What I Tell My Patients:
Faculty Physicians and Nurses Discuss Patient Education About New Treatments and Clinical Trials

Fifteenth Annual RTP Symposium Series Held During the Annual ONS Congress

Prostate Cancer

Saturday, April 29, 2023
12:15 PM – 1:45 PM

Faculty

Neeraj Agarwal, MD, FASCO
Kathy D Burns, RN, MSN, AGACNP-BC, OCN
Susan K Roethke, MSN, CRNP, AOCNP, ANP-BC
Sandy Srinivas, MD

Moderator

Neil Love, MD

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Faculty

Neeraj Agarwal, MD, FASCO
Professor of Medicine
Senior Director for Clinical Research Innovation
Huntsman Cancer Institute Presidential Endowed Chair of Cancer Research
Director, Center of Investigational Therapeutics
Director, Genitourinary Oncology Program
Huntsman Cancer Institute, University of Utah (NCI-CCC)
Salt Lake City, Utah

Kathy D Burns, RN, MSN, AGACNP-BC, OCN
Genitourinary Medical Oncology
City of Hope Comprehensive Cancer Center
Duarte, California

Susan K Roethke, MSN, CRNP, AOCNP, ANP-BC
Genitourinary Medical Oncology
Fox Chase Cancer Center
Philadelphia, Pennsylvania

Sandy Srinivas, MD
Professor of Oncology
Clinical Research Leader, GU Oncology
Stanford University
Stanford, California

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

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Dr Agarwal — Disclosures

Consulting Agreements	Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Calithera Biosciences, Eisai Inc, Exelixis Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Immunomedics Inc, Janssen Biotech Inc, Lilly, MEI Pharma Inc, Merck
Contracted Research	Astellas, AstraZeneca Pharmaceuticals LP, Bavarian Nordic, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Calithera Biosciences, Celldex Therapeutics, Clovis Oncology, Eisai Inc, EMD Serono Inc, Exelixis Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, GSK, Immunomedics Inc, Janssen Biotech Inc, Lilly, Lumos Pharma, Medivation Inc, a Pfizer Company, Merck, Nektar, Novartis, Pfizer Inc, Prometheus Laboratories Inc, Rexahn Pharmaceuticals Inc, Roche Laboratories Inc, Sanofi, Seagen Inc, Takeda Pharmaceuticals USA Inc, TRACON Pharmaceuticals Inc

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Ms Burns — Disclosures

No relevant conflicts of interest to disclose

Ms Roethke — Disclosures

No relevant conflicts of interest to disclose

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Dr Srinivas — Disclosures

Advisory Committee and Consulting Agreements	Janssen Biotech Inc, Merck, Novartis, Seagen Inc
Contracted Research	Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Celgene Corporation, Exelixis Inc, Regeneron Pharmaceuticals Inc, Seagen Inc
Data and Safety Monitoring Board/Committee	Pfizer Inc

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Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Merck, Novartis, and Pfizer Inc.

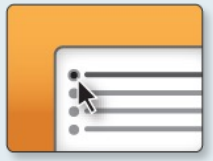
Research To Practice NCPD Planning Committee Members, Staff and Reviewers

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

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 pre- and postmeeting surveys. Survey questions will be 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 NCPD 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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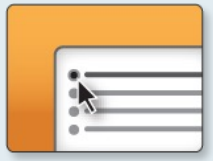
Clinicians Attending via Zoom

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 pre- and postmeeting surveys. Survey questions will be discussed throughout the meeting.

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

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

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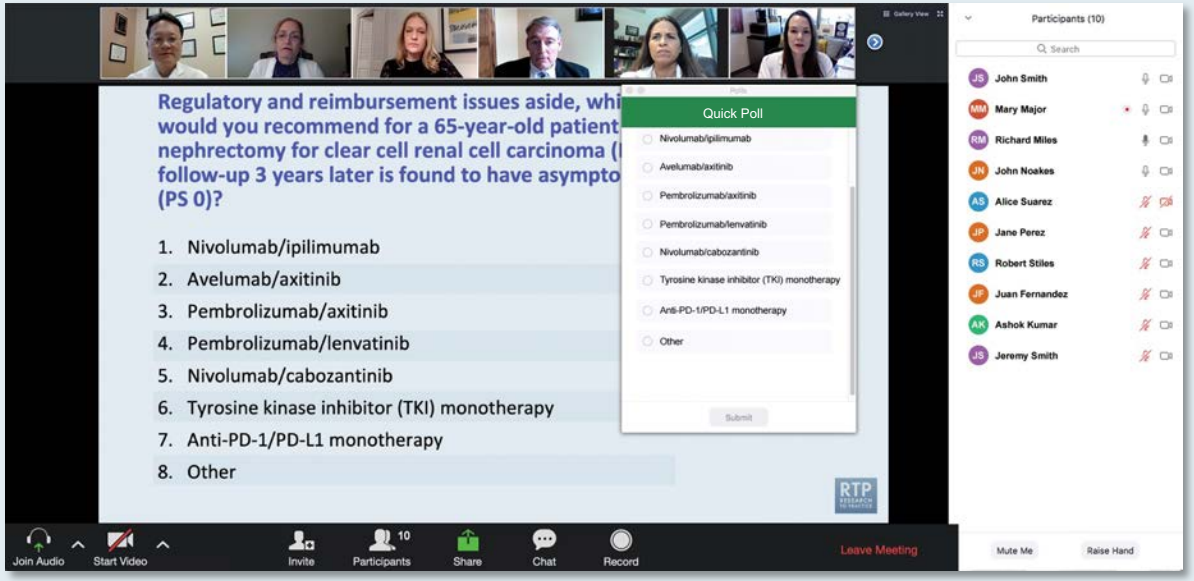
Clinicians, Please Complete the Pre- and Postmeeting Surveys



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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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“What I Tell My Patients”
Fifteenth Annual RTP-ONS NCPD Symposium Series
ONS Congress, San Antonio, Texas — April 26 to 29, 2023

Wednesday April 26	**Cervical and Endometrial Cancer** 11:15 AM – 12:45 PM CT (12:15 PM – 1:45 PM ET)
	Breast Cancer 6:00 PM – 8:00 PM CT (7:00 PM – 9:00 PM ET)
Thursday April 27	**Diffuse Large B-Cell Lymphoma** 6:00 AM – 7:30 AM CT (7:00 AM – 8:30 AM ET)
	Chronic Lymphocytic Leukemia 12:15 PM – 1:45 PM CT (1:15 PM – 2:45 PM ET)
	HER2-Targeted Antibody-Drug Conjugates 6:00 PM – 7:30 PM CT (7:00 PM – 8:30 PM ET)
Friday April 28	**Hepatobiliary Cancers** 6:00 AM – 7:30 AM CT (7:00 AM – 8:30 AM ET)
	Ovarian Cancer 12:15 PM – 1:45 PM CT (1:15 PM – 2:45 PM ET)
	Lung Cancer 6:00 PM – 8:00 PM CT (7:00 PM – 9:00 PM ET)
Saturday April 29	**Acute Myeloid Leukemia, Myelodysplastic Syndromes and Myelofibrosis** 6:00 AM – 7:30 AM CT (7:00 AM – 8:30 AM ET)
	Prostate Cancer 12:15 PM – 1:45 PM CT (1:15 PM – 2:45 PM ET)

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What I Tell My Patients

2023 ONS Congress

San Antonio, Texas

Symposia Themes

- New agents and therapies; ongoing trials related to specific clinical scenarios
- Patient education: Preparing to receive new therapies
- The bond that heals
- THANKS! (Great job)

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How was it different to take care of this patient versus another patient in the same oncologic setting?

What unique biopsychosocial factors (eg, attitude, comorbidities, social support) were considered in the overall management of this case?

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Miami, Florida

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Agenda

Module 1: Overview of Prostate Cancer

Module 2: Intensification of Therapy for Localized Disease

Module 3: Hormone-Sensitive Metastatic Disease

Module 4: PARP Inhibitors

Module 5: Radioligand Therapy

Agenda

Module 1: Overview of Prostate Cancer

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Kathy D Burns, RN, MSN, AGACNP-BC, OCN

72-year-old man with cardiovascular comorbidities and Decipher® high-risk prostate cancer s/p prostatectomy

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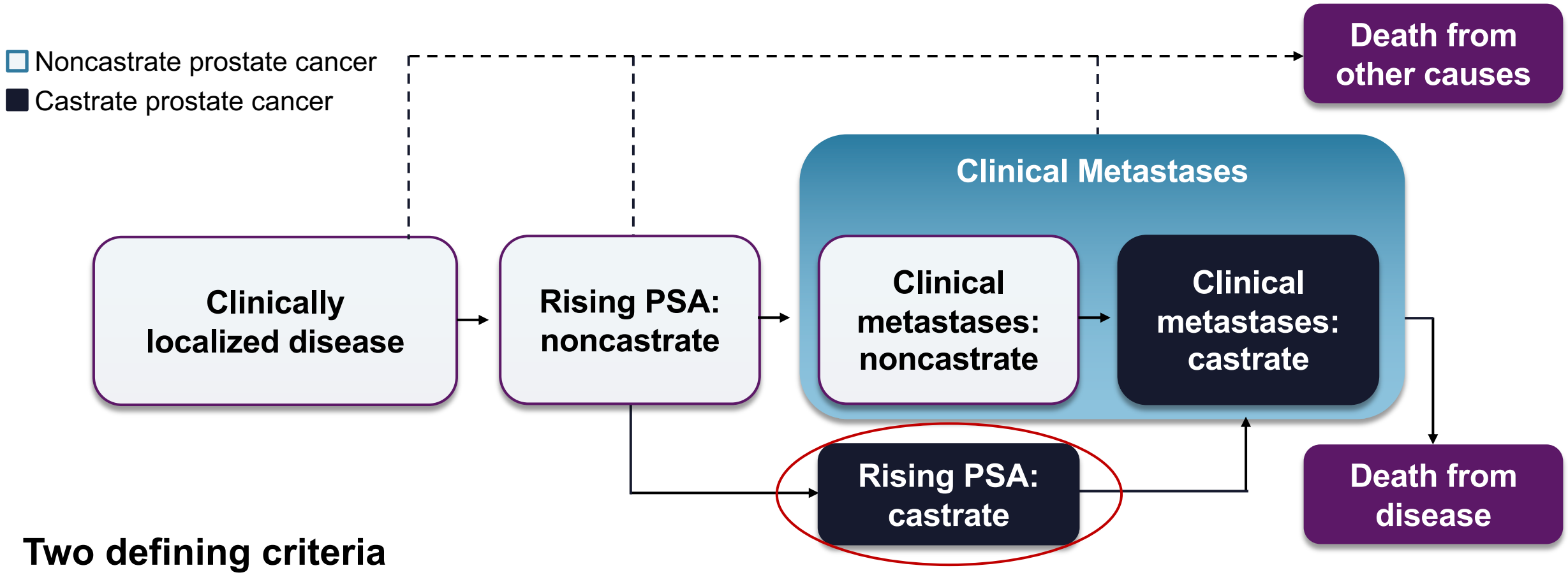
Clinical Research Background

Dr Agarwal
Salt Lake City, Utah

Dr Srinivas
Stanford, California

- **Overview of prostate cancer**
  - **Primary therapy**
  - **Indications for and selection of androgen deprivation therapy (ADT)**
  - **Tolerability of ADT**

Clinical Disease States Model of Prostate Cancer[1]

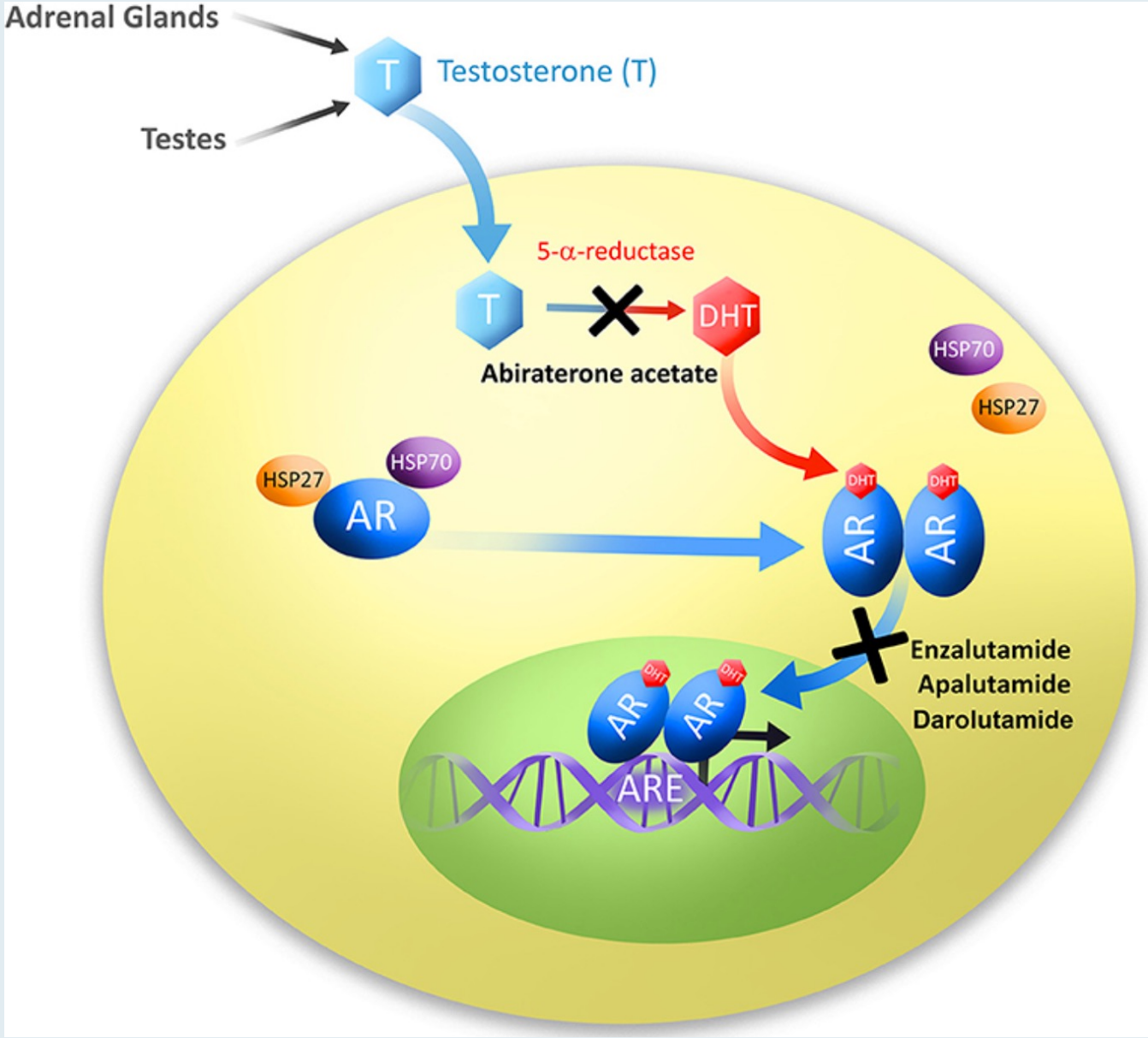


Two defining criteria

- Rising PSA in the setting of castrate testosterone levels (<50 ng/dL)
- No radiographically identifiable metastasis

1. Adapted from Scher HI et al. *J Clin Oncol.* 2008;26:1148-1159.

Diagram of Androgen Production and Its Targeted Inhibition



Rice MA et al. *Front Oncol* 2019; https://doi.org/10.3389/fonc.2019.00801

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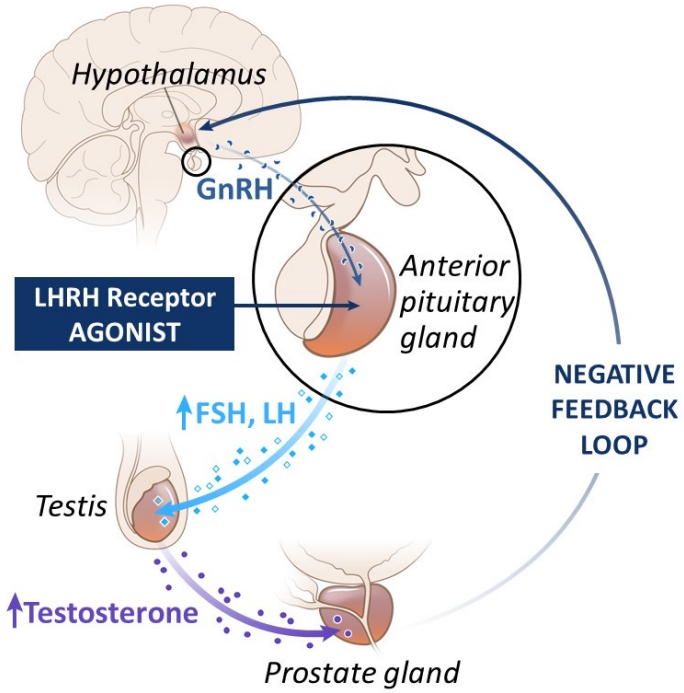
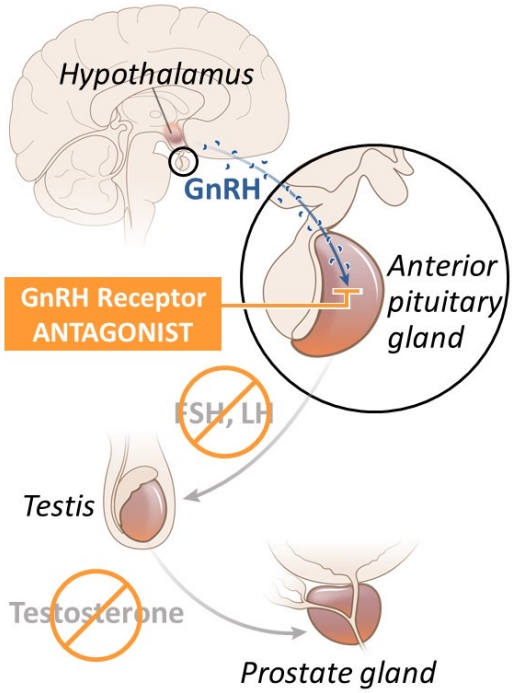
LHRH agonist vs antagonist MOA and side effect profile





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

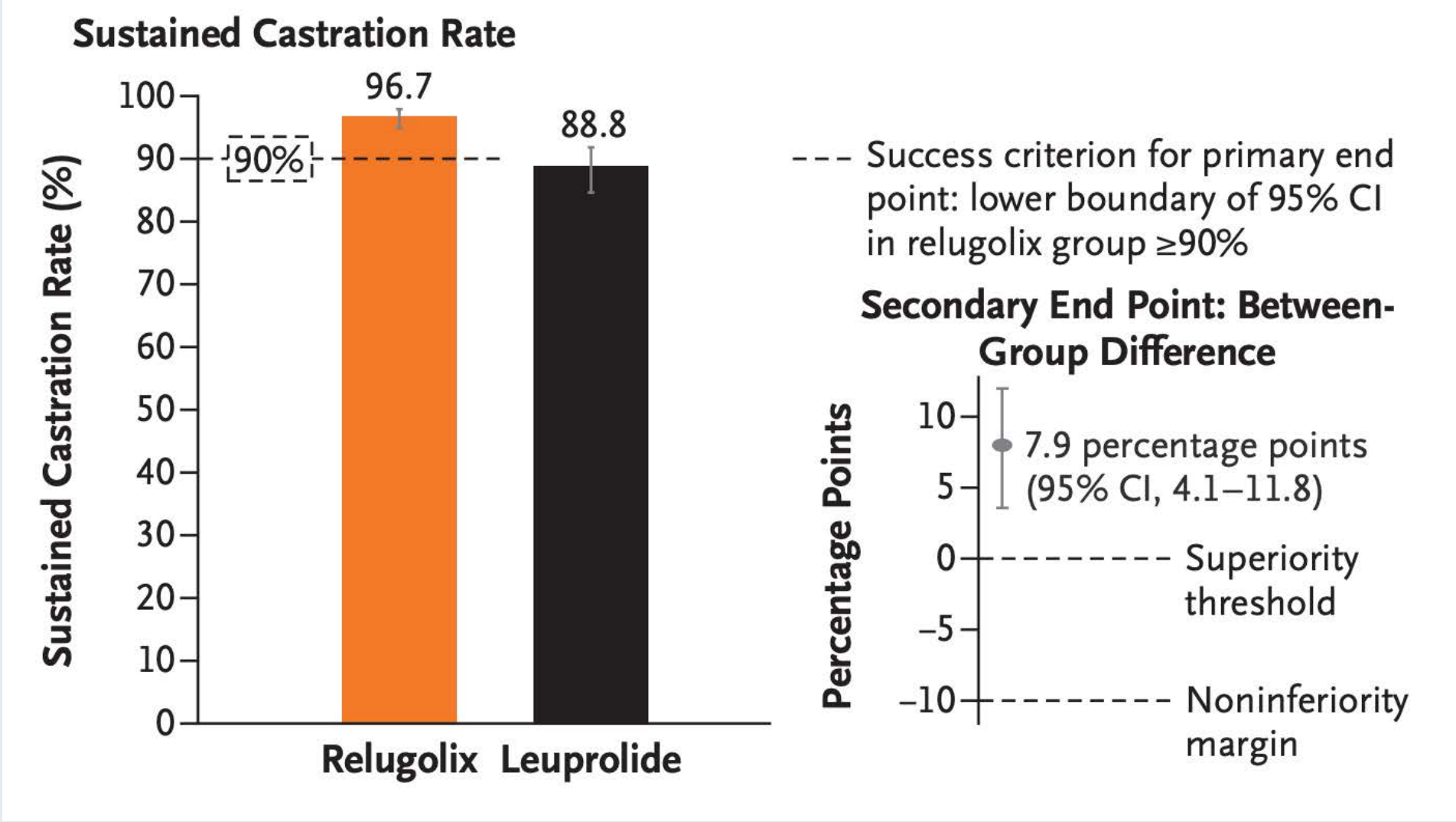
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 4, 2020 VOL. 382 NO. 23

Oral Relugolix for Androgen-Deprivation Therapy in Advanced Prostate Cancer

Neal D. Shore, M.D., Fred Saad, M.D., Michael S. Cookson, M.D., M.M.H.C., Daniel J. George, M.D., Daniel R. Saltzstein, M.D., Ronald Tutrone, M.D., Hideyuki Akaza, M.D., Alberto Bossi, M.D., David F. van Veenhuyzen, M.B., Ch.B., M.Pharm.Med., Bryan Selby, M.S., Xiaolin Fan, Ph.D., Vicky Kang, M.D., Jackie Walling, M.B., Ch.B., Ph.D., and Bertrand Tombal, M.D., Ph.D., for the HERO Study Investigators*

HERO: Oral Relugolix versus Leuprolide Acetate for Androgen-Deprivation Therapy



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

Balancing the benefits/risks of treatment

- Improved survival
- Delayed progression
- Psychological benefits of receiving treatment

Benefits

Shared decision making: goals of patient

- Expense: COST $$$$... ↓ QOL
- ED and ↓ libido
- Hot flashes
- Changes in mood/ ↓cognition
- ↓ strength/ muscle mass
- Osteoporosis
- Anemia, fatigue
- Metabolic syndrome
- Cardiac risk, DM

Risks

Courtesy of Victoria Sinibaldi, RN, MS, CS, CANP, BC

Commentary — Kathy D Burns, RN, MSN, AGACNP-BC, OCN

Side effects – managing expectations

It's important to touch on all of them and give written materials or a reliable website.

- Reduced or absent sexual desire
- Erectile dysfunction (impotence)
- Shrinkage of testicles and penis
- Hot flashes, which may get better or go away with time
- Breast tenderness and growth of breast tissue (gynecomastia)
- Osteoporosis (bone thinning), which can lead to broken bones
- Anemia (low red blood cell counts)
- Decreased mental sharpness/mental fogginess
- Loss of muscle mass
- Weight gain
- Fatigue
- Increased cholesterol levels
- Depression/mood swings

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Agenda

Module 1: Overview of Prostate Cancer

Module 2: Intensification of Therapy for Localized Disease

Module 3: Hormone-Sensitive Metastatic Disease

Module 4: PARP Inhibitors — Monotherapy and Combinations

Module 5: PARP Inhibitors — Toxicity

Module 6: Radioligand Therapy

Susan K Roethke, MSN, CRNP, AOCNP, ANP-BC

90-year-old man with M0 castration-resistant prostate cancer (CRPC) who received enzalutamide

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Dr Agarwal
Salt Lake City, Utah

Clinical Research Background

Dr Srinivas
Stanford, California

- **Intensification of therapy for localized disease**
  - **Current and future role of secondary hormonal therapies**

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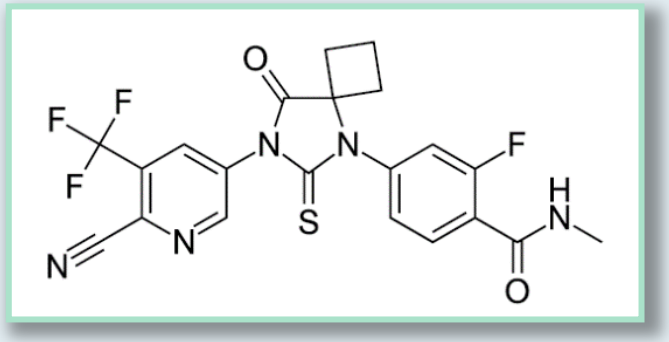
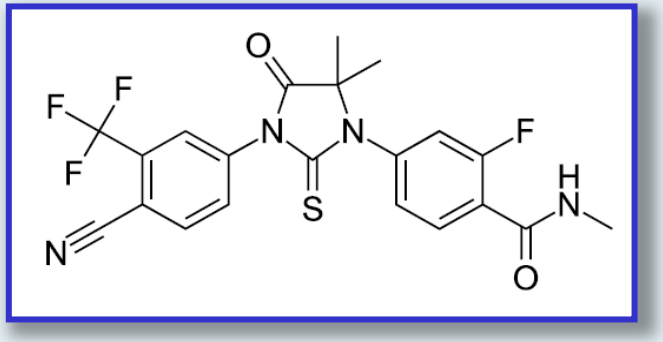
Next-Generation Androgen Receptor Pathway Inhibitors (ARPIs)[1,2]

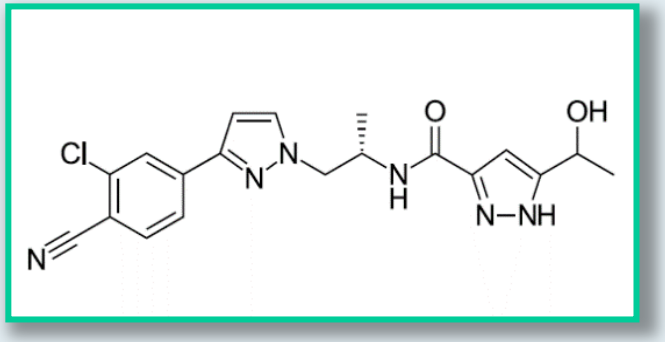
Apalutamide



Enzalutamide



Darolutamide



- Apalutamide and enzalutamide have similar structures
- Darolutamide is structurally distinct from apalutamide and enzalutamide, characterized by low blood–brain barrier penetration[1,2,] and may have improved tolerability

1. Zurth C et al. *J Clin Oncol*. 2018;36(Suppl 6):Abstract 345.
2. Sandmann S et al. American Society of Clinical Oncology 2019 Genitourinary Cancers Symposium (ASCO GU 2019). Abstract 156.

