Meet The Professor

Optimizing the Use of Hormonal Therapy in the Management of Prostate Cancer

Tuesday, October 25, 2022
5:00 PM – 6:00 PM ET

Faculty

Matthew R Smith, MD, PhD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Commercial Support

This activity is supported by an educational grant from Bayer HealthCare Pharmaceuticals.

Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BeyondSpring Pharmaceuticals Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Coherus BioSciences, CTI BioPharma Corp, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Corporation, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Kronos Bio Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, MEI Pharma Inc, Merck, Mersana Therapeutics Inc, Mirati Therapeutics Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi, Seagen Inc, Servier Pharmaceuticals LLC, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, TerSera Therapeutics LLC, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc and Zymeworks Inc.

RTP
RESEARCH
TO PRACTICE

Research To Practice CME Planning Committee Members, Staff and Reviewers

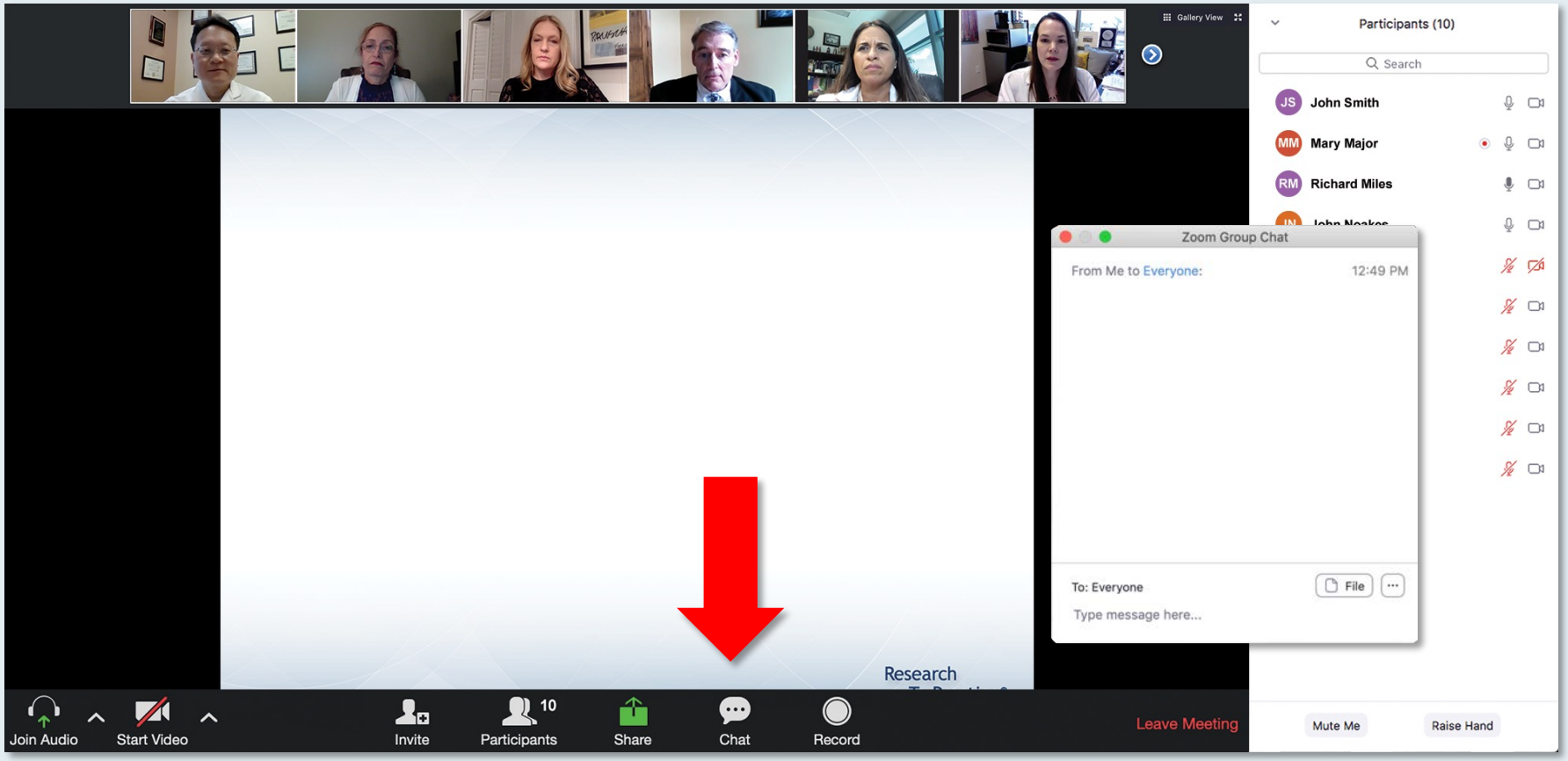
Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

Dr Smith — Disclosures

Advisory Committee, Consulting Agreements and Contracted Research	Bayer HealthCare Pharmaceuticals, Janssen Biotech Inc, Lilly, Pfizer Inc

RTP RESEARCH TO PRACTICE

We Encourage Clinicians in Practice to Submit Questions

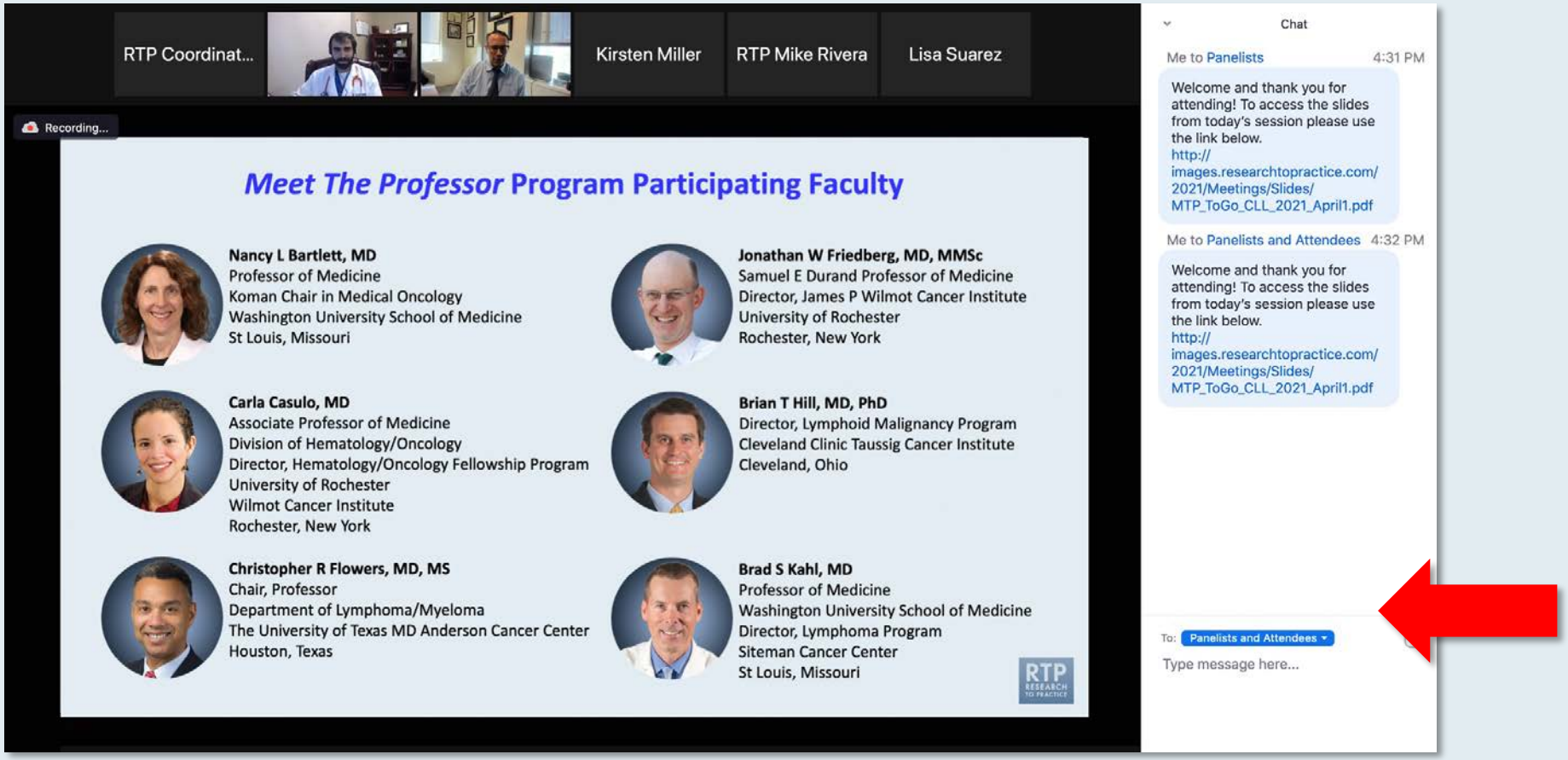


Feel free to submit questions now before the program begins and throughout the program.

RTP RESEARCH TO PRACTICE

Familiarizing Yourself with the Zoom Interface

Expand chat submission box

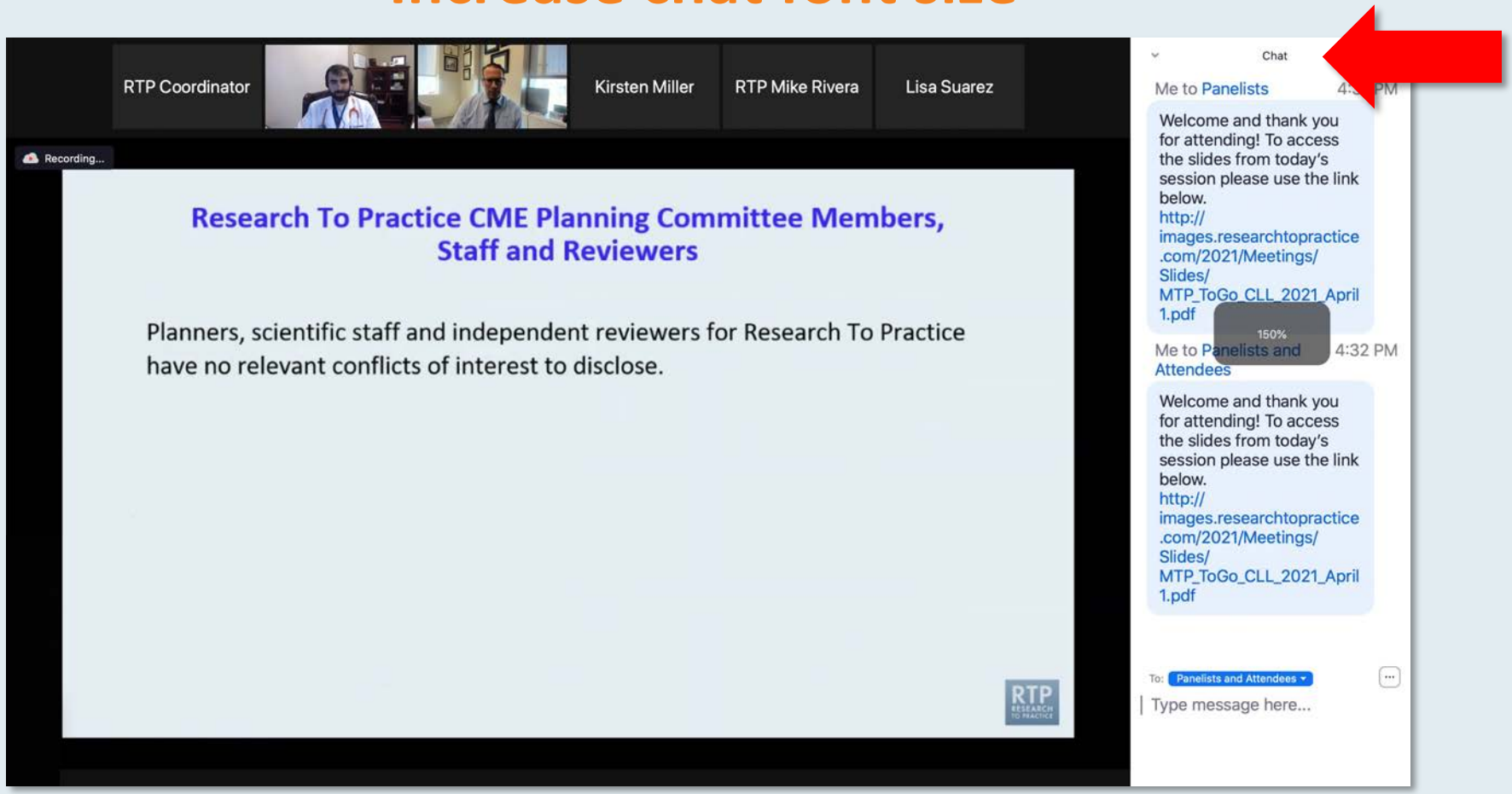


Drag the white line above the submission box up to create more space for your message.

RTP RESEARCH TO PRACTICE

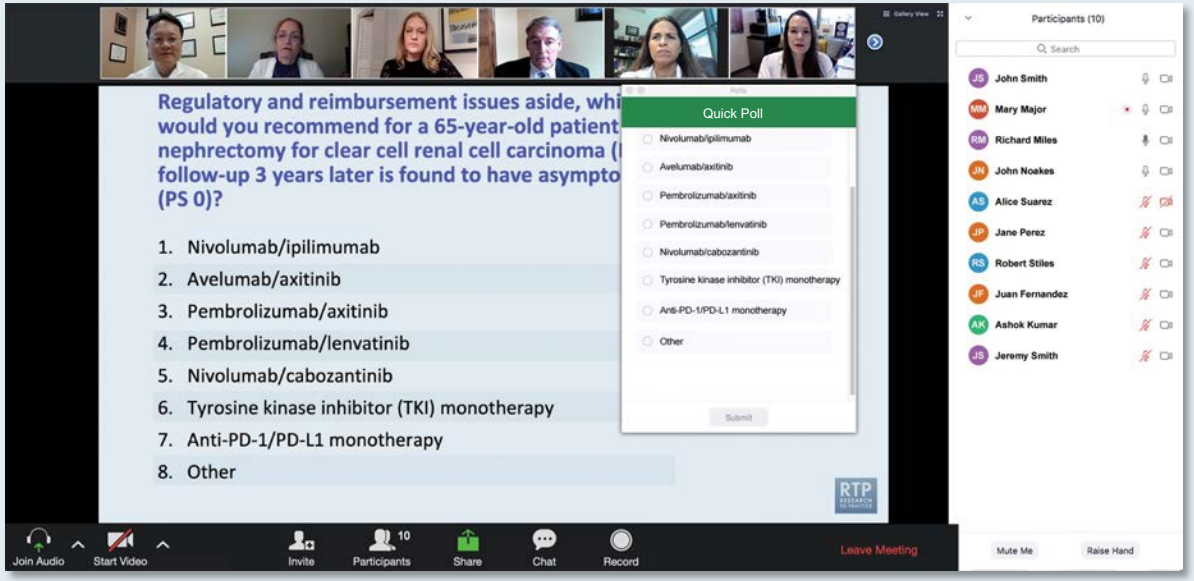
Familiarizing Yourself with the Zoom Interface

Increase chat font size



Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.

Clinicians in the Audience, Please Complete the Pre- and Postmeeting Surveys



ONCOLOGY TODAY

WITH DR NEIL LOVE

Key Presentations on Genitourinary Cancers from the 2022 ASCO Annual Meeting

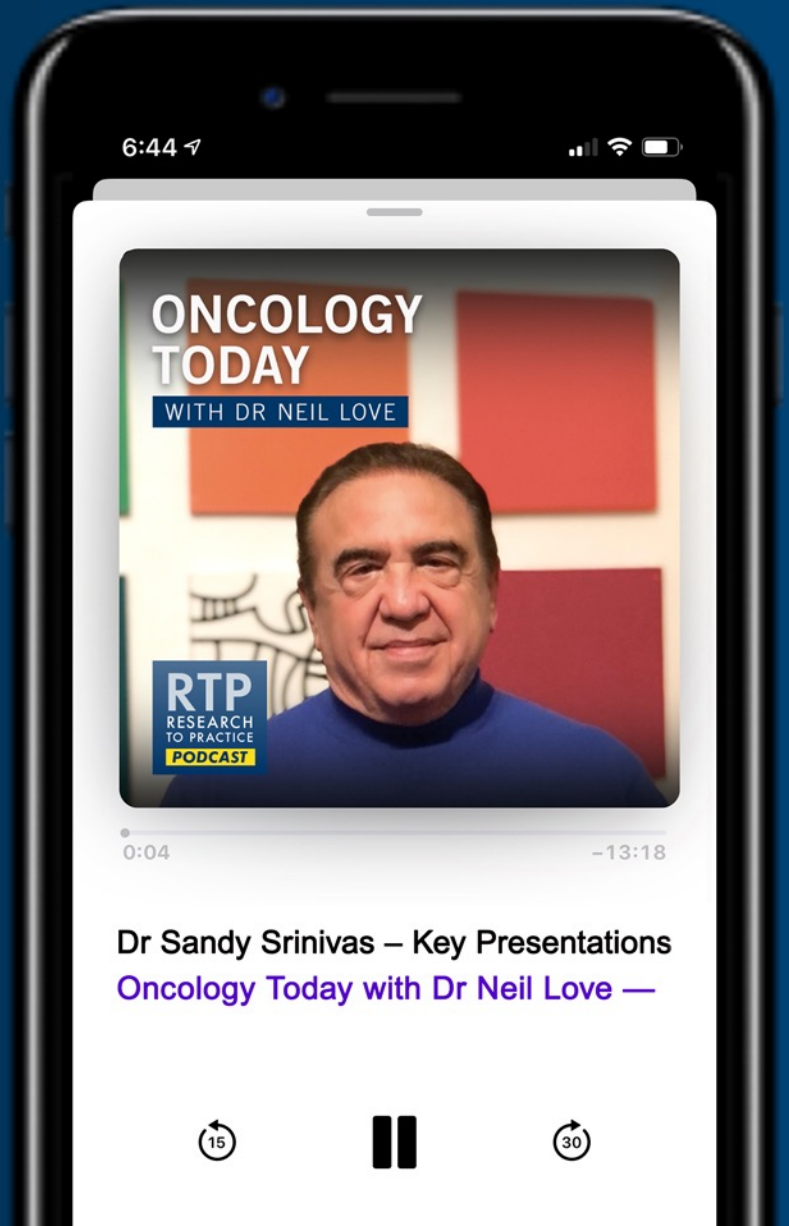
DR SANDY SRINIVAS

STANFORD UNIVERSITY

Listen on Apple Podcasts

Spotify

Listen on Google Podcasts



BCMA-Directed Therapy in Multiple Myeloma — Expert Opinions and Patient Perspectives

Part 1 of a 2-Part CME/MOC-Accredited Virtual Series

Wednesday, October 26, 2022
5:00 PM – 6:00 PM ET

Faculty

Elizabeth O'Donnell, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Current Paradigm and Future Directions for Immunotherapy in the Treatment of Metastatic Non-Small Cell Lung Cancer

A CME/MOC-Accredited Virtual Event

Tuesday, November 1, 2022
5:00 PM – 6:00 PM ET

Faculty

John V Heymach, MD, PhD
Stephen V Liu, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Consensus or Controversy? Documenting and Discussing Clinical Investigators' Practice Patterns in Ovarian Cancer

A CME/MOC-Accredited Virtual Event

Thursday, November 3, 2022
5:00 PM – 6:00 PM ET

Faculty

Ursula Matulonis, MD
Debra L Richardson, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Meet The Professor

Optimizing the Management of HER2-Positive Breast Cancer

Tuesday, November 8, 2022
5:00 PM – 6:00 PM ET

Faculty

Lisa A Carey, MD, ScM

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Meet The Professor
Optimizing the Management of Multiple Myeloma

Tuesday, November 15, 2022
5:00 PM – 6:00 PM ET

Faculty

Paul G Richardson, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Breast Cancer

A 2-Part CME Satellite Symposium Series Held in Conjunction with the 2022 San Antonio Breast Cancer Symposium®

HER2-Positive Breast Cancer

Wednesday, December 7, 2022

7:15 PM – 9:15 PM CT

ER-Positive Breast Cancer

Thursday, December 8, 2022

7:15 PM – 9:15 PM CT

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Addressing Current Questions and Controversies in the Management of Hematologic Cancers — What Clinicians Want to Know

A 3-Part CME Friday Satellite Symposium and Virtual Event Series
Preceding the 64th ASH Annual Meeting

Chronic Lymphocytic Leukemia

Friday, December 9, 2022
11:30 AM – 1:30 PM CT

Hodgkin and Non-Hodgkin Lymphoma

Friday, December 9, 2022
3:15 PM – 5:15 PM CT

Multiple Myeloma

Friday, December 9, 2022
7:00 PM – 9:00 PM CT

Moderator: Neil Love, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us!

