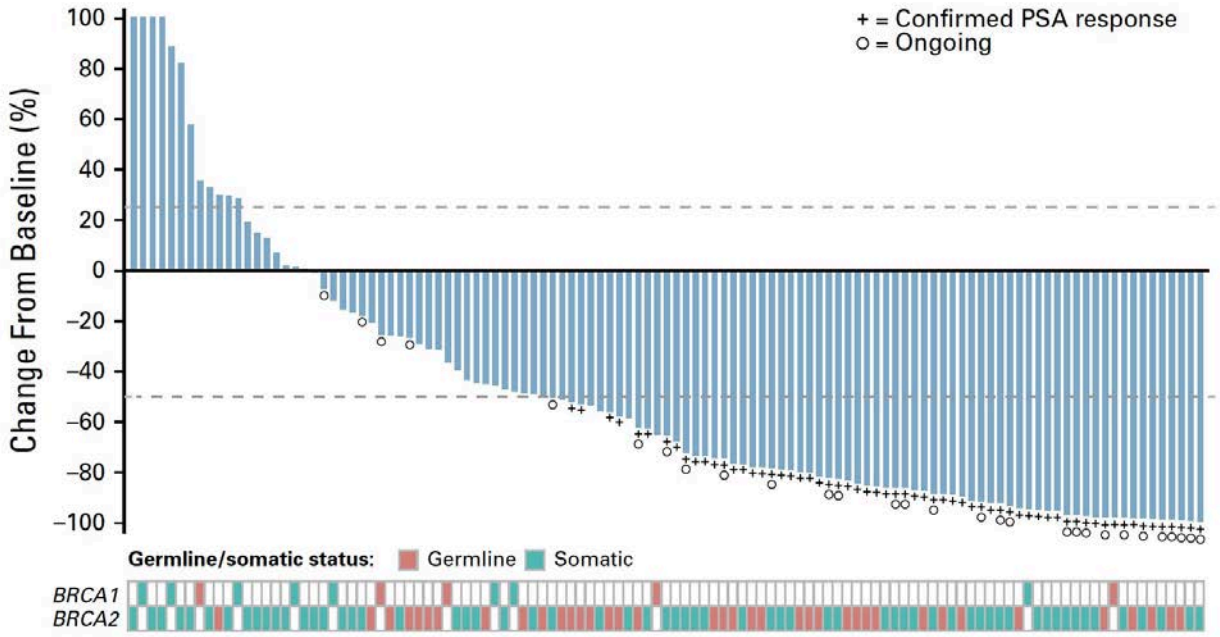
J Clin Oncol 2020;38:3763-72.

TRITON2: Response to Rucaparib in Patients with mCRPC Harboring a BRCA1 or BRCA2 Gene Alteration

ORR per independent radiology review: 43.5%



Confirmed PSA response rate: 54.8%



ORR = objective response rate

Abida W et al; TRITON2 Investigators. *J Clin Oncol* 2020;38(32):3763-72.

PARP Inhibitor Monotherapy with Investigational Agents

Articles

Lancet Oncol 2021;22(9):1250-64

Talazoparib monotherapy in metastatic castration-resistant prostate cancer with DNA repair alterations (TALAPRO-1): an open-label, phase 2 trial

Johann S de Bono, Niven Mehra, Giorgio V Scagliotti, Elena Castro, Tanya Dorff, Adam Stirling, Arnulf Stenzl, Mark T Fleming, Celestia S Higano, Fred Saad, Consuelo Buttigliero, Inge M van Oort, A Douglas Laird, Marielena Mata, Hsiang-Chun Chen, Cynthia G Healy, Akos Czibere, Karim Fizazi

Lancet Oncol 2022;23:362-73

Niraparib in patients with metastatic castration-resistant prostate cancer and DNA repair gene defects (GALAHAD): a multicentre, open-label, phase 2 trial

*Matthew R Smith, Howard I Scher, Shahneen Sandhu, Eleni Efstathiou, Primo N Lara Jr, Evan Y Yu, Daniel J George, Kim N Chi, Fred Saad, Olof Ståhl, David Olmos, Daniel C Danila, Gary E Mason, Byron M Espina, Xin Zhao, Karen A Urtishak, Peter Francis, Angela Lopez-Gitlitz, Karim Fizazi, on behalf of the GALAHAD investigators**

TALAPRO-1 and GALAHAD: PARP Inhibitor Monotherapy Studies with Talazoparib and Niraparib for mCRPC