Phase III EMBARK Trial Meets Primary Endpoint with Enzalutamide Plus Leuprolide for Non-Metastatic HSPC

Press Release: March 16, 2023

"Today, positive topline results [were announced] from the Phase 3 EMBARK trial evaluating enzalutamide in men with non-metastatic hormone-sensitive prostate cancer (nmHSPC; also known as non-metastatic castration-sensitive prostate cancer or nmCSPC) with high-risk biochemical recurrence (BCR). Patients enrolled in the trial were randomized to one of three study arms: enzalutamide plus leuprolide, placebo plus leuprolide, or enzalutamide monotherapy. The study met its primary endpoint with a statistically significant and clinically meaningful improvement in metastasis-free survival (MFS) for patients treated with enzalutamide plus leuprolide versus placebo plus leuprolide.

At the time of the analysis, a positive trend in the key secondary endpoint of overall survival (OS) was also observed, but these data were not yet mature. Patients in the trial will be followed for a subsequent final OS analysis. The study also met a key secondary endpoint with a statistically significant and clinically meaningful improvement in MFS for patients treated with enzalutamide monotherapy versus placebo plus leuprolide. Additional key secondary endpoints reached statistical significance, including time to prostate-specific antigen (PSA) progression and time to first use of new antineoplastic therapy. Other secondary endpoints are being analyzed. No new safety signals have been observed to date in the preliminary safety analysis, which is consistent with the established safety profile of enzalutamide."

https://www.prnewswire.com/news-releases/phase-3-study-shows-xtandi-enzalutamide-plus-leuprolide-significantly-improves-metastasis-free-survival-in-men-with-non-metastatic-prostate-cancer-301774642.html

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The NEW ENGLAND JOURNAL of MEDICINE

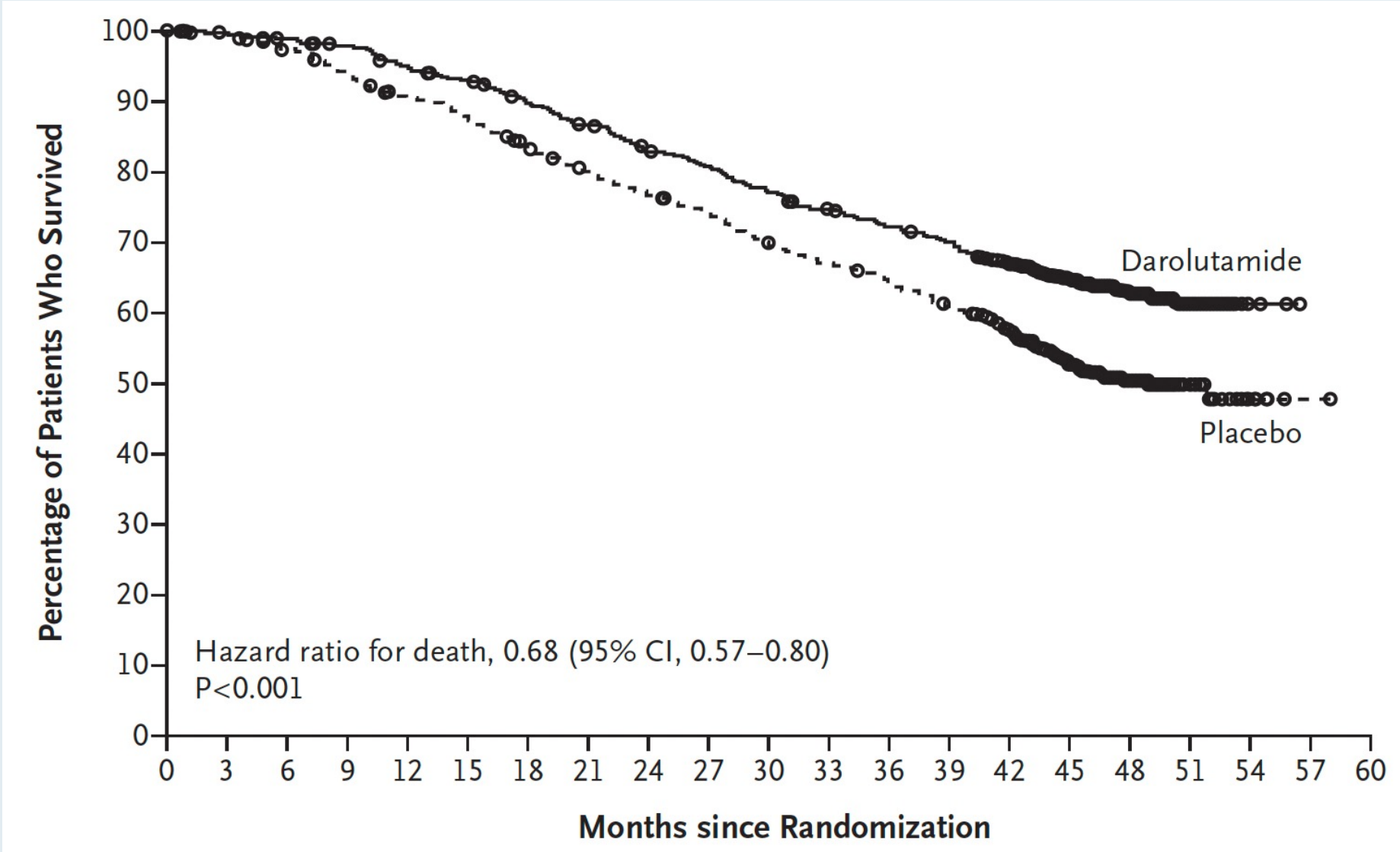
N Engl J Med 2022 Mar;386(12):1132-42.

ORIGINAL ARTICLE

Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer

Matthew R. Smith, M.D., Ph.D., Maha Hussain, M.D., Fred Saad, M.D., Karim Fizazi, M.D., Ph.D., Cora N. Sternberg, M.D., E. David Crawford, M.D., Evgeny Kopyltsov, M.D., Chandler H. Park, M.D., Boris Alekseev, M.D., Álvaro Montesa-Pino, M.D., Dingwei Ye, M.D., Francis Parnis, M.B., B.S., Felipe Cruz, M.D., Teuvo L.J. Tammela, M.D., Ph.D., Hiroyoshi Suzuki, M.D., Ph.D., Tapio Utriainen, M.D., Cheng Fu, M.D., Motohide Uemura, M.D., Ph.D., María J. Méndez-Vidal, M.D., Benjamin L. Maughan, M.D., Pharm.D., Heikki Joensuu, M.D., Silke Thiele, M.D., Rui Li, M.S., Iris Kuss, M.D., and Bertrand Tombal, M.D., Ph.D., for the ARASENS Trial Investigators*

ARASENS: Overall Survival (Primary Endpoint)



Smith MR et al. *N Engl J Med* 2022;386(12):1132-42.

Susan K Roethke, MSN, CRNP, AOCNP, ANP-BC

76-year-old man with metastatic CRPC who received ADT with apalutamide

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Dr Agarwal
Salt Lake City, Utah

Clinical Research Background

Dr Srinivas
Stanford, California

- **Hormone-sensitive metastatic disease**
  - **Selection of cytotoxic therapy, secondary hormonal therapy or both to combine with ADT**

Agenda

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Module 5: Radioligand Therapy

Kathy D Burns, RN, MSN, AGACNP-BC, OCN

69-year-old man with metastatic CRPC and a germline BRCA1 mutation who received olaparib

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Susan K Roethke, MSN, CRNP, AOCNP, ANP-BC

79-year-old man with metastatic CRPC and a somatic CHEK2 mutation who received olaparib

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Dr Agarwal
Salt Lake City, Utah

Clinical Research Background

Dr Srinivas
Stanford, California

- **PARP inhibitors**
  - **Genetic testing**
  - **Monotherapy**
  - **Combination strategies**
  - **Tolerability**

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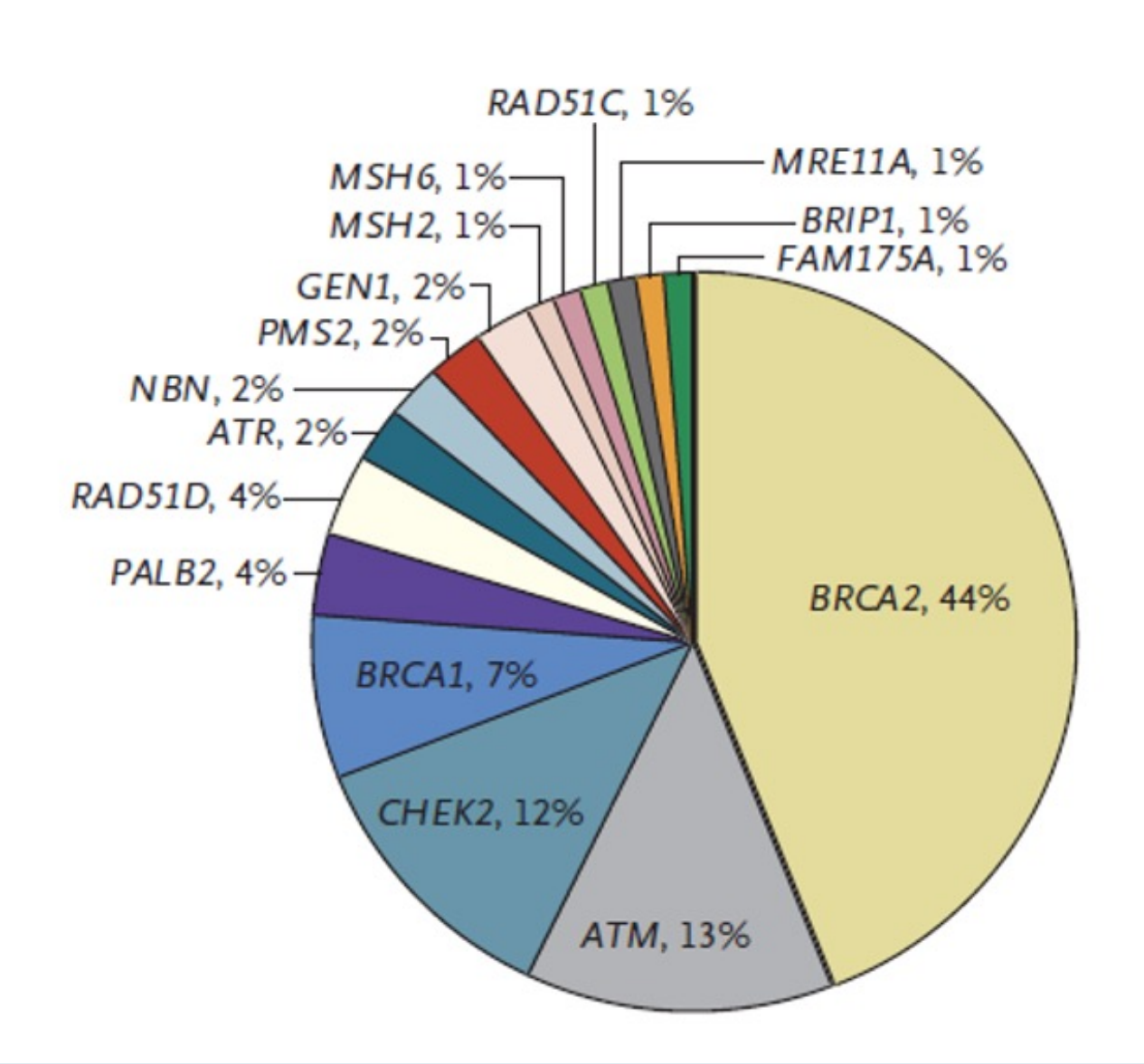
Inherited DNA Repair Gene Mutations in Men with Metastatic Prostate Cancer



- 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

ASCO Genitourinary Cancers Symposium 2023

Abstract LBA16

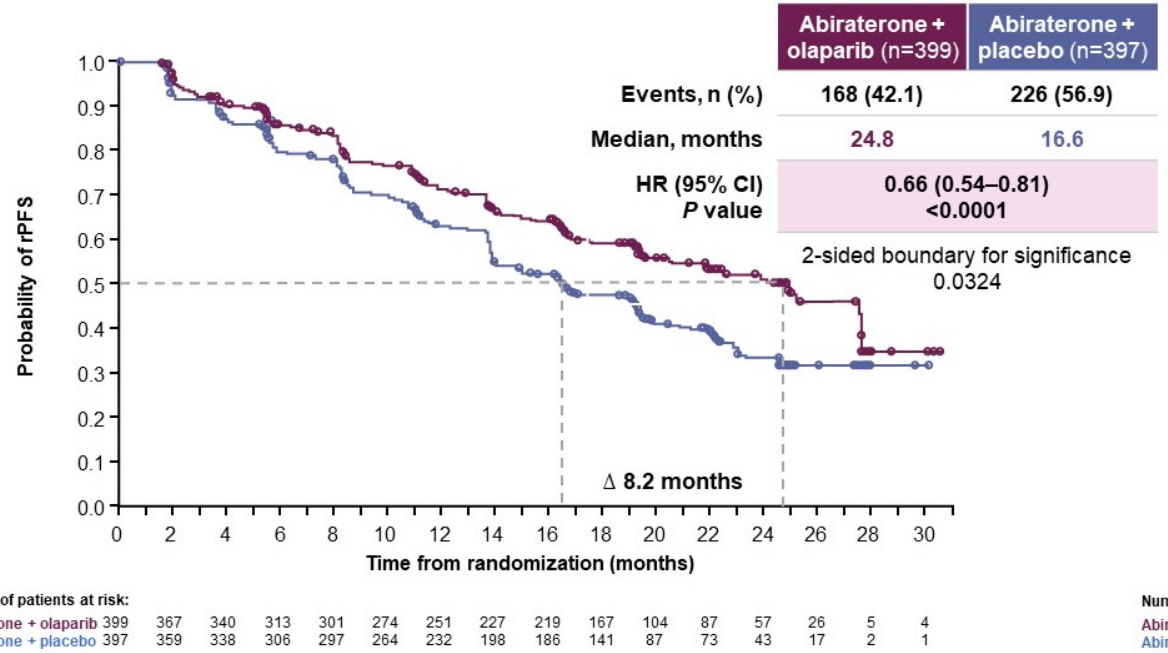
Final pre-specified overall survival in PROpel: abiraterone and olaparib versus abiraterone and placebo as first-line therapy for metastatic castration-resistant prostate cancer

Noel Clarke, Andrew J. Armstrong, Antoine Thiery-Vuillemin, Mototsugu Oya, Neal Shore, Giuseppe Procopio, João Daniel Guedes, Cagatay Arslan, Niven Mehra, Francis Parnis, Emma Brown, Friederike Schlürmann, Jae Young Joung, Mikio Sugimoto, Oliver Sartor, Yu-Zhen Liu, Christian Poehlein, Laura Barker, Paula Michelle del Rosario, Fred Saad

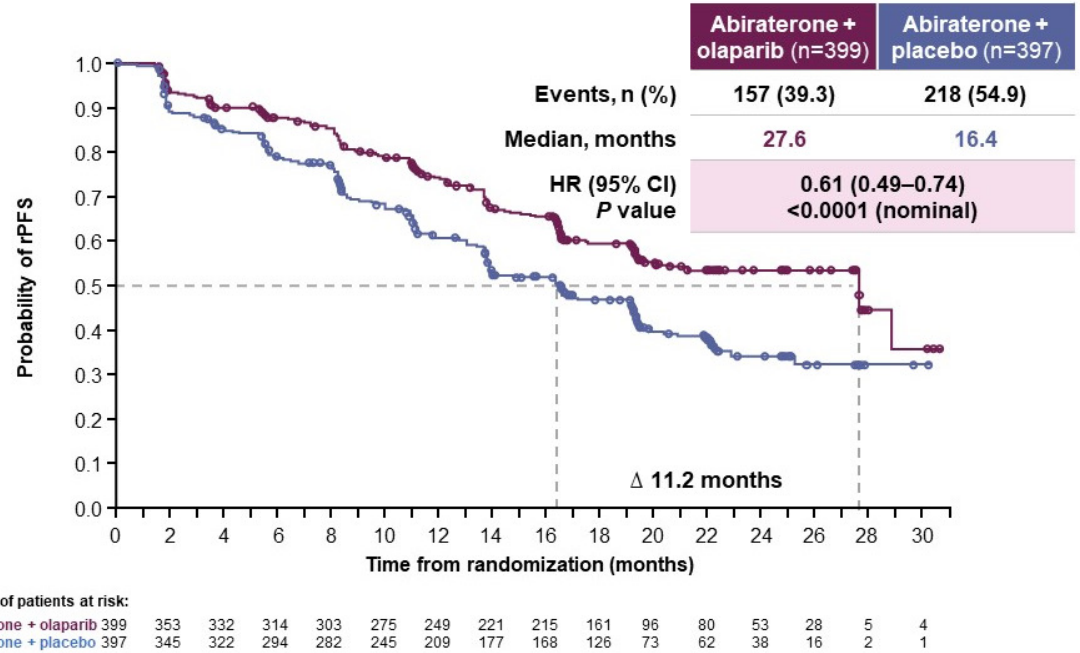
PROpel: Primary Radiographic Progression-Free Survival (rPFS) Results (DCO1)[1]

Abiraterone + olaparib significantly prolonged rPFS versus abiraterone + placebo in the ITT population

rPFS by investigator assessment (INV)



rPFS by blinded independent central review (BICR)



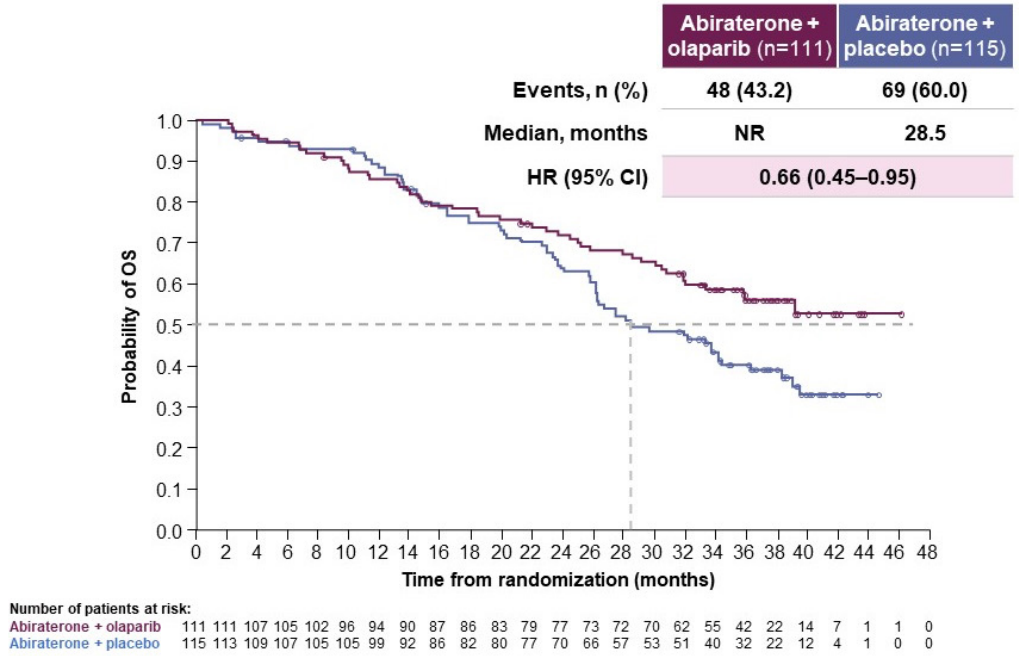
DCO1: 30 July 2021.
Median duration of follow-up for investigator-assessed rPFS for censored patients was 19.3 months in the abiraterone and olaparib arm, and 19.4 months in the abiraterone and placebo arm (19.3 and 19.2 months, respectively, for BICR).
ITT, intention-to-treat.
1. Clarke N *et al*. *NEJM Evidence* 2022;1(9).

Clarke N et al. Genitourinary Cancers Symposium 2023;Abstract LBA16.

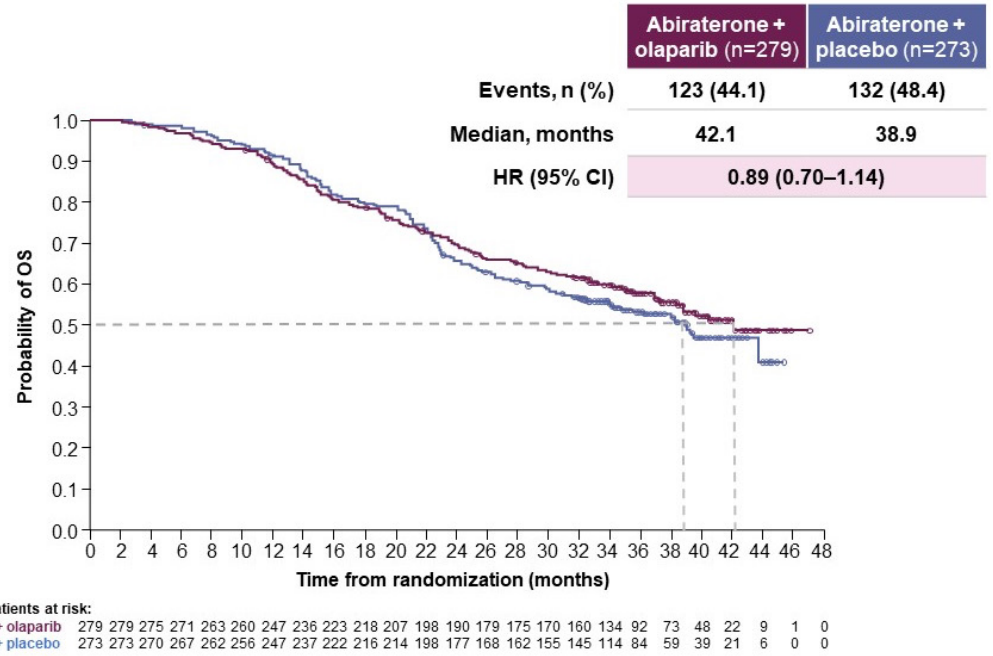
PROpel: Overall Survival (OS) in HRRm and Non-HRRm Subgroups (DCO3)

A trend towards OS benefit was observed across HRRm and non-HRRm subgroups

HRRm (28.4% of ITT population)



Non-HRRm (69.3% of ITT population)



DCO3: 12 October 2022.
The preplanned tumor tissue and plasma ctDNA testing was conducted after randomization and before primary analysis. Results from tumor tissue and plasma ctDNA were combined to determine patients HRRm status (see supplement for more details). 18 patients had unknown HRRm status.

HRRm = homologous recombination repair mutation

Clarke N et al. Genitourinary Cancers Symposium 2023;Abstract LBA16.

original reports

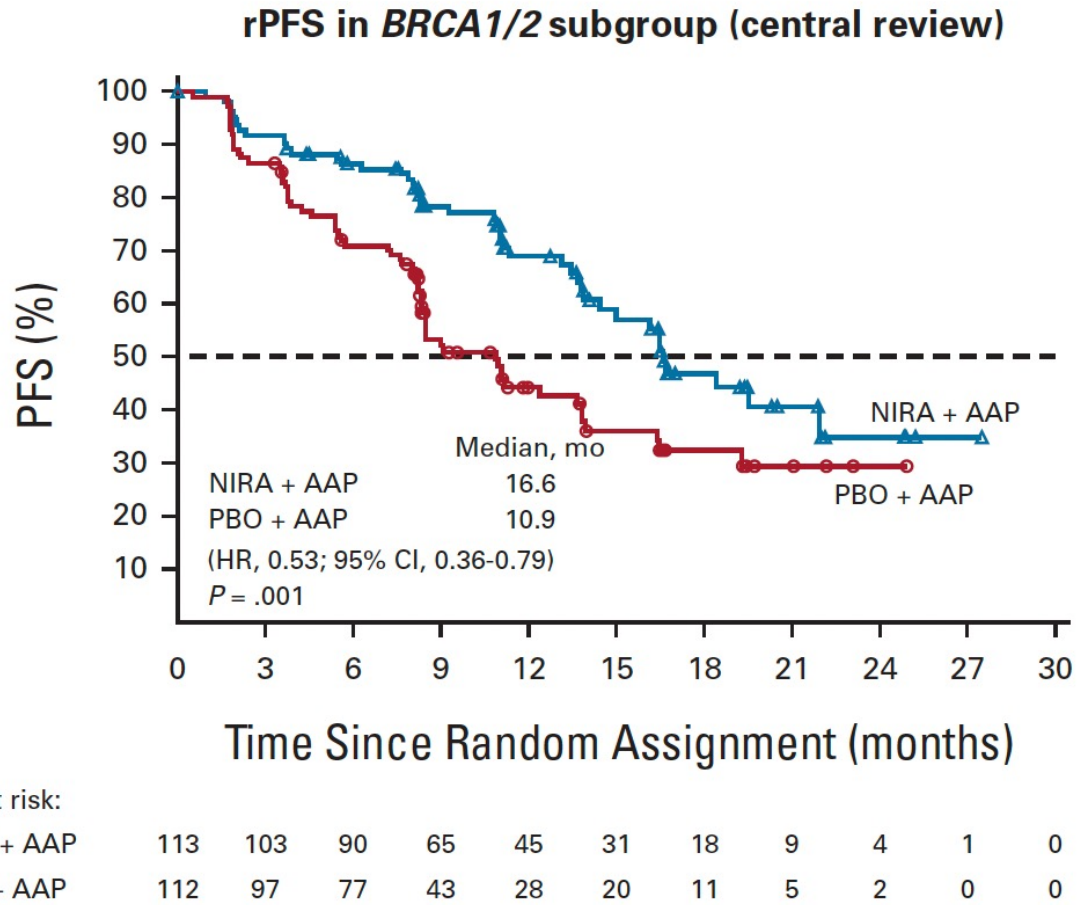
Niraparib and Abiraterone Acetate for Metastatic Castration-Resistant Prostate Cancer

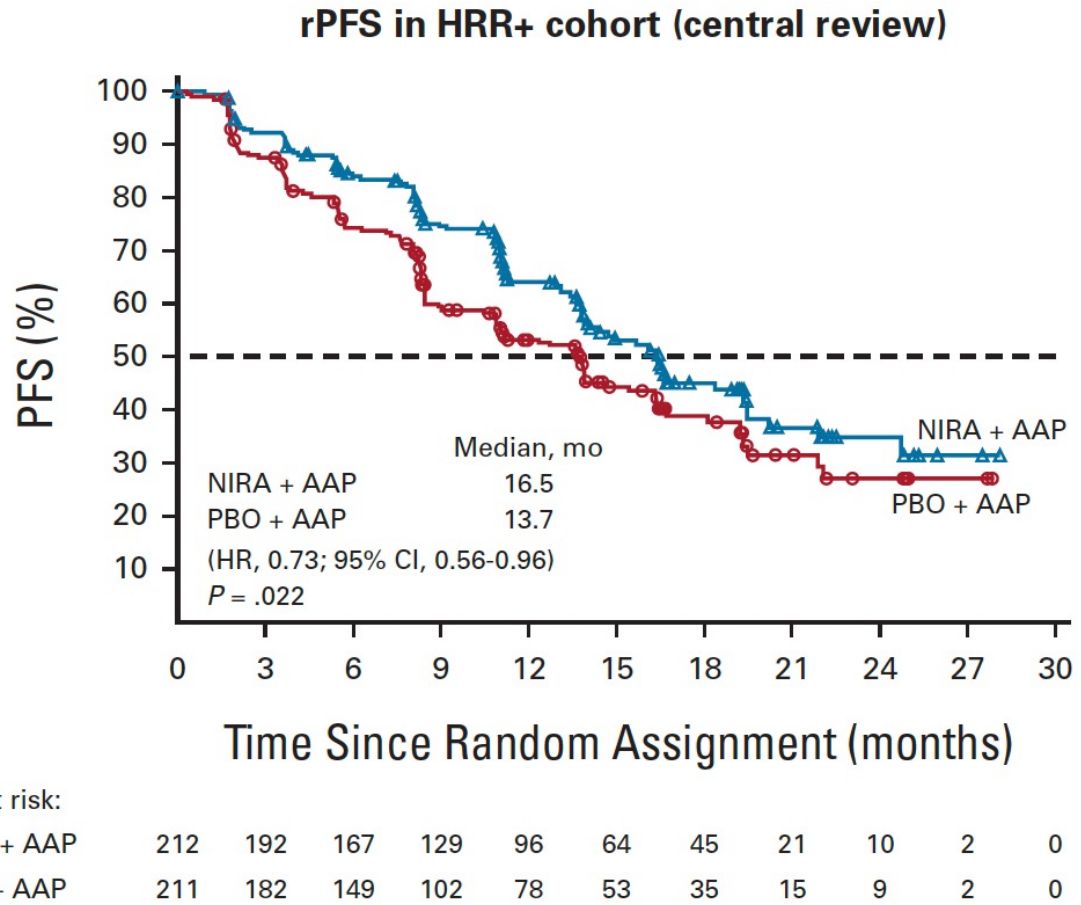
Kim N. Chi, MD[1]; Dana Rathkopf, MD[2]; Matthew R. Smith, MD[3]; Eleni Efstathiou, MD[4]; Gerhardt Attard, MD[5]; David Olmos, MD[6]; Ji Youl Lee, MD[7]; Eric J. Small, MD[8]; Andrea J. Pereira de Santana Gomes, MD[9]; Guilhem Roubaud, MD[10]; Marniza Saad, MD[11]; Bogdan Zurawski, MD[12]; Valerii Sakalo, MD[13]; Gary E. Mason, MD[14]; Peter Francis, MD[15]; George Wang, MS, MAS[14]; Daphne Wu, PhD[16]; Brooke Diorio, PhD[17]; Angela Lopez-Gitlitz, MD[16]; and Shahneen Sandhu, MD[18]; on behalf of the MAGNITUDE Principal Investigators

J Clin Oncol 2023 March 23;[Online ahead of print].