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

RTP
RESEARCH
TO PRACTICE

Meet The Professor

Optimizing the Use of Hormonal Therapy in the Management of Prostate Cancer

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

Meet The Professor Program Participating Faculty

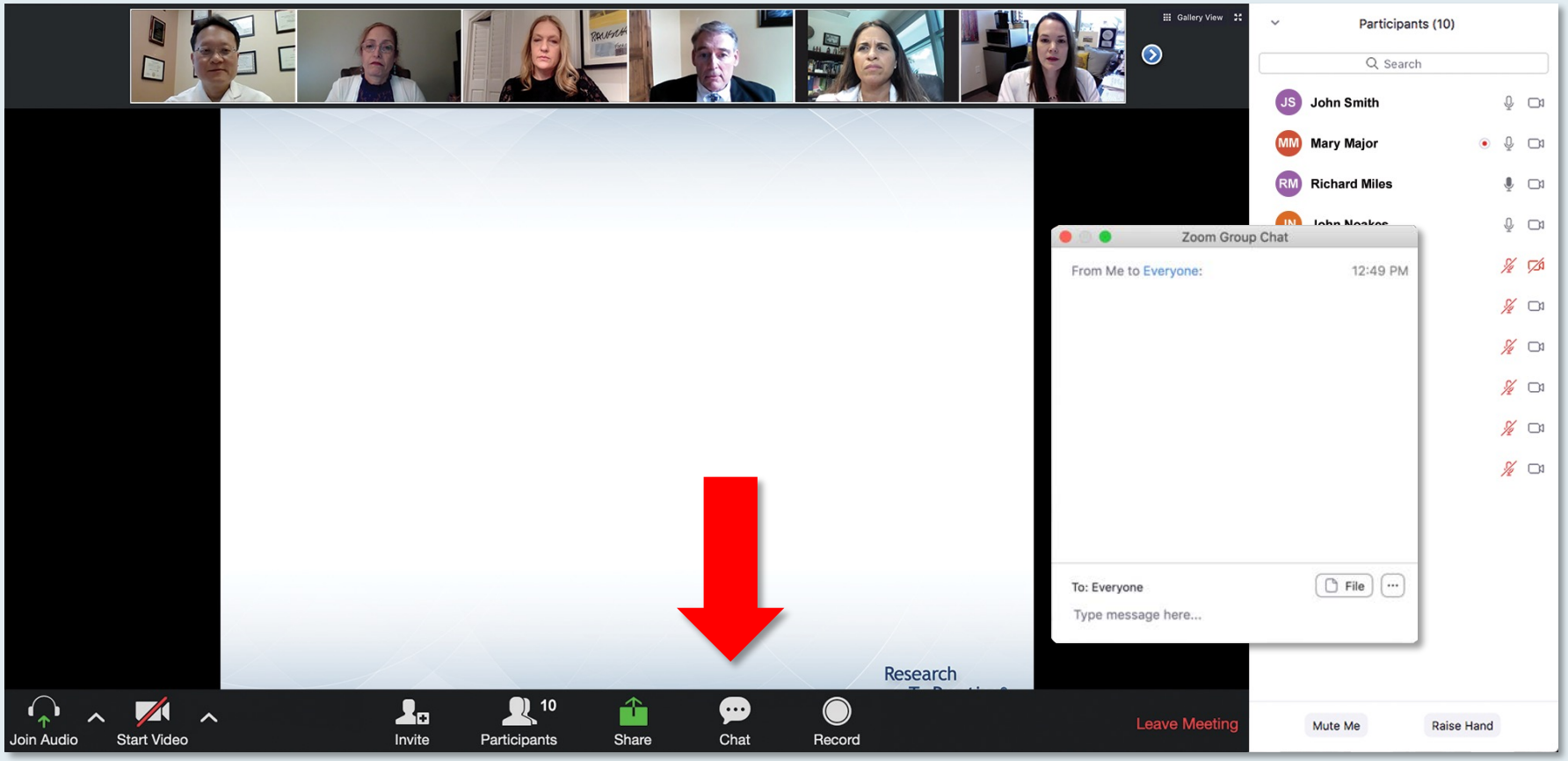
Matthew R Smith, MD, PhD
Claire and John Bertucci Endowed Chair
in Genitourinary Cancers
Professor of Medicine
Harvard Medical School
Director, Genitourinary Malignancies Program
Massachusetts General Hospital Cancer Center
Boston, Massachusetts

MODERATOR
Neil Love, MD
Research To Practice

Additional faculty to be announced.

RTP
RESEARCH
TO PRACTICE

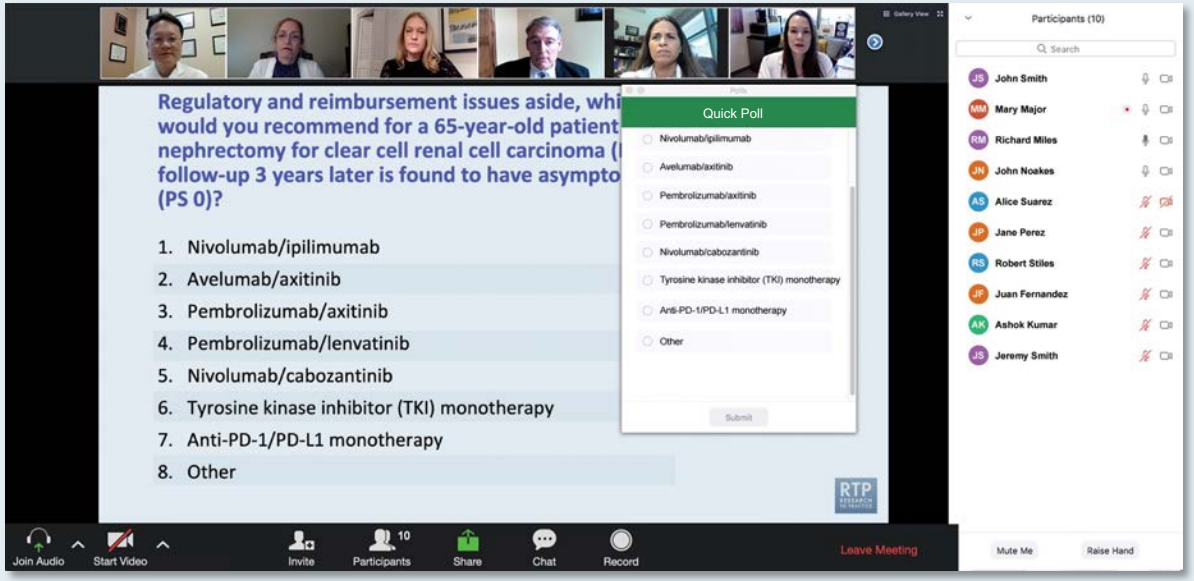
We Encourage Clinicians in Practice to Submit Questions



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

RTP RESEARCH TO PRACTICE

Clinicians in the Audience, Please Complete the Pre- and Postmeeting Surveys



ONCOLOGY TODAY

WITH DR NEIL LOVE

Key Presentations on Genitourinary Cancers from the 2022 ASCO Annual Meeting

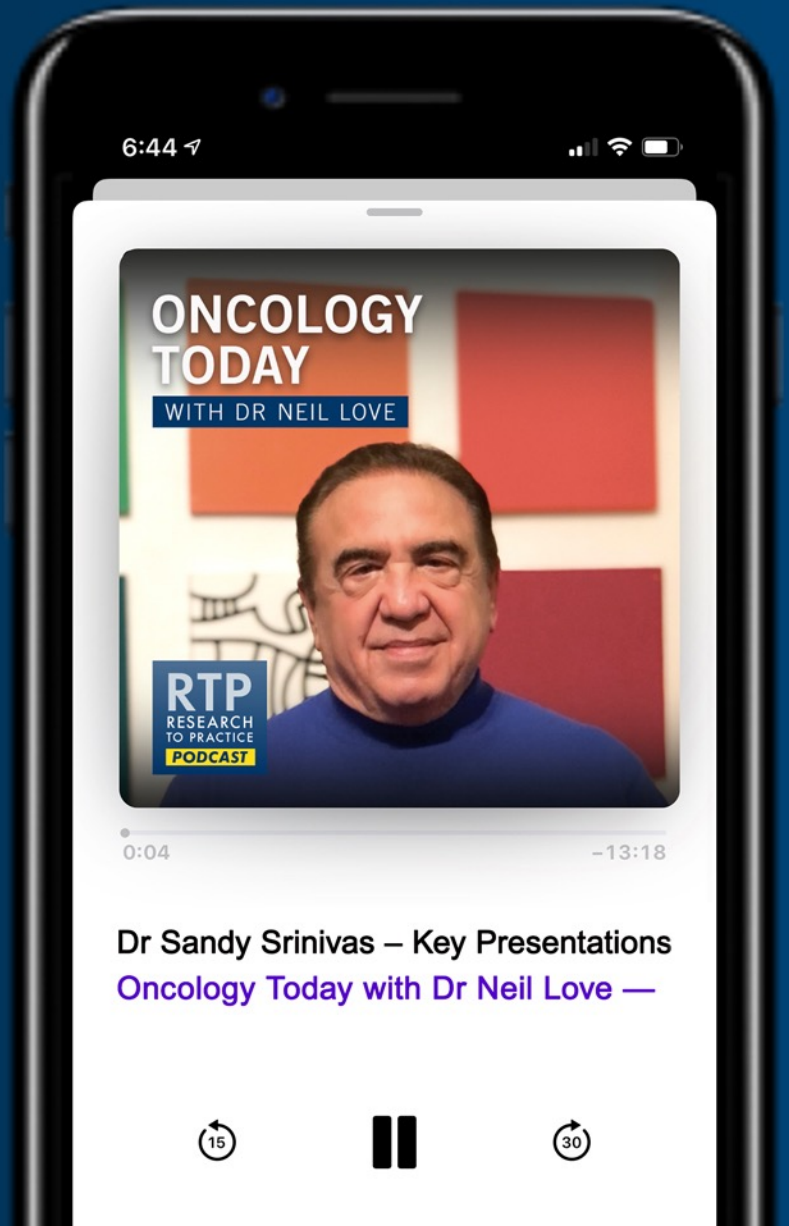
DR SANDY SRINIVAS

STANFORD UNIVERSITY

Listen on Apple Podcasts

Spotify

Listen on Google Podcasts



BCMA-Directed Therapy in Multiple Myeloma — Expert Opinions and Patient Perspectives

Part 1 of a 2-Part CME/MOC-Accredited Virtual Series

Wednesday, October 26, 2022
5:00 PM – 6:00 PM ET

Faculty

Elizabeth O'Donnell, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Current Paradigm and Future Directions for Immunotherapy in the Treatment of Metastatic Non-Small Cell Lung Cancer

A CME/MOC-Accredited Virtual Event

Tuesday, November 1, 2022
5:00 PM – 6:00 PM ET

Faculty

John V Heymach, MD, PhD
Stephen V Liu, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Consensus or Controversy? Documenting and Discussing Clinical Investigators' Practice Patterns in Ovarian Cancer

A CME/MOC-Accredited Virtual Event

Thursday, November 3, 2022
5:00 PM – 6:00 PM ET

Faculty

Ursula Matulonis, MD
Debra L Richardson, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Meet The Professor

Optimizing the Management of HER2-Positive Breast Cancer

Tuesday, November 8, 2022
5:00 PM – 6:00 PM ET

Faculty

Lisa A Carey, MD, ScM

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Meet The Professor
Optimizing the Management of Multiple Myeloma

Tuesday, November 15, 2022
5:00 PM – 6:00 PM ET

Faculty

Paul G Richardson, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Breast Cancer

A 2-Part CME Satellite Symposium Series Held in Conjunction with the 2022 San Antonio Breast Cancer Symposium®

HER2-Positive Breast Cancer

Wednesday, December 7, 2022

7:15 PM – 9:15 PM CT

ER-Positive Breast Cancer

Thursday, December 8, 2022

7:15 PM – 9:15 PM CT

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Addressing Current Questions and Controversies in the Management of Hematologic Cancers — What Clinicians Want to Know

A 3-Part CME Friday Satellite Symposium and Virtual Event Series
Preceding the 64th ASH Annual Meeting

Chronic Lymphocytic Leukemia

Friday, December 9, 2022
11:30 AM – 1:30 PM CT

Hodgkin and Non-Hodgkin Lymphoma

Friday, December 9, 2022
3:15 PM – 5:15 PM CT

Multiple Myeloma

Friday, December 9, 2022
7:00 PM – 9:00 PM CT

Moderator: Neil Love, MD

RTP RESEARCH TO PRACTICE

Meet The Professor

Optimizing the Use of Hormonal Therapy in the Management of Prostate Cancer

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

Commercial Support

This activity is supported by an educational grant from Bayer HealthCare Pharmaceuticals.

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 Smith — Disclosures

Advisory Committee, Consulting Agreements and Contracted Research	Bayer HealthCare Pharmaceuticals, Janssen Biotech Inc, Lilly, Pfizer Inc

RTP RESEARCH TO PRACTICE

Susmitha Apuri, MD
Florida Cancer Specialists
Inverness, Florida

Kapisthalam (KS) Kumar, MD
Florida Cancer Specialists
Trinity, Florida

Jennifer L Dallas, MD
Oncology Specialists of Charlotte
Charlotte, North Carolina

Henna Malik, MD
Texas Oncology
Houston, Texas

Gurveen Kaur, MD
WVU Medicine Wheeling Hospital
Wheeling, West Virginia

David S Morris, MD
Urology Associates
Nashville, Tennessee

RTP
RESEARCH
TO PRACTICE

Meet The Professor with Dr Smith

Introduction: Abemaciclib for Prostate Cancer?

MODULE 1: Rounds

MODULE 2: Ongoing Trials; Reported Data; Review Articles

RTP
RESEARCH
TO PRACTICE

CYCLONE 3: A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of Abemaciclib in Combination with Abiraterone plus Prednisone in Men with High-Risk Metastatic Hormone-Sensitive Prostate Cancer (mHSPC)

McKay RR et al.

ESMO 2022;Abstract 1423TiP.

CYCLONE 2: A Phase 2/3, Randomized, Placebo-Controlled Study of Abiraterone Acetate plus Prednisone with or without Abemaciclib in Patients with Metastatic Castration-Resistant Prostate Cancer

Smith MR et al.

Genitourinary Cancers Symposium 2022;Abstract TPS198.

Meet The Professor with Dr Smith

Introduction: Abemaciclib for Prostate Cancer?

MODULE 1: Rounds

- Dr Dallas: 70-year-old man, PSA 150, Gleason 4 + 4, upper abdominal adenopathy
- Dr Morris: 68-year-old man, Gleason 4 + 4, PSA 147, CT negative
- Dr Kaur: 67-year-old man, CAD, Gleason 4 + 4; 2013 EBRT; increasing PSA now 3.8, 6-month doubling time
- Dr Malik: 66-year-old man, s/p EBRT → ADT, now with M0 progression but patient refuses to continue ADT
- Dr Kumar: 53-year-old man, s/p radical prostatectomy and salvage radiation therapy with a slowly rising PSA now 1.31; PSMA PET scan denied by insurance, now appealed
- Dr Apuri: 77-year-old man, Gleason 5 + 4, PSA 23; EBRT → ADT; cryoablation; enzalutamide → response, now PSA increasing; 18F-fluciclovine PET — subtle focus of uptake in left prostate

MODULE 2: Ongoing Trials; Reported Data; Review Articles

Case Presentation: 70-year-old man, PSA 150, Gleason 4 + 4, upper abdominal adenopathy

Dr Jennifer Dallas (Charlotte, North Carolina)

RTP RESEARCH TO PRACTICE

Discussion Questions

Which systemic therapy would you typically use for a 65-year-old patient presenting de novo with Gleason 8 prostate cancer and 3 asymptomatic bone metastases?

Which systemic therapy would you typically use for an 80-year-old patient presenting de novo with Gleason 8 prostate cancer and 3 asymptomatic bone metastases?

Which systemic therapy would you typically use for a 65-year-old patient presenting de novo with Gleason 8 prostate cancer and multiple bone and liver metastases?