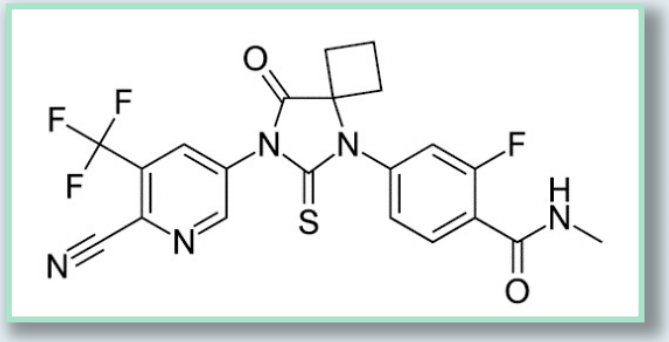
	TALAPRO-1 (talazoparib) (N = 104)	GALAHAD (niraparib) (N = 289)
Eligibility, gene alterations	DDR-HHR gene alterations*	• Germline or somatic BRCA1 or BRCA2 (BRCA cohort) • Other prespecified DNA repair gene defects (non-BRCA cohort)**
Overall response rate BRCA1/2 Non-BRCA1/2	 46% 7%	 34% 11%
rPFS, median (BRCA1/2)	11.2 mo	5.5 mo

*DDR-HHR gene alterations: *ATM*, *ATR*, *BRCA1*, *BRCA2*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, *RAD51C*
** DDR (non-BRCA cohort): *ATM*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *FANCA*, *HDAC2*, and *PALB2*

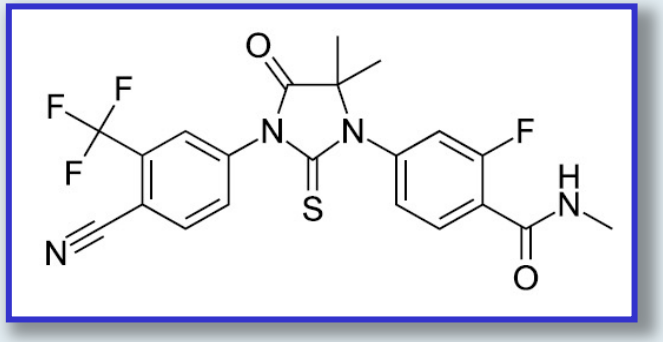
de Bono JS et al. *Lancet Oncol* 2021;22(9):1250-64. Smith MR et al. *Lancet Oncol* 2022;23:362-73.

Next-Generation Androgen Receptor Inhibitors

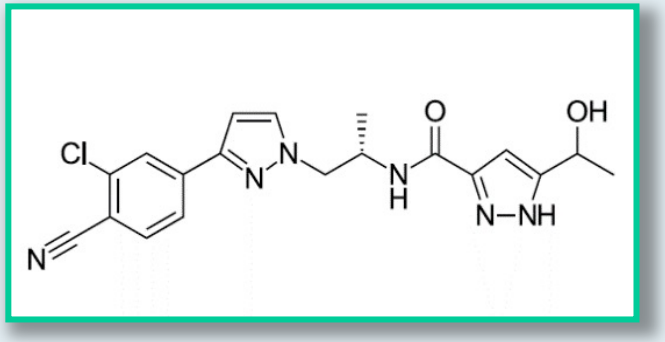
Apalutamide



Enzalutamide



Darolutamide



- Apalutamide and enzalutamide have similar structures
- Darolutamide is structurally distinct from apalutamide and enzalutamide, characterized by low blood-brain barrier penetration, and may have improved tolerability

Zurth C et al. Genitourinary Cancers Symposium 2018;Abstract 345; Sandmann S et al. Genitourinary Cancers Symposium 2019;Abstract 156.

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2020;383:1040-9.

ORIGINAL ARTICLE

Nonmetastatic, Castration-Resistant Prostate Cancer and Survival with Darolutamide

K. Fizazi, N. Shore, T.L. Tammela, A. Ulys, E. Vjaters, S. Polyakov, M. Jievaltas, M. Luz, B. Alekseev, I. Kuss, M.-A. Le Berre, O. Petrenciuc, A. Snapir, T. Sarapohja, and M.R. Smith, for the ARAMIS Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2020;382(23):2197-206.