RTP RESEARCH TO PRACTICE

MAGNITUDE Trial: Radiographic PFS in BRCA1/2 Subgroup and HRR+ Cohort (Central Review)





Chi KN et al. *J Clin Oncol* March 23;Epub ahead of print.

Presentation number LBA17

ASCO Genitourinary Cancers Symposium 2023 | Abstract LBA17

TALAPRO-2: Phase 3 study of talazoparib plus enzalutamide versus placebo plus enzalutamide as first-line treatment in patients with metastatic castration-resistant prostate cancer

Neeraj Agarwal,[1] Arun A. Azad,[2] Joan Carles,[3] Andre P. Fay,[4] Nobuaki Matsubara,[5] Daniel Heinrich,[6] Cezary Szczylik,[7] Ugo De Giorgi,[8] Jae Young Joung,[9] Peter C. Fong,[10] Eric Voog,[11] Robert J. Jones,[12] Neal D. Shore,[13] Curtis Dunshee,[14] Stefanie Zschäbitz,[15] Jan Oldenburg,[16] Xun Lin,[17] Cynthia G. Healy,[18] Nicola Di Santo,[19] Fabian Zohren,[17] Karim Fizazi[20]

[1]Huntsman Cancer Institute (NCI-CCC), University of Utah, Salt Lake City, UT, USA; [2]Peter MacCallum Cancer Centre, Melbourne, Australia; [3]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [4]PUCRS School of Medicine, Porto Alegre, Brazil; [5]National Cancer Center Hospital East, Chiba, Japan; [6]Innlandet Hospital Trust, Gjøvik, Norway; [7]Department of Oncology European Health Center, Otwock, Poland, and Postgraduate Medical Education Center, Warsaw, Poland; [8]IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) Dino Amadori, Meldola, Italy; [9]National Cancer Center, Goyang, Republic of Korea; [10]Auckland City Hospital and University of Auckland, Auckland, New Zealand; [11]Clinique Victor Hugo Centre Jean Bernard, Le Mans, France; [12]School of Cancer Sciences, University of Glasgow, Beatson West of Scotland Cancer Centre, Glasgow, UK; [13]Carolina Urologic Research Center, Myrtle Beach, SC, USA; [14]Arizona Urology Specialists, Tucson, AZ, USA; [15]National Center for Tumor Diseases (NCT), Heidelberg University Hospital, Heidelberg, Germany; [16]Akershus University Hospital (Ahus), Lørenskog, Norway; [17]Pfizer Inc., La Jolla, CA, USA; [18]Pfizer Inc., Collegeville, PA, USA; [19]Pfizer Inc., Durham, NC, USA; [20]Institut Gustave Roussy, University of Paris-Saclay, Villejuif, France

ClinicalTrials.gov identifier: NCT03395197
This study was sponsored by Pfizer Inc. Astellas Pharma Inc. provided enzalutamide

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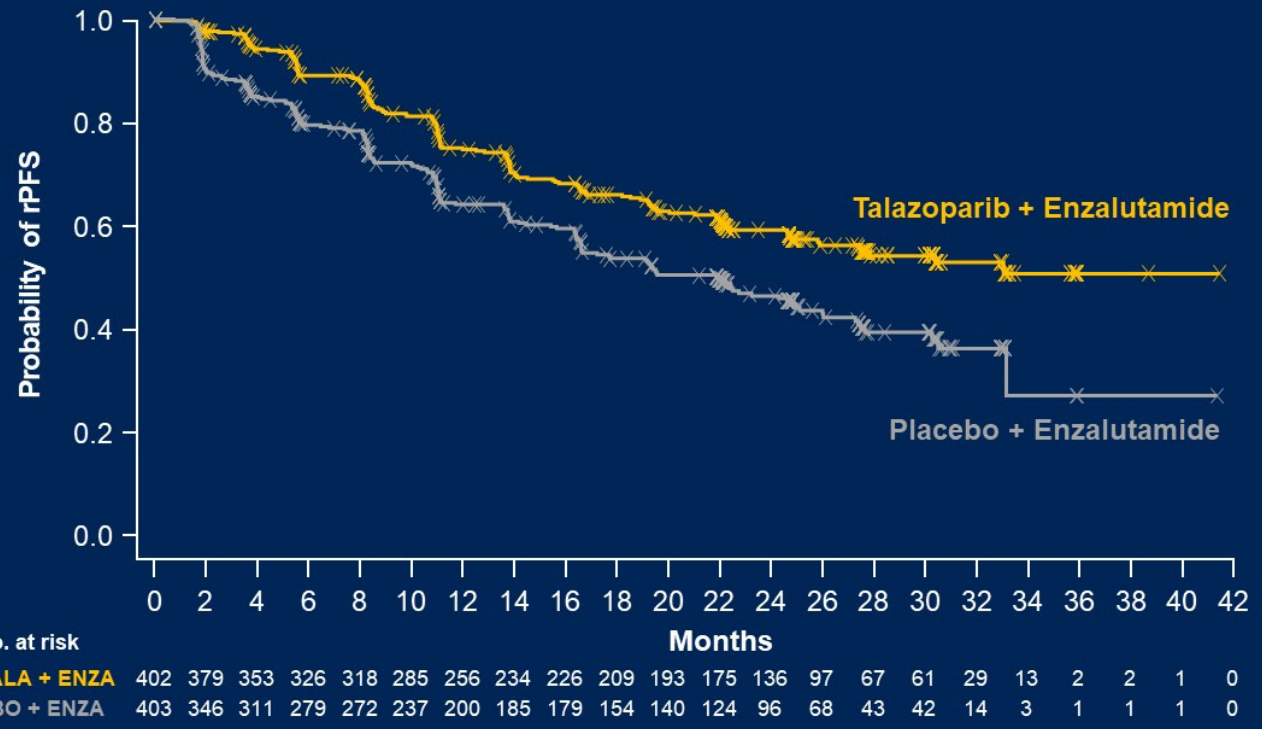
TALAPRO-2 Primary Endpoint: rPFS by BICR

Treatment with talazoparib plus enzalutamide resulted in a 37% reduced risk of progression or death



	TALA + ENZA (N=402)	PBO + ENZA (N=403)
Events, n	151	191
Median (95% CI), months	Not reached (NR) (27.5–NR)	21.9 (16.6–25.1)
HR (95% CI)	0.63 (0.51–0.78); *P* < 0.001	

Median follow-up for rPFS was 24.9 and 24.6 months, respectively

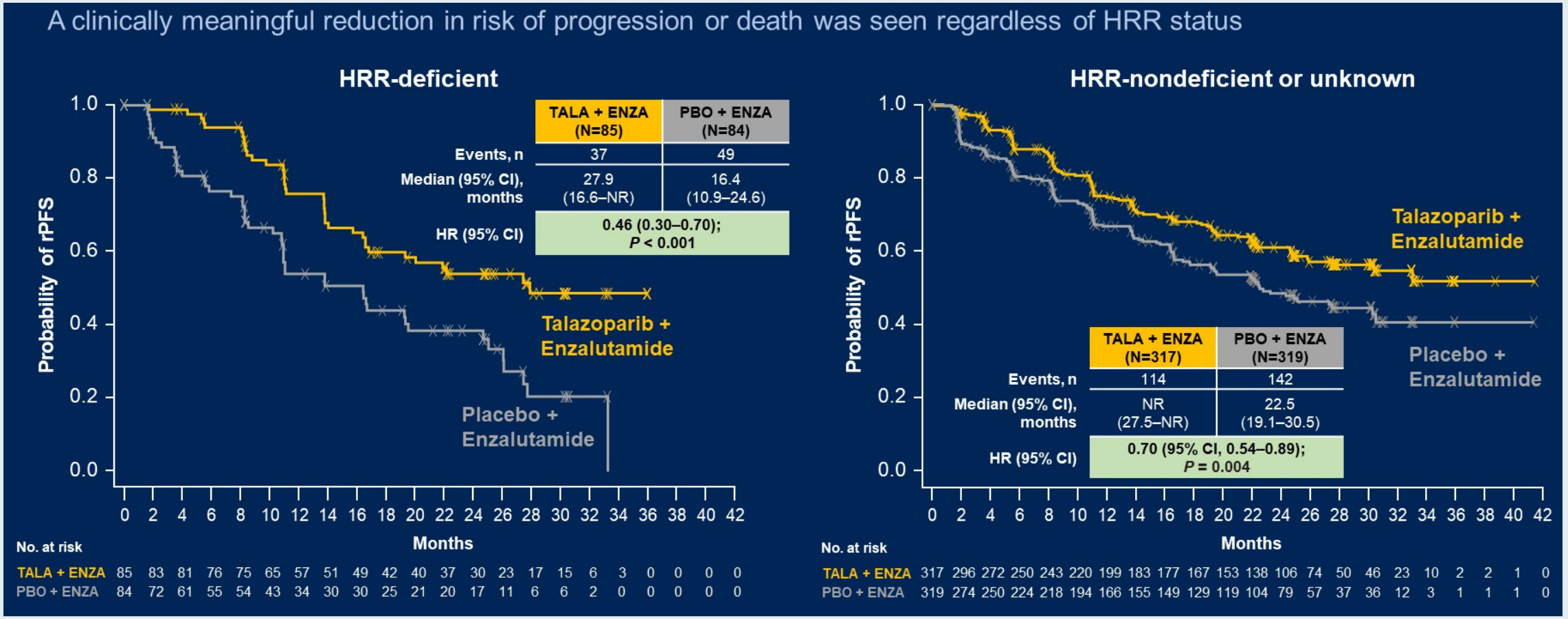
A consistent treatment effect was seen for investigator-assessed rPFS: HR 0.64 (95% CI, 0.50–0.81); *P* < 0.001

Stratified hazard ratios (HRs) and 2-sided *P* values are reported throughout this presentation unless otherwise stated.

Agarwal N et al. Genitourinary Cancers Symposium 2023;Abstract LBA17.

RTP RESEARCH TO PRACTICE

TALAPRO-2: rPFS by BICR by HRR Status



Agarwal N et al. Genitourinary Cancers Symposium 2023;Abstract LBA17.

Agenda

Module 1: Overview of Prostate Cancer

Module 2: Intensification of Therapy for Localized Disease

Module 3: Hormone-Sensitive Metastatic Disease

Module 4: PARP Inhibitors

Module 5: Radioligand Therapy

Kathy D Burns, RN, MSN, AGACNP-BC, OCN

62-year-old man with metastatic CRPC who received cabazitaxel while awaiting availability of ^{177}Lu-PSMA-617

RTP
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TO PRACTICE

Dr Agarwal
Salt Lake City, Utah

Clinical Research Background

Dr Srinivas
Stanford, California

- **Radioligand therapy**
  - **Radium-223**
  - **^{177}Lu-PSMA-617**

RTP
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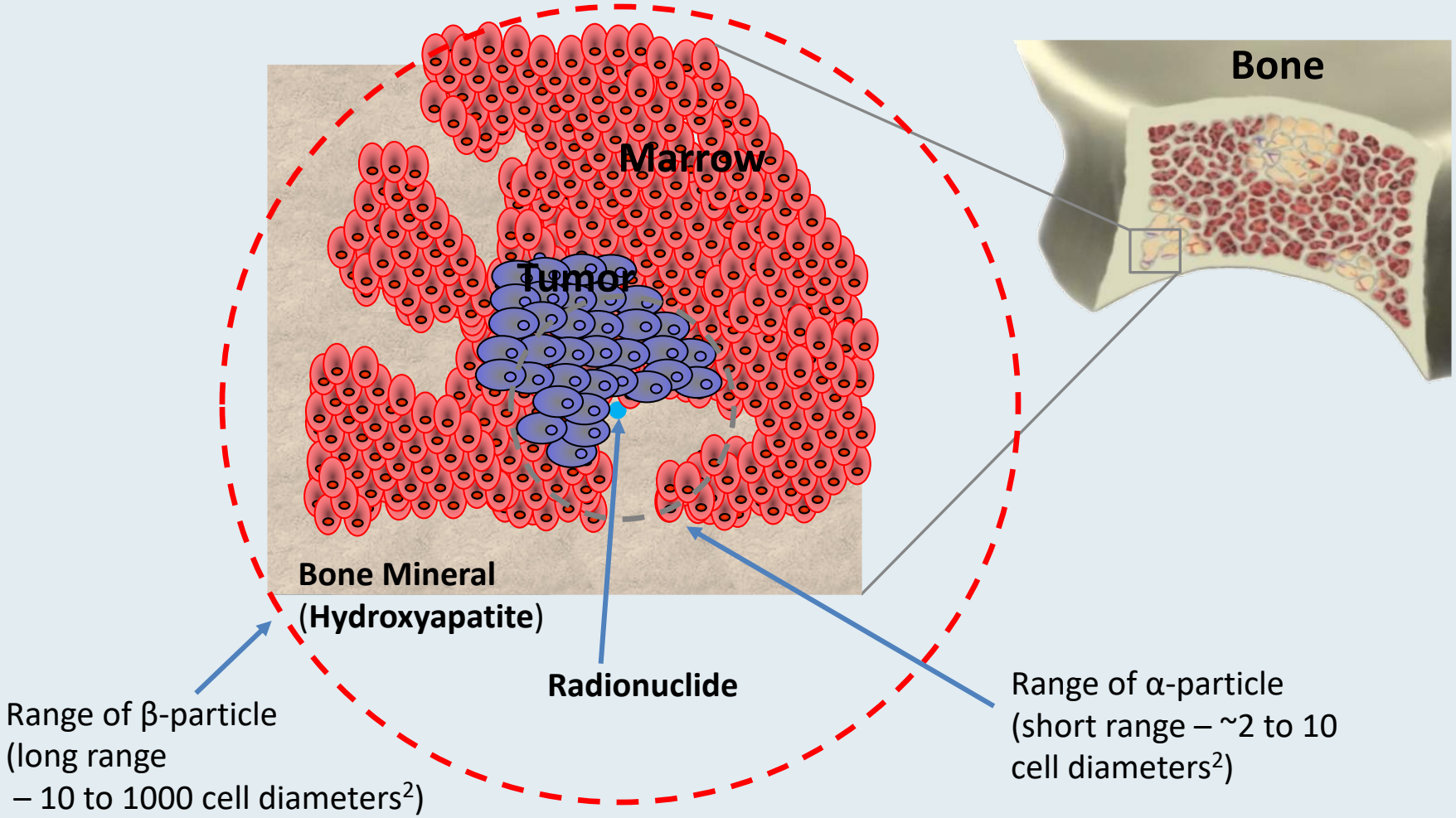
TO PRACTICE

Range of an α-emitting Radiopharmaceutical Compared to a β-emitter

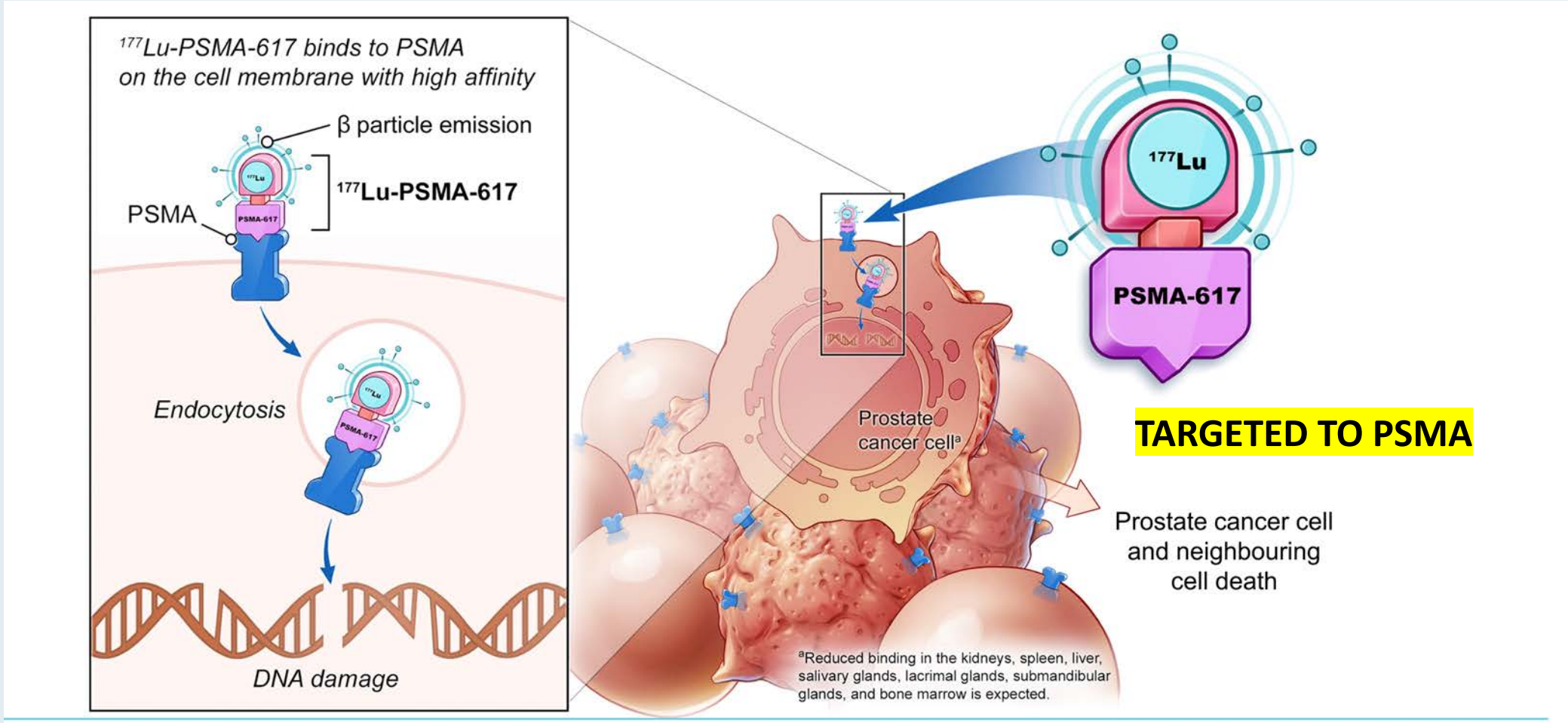
Short range of α-particles could reduce bone marrow exposure[1]



References: 1. Henriksen G, et al. *Cancer Res*. 2002;62:3120–3125. **2.** Brechbiel MW. *Dalton Trans*. 2007;43:4918-4928.

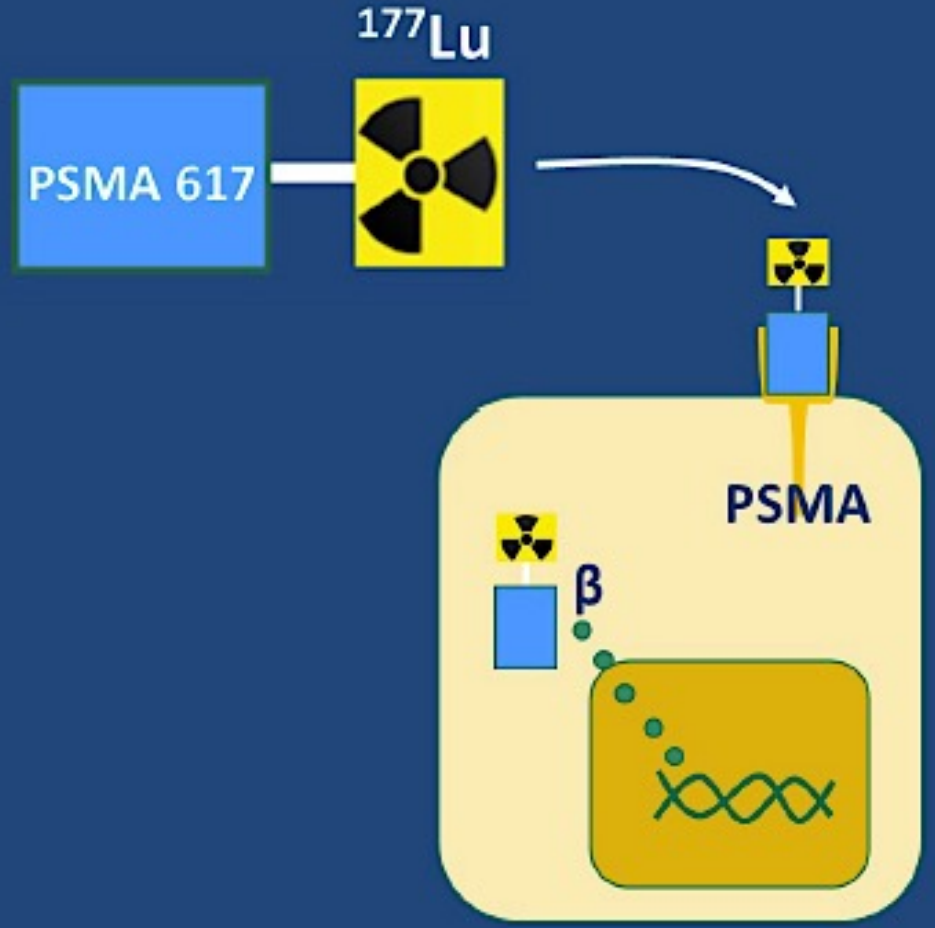
RTP RESEARCH TO PRACTICE

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



Morris MJ et al. ASCO 2021;Abstract LBA4.

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



RLT = radioligand therapy

Hofman S et al. ASCO 2020;Abstract 5500.

^{177}Lu-PSMA-617

Mechanism of action

- **Targeted radioligand**

Indication

- **For adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have received androgen receptor (AR) pathway inhibition and taxane-based chemotherapy**

Recommended dose

- **7.4 GBq (200 mCi) every 6 weeks for up to 6 doses**

Lutetium Lu 177 vipivotide tetraxetan package insert, 10/2022.

Planned/Ongoing Phase III Trials with PSMA in Earlier Settings

	PSMAddition	PSMAfore	SPLASH	ProstAct
Experimental agent	177Lu-PSMA-617	177Lu-PSMA-617	177Lu-PNT2002	177Lu-TLX591
Setting	mCSPC	mCRPC prechemo	mCRPC prechemo	mCRPC post-docetaxel
Primary endpoint	rPFS OS	rPFS OS	rPFS	rPFS
Number of patients	1126	495	415	387

Courtesy of Prof Karim Fizazi, MD, PhD

Phase III PMSAfore Trial Meets Primary Endpoint with ^{177}Lu-PSMA-617 for PSMA-Positive mCRPC

Press Release: December 5, 2022

"Today, [it was announced that] the pivotal Phase III PSMAfore study with ^{177}Lu-PSMA-617, a prostate-specific membrane antigen (PSMA)-targeted radioligand therapy, met its primary endpoint. ^{177}Lu-PSMA-617 demonstrated a statistically significant and clinically meaningful improvement in radiographic progression-free survival (rPFS) in patients with PSMA–positive metastatic castration-resistant prostate cancer (mCRPC) after treatment with androgen-receptor pathway inhibitor (ARPI) therapy, compared to a change in ARPI. No unexpected safety findings were observed in PSMAfore; data are consistent with the already-well established safety profile of ^{177}Lu-PSMA-617.

This is the second positive read-out for ^{177}Lu-PSMA-617 in a Phase III trial following the VISION study, where patients with PSMA–positive mCRPC who received ^{177}Lu-PSMA-617 plus standard of care after being treated with ARPI and taxane-based chemotherapy had a statistically significant reduction in risk of death. The PSMAfore results continue to support the important role of ^{177}Lu-PSMA-617 in treating patients with prostate cancer. The Phase III data will be presented at an upcoming medical meeting and discussed with the US Food and Drug Administration (FDA) in 2023 for regulatory approval."

https://www.globenewswire.com/en/news-release/2022/12/05/2567028/0/en/Novartis-PluvictoTM-shows-statistically-significant-and-clinically-meaningful-radiographic-progression-free-survival-benefit-in-patients-with-PSMA-positive-metastatic-castration-re.html

Radium-223 Chloride

Mechanism of action

- Alpha particle-emitting radioactive therapeutic agent

Indication

- For patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease

Recommended dose

- 55 kBq (1.49 microcurie) per kg body weight, administered at 4-week intervals for 6 injections

Radium-223 package insert, 12/2019.