RTP
RESEARCH
TO PRACTICE

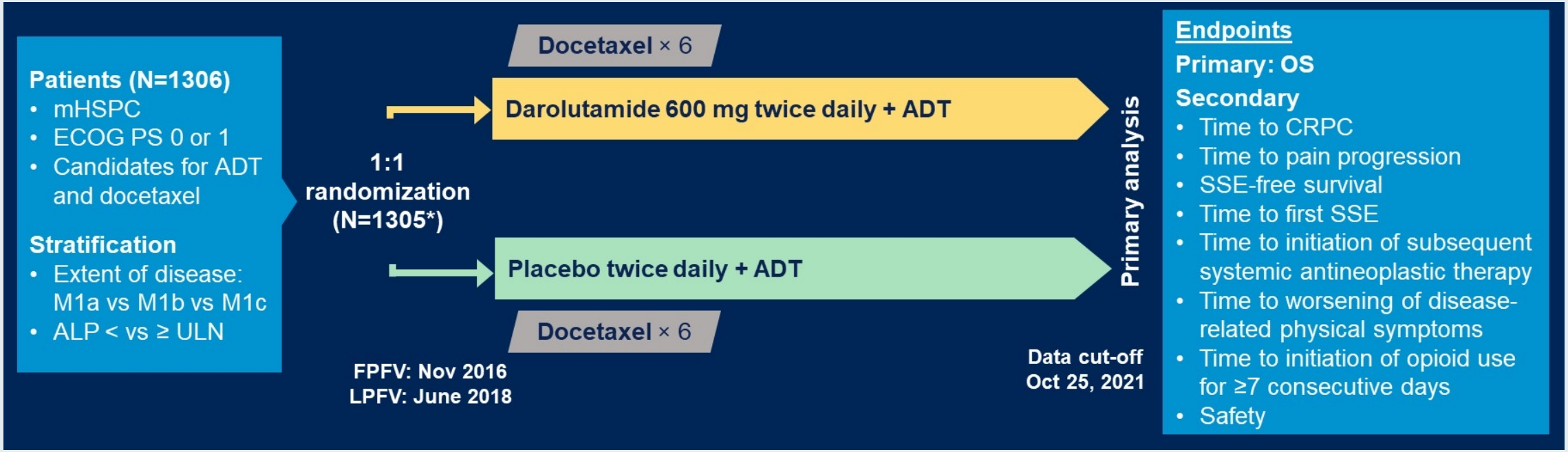
ASCO Genitourinary Cancers Symposium 2022;Abstract 13.

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: Randomized Phase III Trial of Darolutamide vs Placebo in mHSPC



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

The NEW ENGLAND JOURNAL of MEDICINE

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*

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

PARIS 2022 ESMO congress

Abstract 1360MO

Quality of life and patient-relevant endpoints with darolutamide in the phase 3 ARASENS study

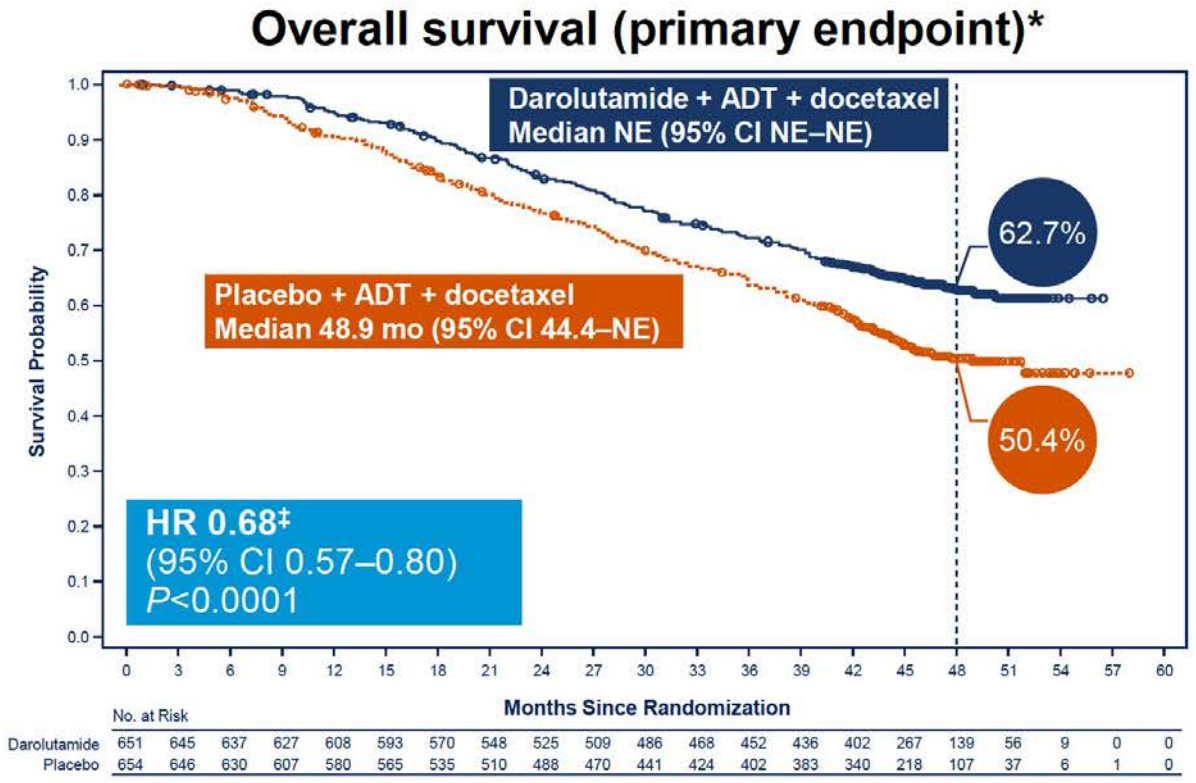
Karim Fizazi[1], Matthew R. Smith[2], Maha Hussain[3], Fred Saad[4], Cora N. Sternberg[5], E. David Crawford[6], Jeanny B. Aragon-Ching[7], Silke Thiele[8], Shivani Kapur[9], Ateesha F. Mohamed[10], Shankar Srinivasan[10], Rui Li[10], Iris Kuss[8], Heikki Joensuu[11], Bertrand Tombal[12]

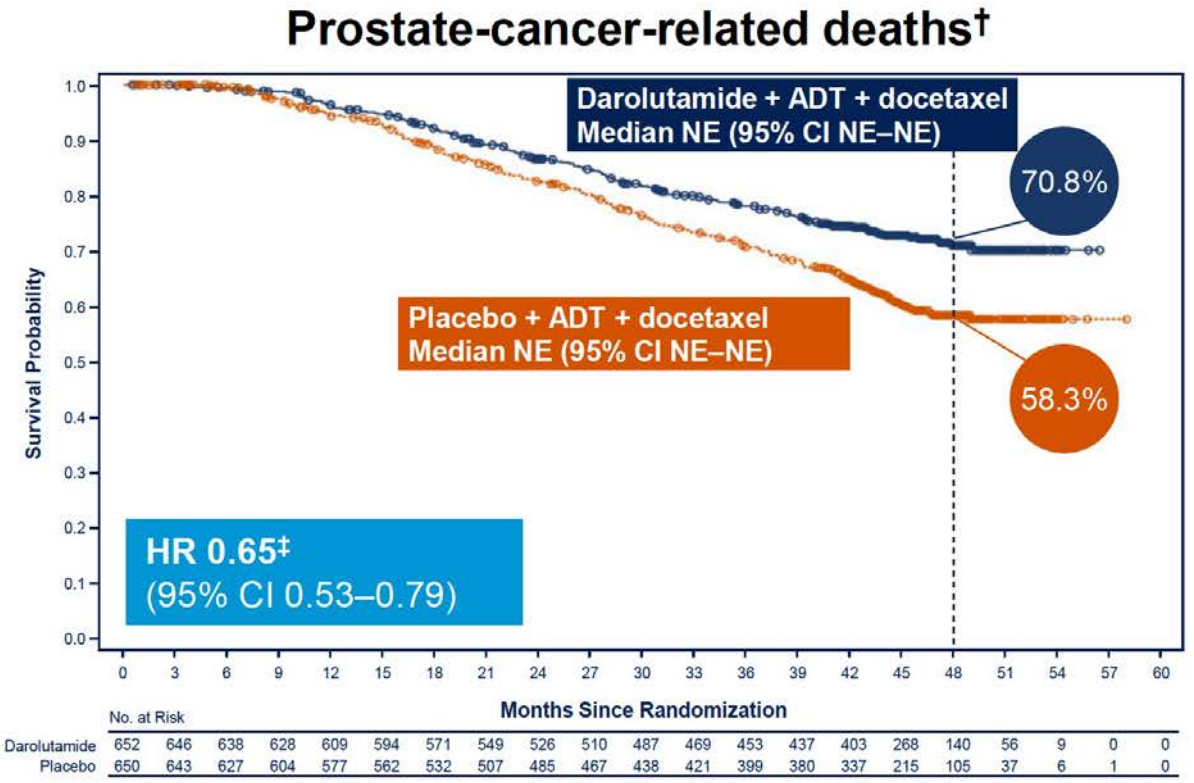
[1]Institut Gustave Roussy, University of Paris-Saclay, Villejuif, France; [2]Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA; [3]Robert H Lurie Comprehensive Cancer Center, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA; [4]University of Montreal Hospital Center, Montreal, Quebec, Canada; [5]Englander Institute for Precision Medicine, Weill Cornell Department of Medicine, Meyer Cancer Center, New York-Presbyterian Hospital, New York, NY, USA; [6]UC San Diego School of Medicine, San Diego, CA, USA; [7]Inova Schar Cancer Institute/Inova Fairfax Hospital, Fairfax, VA, USA; [8]Bayer AG, Berlin, Germany; [9]Bayer SEA, Singapore; [10]Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, USA; [11]Orion Corporation Orion Pharma, Espoo, Finland; [12]Division of Urology, IREC, Cliniques Universitaires Saint Luc, UCLouvain, Brussels, Belgium

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

ARASENS: Overall Survival and Prostate Cancer-Related Deaths

Darolutamide significantly reduced the risk of death by 32.5% vs placebo,[1] and the survival benefit is confirmed by fewer prostate cancer-related deaths with darolutamide vs placebo

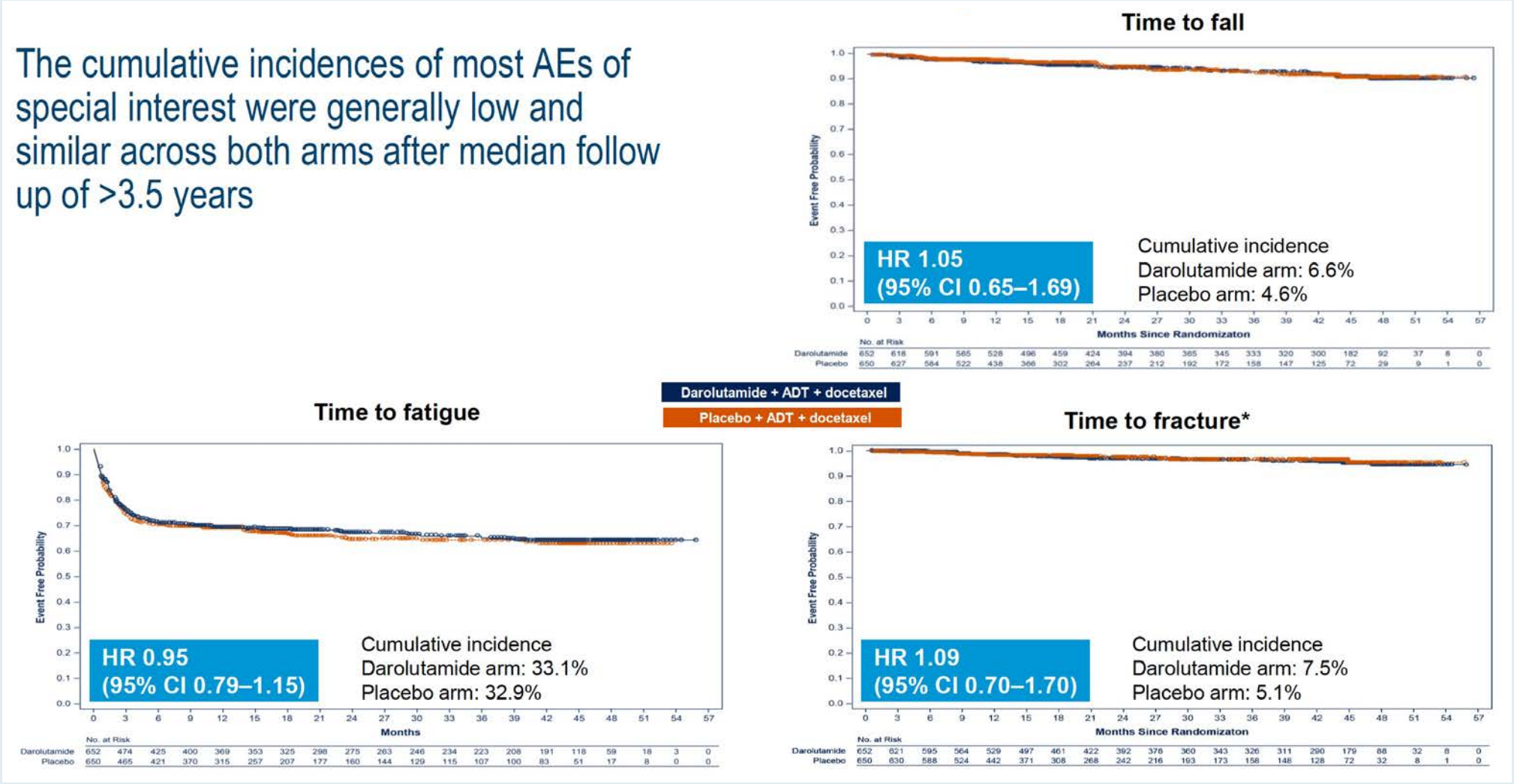




Fizazi K et al. ESMO 2022;Abstract 1360MO.

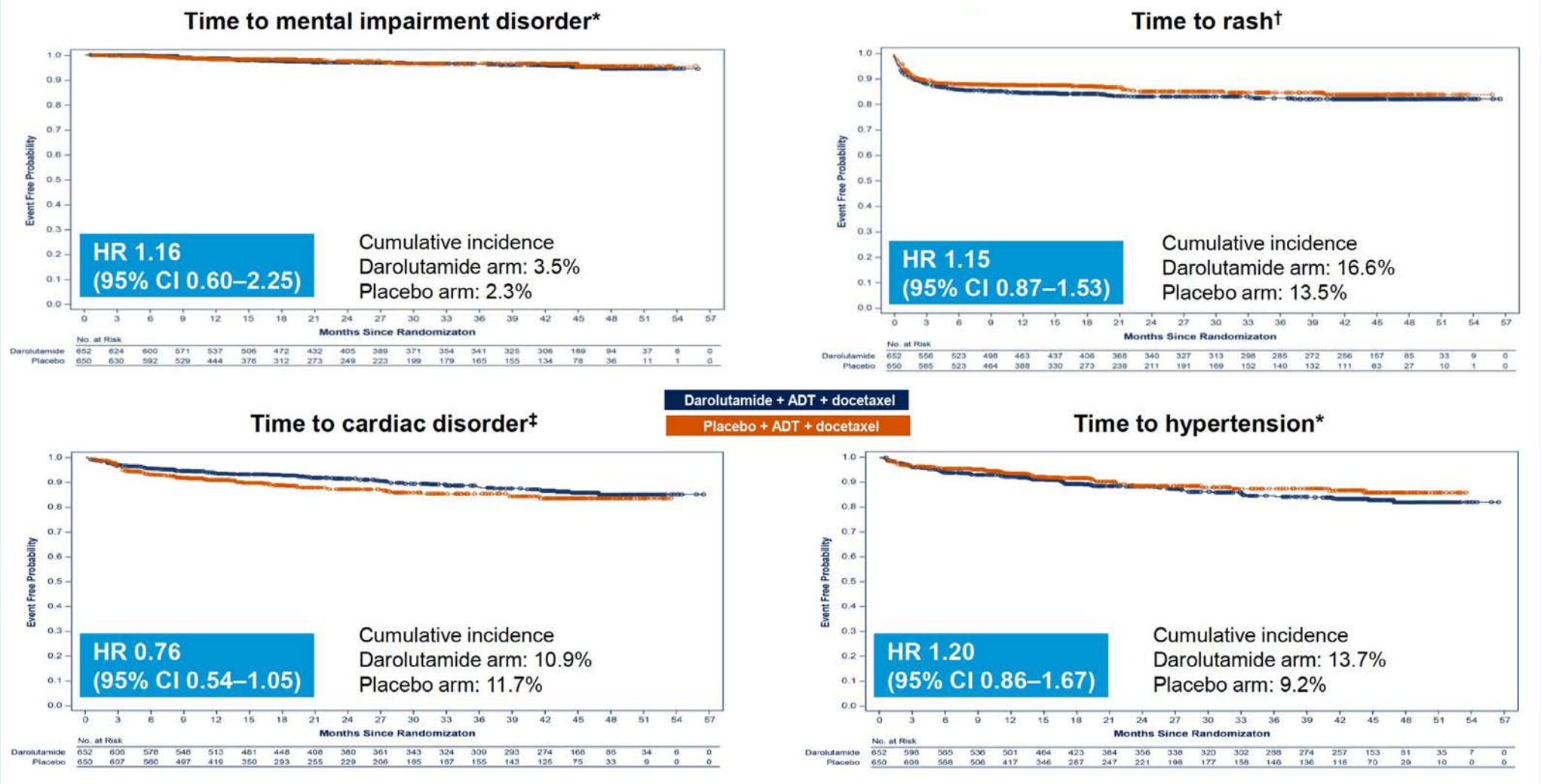
ARASENS: Adverse Events (AEs) of Interest Commonly Associated with Androgen Receptor (AR) Inhibitors

The cumulative incidences of most AEs of special interest were generally low and similar across both arms after median follow up of >3.5 years



Fizazi K et al. ESMO 2022;Abstract 1360MO.

ARASENS: AEs of Interest Commonly Associated with AR Inhibitors (Continued)



Fizazi K et al. ESMO 2022;Abstract 1360MO.