ORIGINAL ARTICLE

Enzalutamide and Survival in Nonmetastatic, Castration-Resistant Prostate Cancer

Cora N. Sternberg, M.D., Karim Fizazi, M.D., Ph.D., Fred Saad, M.D., Neal D. Shore, M.D., Ugo De Giorgi, M.D., Ph.D., David F. Penson, M.D., M.P.H., Ubirajara Ferreira, M.D., Ph.D., Eleni Efstathiou, M.D., Ph.D., Katarzyna Madziarska, M.D., Ph.D., Michael P. Kolinsky, M.D., Daniel I. G. Cubero, M.D., Ph.D., Bettina Noerby, M.D., Fabian Zohren, M.D., Ph.D., Xun Lin, Ph.D., Katharina Modelska, M.D., Ph.D., Jennifer Sugg, M.S., Joyce Steinberg, M.D., and Maha Hussain, M.D., for the PROSPER Investigators*

European Association of Urology

Eur J Cancer 2020;[Online ahead of print].

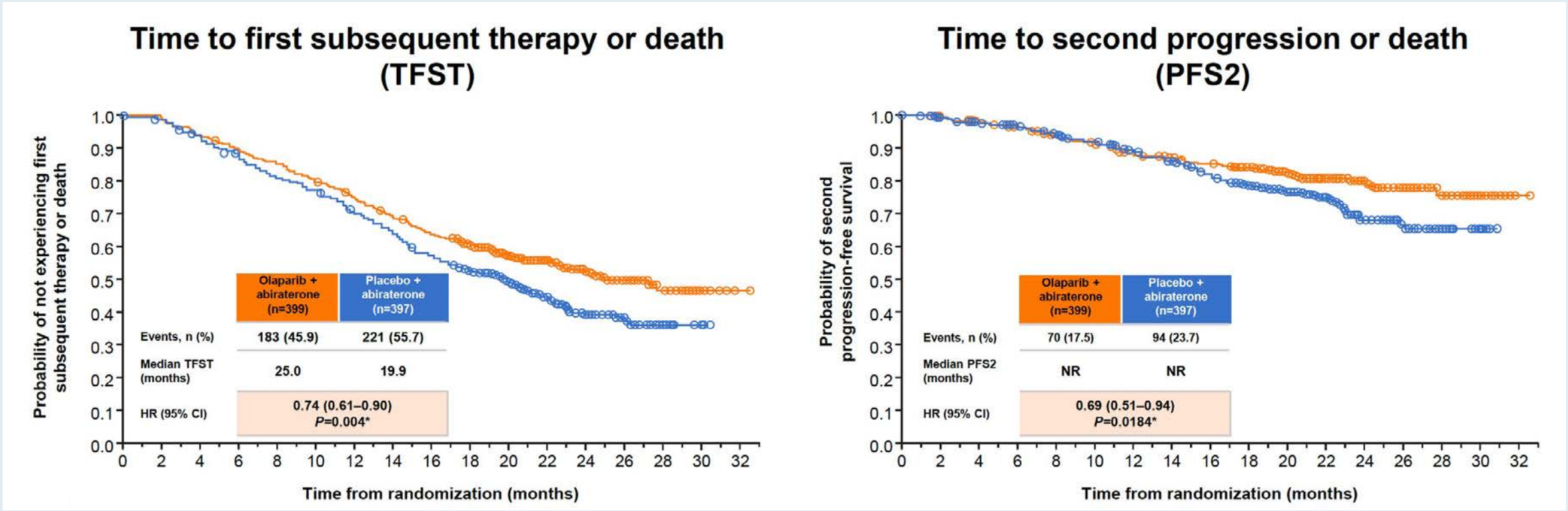
Prostate Cancer

Apalutamide and Overall Survival in Prostate Cancer

Matthew R. Smith[a,], Fred Saad[b], Simon Chowdhury[c], Stéphane Oudard[d], Boris A. Hadaschik[e], Julie N. Graff[f], David Olmos[g], Paul N. Mainwaring[h], Ji Youl Lee[i], Hiroji Uemura[j], Peter De Porre[k], Andressa A. Smith[l], Sabine D. Brookman-May[m,n], Susan Li[l], Ke Zhang[o], Brendan Rooney[p], Angela Lopez-Gitlitz[m], Eric J. Small[q]*