RTP RESEARCH TO PRACTICE

APPENDIX

Relugolix

FDA Approves Relugolix for Advanced Prostate Cancer

Press Release – December 18, 2020

"On December 18, 2020, the 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

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 4, 2020 VOL. 382 NO. 23

Oral Relugolix for Androgen-Deprivation Therapy in Advanced Prostate Cancer

Neal D. Shore, M.D., Fred Saad, M.D., Michael S. Cookson, M.D., M.M.H.C., Daniel J. George, M.D., Daniel R. Saltzstein, M.D., Ronald Tutrone, M.D., Hideyuki Akaza, M.D., Alberto Bossi, M.D., David F. van Veenhuyzen, M.B., Ch.B., M.Pharm.Med., Bryan Selby, M.S., Xiaolin Fan, Ph.D., Vicky Kang, M.D., Jackie Walling, M.B., Ch.B., Ph.D., and Bertrand Tombal, M.D., Ph.D., for the HERO Study Investigators*

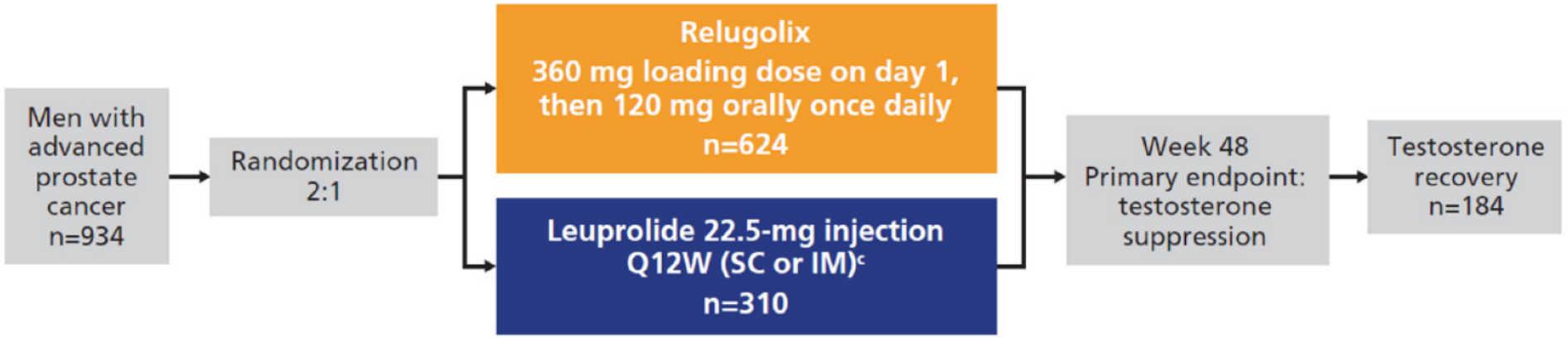
HERO: A Randomized Phase III Study Evaluating Relugolix versus Leuprolide for Advanced Prostate Cancer

Primary objective:

- **US:** Sustained castration[a] rate: lower bound of 95% CI ≥90% in relugolix
- **EU/JAPAN:** Sustained castration[a] rate: non-inferiority of relugolix vs leuprolide

Secondary objectives include:

- Castration[a] rate at day 4
- Castration[a] rate at day 15 (2 weeks)
- Confirmed PSA response rate (>50%) at day 15 (2 weeks)
- Profound castration[b] rate at day 15 (2 weeks)
- FSH level at week 25, day 1 (6 months)
- Castration resistance-free survival
- Time to testosterone recovery

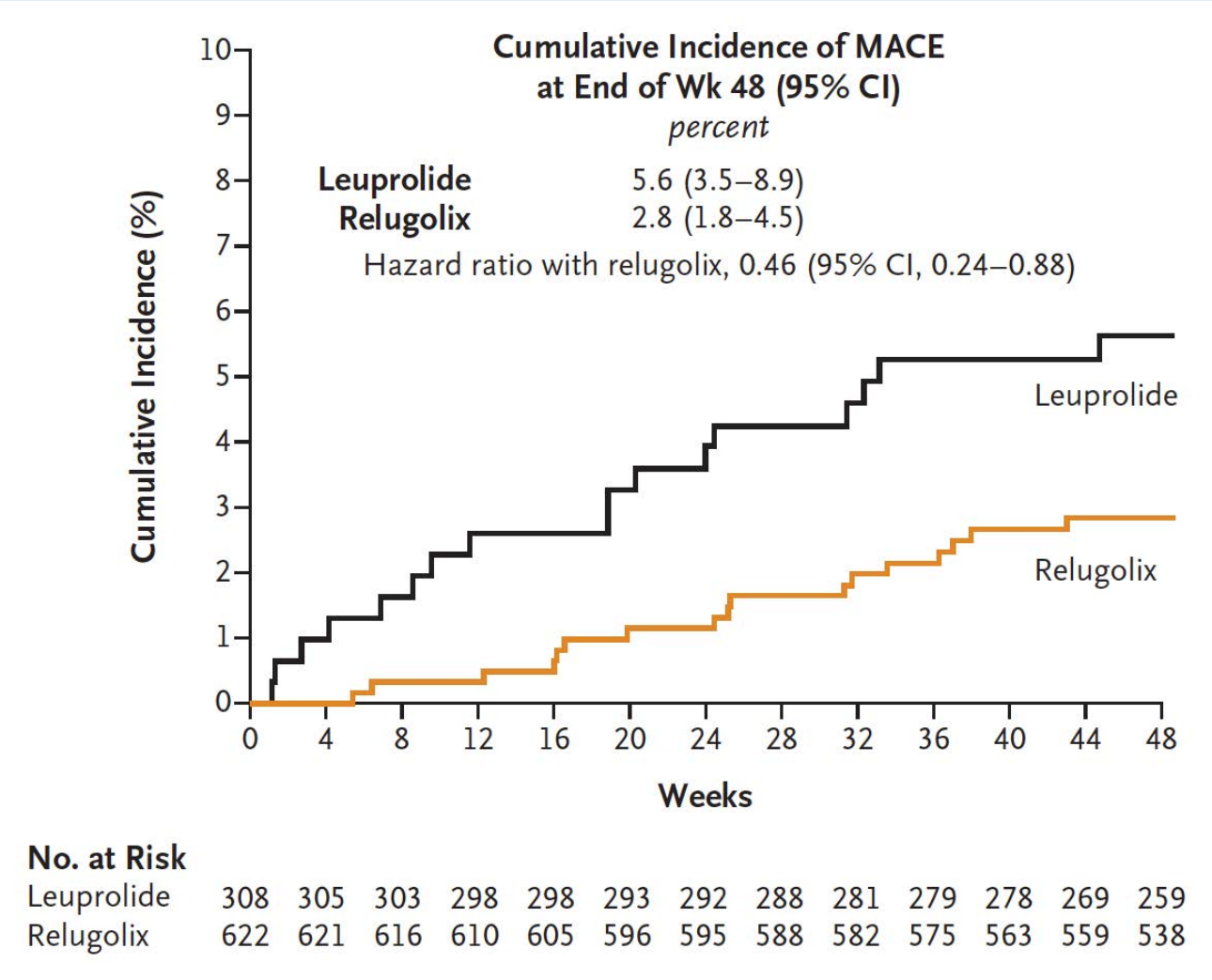


[a]<50 ng/dL; [b]<20 ng/dL; [c]11.25 mg in China, Japan, and Taiwan.

CI, confidence interval; CSPC, castration-sensitive prostate cancer; EU, European Union; FSH, follicle-stimulating hormone; IM, intramuscular; PSA, prostate-specific antigen; Q12W, every 12 weeks; SC, subcutaneous; US, United States.

Saad F et al. *Ther Adv Med Oncol* 2021;13:1-12.

HERO: Cumulative Incidence of Major Adverse Cardiovascular Events (MACE)



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

AUA 2022

MP27-16 ORAL RELUGOLIX FOR ANDROGEN DEPRIVATION THERAPY IN ADVANCED PROSTATE CANCER: DETAILED SAFETY ANALYSIS FROM THE RANDOMIZED PHASE 3 HERO STUDY

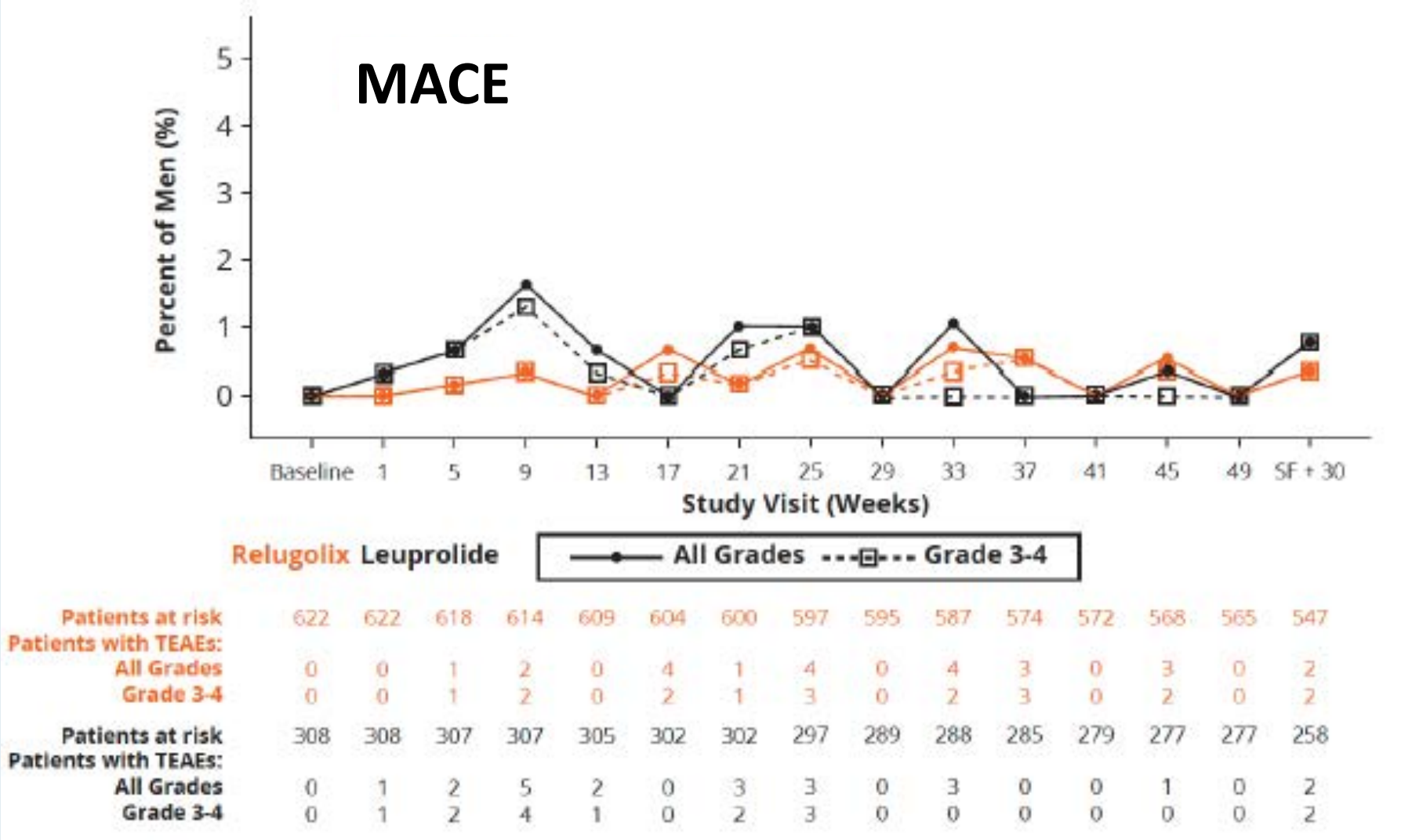
Bryan Mehlhaff, Neal D. Shore, Daniel J. George, Michael S. Cookson, Daniel R. Saltzstein, Ronald Tutrone, James L. Bailen, Bruce Brown, Andria G.M. Langenberg, Mark Fallick, Sophia Lu, Sarah Hanson, Bertrand Tombal, and Fred Saad

HERO: Onset and Duration of Adverse Events (AEs) with Relugolix for Advanced Prostate Cancer

	Relugolix (N = 622)			Leuprolide (N = 308)		
	AE n (%)	Onset (Days)[a] Median (min, max)	Duration (Days)[b] Median (min, max)	AE n (%)	Onset (Days)[a] Median (min, max)	Duration (Days)[b] Median (min, max)
AEs in > 10% of men						
Hot flash	338 (54.3)	19 (1, 343)	342 (15, 477)	159 (51.6)	33 (1, 200)	331 (1, 428)
Fatigue	134 (21.5)	46 (1, 342)	289 (2, 429)	57 (18.5)	41 (1, 326)	274 (3, 426)
Constipation	76 (12.2)	128 (1, 359)	67 (2, 409)	30 (9.7)	61 (1, 273)	92 (3, 410)
Diarrhea[d]	76 (12.2)	76 (1, 338)	9 (1, 370)	21 (6.8)	133 (2, 313)	3 (1, 224)
Arthralgia	75 (12.1)	142 (1, 355)	160 (1, 495)	28 (9.1)	189 (1, 370)	130 (2, 589)
Grade ≥ 3 AEs in ≥ 1% men						
Hypertension[e]	10 (1.6)	206 (15, 334)	15 (1, 328)	2 (0.6)	55 (21, 89)	27 (2, 51)
Diabetes	6 (1.0)	203 (85, 338)	118 (1, 204)	2 (0.6)	32 (29, 34)	192 (53, 330)
Syncope	6 (1.0)	163 (79, 315)	N/A	3 (1.0)	83 (45, 214)	N/A
MACE[c]	18 (2.9)	177 (38, 343)	N/A	19 (6.2)	132 (8, 352)	N/A

Mehlhaff B et al. AUA 2022;Abstract MP27-16.

HERO: MACE by Week During the Study



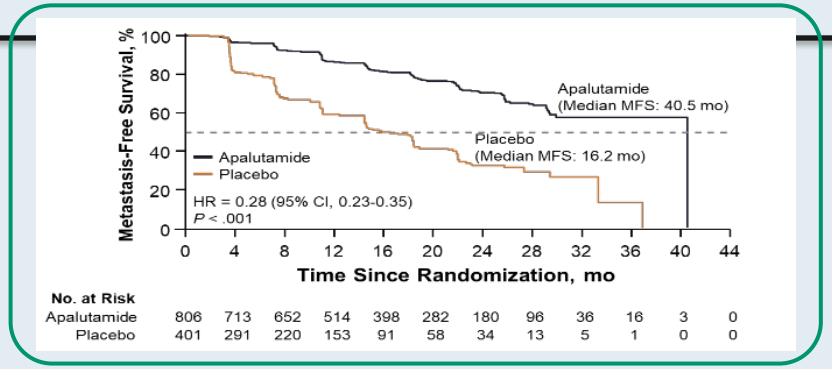
Patients at risk	622	622	618	614	609	604	600	597	595	587	574	572	568	565	547
Patients with TEAEs:															
All Grades	0	0	1	2	0	4	1	4	0	4	3	0	3	0	2
Grade 3-4	0	0	1	2	0	2	1	3	0	2	3	0	2	0	2
Patients at risk	308	308	307	307	305	302	302	297	289	288	285	279	277	277	258
Patients with TEAEs:															
All Grades	0	1	2	5	2	0	3	3	0	3	0	0	1	0	2
Grade 3-4	0	1	2	4	1	0	2	3	0	0	0	0	0	0	2

Mehlhaff B et al. AUA 2022;Abstract MP27-16.

Androgen Receptor Inhibitors

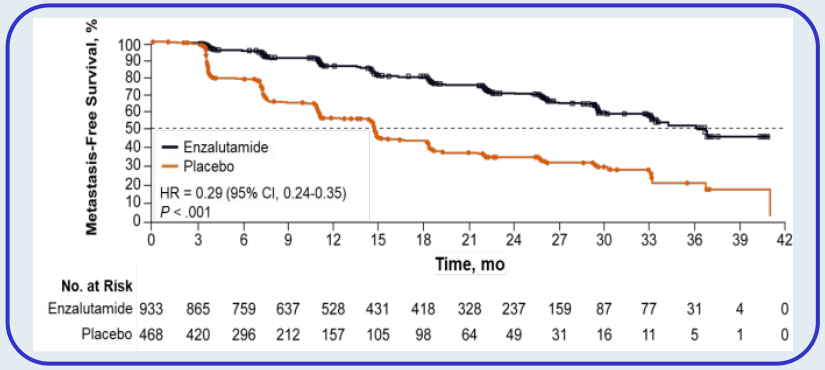
Primary Endpoint: Metastasis-Free Survival (MFS) in Nonmetastatic CRPC

SPARTAN[1]
Apalutamide
(APA)



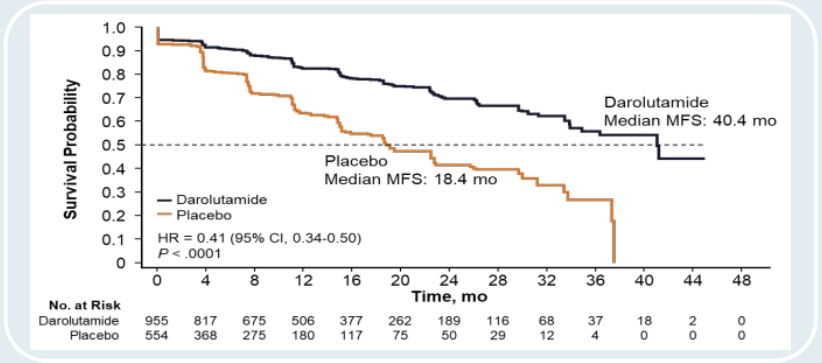
- 72% reduction in distant progression or death
- Median MFS: APA 40.5 vs placebo (PBO) 16.2 months
- 24-month MFS benefit

PROSPER[2]
Enzalutamide
(ENZA)



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

ARAMIS[3]
Darolutamide
(DARO)



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

1. Smith MR et al. *NEJM* 2018;378(15):1408-18. 2. Hussain M et al. *NEJM* 2018;378(26):2465-74. 3. Fizazi K et al. *NEJM* 2019;380(13):1235-46.

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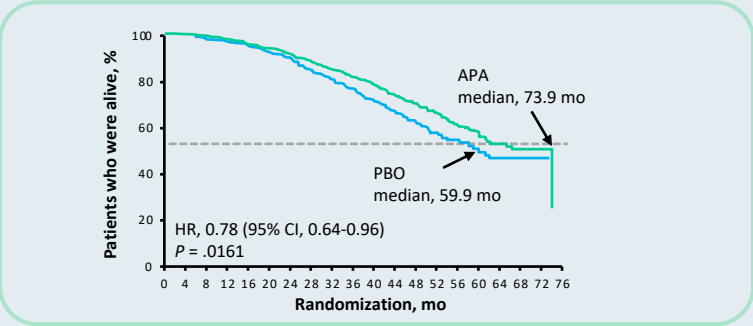
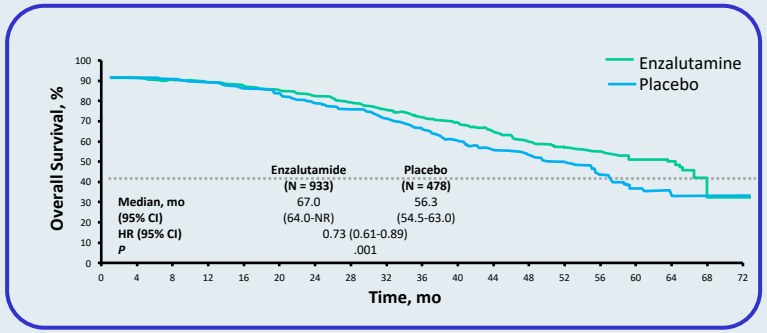
Secondary Endpoint: Overall Survival (OS) in Nonmetastatic HRPC

SPARTAN1[1]
Apalutamide



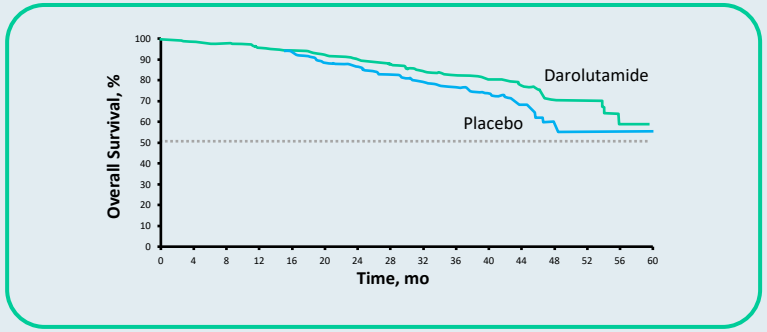
- 22% reduction in risk of death
- Median follow-up of 52.0 months
- Median OS was significantly longer for apalutamide vs placebo
  - 73.9 months vs 59.9 months
  - **HR = 0.78 (95% CI 0.64-0.96); *p* = 0.016**

PROSPER[2]
Enzalutamide



- 27% reduction in risk of death
- Median follow-up of 48 months
- Median OS was significantly longer for enzalutamide vs placebo
  - 67.0 months vs 56.3 months
  - **HR = 0.73 (95% CI 0.61-0.89); *p* = 0.001**

ARAMIS[3]
Darolutamide



- 31% reduction in risk of death
- Median follow-up of 29.0 months
- Median OS was significantly longer for darolutamide vs placebo
  - **HR = 0.69 (95% CI, 0.53-0.88); *p* = 0.003**

1. Smith MR et al. *Eur Urol* 2020;79(1):150-8. 2. Sternberg CN et al. *NEJM* 2020;382(23):2197-206. 3. Fizazi K et al. *NEJM* 2020;383(11):1040-9.

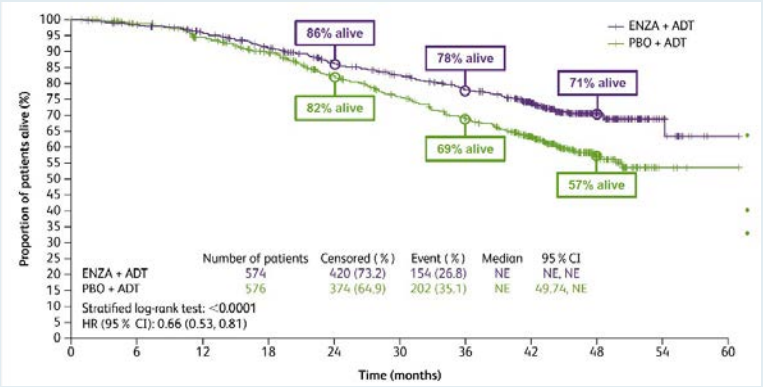
Comparison of Toxicities: Darolutamide, Enzalutamide, Apalutamide for Nonmetastatic HRPC

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(11):1040-9.
Small EJ et al; SPARTAN Investigators. ASCO 2020;Abstract 5516.

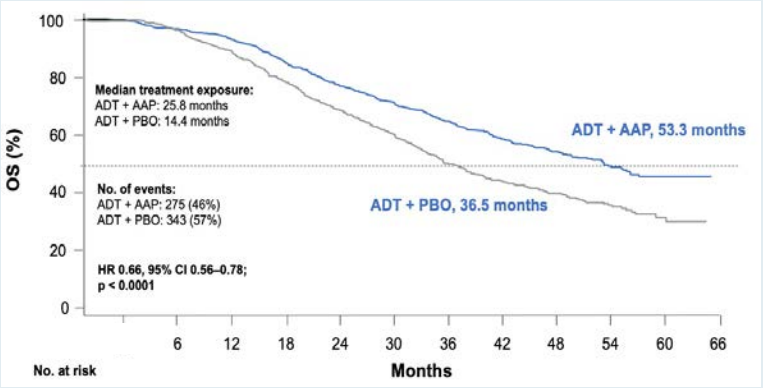
Final Overall Survival (OS) Analyses: Enzalutamide, Abiraterone and Apalutamide for Metastatic Hormone-Sensitive Prostate Cancer

ARCHES[1]
Enzalutamide with androgen deprivation therapy (ADT)



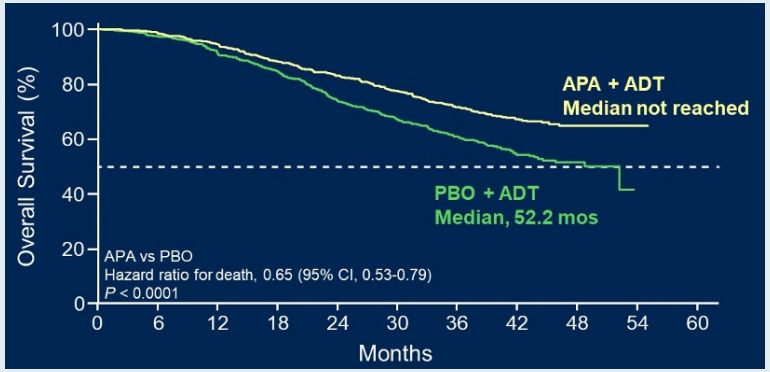
- 34% reduction in risk of death
- Median follow-up of 44.6 months
- Median OS was significantly longer for enzalutamide/ADT vs placebo/ADT
  - 40.2 months vs 13.8 months
  - **HR = 0.66**; $p < 0.0001$

LATITUDE[2]
Abiraterone with ADT



- 34% reduction in risk of death
- Median follow-up of 51.8 months
- Median OS was significantly longer for abiraterone/ADT vs placebo/ADT
  - 53.3 months vs 36.5 months
  - **HR = 0.66**; $p < 0.0001$

TITAN[3]
Apalutatmide with ADT



- 35% reduction in risk of death
- Median follow-up of 44.0 months
- Median OS was significantly longer for apalutamide/ADT vs placebo/ADT
  - Not reached vs 52.2 months
  - **HR = 0.65**; $p < 0.0001$

1. Armstrong AJ et al. ESMO 2021;Abstract LBA25. 2. Fizazi K et al. Genitourinary Cancers Symposium 2019;Abstract 141. 3. Chi KN et al. Genitourinary Cancers Symposium 2021;Abstract 11.

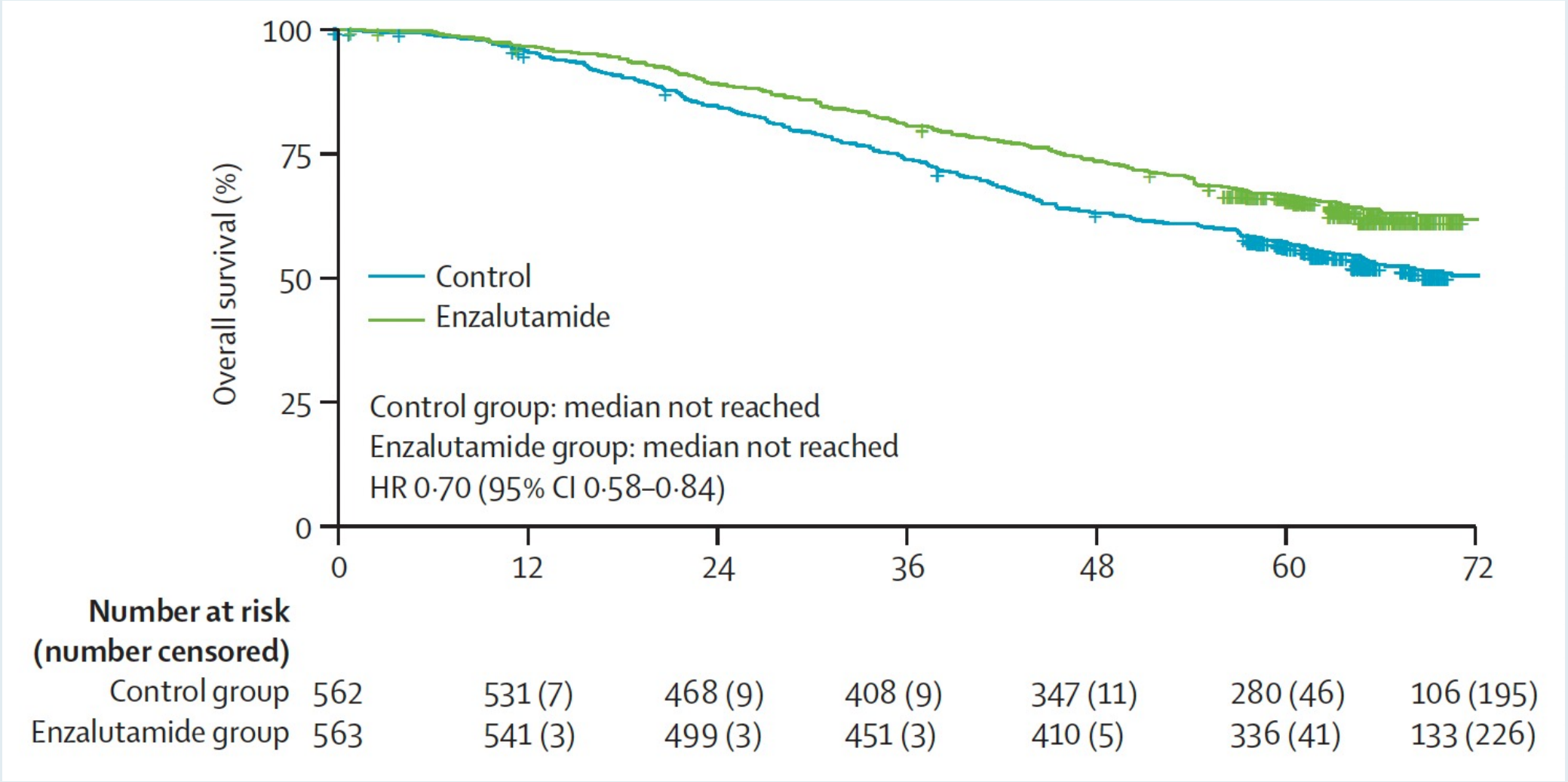
RTP RESEARCH TO PRACTICE

Lancet Oncol 2023; 24: 323–34

Testosterone suppression plus enzalutamide versus testosterone suppression plus standard antiandrogen therapy for metastatic hormone-sensitive prostate cancer (ENZAMET): an international, open-label, randomised, phase 3 trial

Christopher J Sweeney, Andrew J Martin, Martin R Stockler, Stephen Begbie, Leanna Cheung, Kim N Chi, Simon Chowdhury, Mark Frydenberg, Lisa G Horvath, Anthony M Joshua, Nicola J Lawrence, Gavin Marx, John McCaffrey, Ray McDermott, Margaret McJannett, Scott A North, Francis Parnis, Wendy Parulekar, David W Pook, Martin Neil Reaume, Shahneen K Sandhu, Alvin Tan, Thean Hsiang Tan, Alastair Thomson, Francisco Vera-Badillo, Scott G Williams, Diana Winter, Sonia Yip, Alison Y Zhang, Robert R Zielinski, Ian D Davis, for the ENZAMET trial investigators and Australian and New Zealand Urogenital and Prostate Cancer Trials Group*

ENZAMET Primary Endpoint: Overall Survival (ITT Population)



Number at risk (number censored)							
Control group	562	531 (7)	468 (9)	408 (9)	347 (11)	280 (46)	106 (195)
Enzalutamide group	563	541 (3)	499 (3)	451 (3)	410 (5)	336 (41)	133 (226)

Sweeney CJ et al. *Lancet Oncol* 2023; 24: 323–34.