A randomized, controlled, phase 3 study of darolutamide in addition to androgen deprivation therapy (ADT) versus ADT alone in metastatic hormone-sensitive prostate cancer (ARANOTE)

TPS200

KP Haresh,[1] Eglis Vjaters,[2] Daniel Castellano,[3] David Olmos,[3] Neal D. Shore,[4] Liina Nevalaita,[5] Isabella Testa,[5] Christian Kappeler,[7] Iris Kuss,[7] Fred Saad[8]

[1]All India Institute of Medical Sciences, New Delhi, India; [2]P. Stradiņš Clinical University Hospital, Riga, Latvia; [3]Hospital Universitario 12 de Octubre, Madrid, Spain; [4]Carolina Urologic Research Center, Myrtle Beach, SC, USA; [5]Orion Corporation, Espoo, Finland; [6]Bayer S.p.A., Milan, Italy; [7]Bayer AG, Berlin, Germany; [8]Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada

BACKGROUND AND STUDY RATIONALE

- Androgen deprivation therapy (ADT), achieved through surgical or medical castration, has been the standard of care for metastatic hormone-sensitive prostate cancer (mHSPC) for several decades[1,2]
- More recently, the addition of docetaxel, abiraterone acetate, enzalutamide, or apalutamide to ADT has been shown to improve overall survival and/or radiological progression-free survival in phase 3 studies; however, these therapeutic combinations are linked to an increased risk of adverse events[3–6]
- Darolutamide is a well-tolerated, structurally distinct, and highly potent non-steroidal androgen receptor inhibitor (ARI) shown to improve metastasis-free survival by almost 2 years, and reduces the risk of death by 31% versus placebo in patients with nonmetastatic castration-resistant prostate cancer in the pivotal phase 3 ARAMIS trial[7,8]
  - Among patients in the ARAMIS trial, similar incidences of many of the most frequently occurring treatment-emergent adverse events were reported in the two groups, except for fatigue, which was higher in the darolutamide group. Comparable early discontinuation rates were observed in the treatment and placebo arms[7]
- The favorable safety profile of darolutamide, including low potential for drug–drug interactions and low incidence of central nervous system-related adverse events, provides a strong rationale for assessment in combination with ADT in patients with mHSPC

STUDY OBJECTIVE

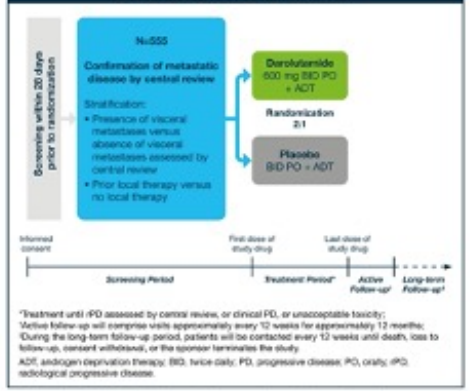
- The ARANOTE trial (NCT04736199, EudraCT 2020-003093-48) was designed to assess the efficacy and safety of darolutamide in combination with standard ADT in patients with mHSPC

METHODS

Study design

- ARANOTE is a global, multicenter, double-blind, randomized, phase 3 trial of darolutamide 600 mg twice daily plus standard ADT versus placebo plus ADT in men with histologically or cytologically confirmed adenocarcinoma of the prostate and documented metastatic disease
- Patients will be randomized 2:1 to receive either 600 mg twice daily darolutamide or matched placebo in combination with ADT of the investigator's choice (luteinizing hormone-releasing hormone agonist/antagonists or orchiectomy) (**Figure 1**)
- Efficacy, safety, and quality of life (using the Functional Assessment of Cancer Therapy–Prostate questionnaire) will be assessed every 12 weeks during the treatment period and the follow-up post-treatment period
- All patients will receive the study drug until radiological disease progression assessed by central review, unacceptable toxicity, or other withdrawal criteria are met
- After discontinuation of study drug, patients will enter the active follow-up period, during which clinic visits will continue for approximately 1 year (12 ± 1 months)
- For long-term follow-up, patients will be contacted by telephone every 12 weeks
- An independent Data Monitoring Committee will regularly monitor the unblinded safety data throughout the trial
- Key inclusion and exclusion criteria are shown in **Table 1**

Figure 1. ARANOTE study design



*Treatment until rPD assessed by central review, or clinical PD, or unacceptable toxicity; †Active follow-up will comprise visits approximately every 12 weeks for approximately 12 months; ‡During the long-term follow-up period, patients will be contacted every 12 weeks until death, loss to follow-up, consent withdrawal, or the sponsor terminates the study.

ADT, androgen deprivation therapy; BID, twice daily; PD, progressive disease; PO, orally; rPD, radiological progressive disease.

Figure 2. ARANOTE study locations[9]

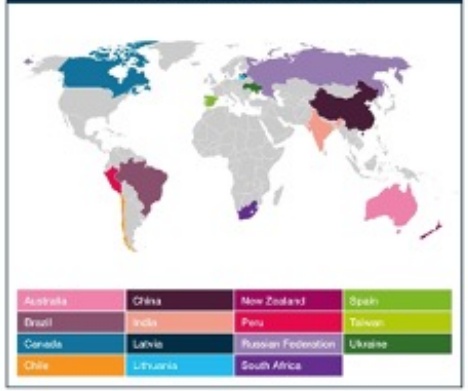


Table 1. ARANOTE key inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Men aged ≥18 years with histologically or cytologically confirmed adenocarcinoma of the prostate	Prior treatment with: • LHRH agonist/antagonist started ≥12 weeks before study treatment starts except neoadjuvant and/or adjuvant therapy for a duration of ≤24 months and completed ≥12 months prior to randomization • Second-generation ARIs or other investigational ARIs • CYP17 enzyme inhibitors as antineoplastic treatment • Chemotherapy including docetaxel or immunotherapy for prostate cancer • Systemic corticosteroids with a dose greater than the equivalent 10 mg of prednisone per day within 28 days prior to randomization
Documented metastatic disease*	Radiotherapy in the 2 weeks prior to randomization
Started ADT (LHRH agonist/antagonist or orchiectomy) with or without first-generation anti-androgen (not longer than 12 weeks before randomization)	Prior malignancy, other than treated basal or squamous cell skin cancer, superficial bladder cancer, or any other cancer in situ currently in complete remission, within 5 years prior to randomization
ECOG performance status 0, 1, or 2	Known leptomeningeal metastases
Adequate bone marrow, liver, and renal function	Inability to swallow oral medications
	Stroke, myocardial infarction, severe or unstable angina pectoris, coronary or peripheral artery bypass graft, or congestive heart failure (New York Heart Association Class III or IV) in the 6 months prior to randomization
	A gastrointestinal disorder or procedure that may interfere with absorption of the study drug

*Metastatic disease confirmed by conventional imaging method either by a positive ^{99m}Tc-phosphonate bone scan, or soft tissue or visceral metastases, either by contrast-enhanced abdominal/pelvic/chest CT or MRI scan assessed by central review.

ADT, androgen deprivation therapy; ARI, androgen receptor inhibitor; CT, computed tomography; CYP17, cytochrome P17; ECOG, Eastern Cooperative Oncology Group; LHRH, luteinizing hormone-releasing hormone; MRI, magnetic resonance imaging.

ARANOTE OBJECTIVES AND ENDPOINTS*

OBJECTIVES

Primary

- To determine if darolutamide plus ADT is superior to placebo plus ADT at improving rPFS in patients with mHSPC

Secondary

- To evaluate the efficacy of darolutamide plus ADT compared with placebo plus ADT at improving OS, time to progression to CRPC, time to initiation of subsequent antineoplastic therapy, time to PSA progression, and determination of rates of undetectable PSA
- To estimate the patients' quality of life benefit of darolutamide plus ADT compared with placebo plus ADT by improving symptomatic time to pain progression
- To assess the safety of darolutamide plus ADT compared with placebo plus ADT in patients with mHSPC

ENDPOINTS

Primary

- rPFS assessed by central review based on RECIST v1.1 for soft tissue metastases and PCWG3 criteria for bone metastases

Secondary

- OS – key secondary endpoint
- Time to CRPC
- Time to initiation of subsequent antineoplastic therapy
- Time to PSA progression
- Rates of undetectable PSA (<0.2 ng/mL)
- Time to pain progression (BPI-SF)
- AE assessments using NCI-CTCAE v5.0

*Objective and endpoint abbreviation definitions. ADT, androgen deprivation therapy; AE, adverse event; BPI-SF, Brief Pain Inventory-Short Form; CRPC, castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; NCI-CTCAE, National Cancer Institute–Common Terminology Criteria for Adverse Events; OS, overall survival; PCWG3, Prostate Cancer Working Group 3; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors; rPFS, radiological progression-free survival (defined as time interval between randomization and date of radiological progression, assessed by central review based on RECIST v1.1 for soft tissue metastases and PCWG3 criteria for bone metastases).

ARANOTE TRIAL STATUS

- The ARANOTE study is currently recruiting patients at 150 study locations across 15 countries with an estimated enrollment of 555 patients[9]
- The trial will be conducted at sites in Australia, Brazil, Canada, Chile, China, India, Latvia, Lithuania, New Zealand, Peru, Russian Federation, South Africa, Spain, Taiwan, and Ukraine (**Figure 2**)[9]
- The first patient visit was on February 23, 2021[9]
- The projected primary completion date is March 27, 2024, with an estimated study completion date of September 26, 2025[9]

Scan QR code to download the poster

References: 1. Francini E, et al. *Prostate* 2018;78:889–895; 2. Perlmutter MA, Lepor H. *Rev Urol* 2007;9(Suppl 1):S3–S8; 3. Sweeney CJ, et al. *N Engl J Med* 2015;373:737–746; 4. Chi KN, et al. *N Engl J Med* 2019;381:13–24; 5. Rydzewska LHM, et al. *Eur J Cancer* 2017;81:88–101; 6. Armstrong AJ, et al. *J Clin Oncol* 2019;37:2974–2986; 7. Fizazi K, et al. *N Engl J Med* 2019;380:1235–1246; 8. Fizazi K, et al. *N Engl J Med* 2020;383:1040–1049; 9. ClinicalTrials.gov. NCT04736199 (accessed February 2022).

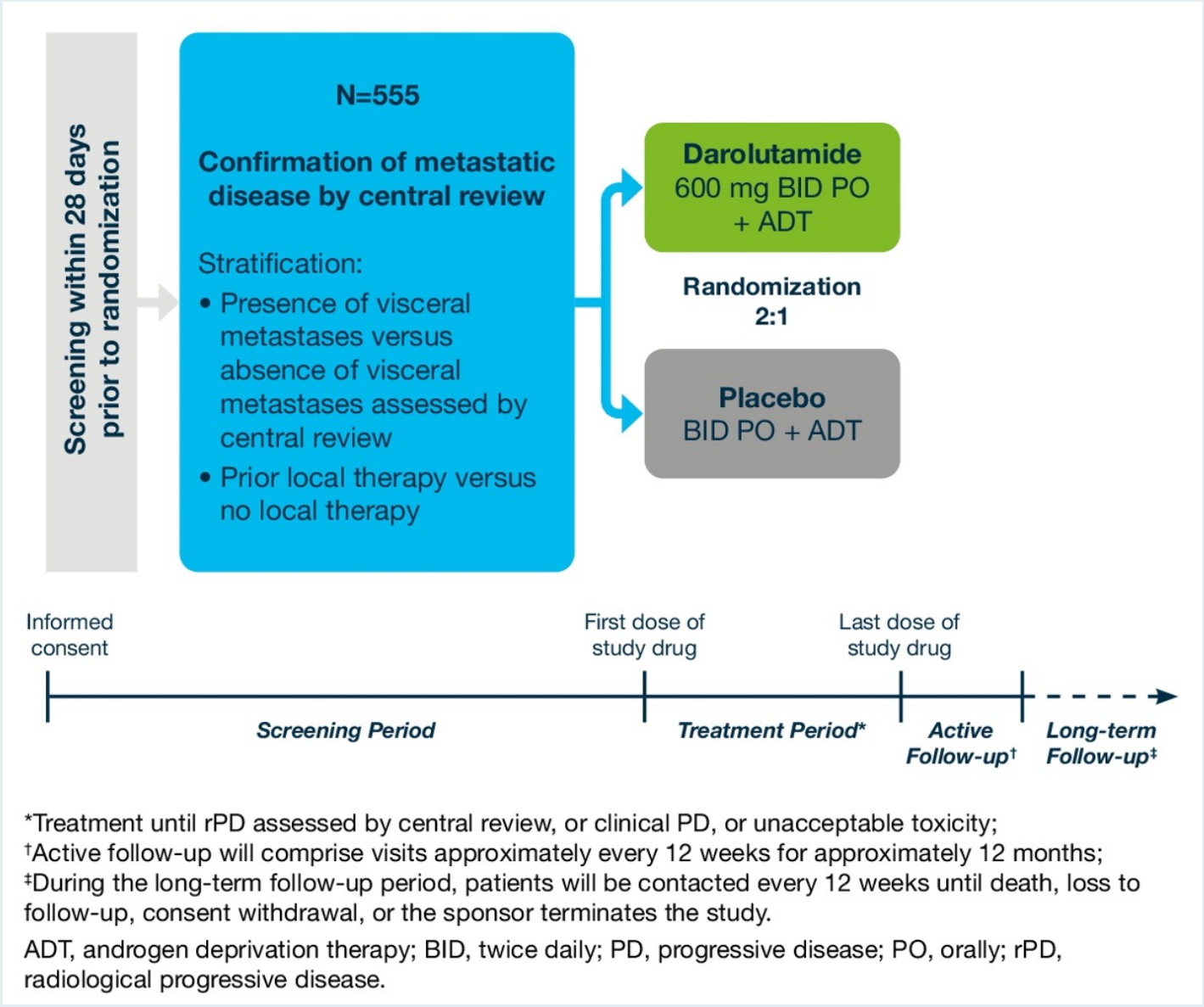
Acknowledgments: The authors thank the patients, their families, and all investigators involved in the ARANOTE study. This trial is supported by Orion Corporation, and Bayer AG. Medical writing support was provided by Yasmine Dufani of OPEN Health Communications (London, UK), with financial support from Bayer HealthCare Pharmaceuticals (Whippany, NJ, USA).

Presented at the American Society of Clinical Oncology Genitourinary Cancers Symposium, San Francisco, CA, USA and online, February 17–19, 2022

Corresponding author contact: drkpharesh@gmail.com

Haresh KP et al. Genitourinary Cancers Symposium 2022;Abstract TPS200.

ARANOTE Phase III Study Design

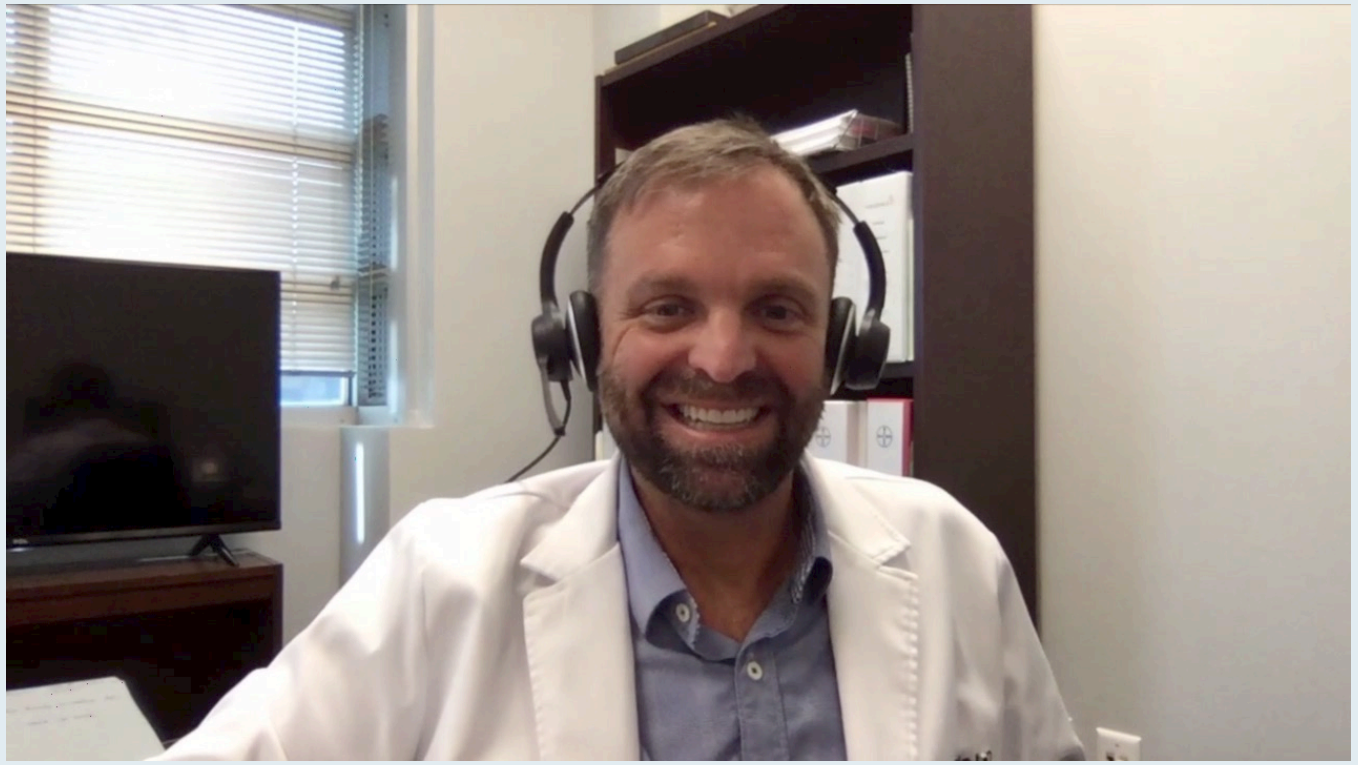


*Treatment until rPD assessed by central review, or clinical PD, or unacceptable toxicity;
†Active follow-up will comprise visits approximately every 12 weeks for approximately 12 months;
‡During the long-term follow-up period, patients will be contacted every 12 weeks until death, loss to follow-up, consent withdrawal, or the sponsor terminates the study.

ADT, androgen deprivation therapy; BID, twice daily; PD, progressive disease; PO, orally; rPD, radiological progressive disease.

Haresh KP et al. Genitourinary Cancers Symposium 2022;Abstract TPS200.