RTP RESEARCH TO PRACTICE

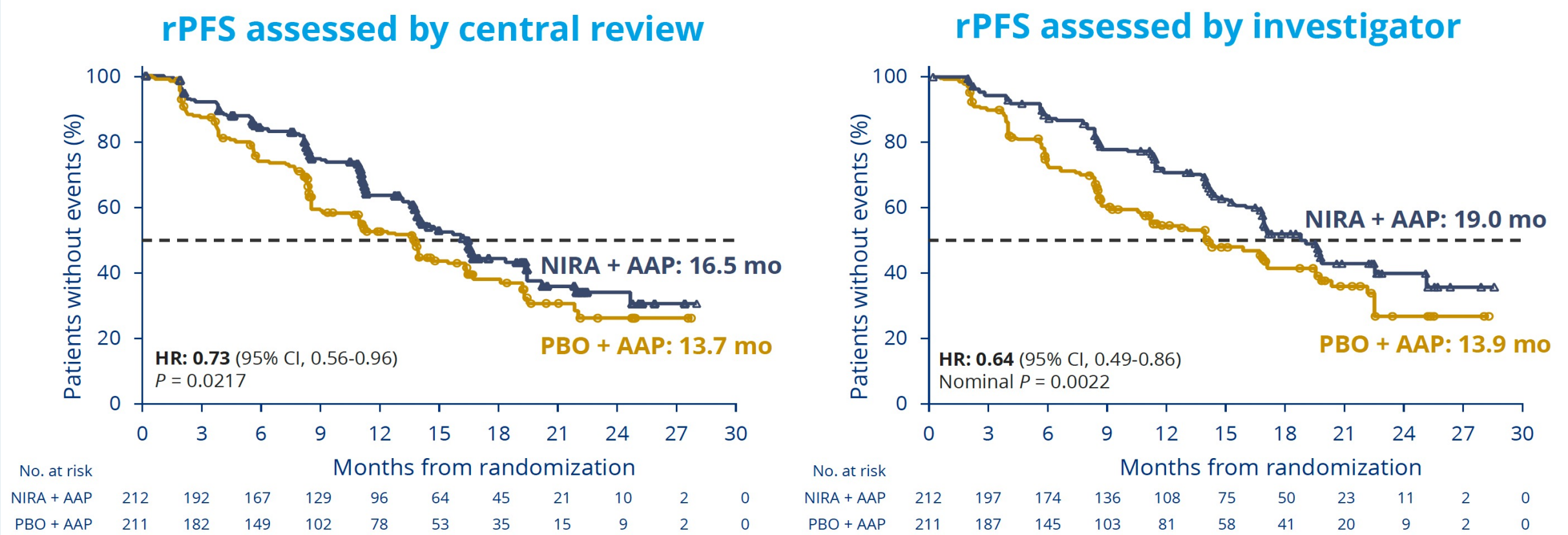
PROpel: TFST and PFS2



Saad F et al. Genitourinary Cancers Symposium 2022;Abstract 11.

RTP RESEARCH TO PRACTICE

MAGNITUDE: All HRR Biomarker-Positive — Primary Endpoint Niraparib with Abiraterone Acetate Significantly Reduced the Risk of Disease Progression or Death by 27% in mCRPC



Chi KN et al. Genitourinary Cancers Symposium 2022;Abstract 12.

RTP RESEARCH TO PRACTICE

MAGNITUDE HRR Biomarker-Positive: Summary of TEAEs

Overall summary, n (%)	NIRA + AAP n = 212	PBO + AAP n = 211
All TEAEs	210 (99.1)	199 (94.3)
Drug related	162 (76.4)	116 (55.0)
Grade 3/4 TEAEs	142 (67.0)	98 (46.4)
SAEs	76 (35.8)	52 (24.6)
Drug related[a]	24 (11.3)	6 (2.8)
Dose reduction due to an AE	42 (19.8)	7 (3.3)
Discontinuation of niraparib or placebo due to AE	23 (10.8)	10 (4.7)
All deaths within 30 days of last dose	19 (9.0)	19 (9.0)
Death due to prostate cancer	8 (3.8)	12 (5.7)
AE	11 (5.2)	7 (3.3)

- The most common AEs leading to dose reduction in the niraparib group were anemia (13.2%) and thrombocytopenia (2.8%), consistent with established safety profile for NIRA
- Median relative dose intensity was 99% in the NIRA + AAP group

Chi KN et al. Genitourinary Cancers Symposium 2022;Abstract 12.

Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Gastrointestinal Cancers

A CME Hybrid Symposium Held in Conjunction with the 2022 ASCO Annual Meeting

Saturday, June 4, 2022
7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)

Faculty

Tanios Bekaii-Saab, MD
Kristen K Ciombor, MD, MSCI
Eileen M O'Reilly, MD
Philip A Philip, MD, PhD, FRCP
John Strickler, MD
Eric Van Cutsem, MD, PhD

Moderator

Neil Love, MD

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Thank you for joining us!

CME links will be posted in the chat (Zoom participants only) and emailed to all participants within 24 hours of the program.

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