Olaparib

RTP
RESEARCH
TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

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

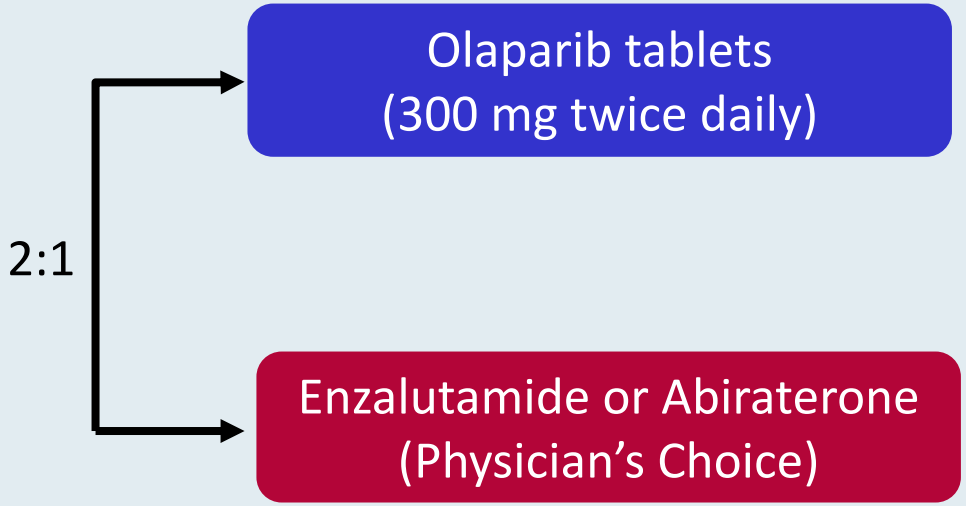
ORIGINAL ARTICLE

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

PROfound: Randomized Phase III Trial of Olaparib versus Enzalutamide or Abiraterone for mHRPC

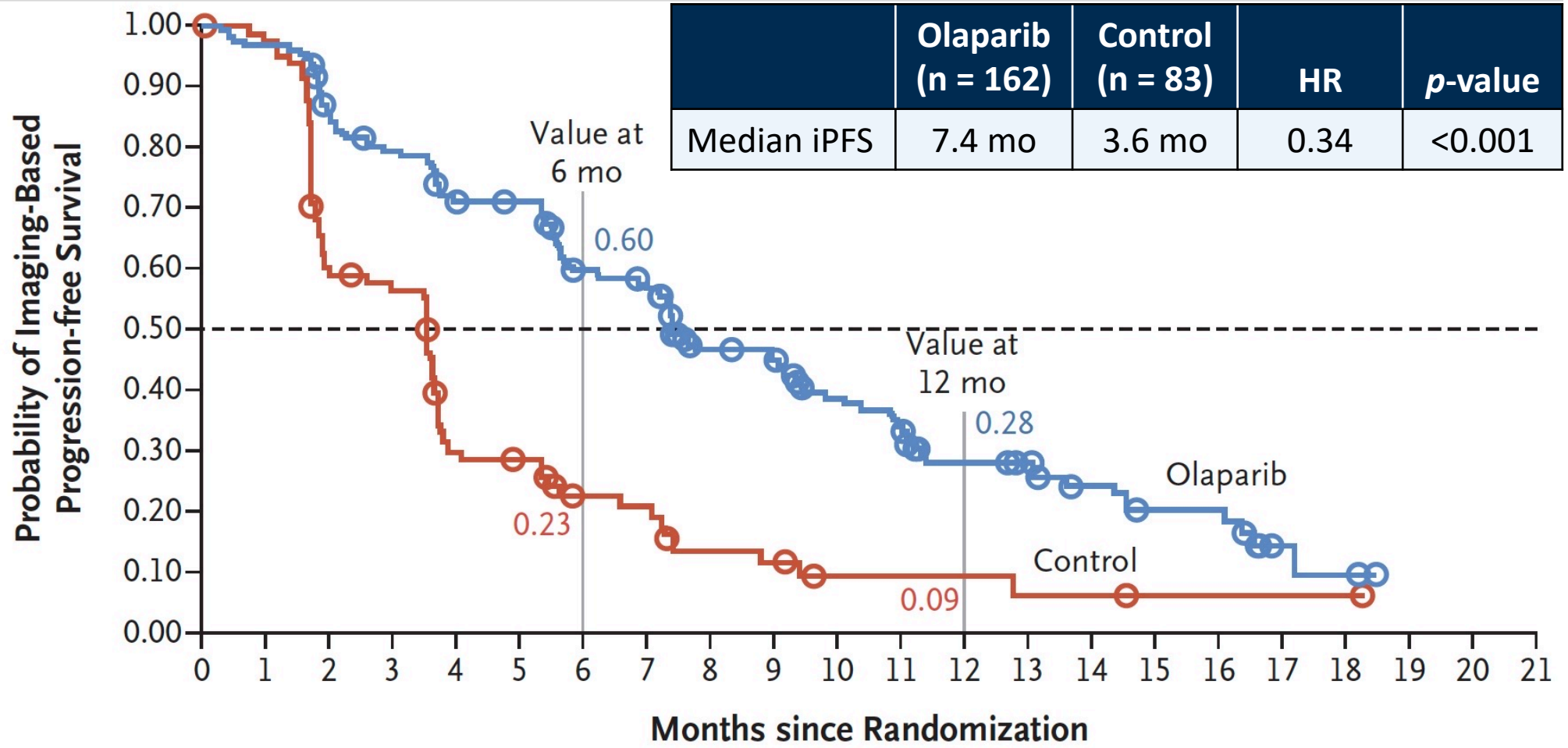
- Cohort A (n = 245) had ≥1 alteration in BRCA1, BRCA2 or ATM
- Cohort B (n = 142) had ≥1 alteration in BARD1, BRIP1, CDK12, CHEK1/2, FANCL, PALB2, PPP2R2A, RAD51B/C/D or RAD54L



de Bono J et al. *N Engl J Med* 2020;382:2091-102.

PROfound Primary Endpoint: Imaging-Based PFS with Olaparib in Cohort A (≥1 Alteration in BRCA1, BRCA2 or ATM)

	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. *N Engl J Med* 2020;382:2091.

RTP RESEARCH TO PRACTICE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

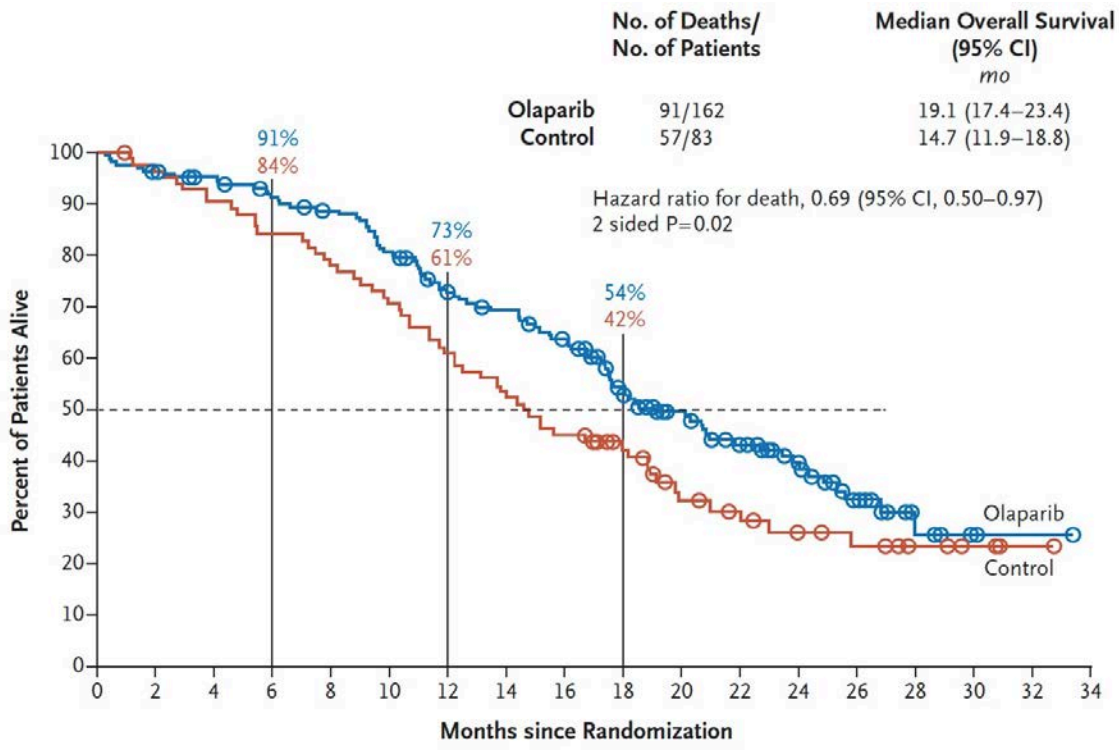
Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer

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*

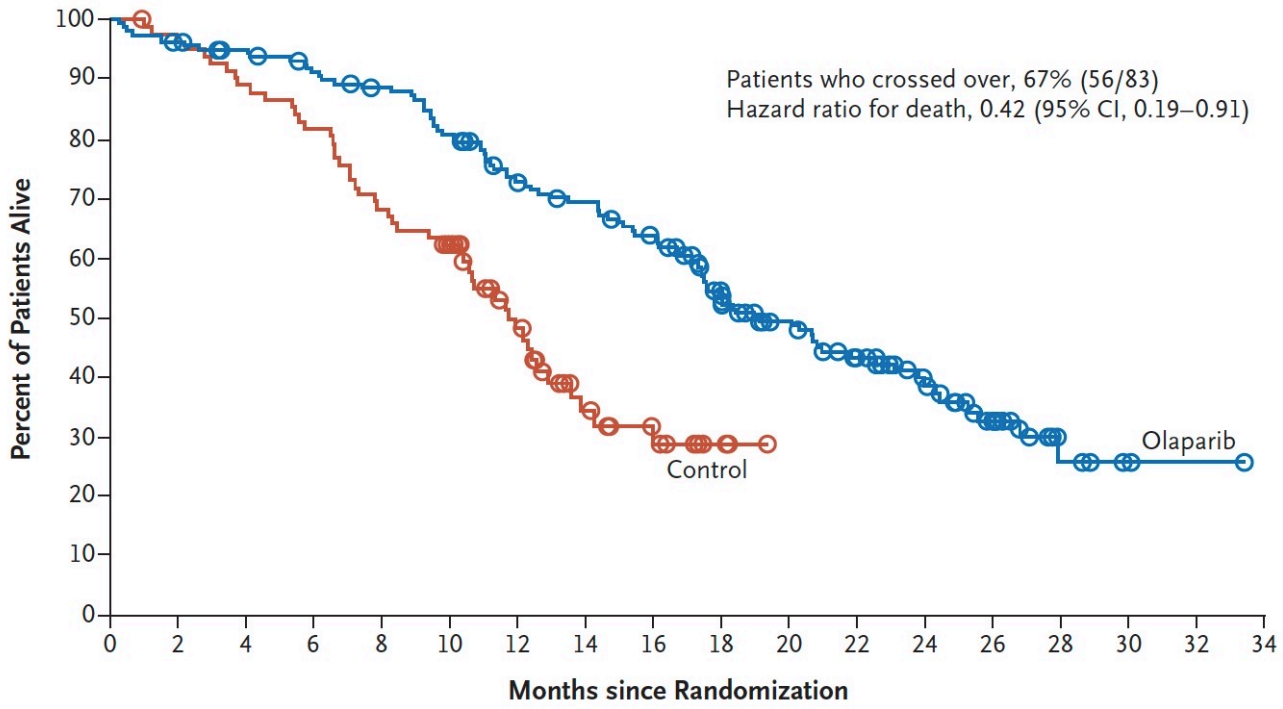
N Engl J Med 2020;383:2345-57.

PROfound: OS with Olaparib in Cohort A (≥1 Alteration in BRCA1, BRCA2 or ATM)

Overall survival



Crossover-adjusted overall survival



Hussain M et al. *N Engl J Med* 2020;383:2345-57.

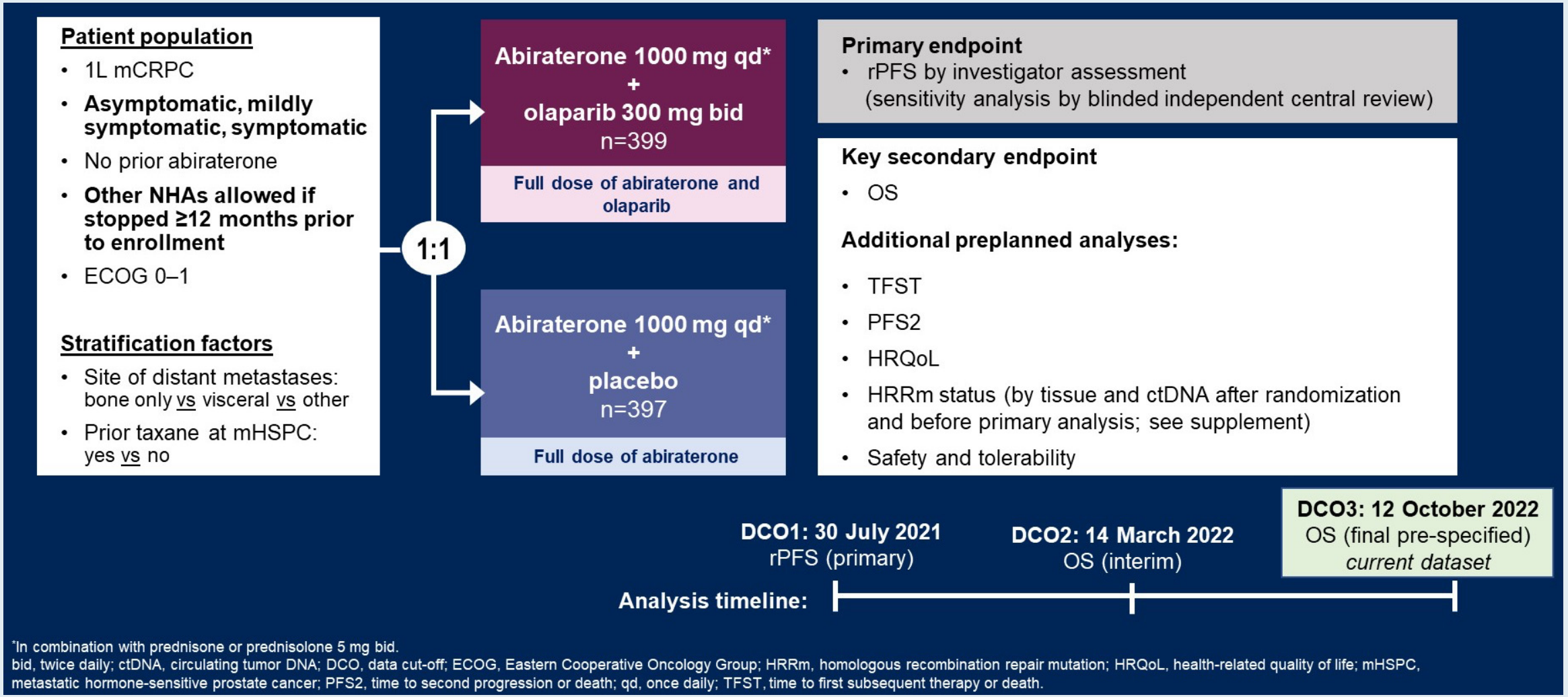
ASCO Genitourinary Cancers Symposium 2023

Abstract LBA16

Final pre-specified overall survival in PROpel: abiraterone and olaparib versus abiraterone and placebo as first-line therapy for metastatic castration-resistant prostate cancer

Noel Clarke, Andrew J. Armstrong, Antoine Thiery-Vuillemin, Mototsugu Oya, Neal Shore, Giuseppe Procopio, João Daniel Guedes, Cagatay Arslan, Niven Mehra, Francis Parnis, Emma Brown, Friederike Schlürmann, Jae Young Joung, Mikio Sugimoto, Oliver Sartor, Yu-Zhen Liu, Christian Poehlein, Laura Barker, Paula Michelle del Rosario, Fred Saad

PROpel: Phase III Trial Design



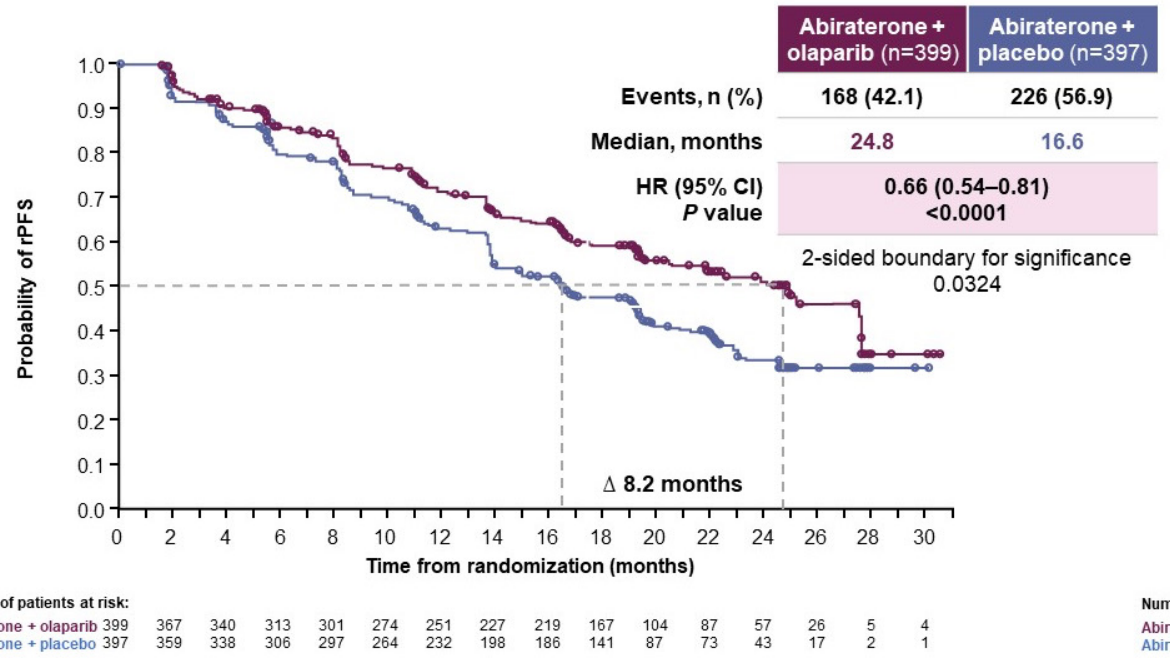
*In combination with prednisone or prednisolone 5 mg bid.
bid, twice daily; ctDNA, circulating tumor DNA; DCO, data cut-off; ECOG, Eastern Cooperative Oncology Group; HRRm, homologous recombination repair mutation; HRQoL, health-related quality of life; mHSPC, metastatic hormone-sensitive prostate cancer; PFS2, time to second progression or death; qd, once daily; TFST, time to first subsequent therapy or death.

Clarke N et al. Genitourinary Cancers Symposium 2023;Abstract LBA16.

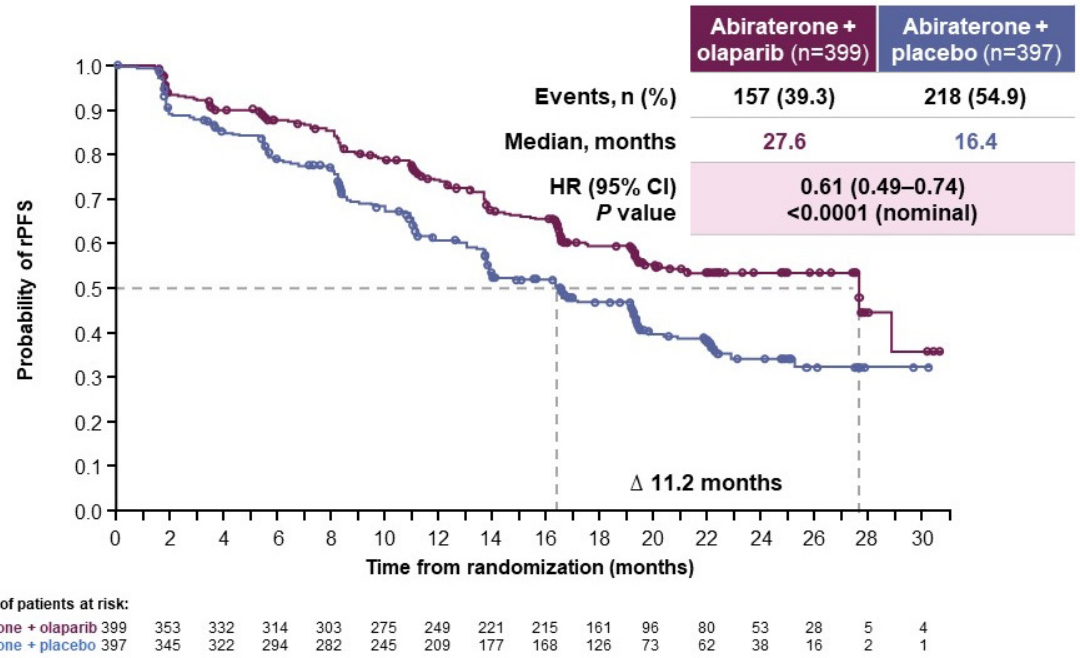
PROpel: Primary Radiographic Progression-Free Survival (rPFS) Results (DCO1)[1]

Abiraterone + olaparib significantly prolonged rPFS versus abiraterone + placebo in the ITT population

rPFS by investigator assessment (INV)



rPFS by blinded independent central review (BICR)



DCO1: 30 July 2021.
Median duration of follow-up for investigator-assessed rPFS for censored patients was 19.3 months in the abiraterone and olaparib arm, and 19.4 months in the abiraterone and placebo arm (19.3 and 19.2 months, respectively, for BICR).
ITT, intention-to-treat.
1. Clarke N *et al*. *NEJM Evidence* 2022;1(9).

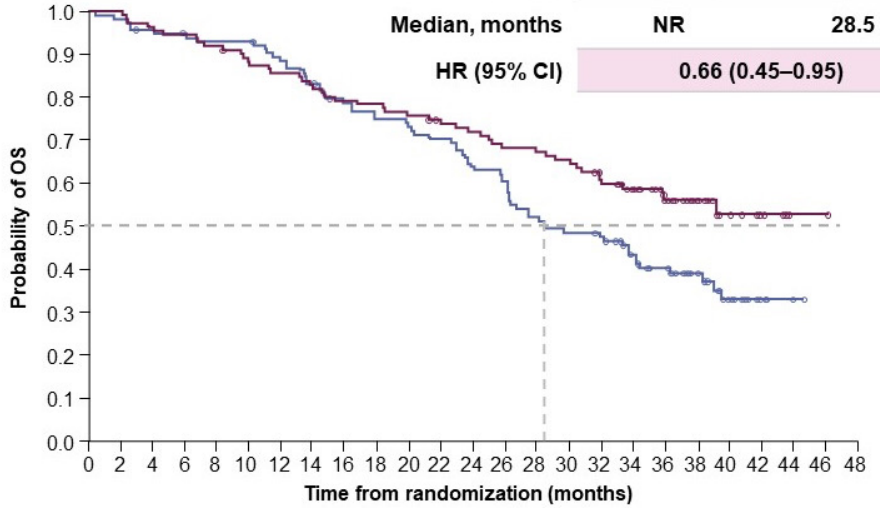
Clarke N et al. Genitourinary Cancers Symposium 2023;Abstract LBA16.