Case Presentation: 68-year-old man, Gleason 4 + 4, PSA 147, CT negative



Dr David Morris (Nashville, Tennessee)

RTP
RESEARCH
TO PRACTICE

Case Presentation: 67-year-old man, CAD, Gleason 4 + 4; 2013 EBRT; increasing PSA now 3.8, 6-month doubling time

Dr Gurveen Kaur (Wheeling, West Virginia)

RTP
RESEARCH
TO PRACTICE

Case Presentation: 66-year-old man, s/p EBRT → ADT, now with M0 progression but patient refuses to continue ADT

Dr Henna Malik (Houston, Texas)

RTP
RESEARCH
TO PRACTICE

Case Presentation: 53-year-old man, s/p radical prostatectomy and salvage radiation therapy with a slowly rising PSA now 1.31; PSMA PET scan denied by insurance, now appealed

Dr KS Kumar (Trinity, Florida)

RTP
RESEARCH
TO PRACTICE

Case Presentation: 77-year-old man, Gleason 5 + 4, PSA 23; EBRT → ADT; cryoablation; enzalutamide → response, now PSA increasing; 18F-fluciclovine PET — subtle focus of uptake in left prostate

Dr Susmitha Apuri (Lutz, Florida)

RTP
RESEARCH
TO PRACTICE

Discussion Question

Regulatory and reimbursement issues aside, which of the following therapies would you most likely recommend for a 65-year-old man with mHSPC who experiences disease progression after receiving an LHRH agonist with abiraterone and docetaxel ?

- ^{177}Lu-PSMA-617
- ^{177}Lu-PSMA-617 and antiandrogen
- Radium-223
- Radium-223 and antiandrogen
- Cabazitaxel
- Apalutamide
- Darolutamide
- Enzalutamide
- Other

RTP RESEARCH TO PRACTICE

Discussion Question

A 65-year-old man receiving ADT for M0 recurrence presents with metastases to bone and lungs. A germline BRCA2 mutation is detected. Regulatory and reimbursement issues aside, what is your likely strategy in addition to continuing ADT?

- Abiraterone/prednisone
- Abiraterone/prednisone + PARP inhibitor (PARPi)
- Enzalutamide
- Enzalutamide + PARPi
- Apalutamide
- Apalutamide + PARPi
- Darolutamide
- Darolutamide + PARPi
- PARPi alone
- Other

RTP RESEARCH TO PRACTICE

Discussion Question

A 65-year-old man receiving ADT for M0 recurrence with no HRR mutations presents with metastases to bone and lungs. Regulatory and reimbursement issues aside, what is your likely strategy in addition to continuing ADT?

- Abiraterone/prednisone
- Abiraterone/prednisone + PARPi
- Enzalutamide
- Enzalutamide + PARPi
- Apalutamide
- Apalutamide + PARPi
- Darolutamide
- Darolutamide + PARPi
- PARPi alone
- Other

RTP RESEARCH TO PRACTICE

Meet The Professor with Dr Smith

Introduction: Abemaciclib for Prostate Cancer?

MODULE 1: Rounds

MODULE 2: Ongoing Trials; Reported Data; Review Articles

RTP
RESEARCH
TO PRACTICE

Hormonal Treatment for Nonmetastatic Prostate Cancer

RTP
RESEARCH
TO PRACTICE

CLINICAL UPDATE

Current Developments in the Management of Prostate Cancer

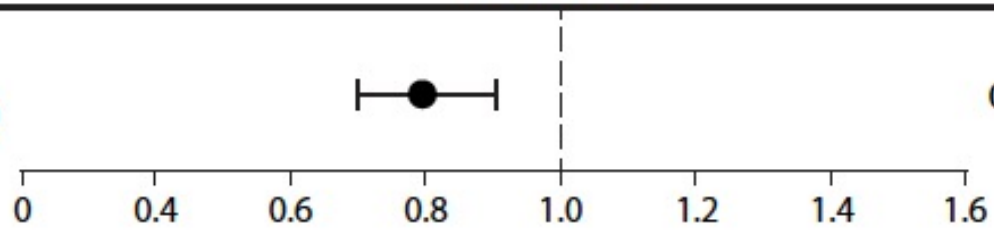
Clinical Update

How Quality of Life Can Help Guide Selection of Androgen Receptor Inhibitors in Nonmetastatic Castration-Resistant Prostate Cancer

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

Hematol Oncol 2021;19(10):627-30.

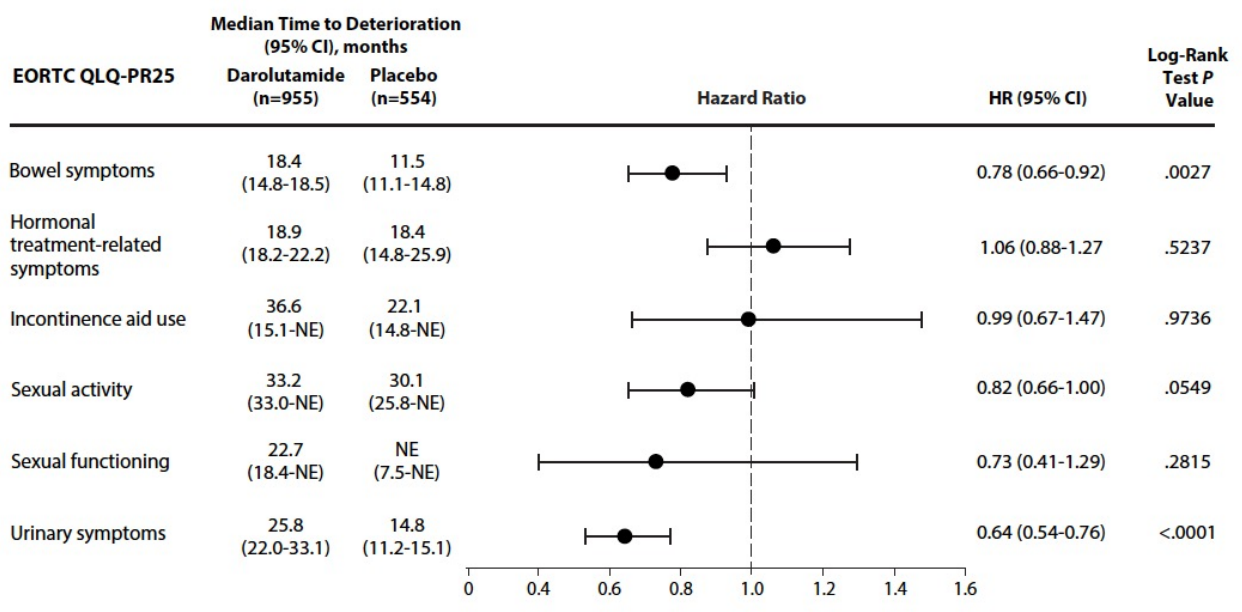
Cox Regression Analysis of Time to Deterioration in FACT-P PCS Scores in an Analysis of the Phase III ARAMIS Trial

FACT-P PCS	Median Time to Deterioration (95% CI), months: Darolutamide (n=955)	Median Time to Deterioration (95% CI), months: Placebo (n=554)	Hazard Ratio	HR (95% CI)	Log-Rank Test *P* Value
	11.07 (11.04-11.14)	7.88 (7.46-11.07)		0.80 (0.70-0.91)	.0005

FACT-P PCS	Treatment Group	Events	Censored	Total
	Darolutamide	590	365	955
	Placebo	354	200	554

Smith MR. *Clin Adv Hematol Oncol* 2021;19(10):627-30.

Cox Regression Analysis of Time to Deterioration in EORTC QLQ-PR25 Subscale Scores in an Analysis of the Phase III ARAMIS Trial



EORTC QLQ-PR25	Treatment Group	Events	Censored	Total
Bowel symptoms	Darolutamide	415	540	955
	Placebo	235	319	554
Hormonal treatment-related symptoms	Darolutamide	385	570	955
	Placebo	172	382	554
Incontinence aid use	Darolutamide	83	169	252
	Placebo	36	93	129
Sexual activity	Darolutamide	253	702	955
	Placebo	143	411	554
Sexual functioning	Darolutamide	29	71	100
	Placebo	22	48	70
Urinary symptoms	Darolutamide	321	634	955
	Placebo	215	339	554

Smith MR. *Clin Adv Hematol Oncol* 2021;19(10):627-30.

Eur Urol 2022 September 8;[Online ahead of print].

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

European Association of Urology

Prostate Cancer

Efficacy and Safety of Darolutamide in Patients with Nonmetastatic Castration-resistant Prostate Cancer Stratified by Prostate-specific Antigen Doubling Time: Planned Subgroup Analysis of the Phase 3 ARAMIS Trial

Martin Bögemann[a,*], *Neal D. Shore*[b], *Matthew R. Smith*[c], *Teuvo L.J. Tammela*[d], *Albertas Ulys*[e], *Egils Vjaters*[f], *Sergey Polyakov*[g], *Mindaugas Jievaltas*[h], *Murilo Luz*[i], *Boris Alekseev*[j], *Thierry Lebret*[k], *Martin Schostak*[l], *Frank Verholen*[m], *Marie-Aude Le Berre*[n], *Shankar Srinivasan*[o], *Jorge Ortiz*[o], *Ateesha F. Mohamed*[o], *Toni Sarapohja*[p], *Karim Fizazi*[q]

Efficacy and Safety Outcomes of Darolutamide in Patients with Nonmetastatic Castration-Resistant Prostate Cancer with Comorbidities and Concomitant Medications from ARAMIS

Fizazi K et al.

Genitourinary Cancers Symposium 2022;Abstract 256.

PARIS 2022 ESMO congress

Abstract LBA9

Duration of androgen deprivation therapy (ADT) with post-operative radiotherapy (RT) for prostate cancer: first results of the RADICALS-HD trial

C.C. Parker

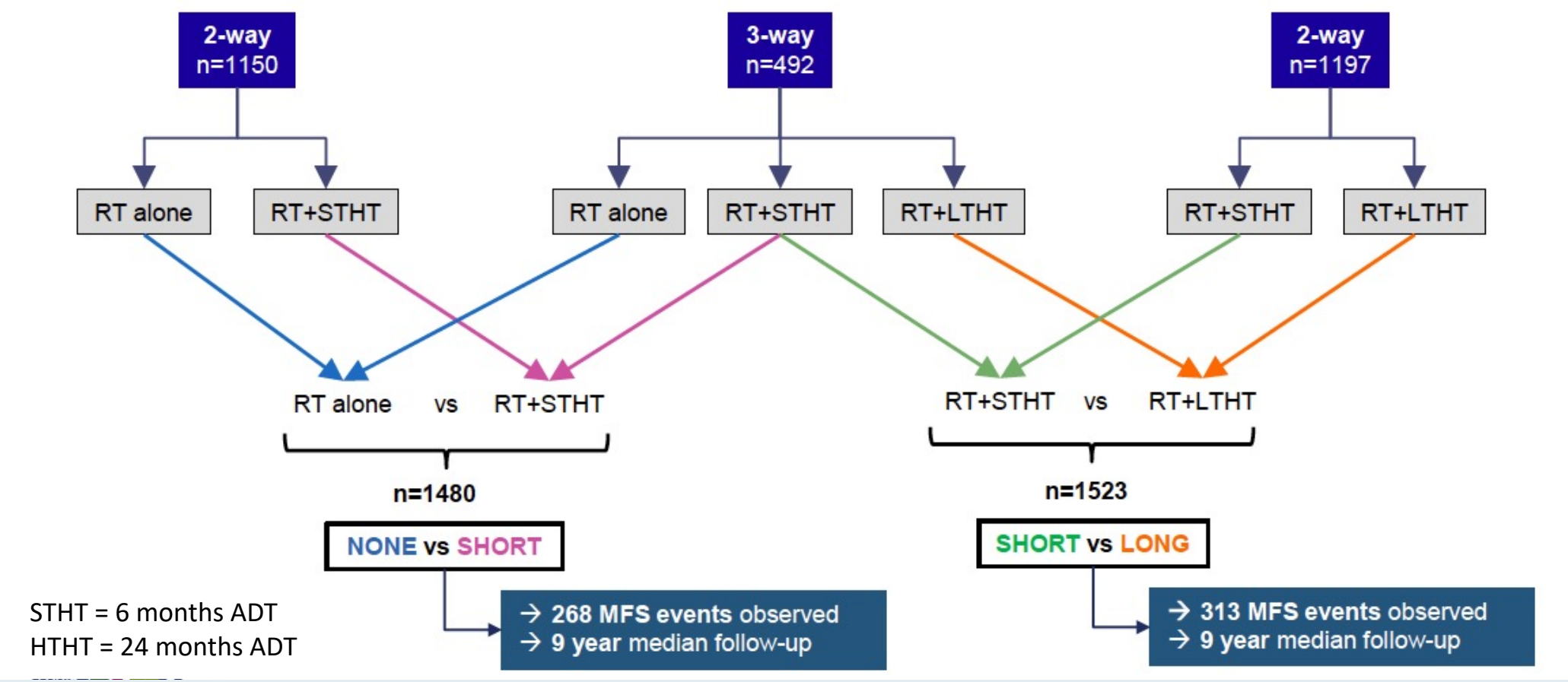
N.W. Clarke, A. Cook, C. Catton, W. Cross, H. Kynaston, J. Logue, P.M. Petersen, P. Neville, R. Persad, H. Payne, F. Saad, A. Stirling, W.R. Parulekar, M.K.B. Parmar, M.R. Sydes

Paris, September 2022

RTP RESEARCH TO PRACTICE

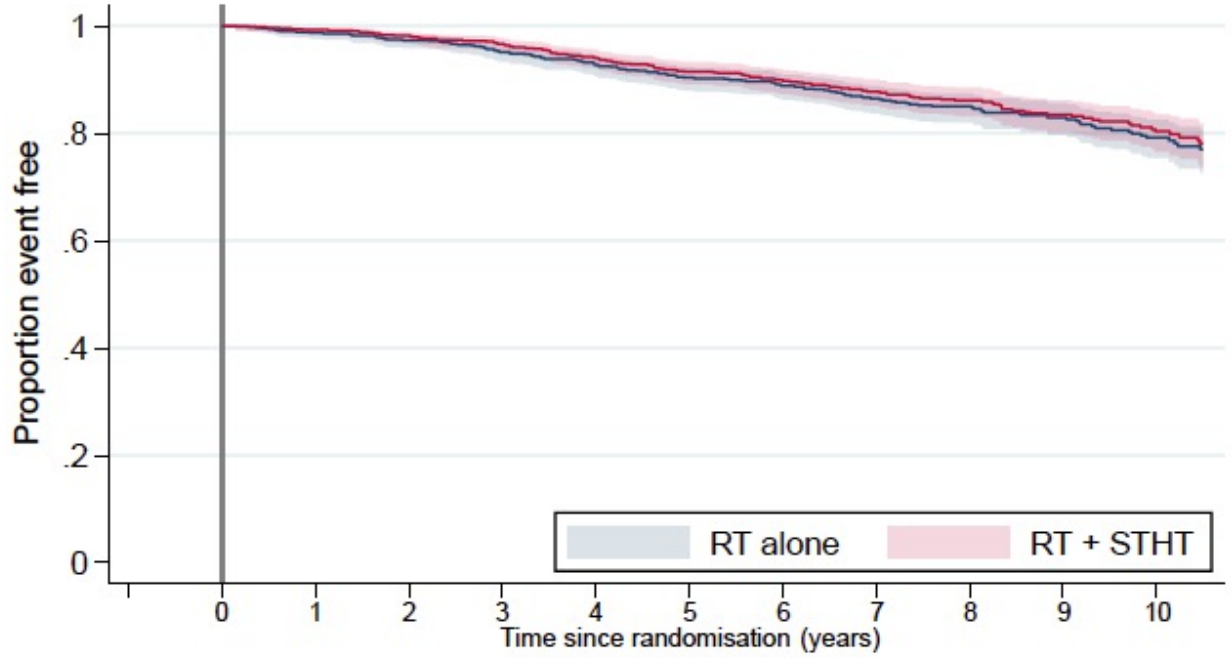
RADICALS-HD Phase III Trial: Recruitment and Randomization

- RADICALS-HD is part of the RADICALS protocol and was designed to assess the use and duration of ADT with postoperative radiation therapy (RT) for prostate cancer
- Key eligibility criteria were indication for RT after previous radical prostatectomy and no previous post-operative ADT



Parker CC et al. ESMO 2022;Abstract LBA9.

RADICALS-HD Metastasis-Free Survival: None versus Short ADT



NONE vs SHORT

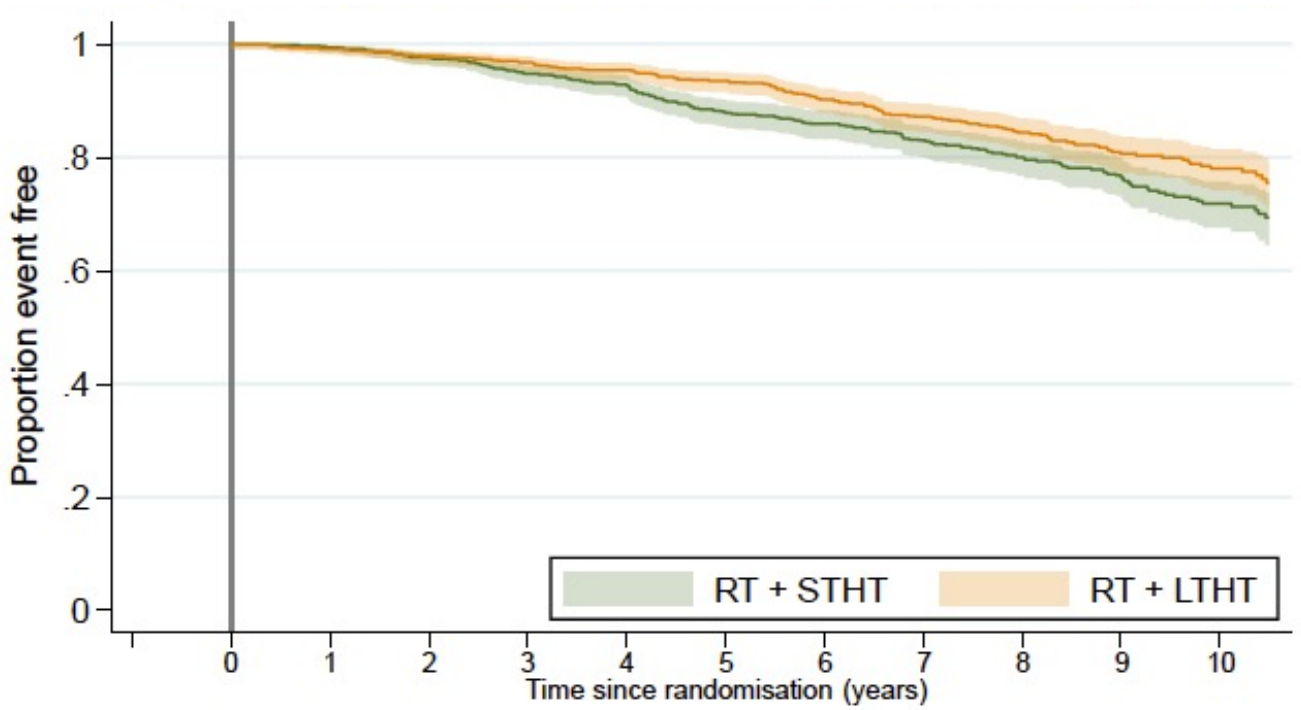
	RT alone (n=737)	RT+STHT (n=743)
Events	142	126
HR (95%CI)	0.89 (0.69 to 1.14)	
P-value	0.35	
10yr event free	79%	80%

Note: HR < 1 favour RT+STHT
Note: predicted 10yr MFS = 80%

Parker CC et al. ESMO 2022;Abstract LBA9.

RTP RESEARCH TO PRACTICE

RADICALS-HD Metastasis-Free Survival: Short versus Long ADT



SHORT vs LONG

	RT+STHT (n=761)	RT+LTHT (n=762)
Events	174	139
HR (95%CI)	**0.77** (0.61 to 0.97)	
P-value	0.03	
10yr event free	72%	78%

Note: HR < 1 favour RT+LTHT
Note: predicted 10yr MFS = 75%

Parker CC et al. ESMO 2022;Abstract LBA9.

RTP RESEARCH TO PRACTICE

RADICALS-HD: Adverse Events

	NONE vs SHORT			SHORT vs LONG		
Maximum grade	**RT alone**	**RT+STHT**	**p**	**RT+STHT**	**RT+LTHT**	**p**
0-2	612 (83%)	635 (85%)	0.25	650 (85%)	615 (81%)	0.06
3	114 (16%)	90 (12%)		99 (13%)	138 (18%)	
4*	7 (1%)	10 (1%)		6 (1%)	4 (1%)	

* No grade 5 events

Most common grade 3+ adverse events reported within 2 years after randomisation:

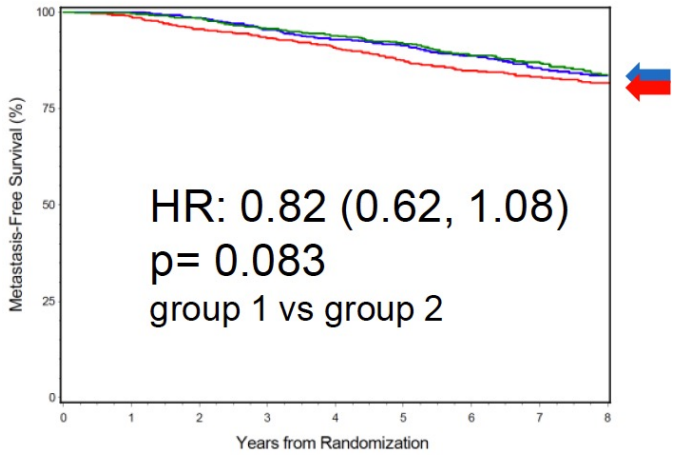
6% - Urethral stricture
4% - Haematuria

Parker CC et al. ESMO 2022;Abstract LBA9.

Randomized Trials Assessing the Addition of Short-Term ADT to Postoperative RT

RTOG 0534 (SPPORT)
100% salvage

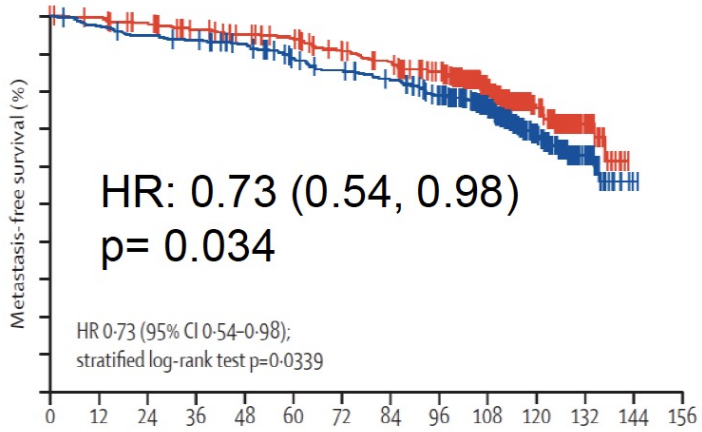
Metastases-free survival



Post-hoc analysis

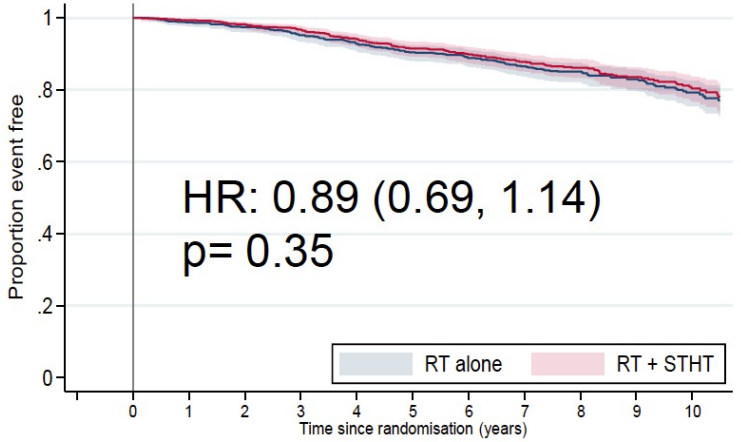
GETUG-AFU 16
100% salvage

Metastases-free survival



RADICALS-HD
71% salvage

Metastases-free survival



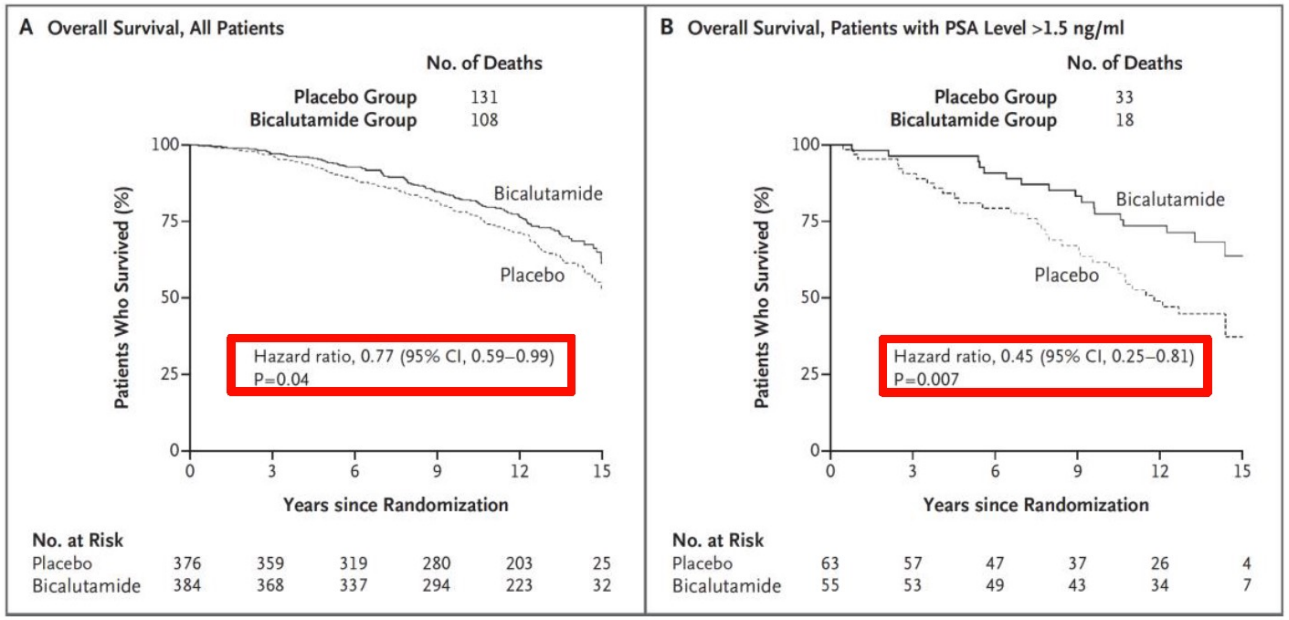
Mixed results when assessing the benefit of short-term ADT

Gillessen S et al. ESMO 2022;Discussant LBA9.

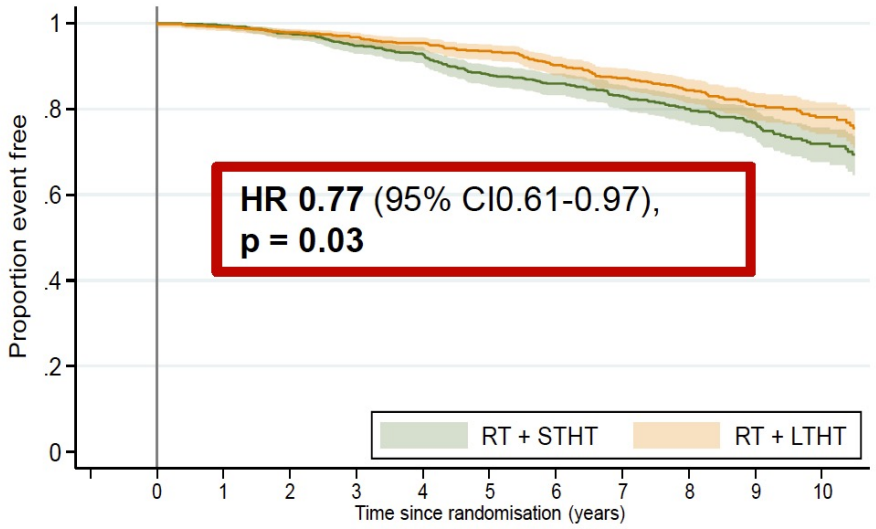
RTP RESEARCH TO PRACTICE

Addition of Long-Term Hormonal Therapy to Postoperative RT

RTOG 9601
100% salvage
Overall survival



RADICALS-HD
57% salvage
Metastases-free survival



Benefit of long hormonal treatment (vs no and vs short)

Gillessen S et al. ESMO 2022;Discussant LBA9.

What have we learned

Adding short-term ADT to salvage RT in a better risk population likely results in a very small improvement in MFS (meta-analysis),

- however many patients in RTOG 0534/ GETUG 16/RADICALS HD seem to do well in terms of MFS with RT alone, longer follow-up interesting

Adding long-term (vs short-term) ADT in the higher risk population to «post-operative» RT resulted in an improvement in MFS,

- however majority of patients in RADICALS HD did well with short term ADT in terms of MFS
- ADT has toxicity, quality of life data would be interesting
- Patient preference, balance of side effects from long term hormonal therapy vs reducing events

Gillessen S et al. ESMO 2022;Discussant LBA9.

RTP RESEARCH TO PRACTICE

Oral Relugolix for Androgen Deprivation Therapy in Advanced Prostate Cancer: Detailed Safety Analysis from the Randomized Phase 3 HERO Study

Mehlhaff B et al.

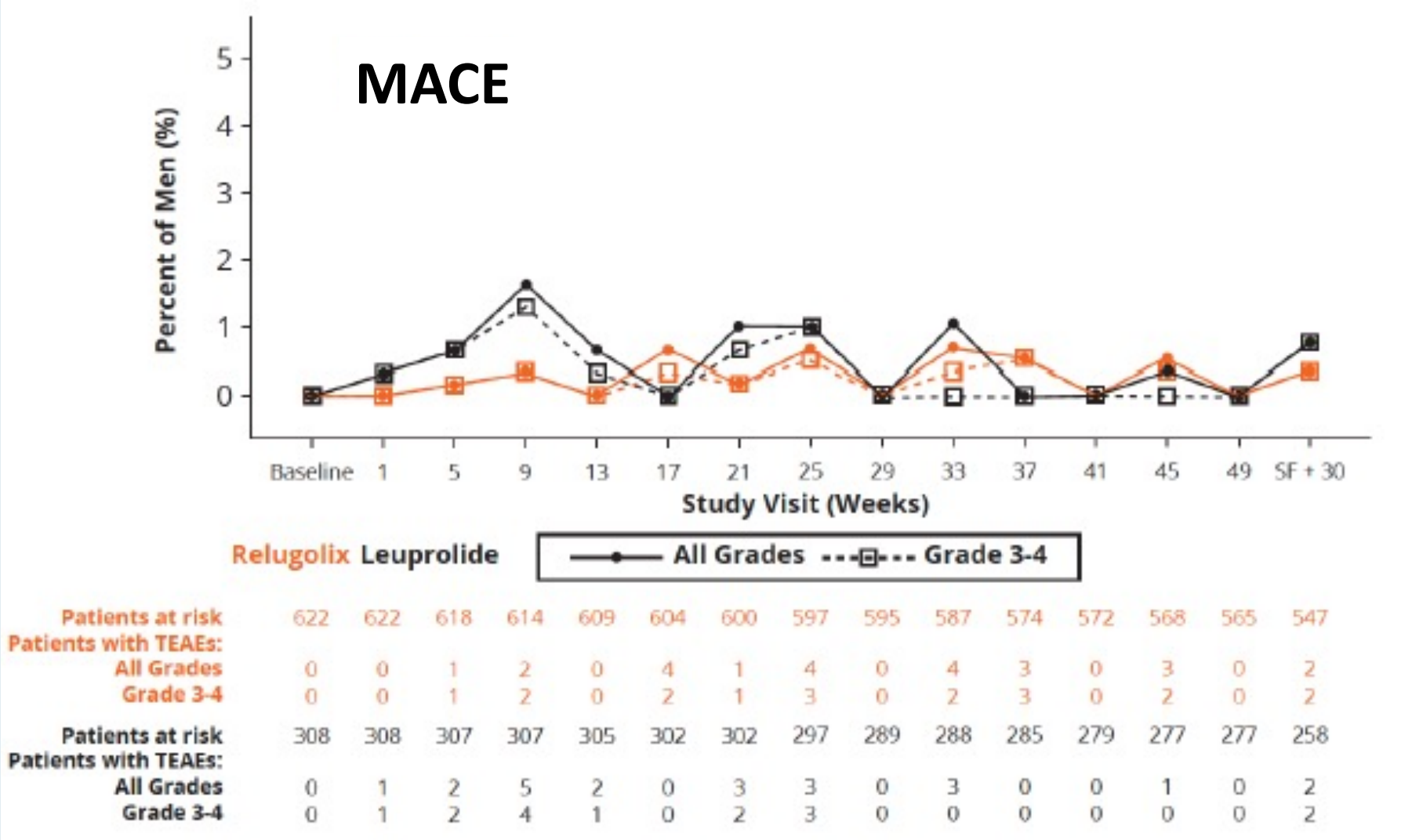
AUA 2022;Abstract MP27-16.

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.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 4, 2020 VOL. 382 NO. 23 :2187-96.

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*

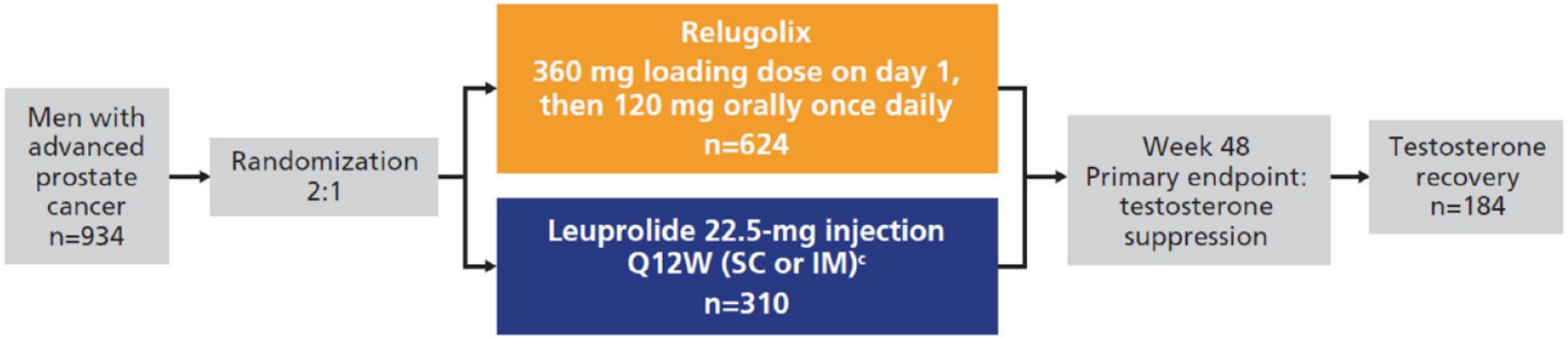
HERO: Randomized Phase III Study Evaluating Relugolix versus Leuprolide for Advanced Prostate Cancer

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

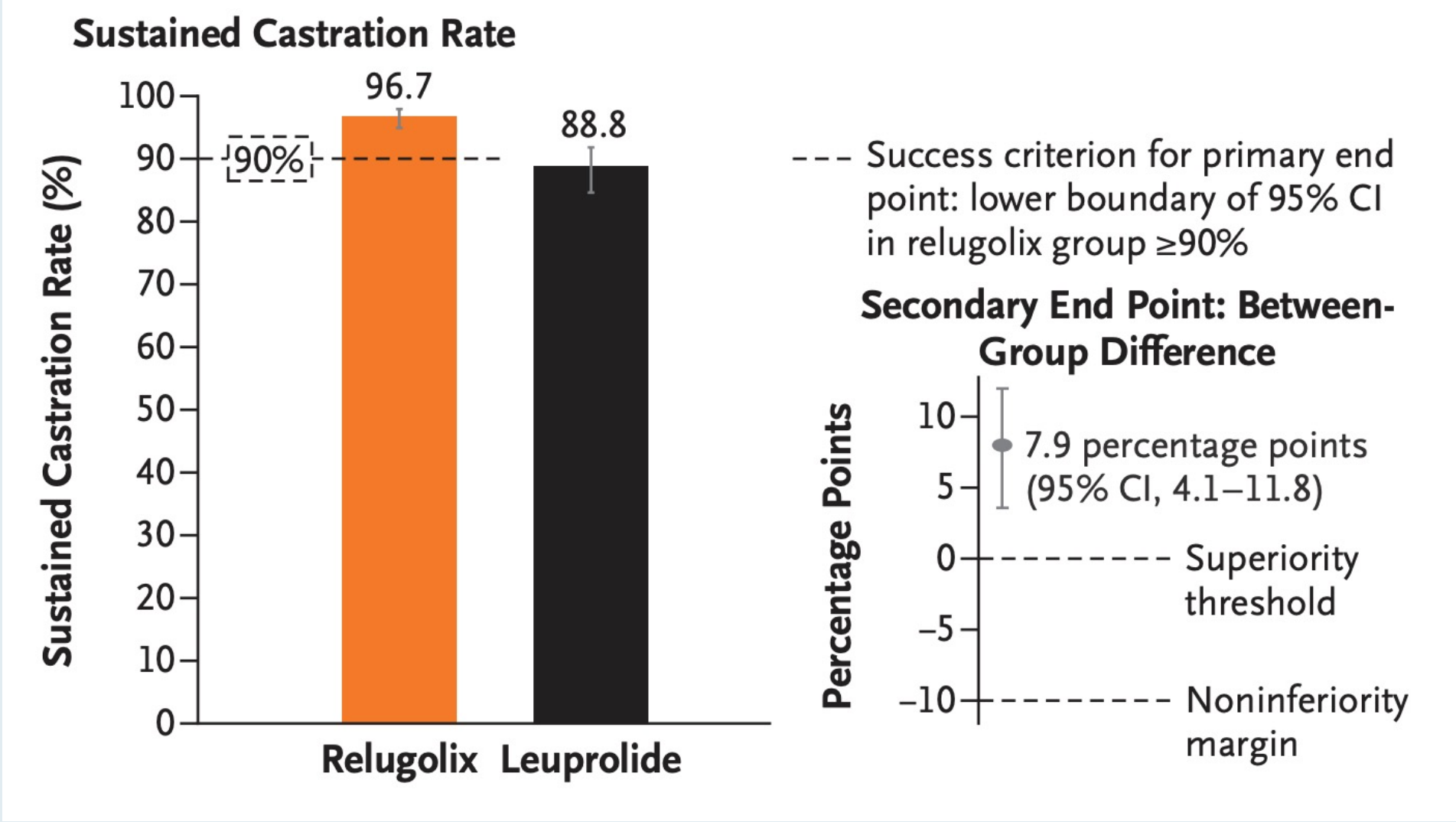


[a]<50 ng/dL; [b]<20 ng/dL; [c]11.25 mg in China, Japan, and Taiwan.