PROpel: Overall Survival (OS) in HRRm and Non-HRRm Subgroups (DCO3)

A trend towards OS benefit was observed across HRRm and non-HRRm subgroups

HRRm (28.4% of ITT population)

	Abiraterone + olaparib (n=111)	Abiraterone + placebo (n=115)
Events, n (%)	48 (43.2)	69 (60.0)
Median, months	NR	28.5
HR (95% CI)	0.66 (0.45–0.95)	

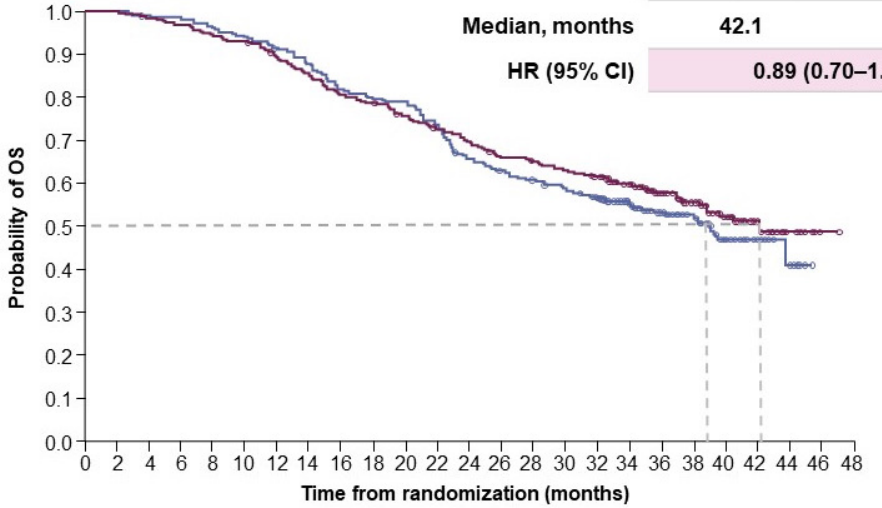


Number of patients at risk:

Abiraterone + olaparib	111	111	107	105	102	96	94	90	87	86	83	79	77	73	72	70	62	55	42	22	14	7	1	1	0
Abiraterone + placebo	115	113	109	107	105	105	99	92	86	82	80	77	70	66	57	53	51	40	32	22	12	4	1	0	0

Non-HRRm (69.3% of ITT population)

	Abiraterone + olaparib (n=279)	Abiraterone + placebo (n=273)
Events, n (%)	123 (44.1)	132 (48.4)
Median, months	42.1	38.9
HR (95% CI)	0.89 (0.70–1.14)	



Number of patients at risk:

Abiraterone + olaparib	279	279	275	271	263	260	247	236	223	218	207	198	190	179	175	170	160	134	92	73	48	22	9	1	0
Abiraterone + placebo	273	273	270	267	262	256	247	237	222	216	214	198	177	168	162	155	145	114	84	59	39	21	6	0	0

DCO3: 12 October 2022.
The preplanned tumor tissue and plasma ctDNA testing was conducted after randomization and before primary analysis. Results from tumor tissue and plasma ctDNA were combined to determine patients HRRm status (see supplement for more details). 18 patients had unknown HRRm status.

Clarke N et al. Genitourinary Cancers Symposium 2023;Abstract LBA16.

PROpel: Overall Safety Profile (DCO3)

No new safety signals with longer treatment duration and follow-up

N (%)	Abiraterone + olaparib (n=398)	Abiraterone + placebo (n=396)
Any AE	389 (97.7)	380 (96.0)
Any AE CTCAE Grade ≥3	222 (55.8)	171 (43.2)
Death due to an AE	**26 (6.5)**	**20 (5.1)**
Any AE leading to:		
Dose interruption of **olaparib** or **placebo**	195 (49.0)	112 (28.3)
Dose reduction of **olaparib** or **placebo**	90 (22.6)	24 (6.1)
Discontinuation of olaparib or **placebo**	**69 (17.3)**	**34 (8.6)**
Discontinuation of abiraterone	**45 (11.3)**	**37 (9.3)**

AEs of special interest for olaparib

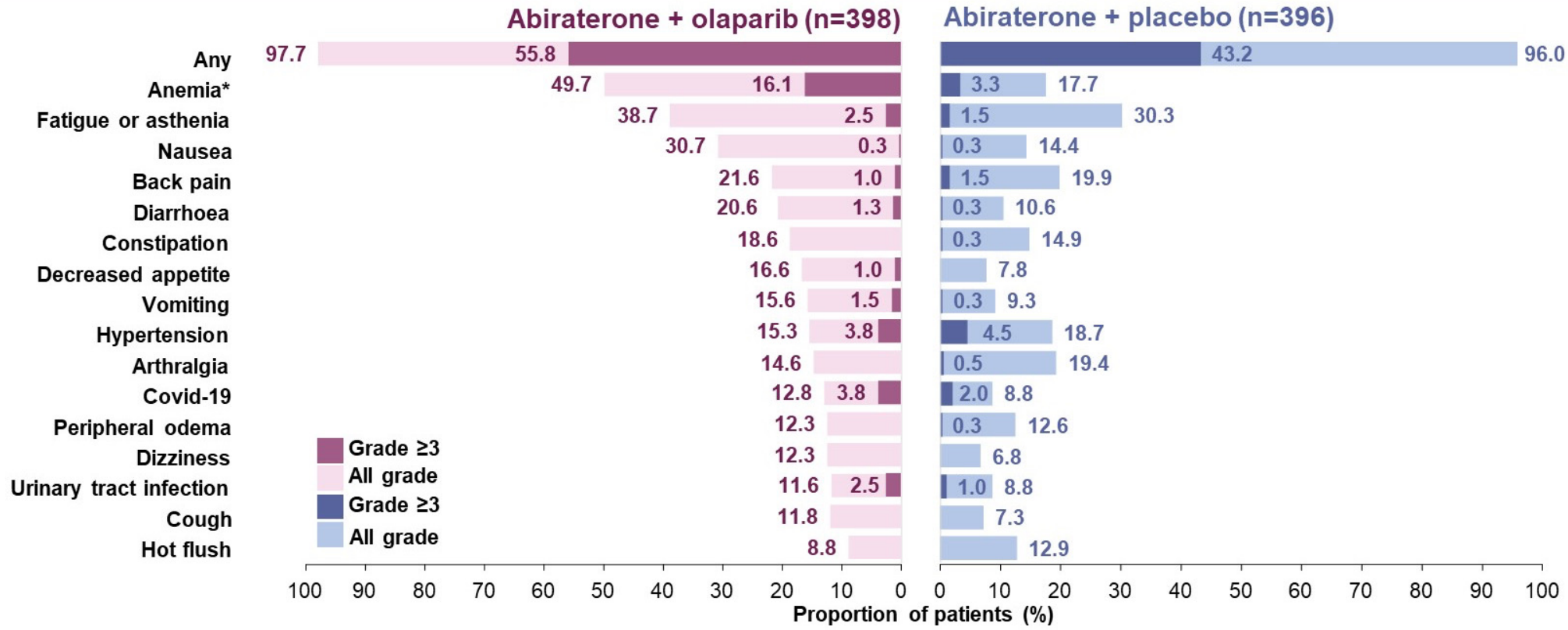
- Two cases of MDS/AML in the olaparib and abiraterone arm
- Incidence of new primary malignancies (NPM) and pneumonitis was balanced between treatment arms (see supplement)

DCO3: 12 October 2022.
At DCO3, median total treatment duration of olaparib was 18.5 months, placebo was 15.7 months, abiraterone in the abiraterone + olaparib arm was 20.1 months and in the abiraterone + placebo arm was 15.7 months.
AE, adverse event; AML, acute myeloid leukemia; CTCAE, Common Terminology Criteria for Adverse Events v4.03; MDS, myelodysplastic syndrome.

Clarke N et al. Genitourinary Cancers Symposium 2023;Abstract LBA16.

PROpel: Most Common AEs (>10% Patients; DCO3)

Consistent with the known safety profiles of abiraterone and olaparib



Pulmonary embolism (7.3% vs 2.3%) and cardiac failure events (1.8% vs 1.8%) were similar to earlier data cut-offs (see supplement)

DCO3: 12 October 2022. Safety was assessed through the reporting of AEs according to NCI CTCAE v4.03 and laboratory assessments. *Grouped term anemia category includes anemia, decreased hemoglobin level, decreased red-cell count, decreased hematocrit level, erythropenia, macrocytic anemia, normochromic anemia, normochromic normocytic anemia and normocytic anemia.

Clarke N et al. Genitourinary Cancers Symposium 2023;Abstract LBA16.

RTP RESEARCH TO PRACTICE

Niraparib

original reports

Niraparib and Abiraterone Acetate for Metastatic Castration-Resistant Prostate Cancer

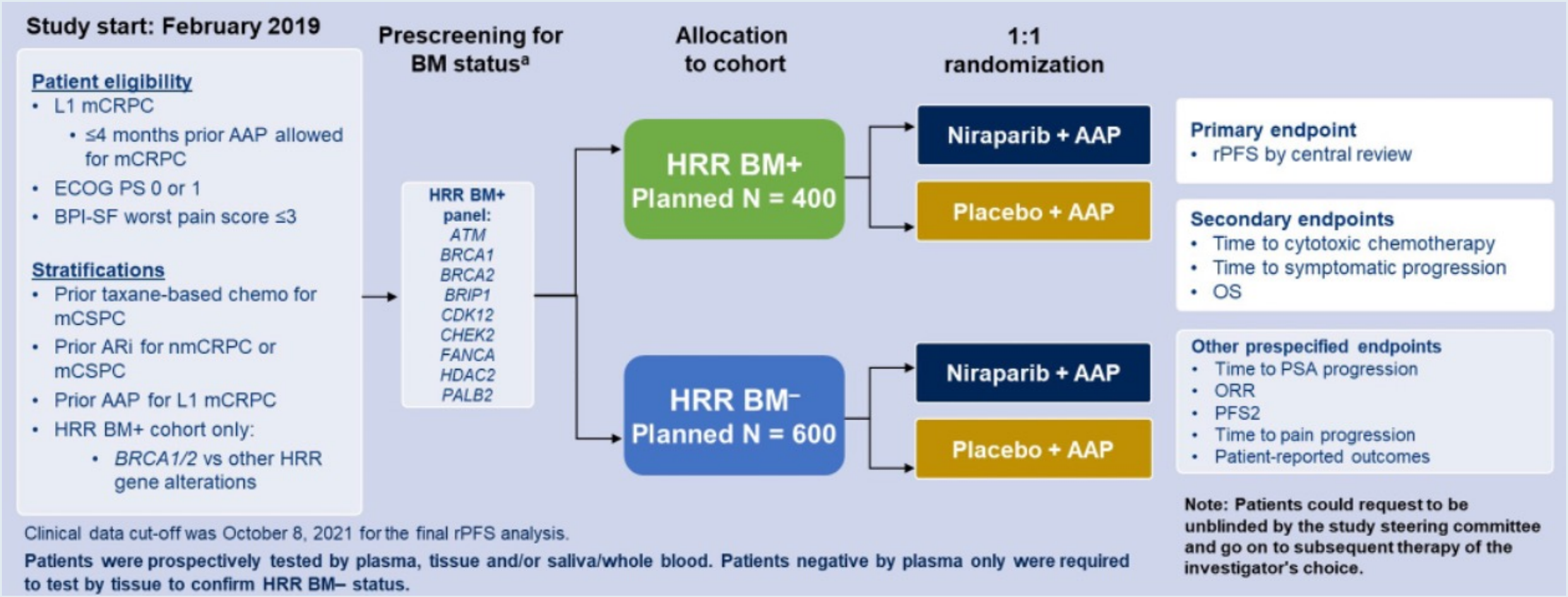
Kim N. Chi, MD[1]; Dana Rathkopf, MD[2]; Matthew R. Smith, MD[3]; Eleni Efstathiou, MD[4]; Gerhardt Attard, MD[5]; David Olmos, MD[6]; Ji Youl Lee, MD[7]; Eric J. Small, MD[8]; Andrea J. Pereira de Santana Gomes, MD[9]; Guilhem Roubaud, MD[10]; Marniza Saad, MD[11]; Bogdan Zurawski, MD[12]; Valerii Sakalo, MD[13]; Gary E. Mason, MD[14]; Peter Francis, MD[15]; George Wang, MS, MAS[14]; Daphne Wu, PhD[16]; Brooke Diorio, PhD[17]; Angela Lopez-Gitlitz, MD[16]; and Shahneen Sandhu, MD[18]; on behalf of the MAGNITUDE Principal Investigators

J Clin Oncol 2023 Mar 23; Epub ahead of print

RTP RESEARCH TO PRACTICE

MAGNITUDE: Randomized, Double-Blind, Placebo-Controlled Study

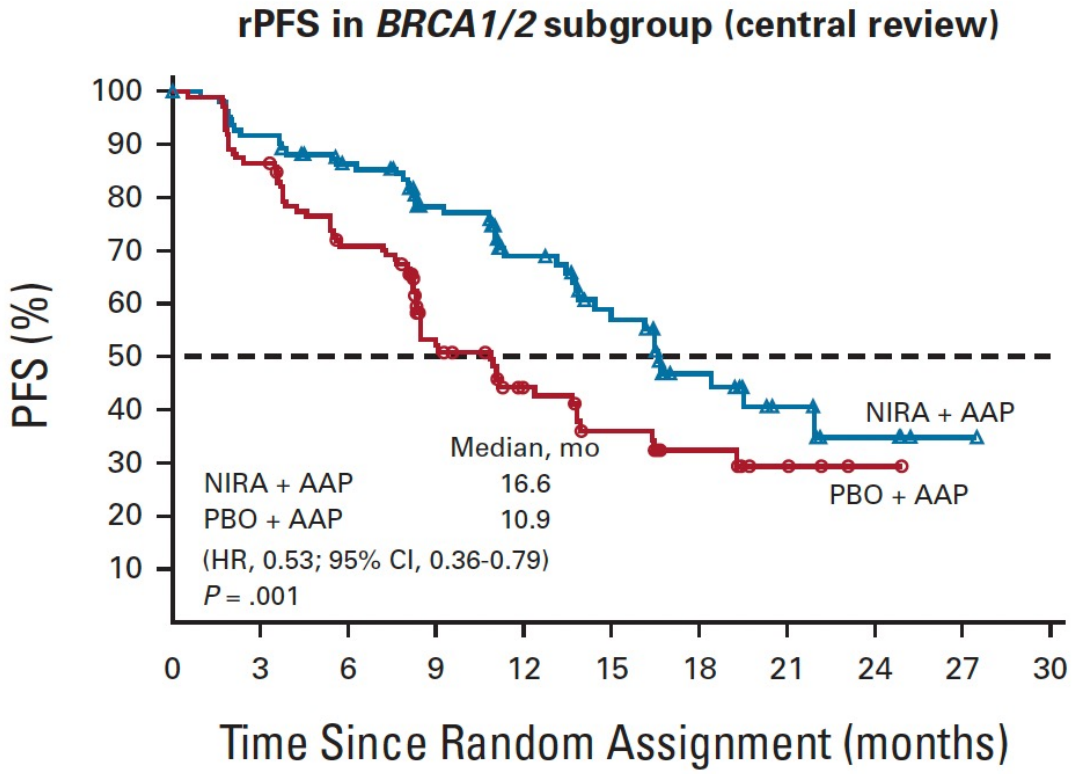
Prospectively Selected Biomarker (BM) Cohorts Designed to Test HRR BM+ and HRR BM-



HRR = homologous recombination repair; BM = biomarker; mCRPC = metastatic castration-resistant prostate cancer; mCSPC = metastatic castration-sensitive prostate cancer; nmCRPC = nonmetastatic castration-resistant prostate cancer; AAP = abiraterone acetate and prednisone; rPFS = radiographic progression-free survival; OS = overall survival; PSA = prostate-specific antigen; ORR = objective response rate

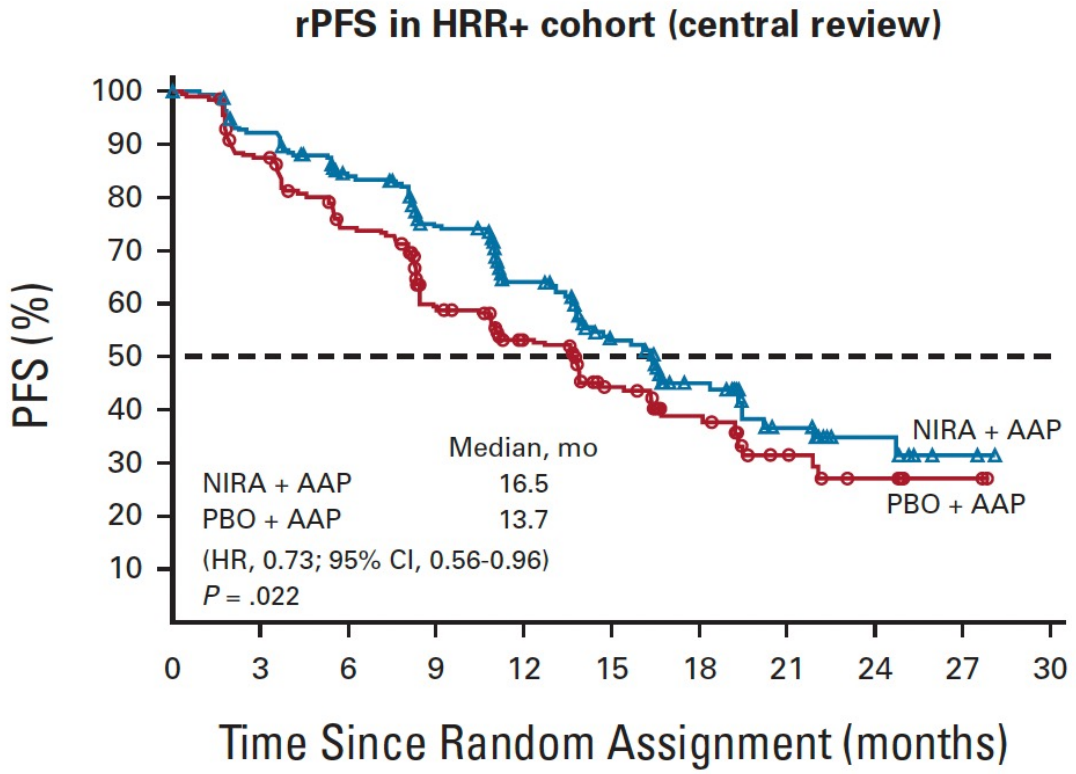
Chi KN et al. Genitourinary Cancers Symposium 2022;Abstract 12.

MAGNITUDE: Radiographic PFS in BRCA1/2 Subgroup and HRR-Positive Cohort (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

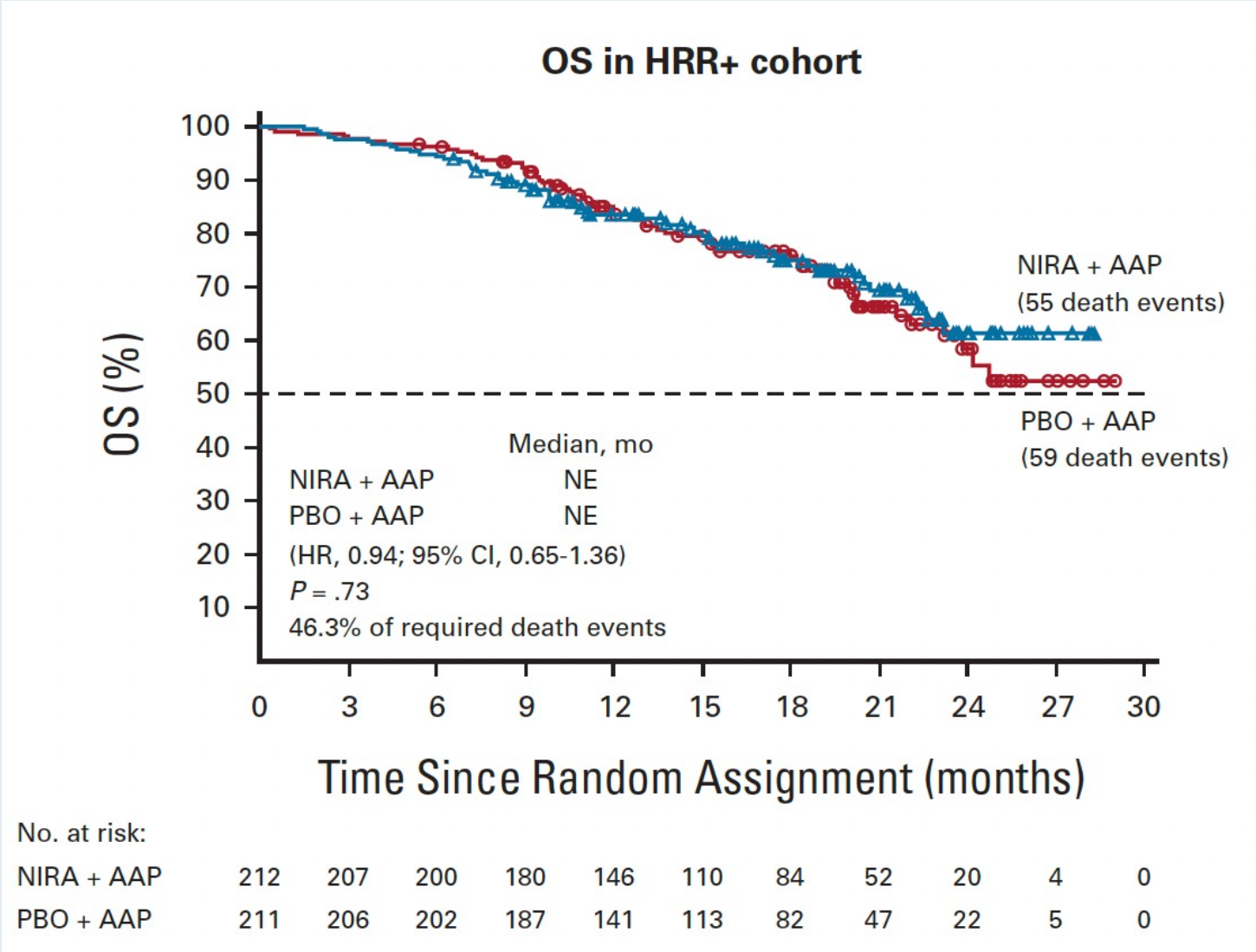


No. at risk:

NIRA + AAP	212	192	167	129	96	64	45	21	10	2	0
PBO + AAP	211	182	149	102	78	53	35	15	9	2	0

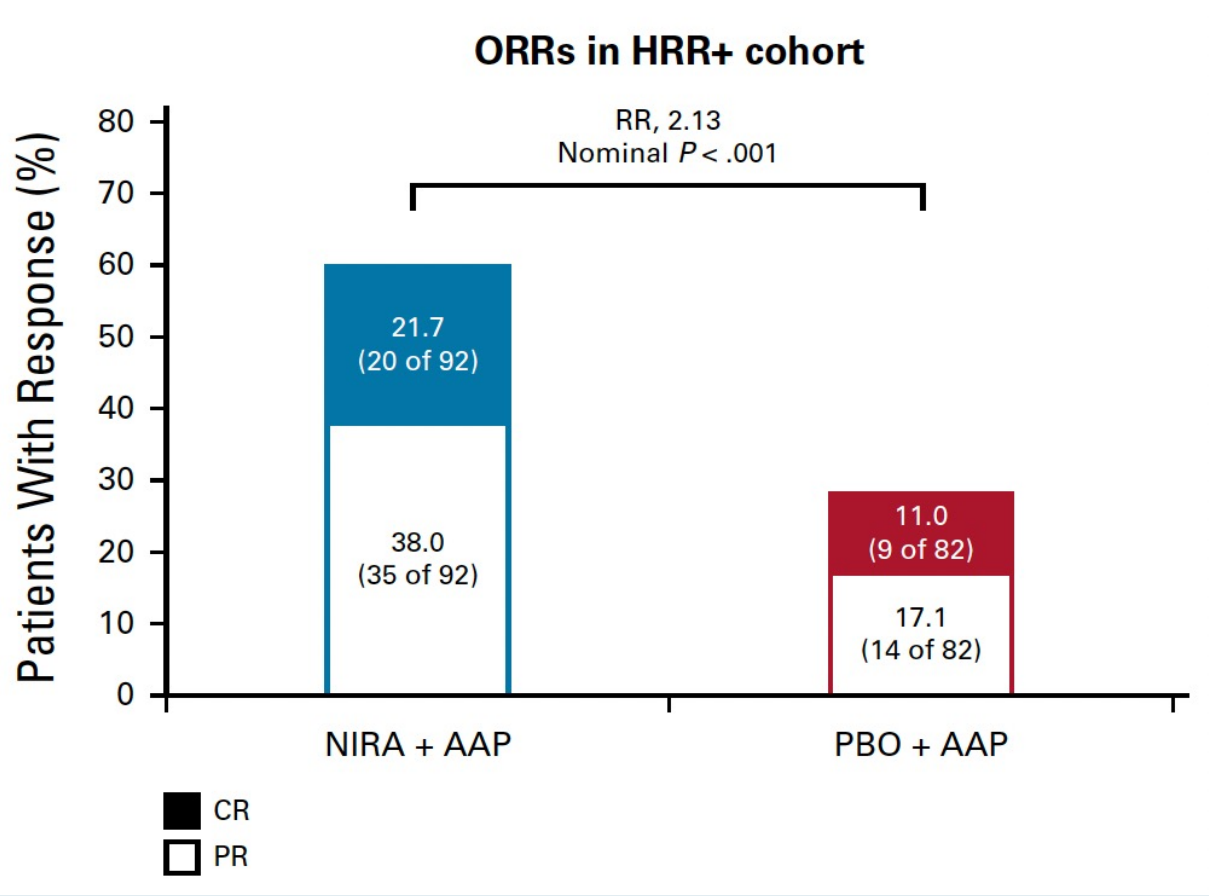
Chi KN et al. *J Clin Oncol* 2023 March 23;Epub ahead of print.

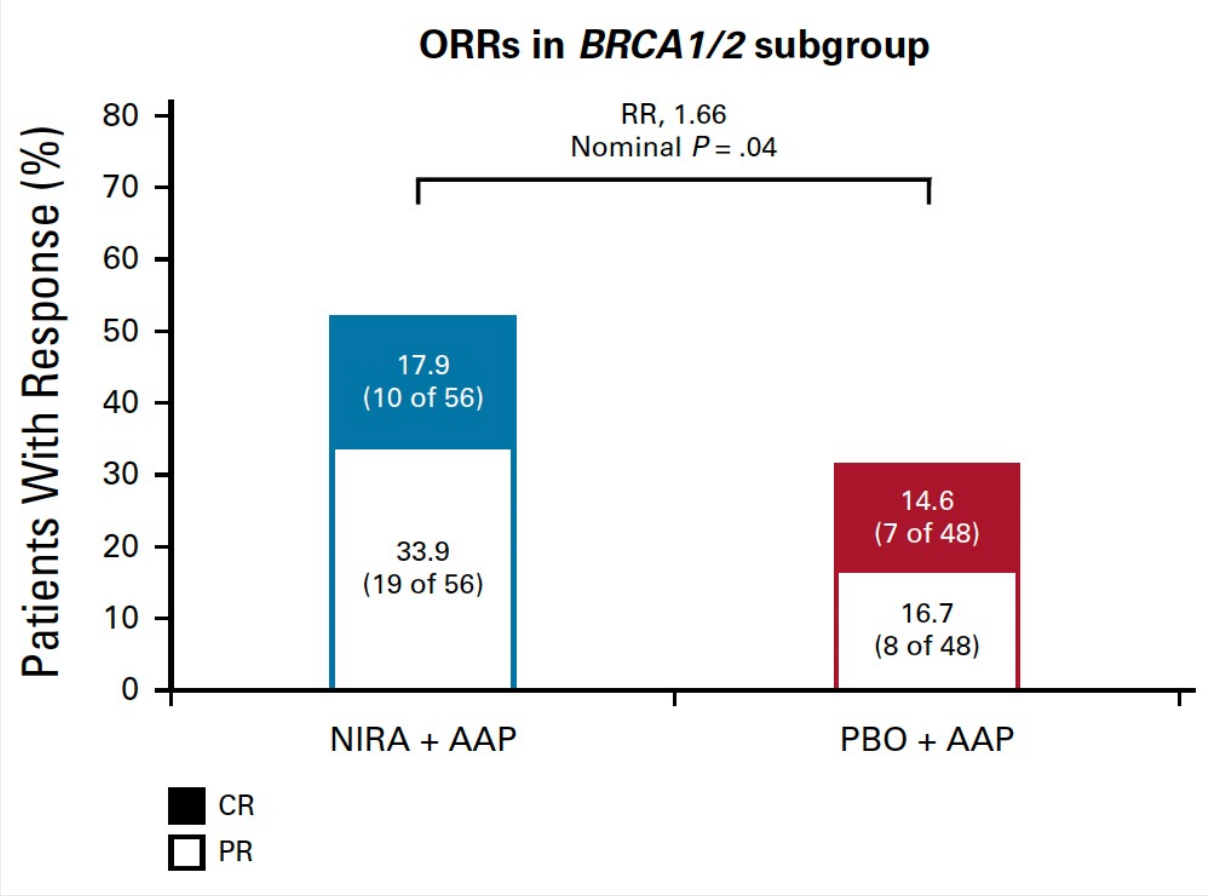
MAGNITUDE: Overall Survival in the HRR-Positive Cohort (Central Review)



Chi KN et al. *J Clin Oncol* 2023 March 23;Epub ahead of print.