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.

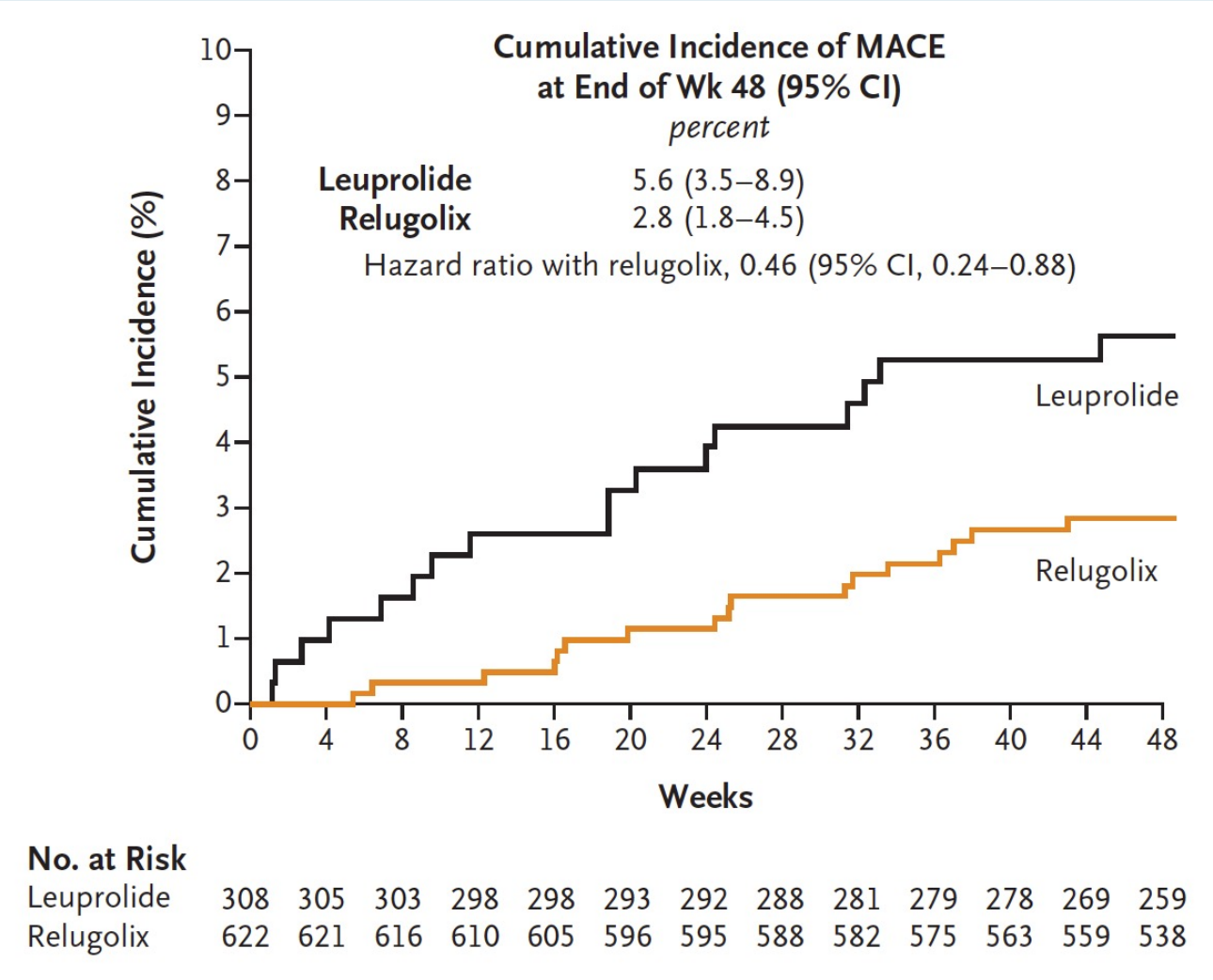
Saad F et al. *Ther Adv Med Oncol* 2021;13:1-12.

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



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

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



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

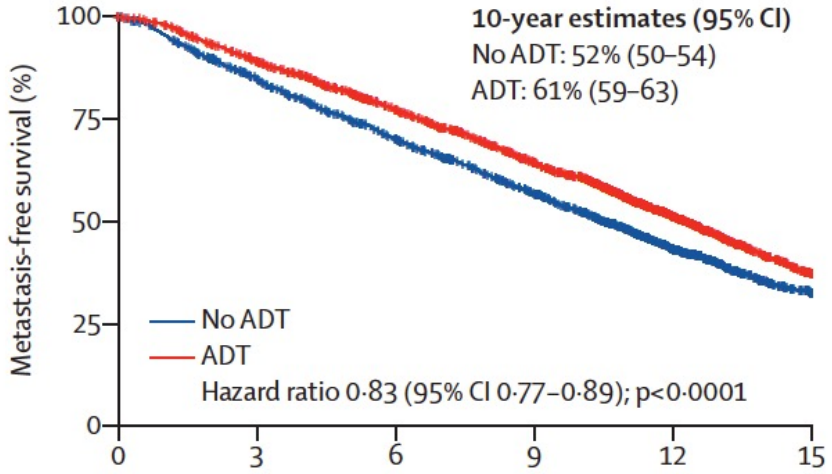
Lancet Oncol 2022;23(2):304-16.

Articles

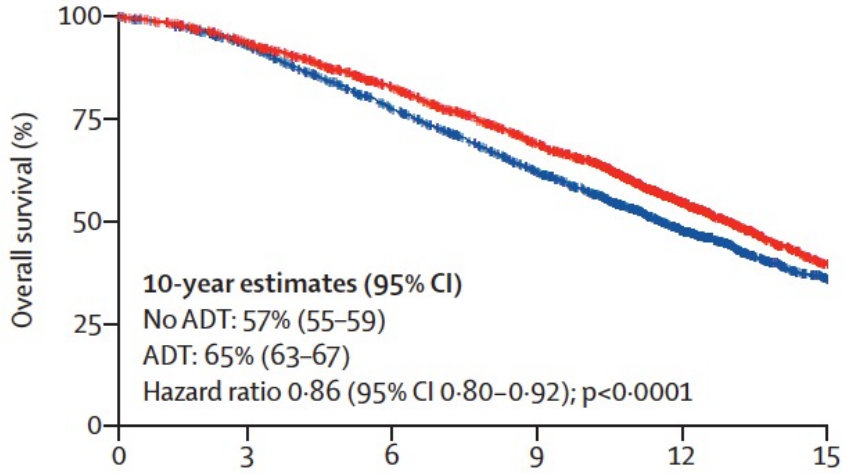
Androgen deprivation therapy use and duration with definitive radiotherapy for localised prostate cancer: an individual patient data meta-analysis

Amar U Kishan, Yilun Sun*, Holly Hartman, Thomas M Pisansky, Michel Bolla, Anouk Neven, Allison Steigler, James W Denham, Felix Y Feng, Almudena Zapatero, John G Armstrong, Abdenour Nabid, Nathalie Carrier, Luis Souhami, Mary T Dunne, Jason A Efstathiou, Howard M Sandler, Araceli Guerrero, David Joseph, Philippe Maingon, Theo M de Reijke, Xavier Maldonado, Ting Martin Ma, Tahmineh Romero, Xiaoyan Wang, Matthew B Rettig, Robert E Reiter, Nicholas G Zaorsky, Michael L Steinberg, Nicholas G Nickols, Angela Y Jia, Jorge A Garcia, Daniel E Spratt, the MARCAP Consortium group†*

Metastasis-Free and Overall Survival Curves for Androgen Deprivation Therapy (ADT) Use



Number at risk (number censored)						
No ADT (1600 events)	2576 (2)	2128 (63)	1695 (133)	1289 (224)	722 (514)	335 (761)
ADT (1399 events)	2555 (4)	2226 (56)	1828 (166)	1415 (282)	754 (689)	332 (951)

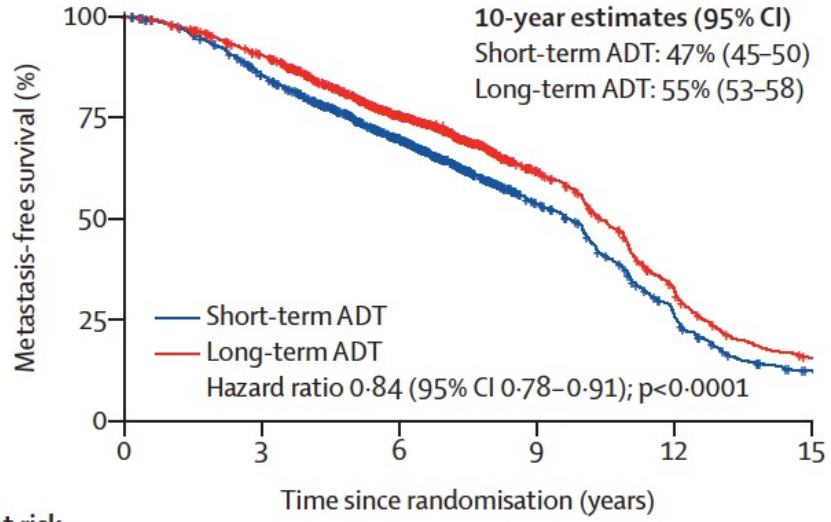


Number at risk (number censored)						
No ADT (1489 events)	2579 (2)	2304 (64)	1848 (147)	1392 (245)	782 (576)	353 (862)
ADT (1316 events)	2557 (4)	2314 (58)	1937 (172)	1509 (292)	796 (739)	344 (1024)

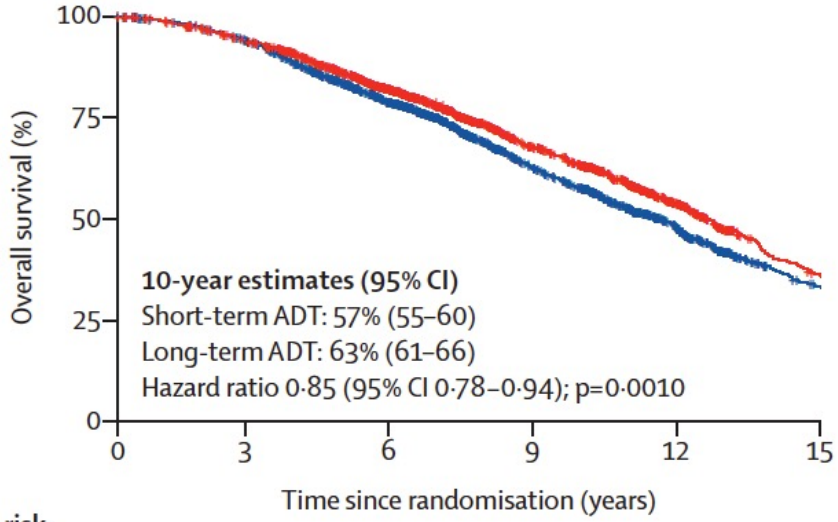
Kishan AU et al. *Lancet Oncol* 2022;23(2):304-16.

RTP RESEARCH TO PRACTICE

Metastasis-Free and Overall Survival Curves for Adjuvant ADT Prolongation



Number at risk (number censored)						
Short-term ADT (1294 events)	1874 (3)	1575 (30)	1105 (225)	627 (485)	294 (508)	128 (522)
Long-term ADT (1224 events)	1900 (1)	1687 (31)	1190 (267)	711 (565)	361 (588)	169 (595)



Number at risk (number censored)						
Short-term ADT (903 events)	1874 (3)	1703 (40)	1231 (256)	722 (550)	338 (791)	146 (908)
Long-term ADT (839 events)	1900 (1)	1733 (41)	1279 (288)	773 (610)	382 (867)	179 (975)

Kishan AU et al. *Lancet Oncol* 2022;23(2):304-16.

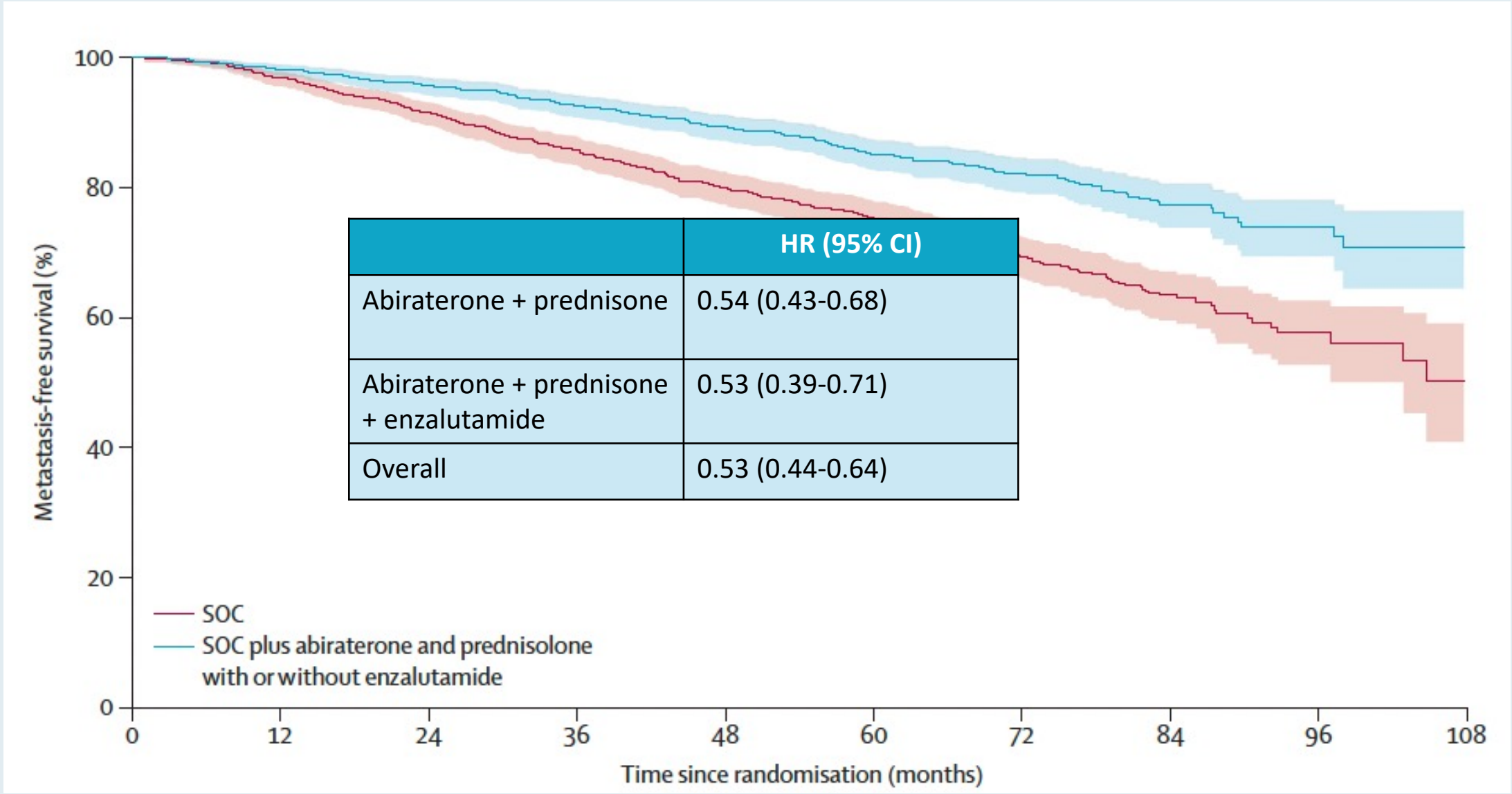
RTP RESEARCH TO PRACTICE

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 Platform Protocol Meta-Analysis: Metastasis-Free Survival