MAGNITUDE: Overall Response Rate





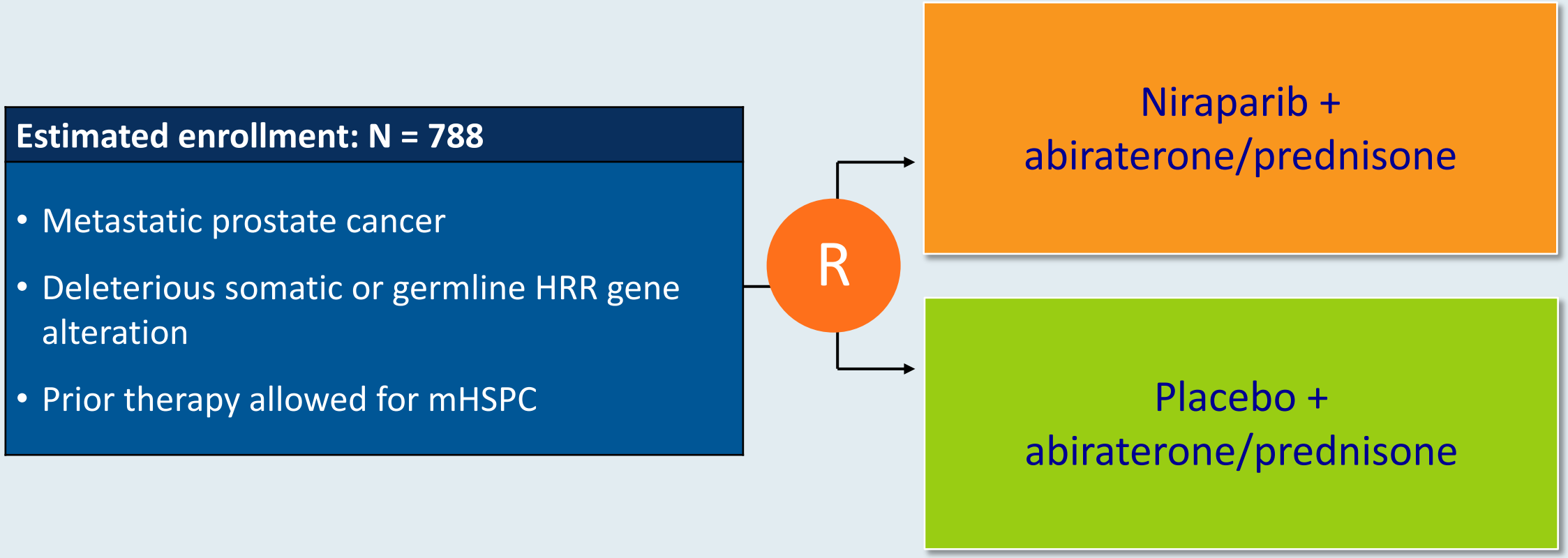
Chi KN et al. *J Clin Oncol* 2023 March 23;Epub ahead of print.

MAGNITUDE: Select TEAEs in HRR-Positive Patients

	NIRA + AAP (n = 212)			PBO + AAP (n = 211)		
Event	**All Grades, No. (%)**	**Grade 3, No. (%)**	**Grade 4, No. (%)**	**All Grades, No. (%)**	**Grade 3, No. (%)**	**Grade 4, No. (%)**
Patients with ≥1 SAE	76 (35.8)			52 (24.6)		
Any TEAEs	210 (99.1)	119 (56.1)	23 (10.8)	199 (94.3)	90 (42.7)	8 (3.8)
Anemia	98 (46.2)	60 (28.3)	3 (1.4)	43 (20.4)	16 (7.6)	0
Hypertension	66 (31.1)	31 (14.6)	0	44 (20.9)	26 (12.3)	0
Constipation	65 (30.7)	0	0	29 (13.7)	0	0
Fatigue	56 (26.4)	7 (3.3)	0	35 (16.6)	9 (4.3)	0
Nausea	50 (23.6)	1 (0.5)	0	29 (13.7)	0	0
Thrombocytopenia	45 (21.2)	6 (2.8)	8 (3.8)	18 (8.5)	5 (2.4)	0
Dyspnea	34 (16.0)	4 (1.9)	0	12 (5.7)	2 (0.9)	0
Asthenia	33 (15.6)	1 (0.5)	1 (0.5)	19 (9.0)	1 (0.5)	0
Back pain	31 (14.6)	5 (2.4)	0	44 (20.9)	2 (0.9)	0
Decreased appetite	30 (14.2)	1 (0.5)	0	13 (6.2)	1 (0.5)	0
Hypokalemia	29 (13.7)	6 (2.8)	0	20 (9.5)	6 (2.8)	0
Neutropenia	29 (13.7)	11 (5.2)	3 (1.4)	12 (5.7)	3 (1.4)	0

Chi KN et al. *J Clin Oncol* 2023 March 23;Epub ahead of print.

AMPLITUDE Phase III Study Design



Primary endpoint: rPFS

Secondary endpoints: OS, symptomatic PFS, time to subsequent therapy, adverse events

www.clinicaltrials.gov. NCT04497844. Accessed September 2022

Talazoparib

RTP
RESEARCH
TO PRACTICE

Presentation number LBA17

ASCO Genitourinary Cancers Symposium 2023 | Abstract LBA17

TALAPRO-2: Phase 3 study of talazoparib plus enzalutamide versus placebo plus enzalutamide as first-line treatment in patients with metastatic castration-resistant prostate cancer

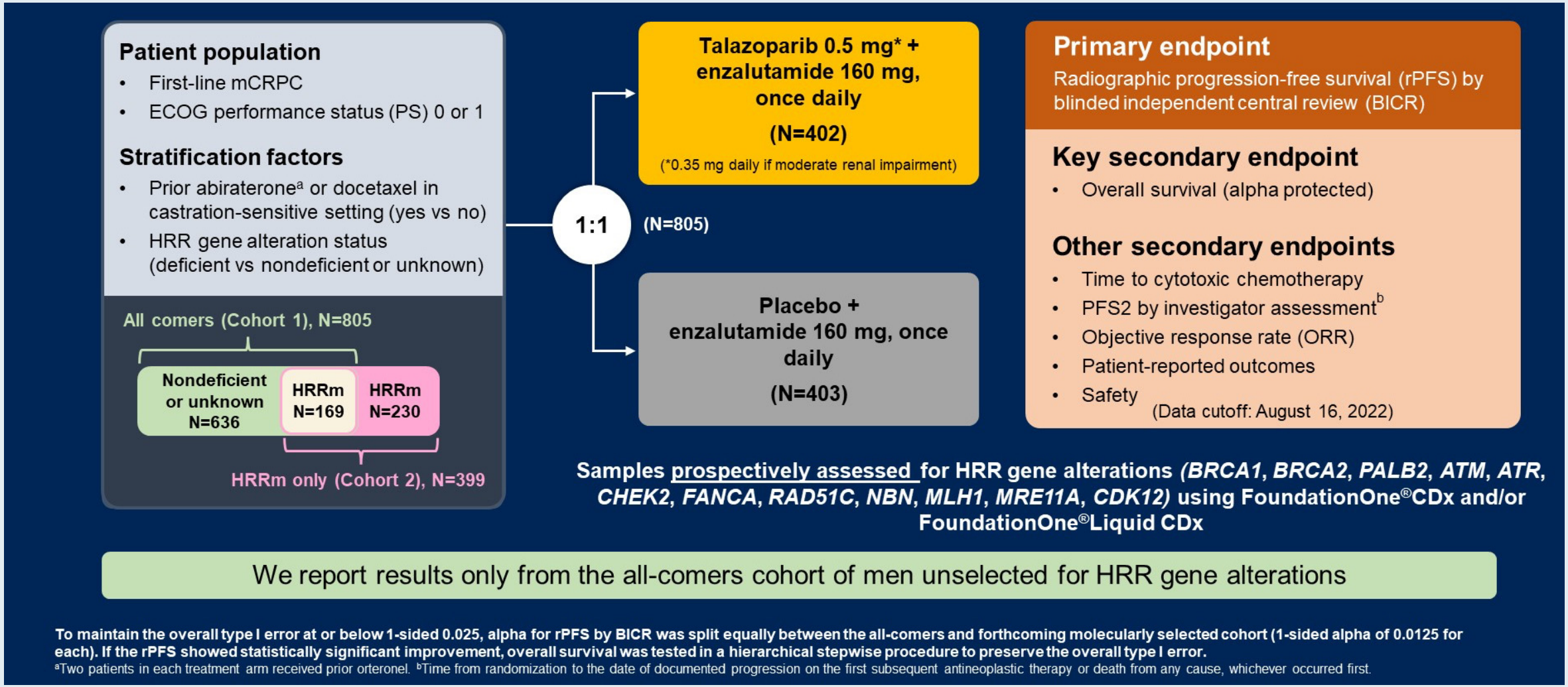
Neeraj Agarwal,[1] Arun A. Azad,[2] Joan Carles,[3] Andre P. Fay,[4] Nobuaki Matsubara,[5] Daniel Heinrich,[6] Cezary Szczylik,[7] Ugo De Giorgi,[8] Jae Young Joung,[9] Peter C. Fong,[10] Eric Voog,[11] Robert J. Jones,[12] Neal D. Shore,[13] Curtis Dunshee,[14] Stefanie Zschäbitz,[15] Jan Oldenburg,[16] Xun Lin,[17] Cynthia G. Healy,[18] Nicola Di Santo,[19] Fabian Zohren,[17] Karim Fizazi[20]

[1]Huntsman Cancer Institute (NCI-CCC), University of Utah, Salt Lake City, UT, USA; [2]Peter MacCallum Cancer Centre, Melbourne, Australia; [3]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [4]PUCRS School of Medicine, Porto Alegre, Brazil; [5]National Cancer Center Hospital East, Chiba, Japan; [6]Innlandet Hospital Trust, Gjøvik, Norway; [7]Department of Oncology European Health Center, Otwock, Poland, and Postgraduate Medical Education Center, Warsaw, Poland; [8]IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) Dino Amadori, Meldola, Italy; [9]National Cancer Center, Goyang, Republic of Korea; [10]Auckland City Hospital and University of Auckland, Auckland, New Zealand; [11]Clinique Victor Hugo Centre Jean Bernard, Le Mans, France; [12]School of Cancer Sciences, University of Glasgow, Beatson West of Scotland Cancer Centre, Glasgow, UK; [13]Carolina Urologic Research Center, Myrtle Beach, SC, USA; [14]Arizona Urology Specialists, Tucson, AZ, USA; [15]National Center for Tumor Diseases (NCT), Heidelberg University Hospital, Heidelberg, Germany; [16]Akershus University Hospital (Ahus), Lørenskog, Norway; [17]Pfizer Inc., La Jolla, CA, USA; [18]Pfizer Inc., Collegeville, PA, USA; [19]Pfizer Inc., Durham, NC, USA; [20]Institut Gustave Roussy, University of Paris-Saclay, Villejuif, France

ClinicalTrials.gov identifier: NCT03395197
This study was sponsored by Pfizer Inc. Astellas Pharma Inc. provided enzalutamide

RTP RESEARCH TO PRACTICE

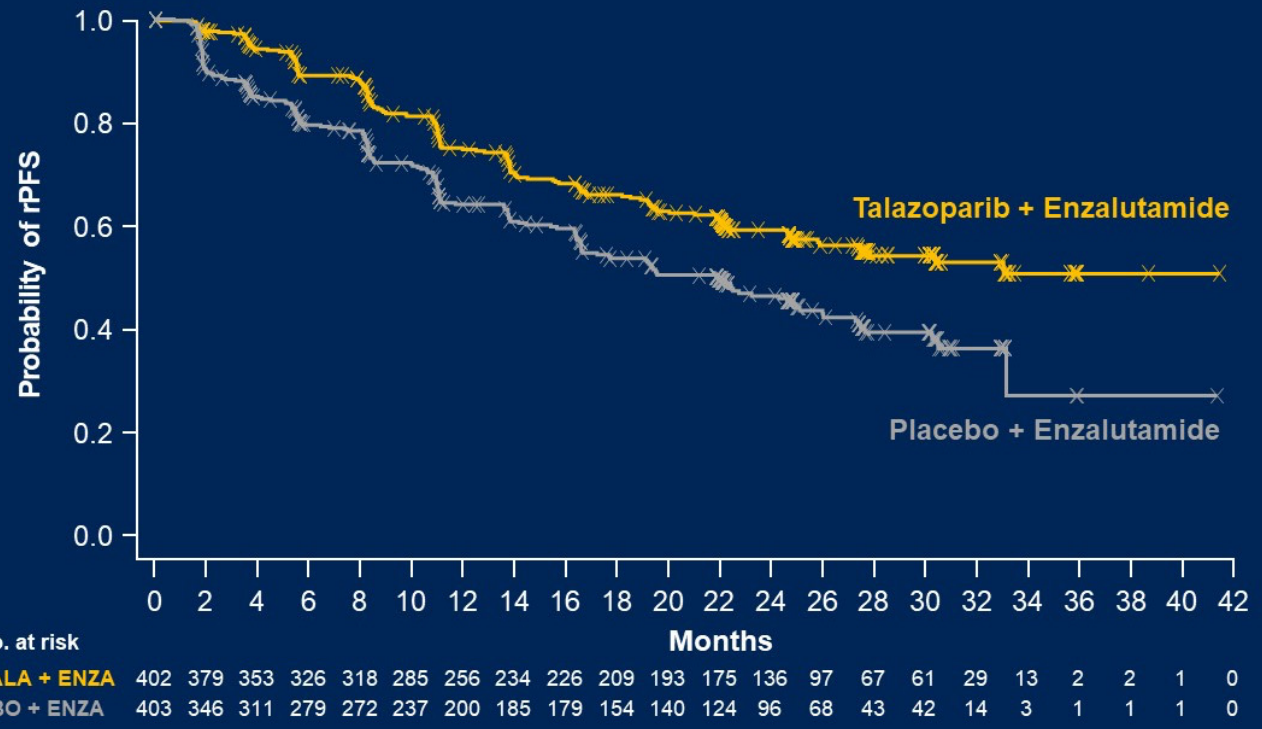
TALAPRO-2: A Phase III Trial of First-Line Talazoparib/Enzalutamide for mHRPC with or without DNA Damage Repair Mutations



Agarwal N et al. Genitourinary Cancers Symposium 2023;Abstract LBA17.

TALAPRO-2 Primary Endpoint: rPFS by BICR

Treatment with talazoparib plus enzalutamide resulted in a 37% reduced risk of progression or death



	TALA + ENZA (N=402)	PBO + ENZA (N=403)
Events, n	151	191
Median (95% CI), months	Not reached (NR) (27.5–NR)	21.9 (16.6–25.1)
HR (95% CI)	0.63 (0.51–0.78); *P* < 0.001	

Median follow-up for rPFS was 24.9 and 24.6 months, respectively

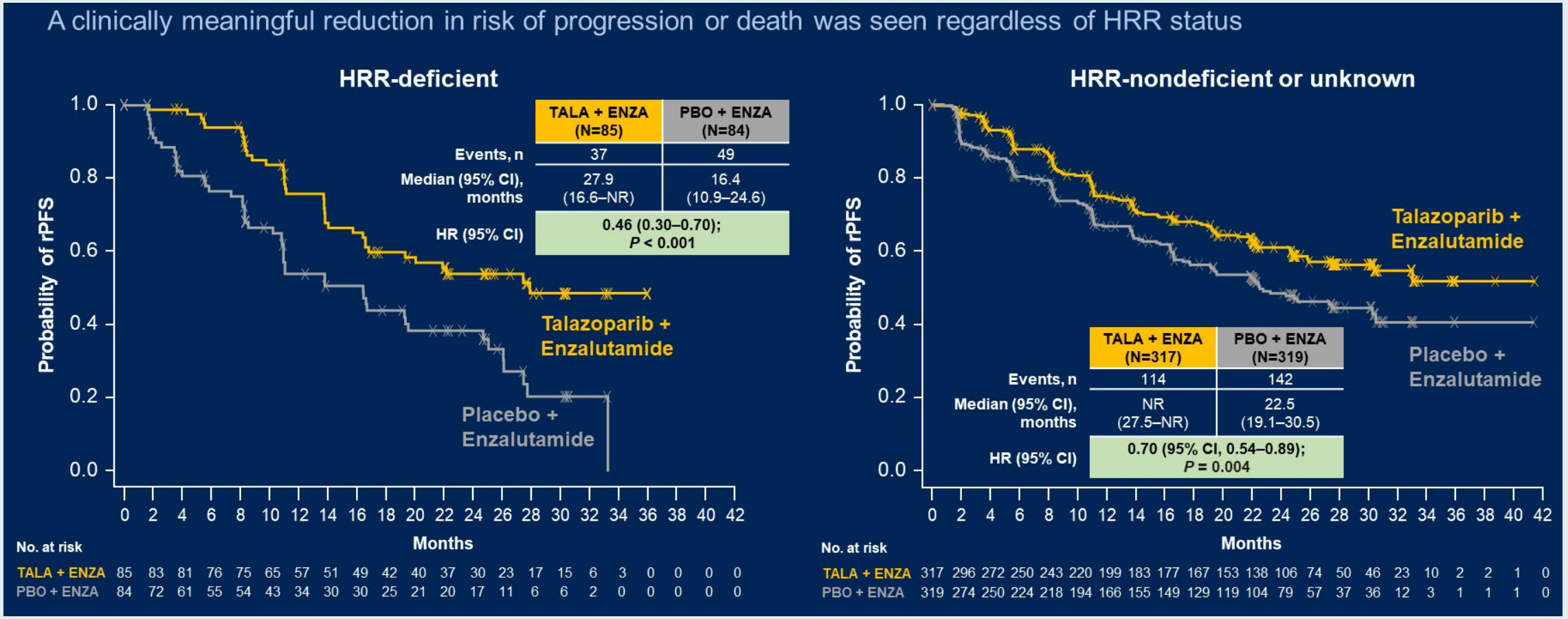
A consistent treatment effect was seen for investigator-assessed rPFS: HR 0.64 (95% CI, 0.50–0.81); *P* < 0.001

Stratified hazard ratios (HRs) and 2-sided *P* values are reported throughout this presentation unless otherwise stated.

Agarwal N et al. Genitourinary Cancers Symposium 2023;Abstract LBA17.

RTP RESEARCH TO PRACTICE

TALAPRO-2: rPFS by BICR, by HRR Status



Agarwal N et al. Genitourinary Cancers Symposium 2023;Abstract LBA17.

TALAPRO-2: Safety Summary

TEAEs, n (%)	TALA + ENZA (N=398)	PBO + ENZA (N=401)
Any TEAE	392 (98.5)	379 (94.5)
Treatment-related	357 (89.7)	279 (69.6)
SAEs	157 (39.4)	107 (26.7)
Treatment-related	78 (19.6)	12 (3.0)
Grade 3–4 TEAEs	286 (71.9)	163 (40.6)
Grade 5 TEAEs	13 (3.3)	18 (4.5)
Treatment-related	0	2 (0.5)
Dose interruption of talazoparib or placebo due to AE	300 (75.4)	94 (23.4)
Dose reduction of talazoparib or placebo due to AE*	223 (56.0)	29 (7.2)
Discontinuation of talazoparib or placebo due to AE	76 (19.1)	49 (12.2)

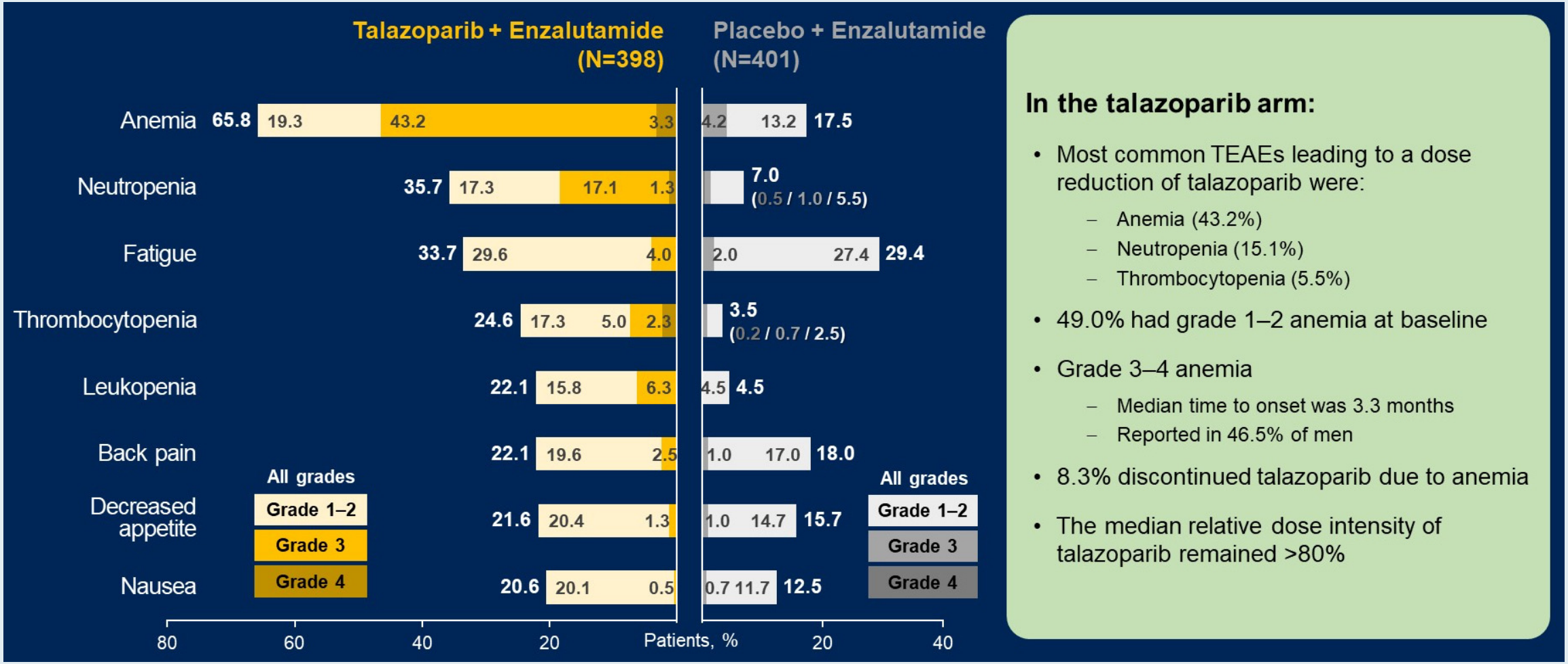
*The median relative dose intensity of talazoparib remained >80%

TEAEs of special interest for talazoparib

- Myelodysplastic syndrome was reported in 1 patient during the safety reporting period and acute myeloid leukemia was reported in 1 patient during the follow-up period (both in the talazoparib plus enzalutamide arm)
- Pulmonary embolism was reported in 10 (2.5%) patients (grade 3 in 9 patients) in the talazoparib plus enzalutamide arm and in 3 (0.7%) patients (all grade 3) in the placebo plus enzalutamide arm

Agarwal N et al. Genitourinary Cancers Symposium 2023;Abstract LBA17.

TALAPRO-2: Most Common TEAEs



In the talazoparib arm:

- Most common TEAEs leading to a dose reduction of talazoparib were:
  - Anemia (43.2%)
  - Neutropenia (15.1%)
  - Thrombocytopenia (5.5%)
- 49.0% had grade 1–2 anemia at baseline
- Grade 3–4 anemia
  - Median time to onset was 3.3 months
  - Reported in 46.5% of men
- 8.3% discontinued talazoparib due to anemia
- The median relative dose intensity of talazoparib remained >80%

Agarwal N et al. Genitourinary Cancers Symposium 2023;Abstract LBA17.

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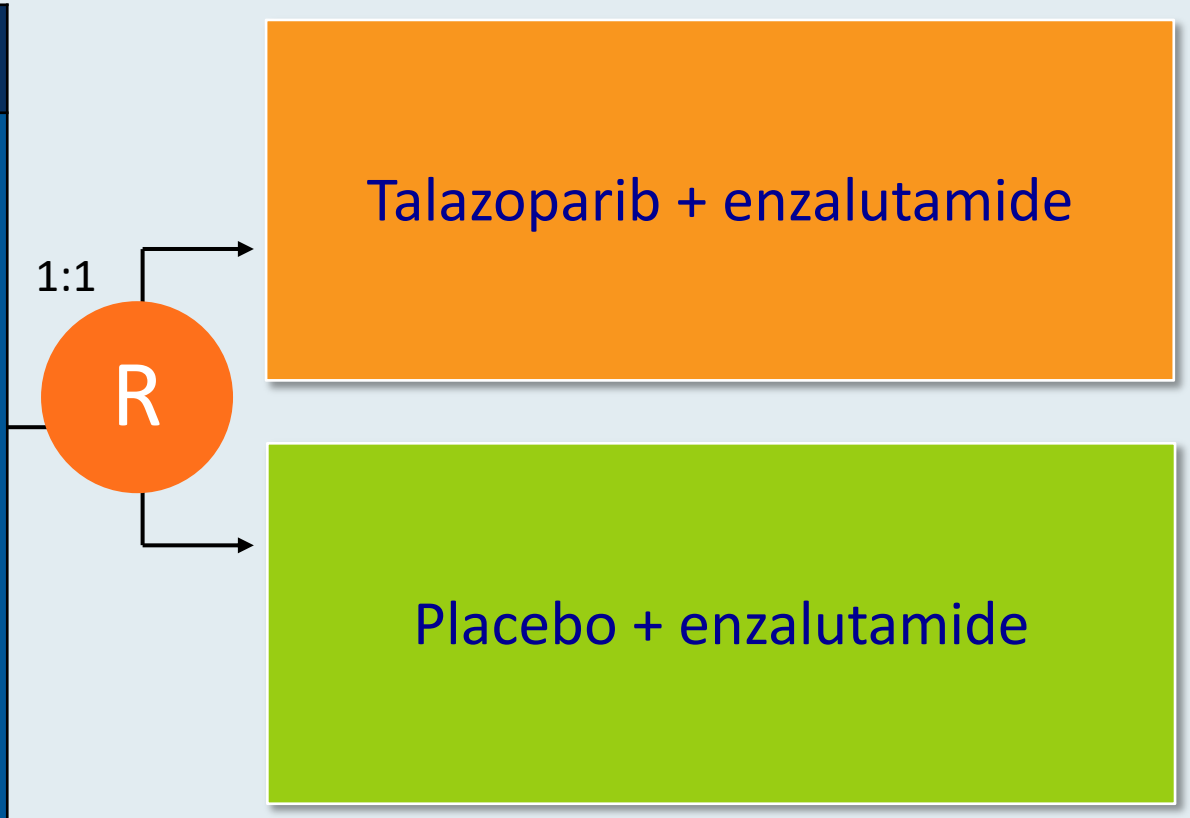
TALAPRO-3 Phase III Study Design

Estimated enrollment: N = 550

- Metastatic prostate cancer
- DNA damage response (DDR)-HRR gene alteration
- Prior therapy allowed for mHSPC; ≤3 months of ADT with or without approved novel hormonal therapy for mHSPC, if required prior to randomization, with no radiographic evidence of disease progression or rising PSA prior to Day 1



Primary endpoint: rPFS by investigator assessment

Secondary endpoints: OS, objective response in measurable soft tissue disease, duration of soft tissue response, time to first symptomatic skeletal event, time to PSA progression, time to antineoplastic therapy, others

Agarwal N et al. ASCO 2022;Abstract TPS5096.

^{177}Lu-PSMA-617

FDA Approves ^{177}Lu-PSMA-617 for the Treatment of mHRPC

Press Release: March 23, 2022

"On March 23, 2022, the Food and Drug Administration approved [the radio-ligand therapy ^{177}Lu-PSMA-617] for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) 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 lutetium Lu 177 vipivotide tetraxetan PSMA-directed therapy is indicated. Gallium Ga 68 gozetotide is the first radioactive diagnostic agent approved for patient selection in the use of 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 rPFS. 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 plus BSoC versus BSoC. Median OS was 15.3 months (95% CI: 14.2, 16.9) in the ^{177}Lu-PSMA-617 plus BSoC arm and 11.3 months (95% CI: 9.8, 13.5) in the BSoC arm, respectively."

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

RTP RESEARCH TO PRACTICE

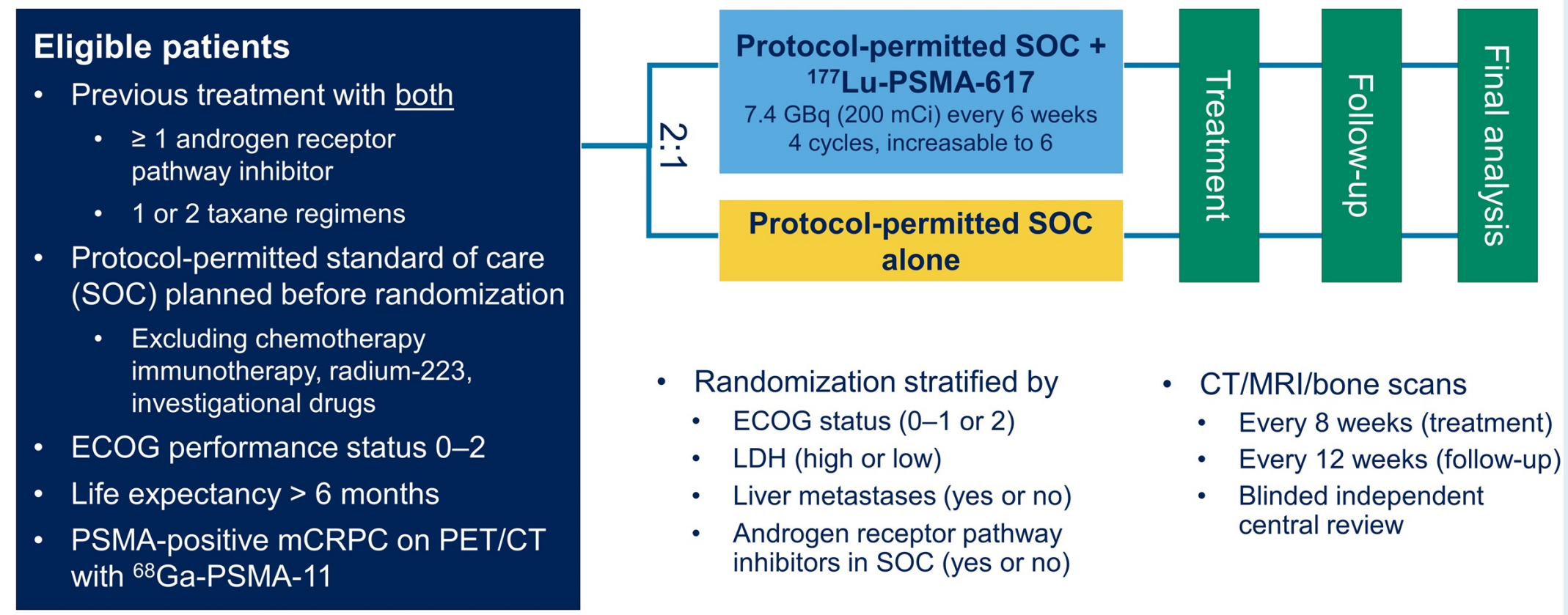
N Engl J Med 2021;385(12):1091-103
The NEW ENGLAND JOURNAL of MEDICINE

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*

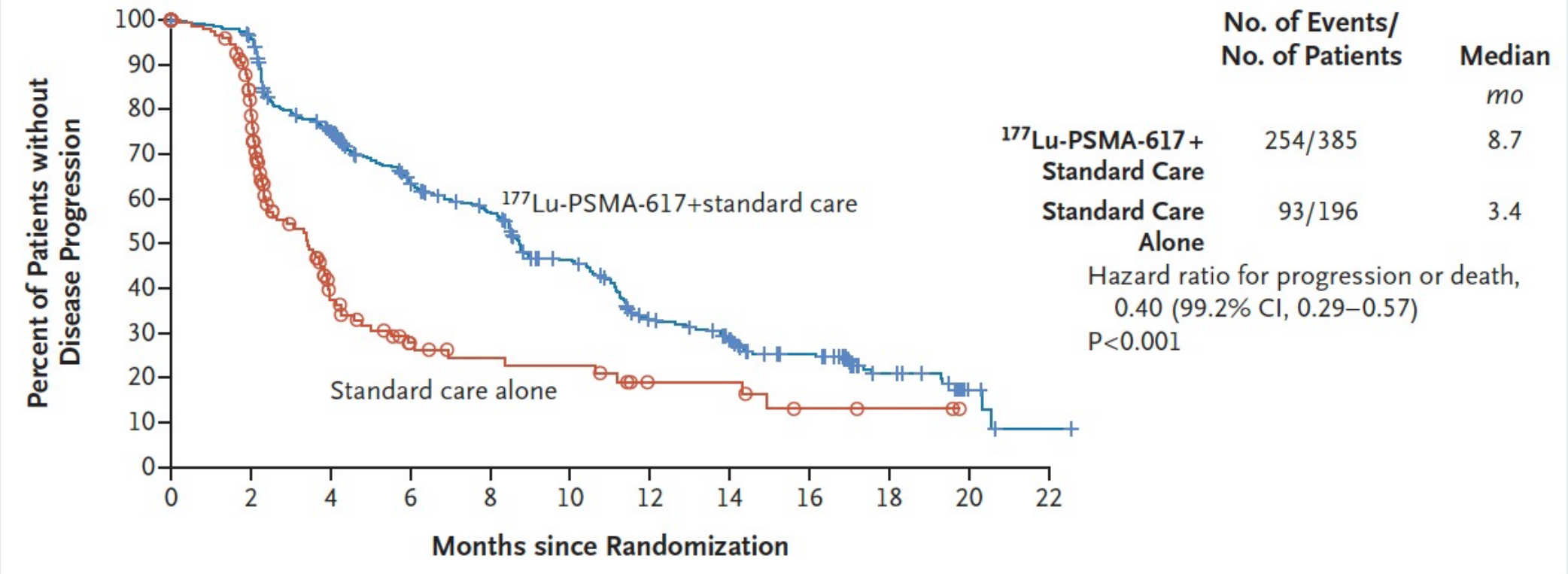
VISION: Pivotal Phase III Trial of ^{177}Lu-PSMA-617 for mHRPC



Morris MJ et al. ASCO 2021;Abstract LBA4. Sartor O et al. *N Engl J Med* 2021;385(12):1091-103.

RTP RESEARCH TO PRACTICE

VISION: Imaging-Based Progression-Free Survival by Independent Central Review

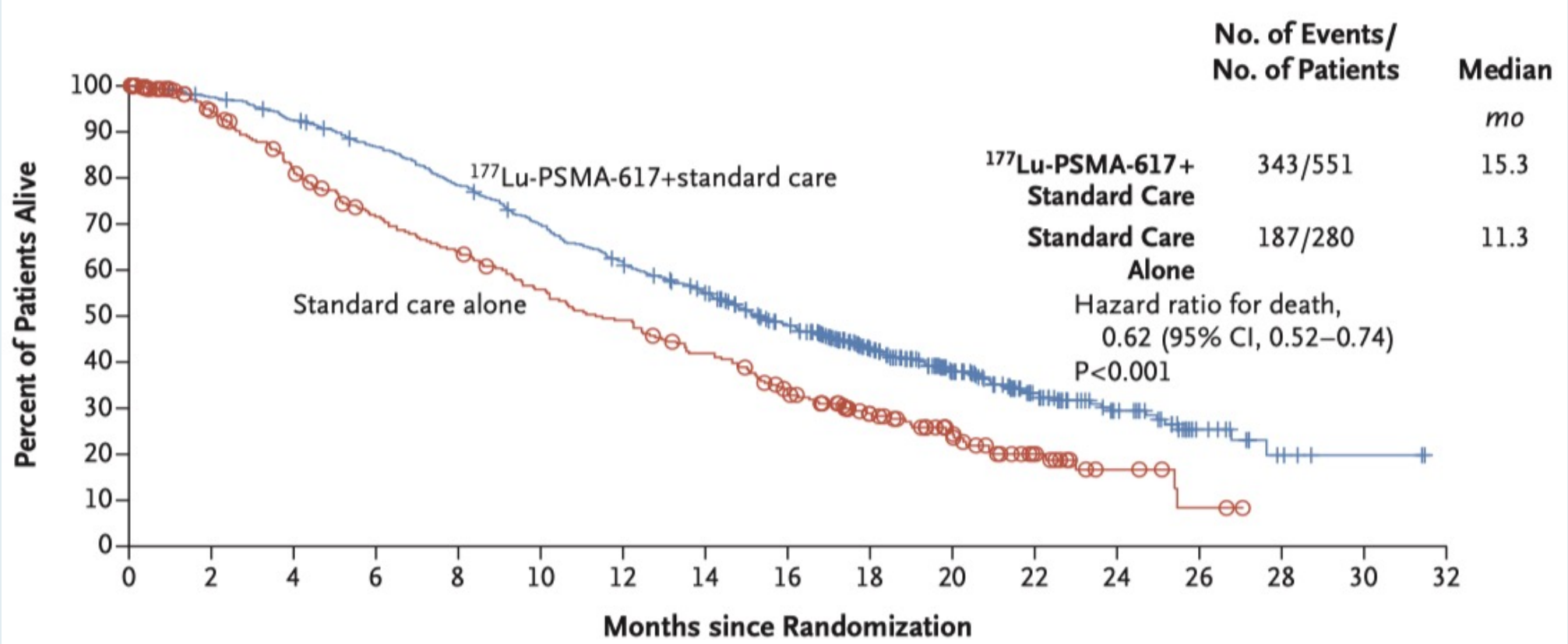


- Median OS (^{177}Lu-PSMA-617 versus standard therapy): 15.3 months versus 11.3 months (HR 0.62, $p < 0.001$)
- Time to first symptomatic skeletal event OS (^{177}Lu-PSMA-617 versus standard therapy): 11.5 months versus 6.8 months (HR 0.50, $p < 0.001$)

Sartor O et al. *N Engl J Med* 2021;385(12):1091-103.

RTP RESEARCH TO PRACTICE

VISION: Overall Survival



Sartor O et al. *N Engl J Med* 2021;385(12):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(12):1091-103.

RTP RESEARCH TO PRACTICE

PRINCE: Phase I trial of ^{177}Lu-PSMA-617 in combination with pembrolizumab in patients with metastatic castration-resistant prostate cancer (mCRPC)

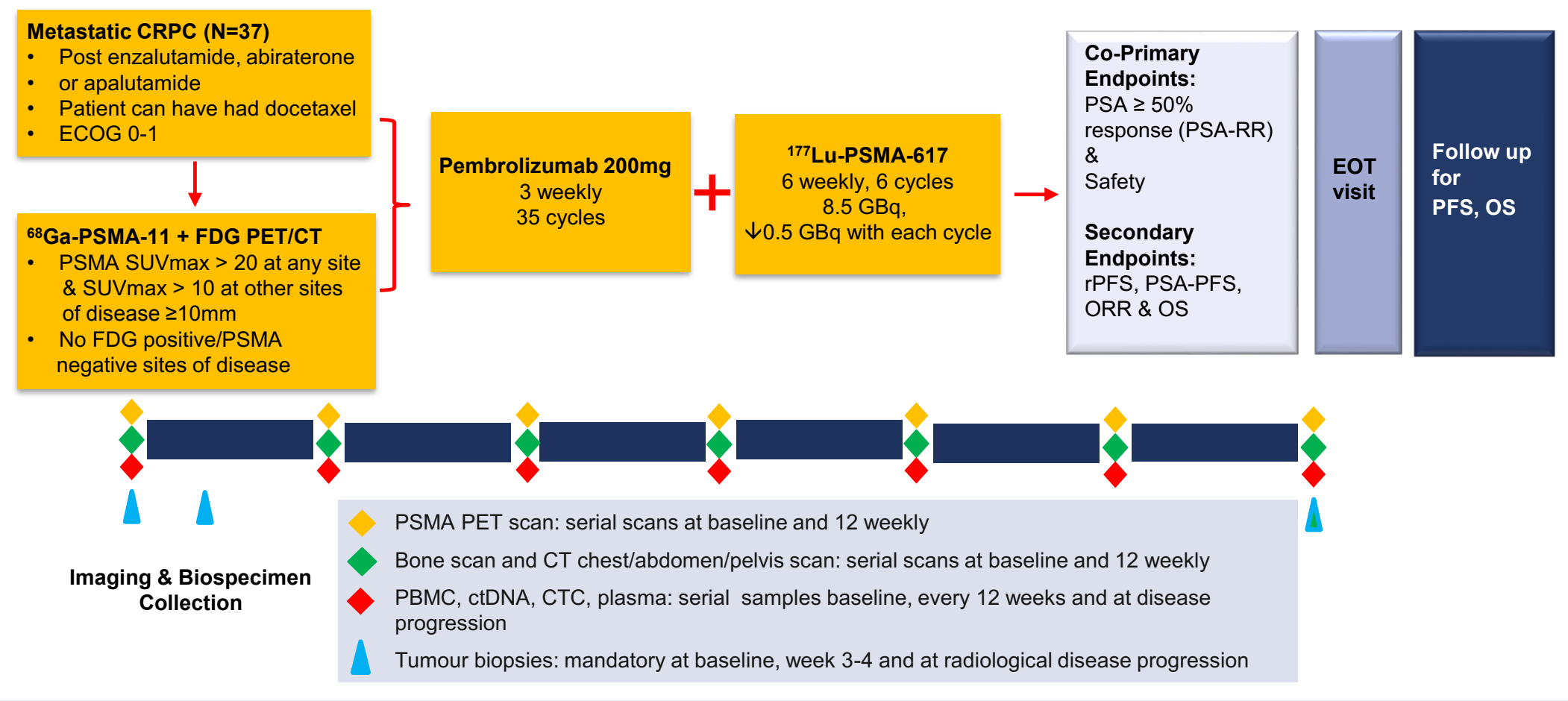
Authors: Shahneen Sandhu[1,2], Anthony M. Joshua[3], Louise Emmett[3], Lavinia Spain[1,4], Lisa G. Horvath[5], Megan Crumbaker[3], Arsha Anton[4], Roslyn Wallace[1], Anupama Pasam[1], Mathias Bressel[1,2], Erin Cassidy[1], Patricia Banks[1], Nattakorn Dhiantravan[1], Timothy J. Akhurst[1], Aravind Ravi Kumar[1], Ramin Alipour[1], Mark Scalzo[1], Scott Williams[1,2], Rod J. Hicks[6], Michael S. Hofman[1,2]

[1]Peter MacCallum Cancer Centre, Melbourne; [2]Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne; [3]St Vincent's Hospital, Sydney; [4]Eastern Health, Melbourne; [5]Chris O'Brien Lifehouse, Sydney; [6]St Vincent's Medical School, University of Melbourne, Melbourne

ASCO 2022; Abstract 5017

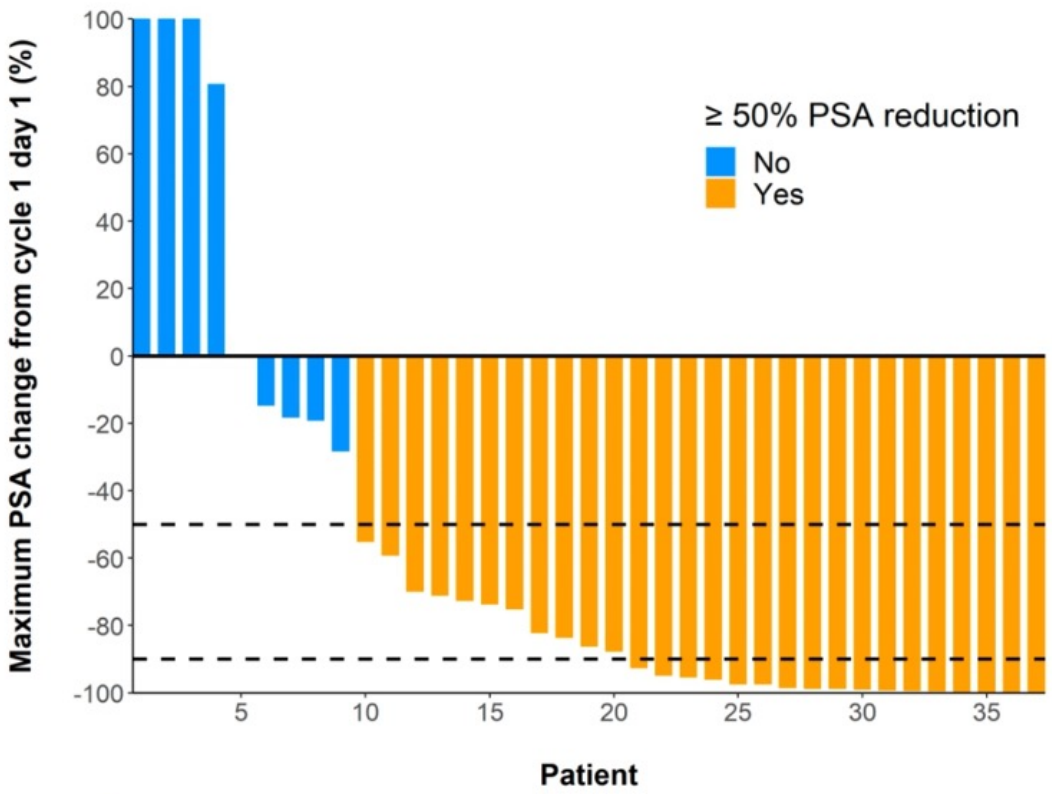
RTP RESEARCH TO PRACTICE

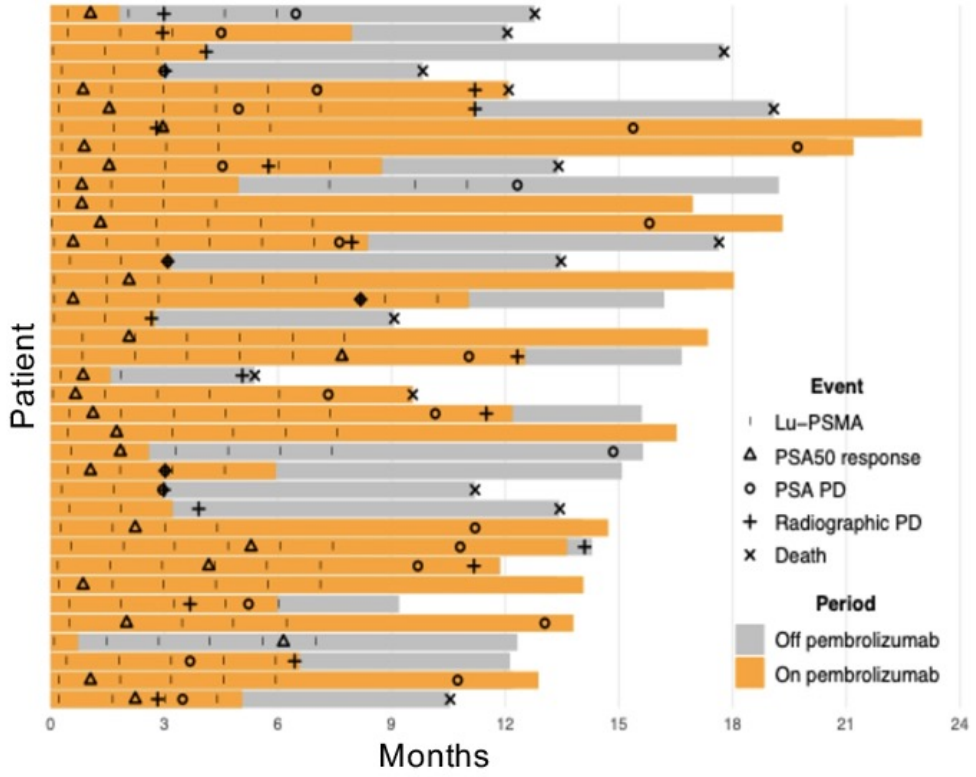
PRINCE: Phase Ib Study of Pembrolizumab with ^{177}Lu-PSMA-617 for mHRPC



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

PRINCE Primary Endpoint: PSA Response Rate





PSA ≥ 50% response = 76% (28/37 95% CI:59-88)
ORR by RECIST 1.1 = 78% (7/9)

median follow up: 16 months at data cut off

Sandhu S et al. ASCO 2022; Abstract 5017.

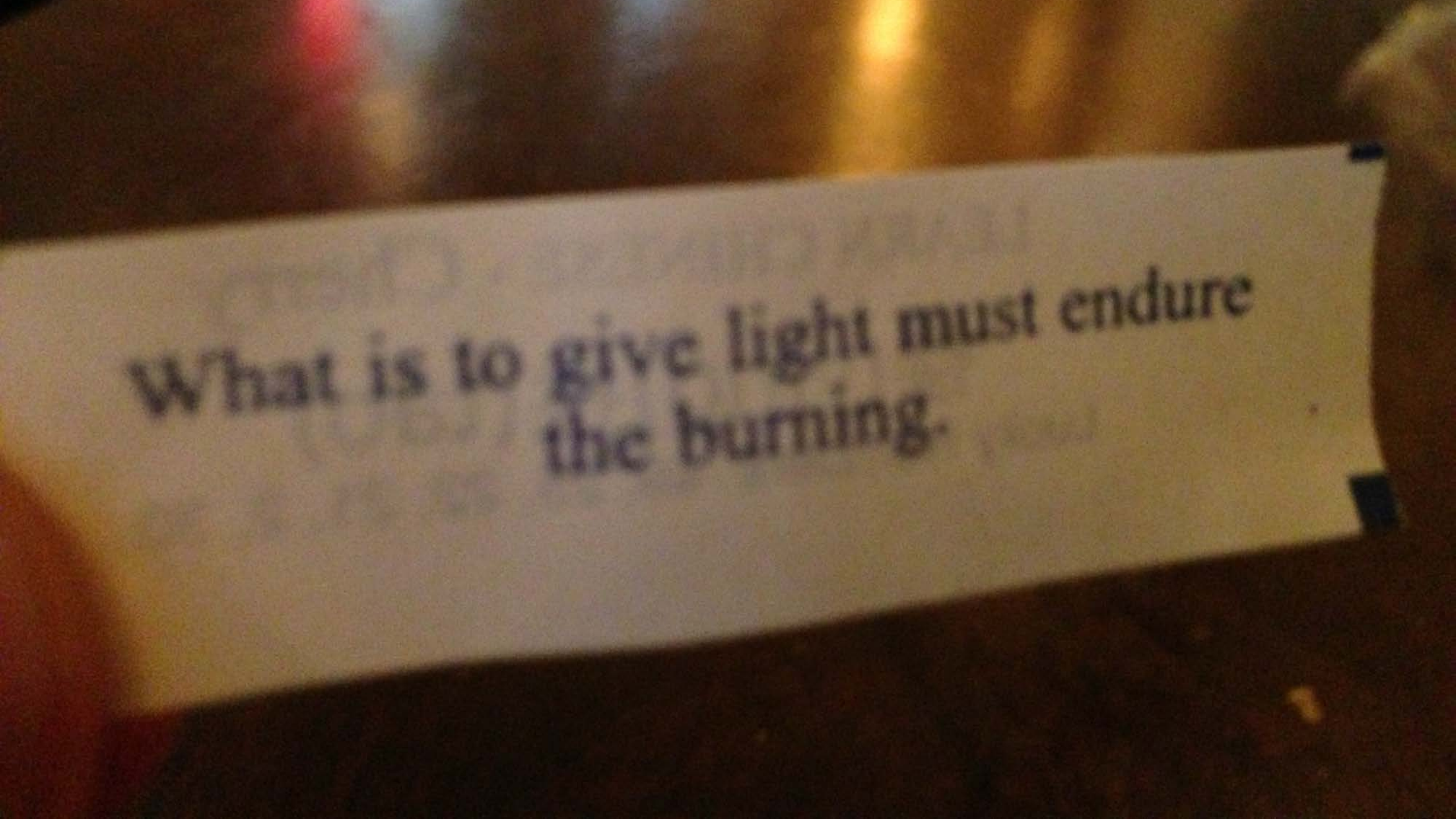
PRINCE: Treatment-Related Adverse Events

Table 1: TRAE	Any grade n (%)	Grade 3, n (%)
Xerostomia	29 (78%)	
Fatigue	16 (43%)	2 (5%)
Rash	9 (24%)	
Nausea	10 (27%)	
Pruritis	10 (27%)	
Anorexia	6 (16%)	
Thrombocytopenia	6 (16%)	
Diarrhea	5 (14%)	
Bone pain (flare)	4 (11%)	
Alanine aminotransferase elevation	4 (11%)	
Dry eye	3 (8%)	
Dysgeusia	3 (8%)	
Weight loss	3 (8%)	
Anemia	3 (8%)	1(3%)
Aspartate aminotransferase elevation	3 (8%)	
Amylase elevation	3 (8%)	1 (3%)
Arthralgia	4 (11%)	
Myalgia	3 (8%)	
Neutropenia	1 (3%)	

Table 2: Immune Related Adverse Events (irAEs)	Grade 2 n (%)	Grade 3 n (%)
Fatigue	2 (5%)	2 (5%)
Amylase elevation	-	1 (3%)
Colitis *	-	2 (5%)
Pancreatitis	-	1(3%)
Nephritis	-	1(3%)
Type I Diabetes	-	1 (3%)
Mucosal Pemphigus #	-	1 (3%)
Ocular Myasthenia Gravis *	-	1 (3%)
Optic Neuritis #	1 (3%)	-
Myocarditis *		1 (3%)
Pneumonitis	1 (3%)	1(3%)

Discontinuation for toxicity:
Pembrolizumab, n (%): 5 (19%)
^{177}Lu-PSMA-617, n (%): 0 (0%)

Sandhu S et al. ASCO 2022; Abstract 5017.


What is to give light must endure
the burning.

What I Tell My Patients:
Faculty Physicians and Nurses Discuss Patient Education About New Treatments and Clinical Trials

Fifteenth Annual RTP Symposium Series Held During the Annual ONS Congress

Prostate Cancer

Saturday, April 29, 2023
12:15 PM – 1:45 PM

Faculty

Neeraj Agarwal, MD, FASCO
Kathy D Burns, RN, MSN, AGACNP-BC, OCN
Susan K Roethke, MSN, CRNP, AOCNP, ANP-BC
Sandy Srinivas, MD

Moderator

Neil Love, MD

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