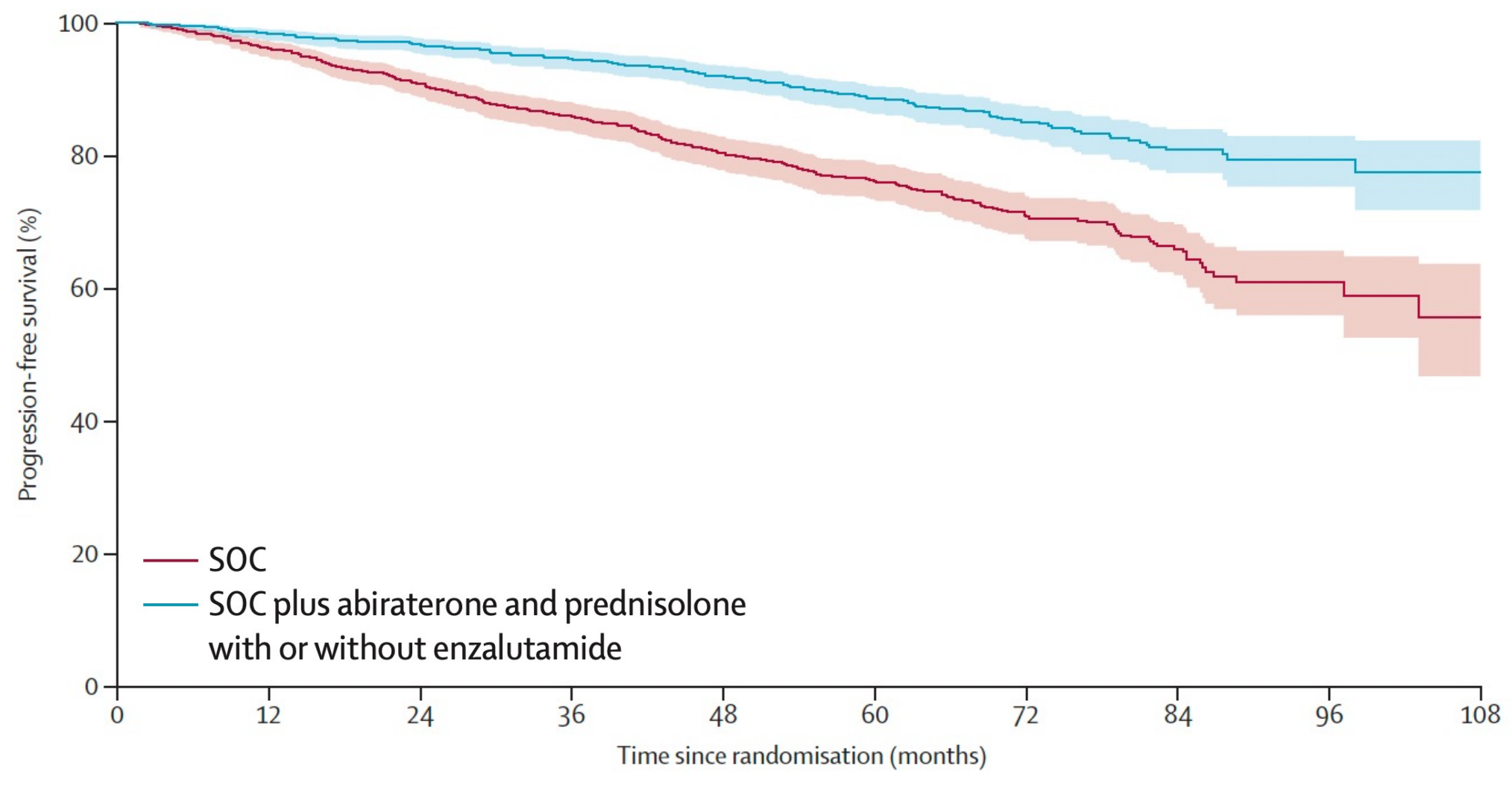


	HR (95% CI)
Abiraterone + prednisone	0.54 (0.43-0.68)
Abiraterone + prednisone + enzalutamide	0.53 (0.39-0.71)
Overall	0.53 (0.44-0.64)

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

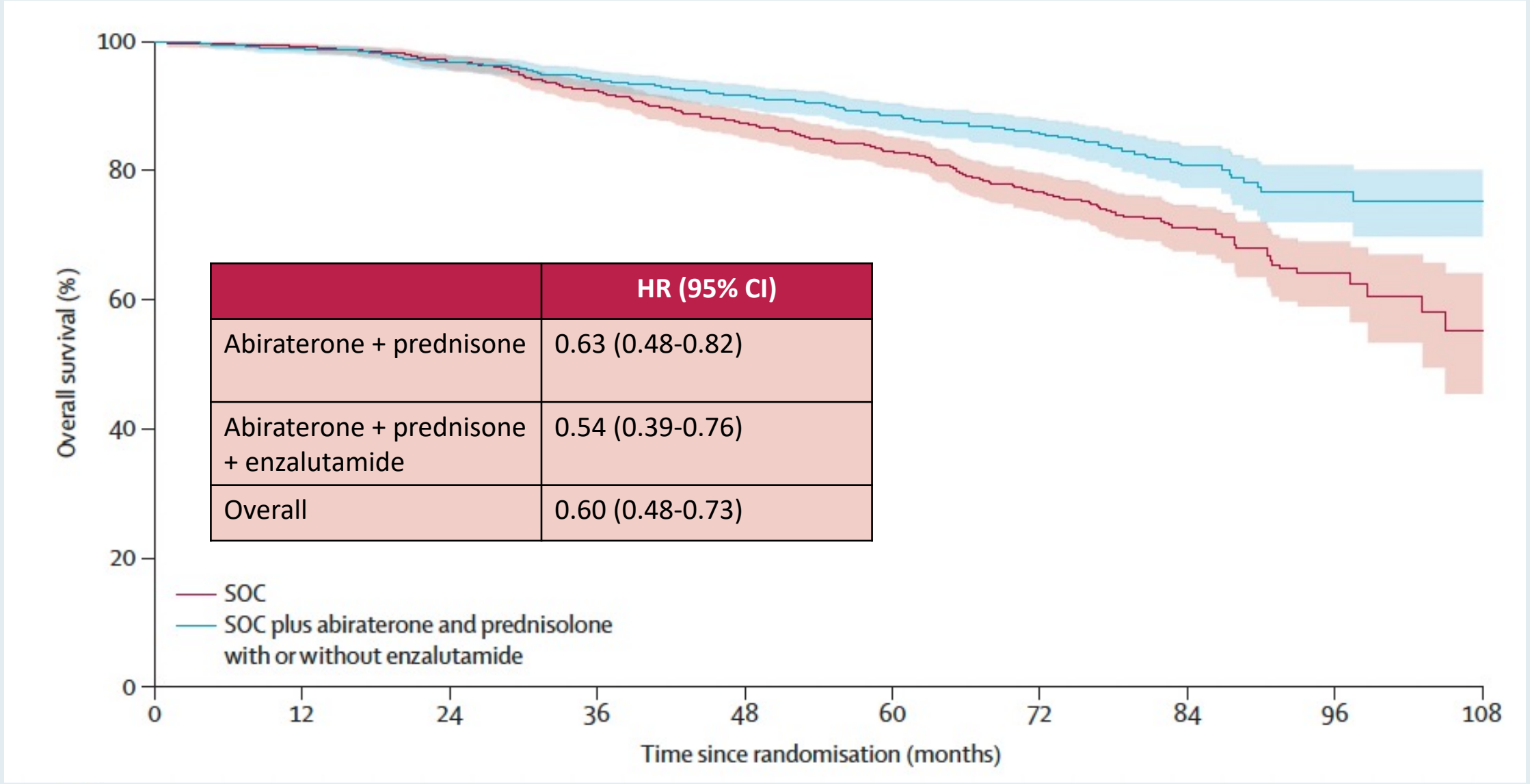
RTP RESEARCH TO PRACTICE

STAMPEDE Platform Protocol Meta-Analysis: Progression-Free Survival



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

STAMPEDE Platform Protocol Meta-Analysis: Overall Survival



	HR (95% CI)
Abiraterone + prednisone	0.63 (0.48-0.82)
Abiraterone + prednisone + enzalutamide	0.54 (0.39-0.76)
Overall	0.60 (0.48-0.73)

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

RTP RESEARCH TO PRACTICE

STAMPEDE Platform Protocol Meta-Analysis: Select Adverse Events

	Control group in the abiraterone trial (n=455)			Control group in the abiraterone and enzalutamide trial (n=533)			Combination therapy in the abiraterone trial (n=451)			Combination therapy in the abiraterone and enzalutamide trial (n=513)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Erectile dysfunction	211 (46%)	48 (11%)	0	237 (44%)	55 (10%)	0	209 (46%)	41 (9%)	0	243 (47%)	71 (14%)	0
Hypertension	65 (14%)	6 (1%)	0	74 (14%)	8 (2%)	0	108 (24%)	23 (5%)	0	189 (37%)	73 (14%)	0
ALT increased	51 (11%)	0	0	72 (14%)	4 (1%)	0	82 (18%)	23 (5%)	2 (<1%)	145 (28%)	59 (12%)	5 (1%)
Fatigue	279 (61%)	4 (1%)	NM	371 (70%)	12 (2%)	NM	299 (66%)	10 (2%)	NM	411 (80%)	49 (10%)	NM
AST increased	14 (3%)	1 (<1%)	0	17 (3%)	0	0	33 (7%)	2 (<1%)	0	61 (12%)	17 (3%)	2 (<1%)
Insomnia	126 (28%)	1 (<1%)	NM	162 (30%)	1 (<1%)	NM	133 (29%)	8 (2%)	NM	200 (39%)	7 (1%)	NM
Hypokalemia	4 (1%)	1 (<1%)	0	9 (2%)	1 (<1%)	0	50 (11%)	4 (1%)	1 (<1%)	56 (11%)	6 (1%)	0
Anaemia	142 (31%)	3 (1%)	2 (<1%)	211 (40%)	2 (<1%)	0	185 (41%)	1 (<1%)	1 (<1%)	225 (44%)	2 (<1%)	0
Dizziness	53 (12%)	0	NM	70 (13%)	1 (<1%)	NM	72 (16%)	1 (<1%)	NM	126 (25%)	4 (1%)	NM
Constipation	104 (23%)	3 (1%)	0	149 (28%)	0	0	128 (28%)	1 (<1%)	0	181 (35%)	1 (<1%)	0
Cough	72 (16%)	0	0	107 (20%)	0	0	103 (23%)	5 (1%)	0	103 (20%)	0	0
Nausea	43 (9%)	1 (<1%)	NM	67 (13%)	0	NM	60 (13%)	0	NM	130 (25%)	3 (1%)	NM

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

RTP RESEARCH TO PRACTICE

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

Trial identifier	N	Study arms	Estimated primary completion date
DASL-HiCaP (NCT04136353)	1,100	• Darolutamide + androgen deprivation therapy (ADT) + external beam radiation therapy (EBRT) • Placebo + ADT + EBRT	January 2028
ERADICATE (NCT04484818)	810	For patients with high risk score by genomic testing • Darolutamide + ADT • Placebo + ADT	May 2028
EMBARK (NCT02319837)	1,068	• Enzalutamide • Enzalutamide + ADT • Placebo + ADT	December 2022
NCT03009981	504	• ADT • Apalutamide + ADT • Apalutamide + abiraterone acetate/prednisone + ADT	January 2024
PRIMORDIUM (NCT04557059)	412	PSMA-PET positive patients • Apalutamide + ADT + radiation therapy (RT) • Placebo + ADT + RT	January 2028

www.clinicaltrials.gov. Accessed September 2022.

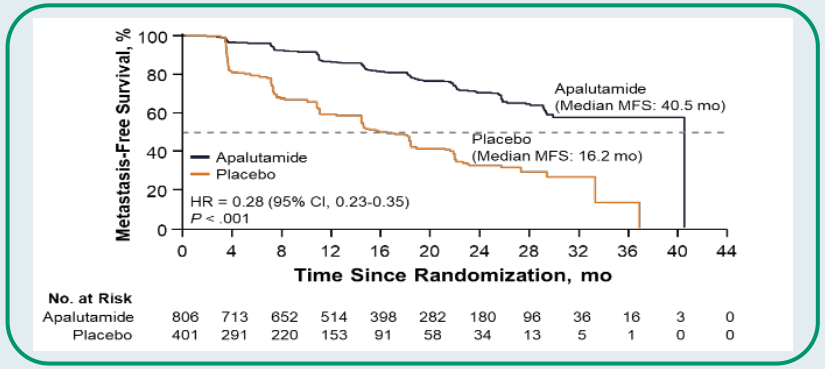
FDA Approvals of Next-Generation Antiandrogens for Nonmetastatic Castration-Resistant Prostate Cancer (CRPC)

Agent	Approval date	Pivotal study
Darolutamide	July 30, 2019	ARAMIS
Enzalutamide	July 12, 2018	PROSPER
Apalutamide	February 14, 2018	SPARTAN

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

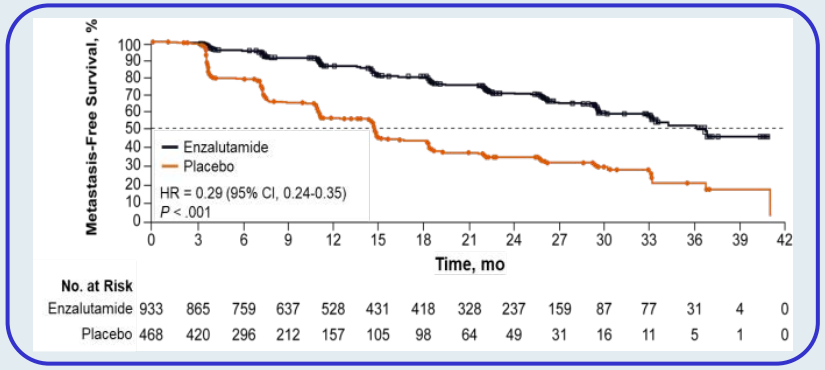
Primary Endpoint: Metastasis-Free Survival (MFS) in Nonmetastatic CRPC

SPARTAN[1] apalutamide (APA)



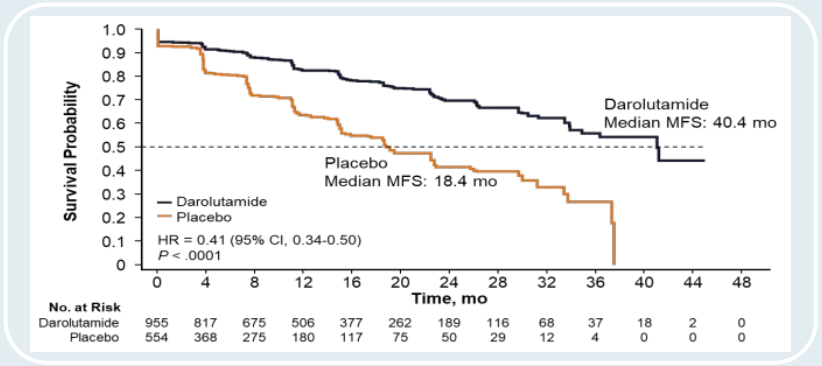
- 72% reduction in distant progression or death
- Median MFS: APA 40.5 vs placebo (PBO) 16.2 months
- 24-month MFS benefit

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)



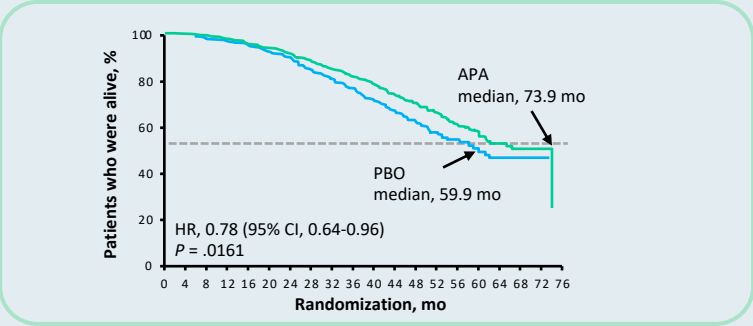
- 59% reduction in distant progression or death
- Median MFS: DARO 40.4 vs PBO 18.4 months
- 22-month MFS benefit

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.

RTP RESEARCH TO PRACTICE

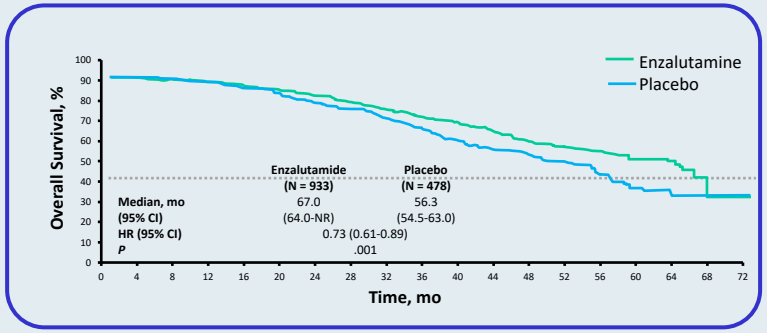
Secondary Endpoint: Overall Survival (OS) in Nonmetastatic CRPC

SPARTAN1[1]
apalutamide



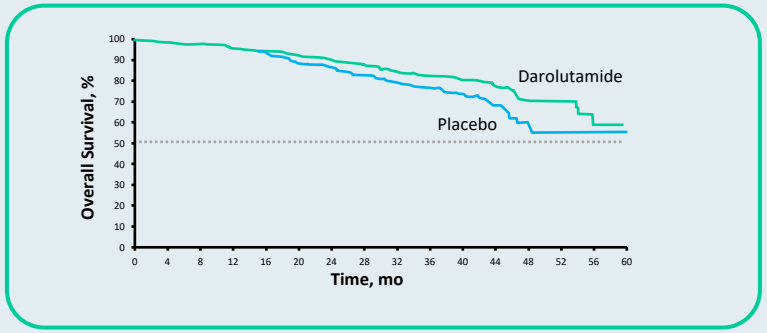
- 22% reduction in risk of death
- Median follow-up of 52.0 months
- Median OS was significantly longer for apalutamide vs placebo
  - 73.9 months vs 59.9 months
  - **HR = 0.78 (95% CI 0.64-0.96); *p* = 0.016**

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

Optimal Use of Secondary Hormonal Therapy for Patients with Metastatic Hormone-Sensitive Prostate Cancer (mHSPC)

FDA Approves Darolutamide for Metastatic Hormone-Sensitive Prostate Cancer

Press Release: August 5, 2022

"The FDA approved darolutamide in combination with docetaxel chemotherapy for patients with metastatic hormone-sensitive prostate cancer (mHSPC).

The approval is based on the results of a large Phase 3 clinical trial called ARASENS. This trial compared outcomes among 1300 patients who received docetaxel + standard ADT + darolutamide vs. patients who received docetaxel + standard ADT + placebo. 86% of the patients were newly diagnosed with prostate cancer that had metastasized to the bones or other organs.

Patients treated with the addition of darolutamide were 32% less likely to die during the study follow-up period compared to patients treated with docetaxel + ADT alone. These patients also had improved time to castration resistance (when the PSA increases and disease worsens, despite hormone therapy), time to pain progression, time to symptomatic skeletal related events (i.e., bone fractures, needing radiation to the bones, etc.), and time to next cancer therapy. Importantly, these improved outcomes of triplet therapy intensification were associated with only a modest increase in adverse events."

https://www.pcf.org/c/breaking-news-fda-approves-darolutamide-for-metastatic-hormone-sensitive-prostate-cancer/

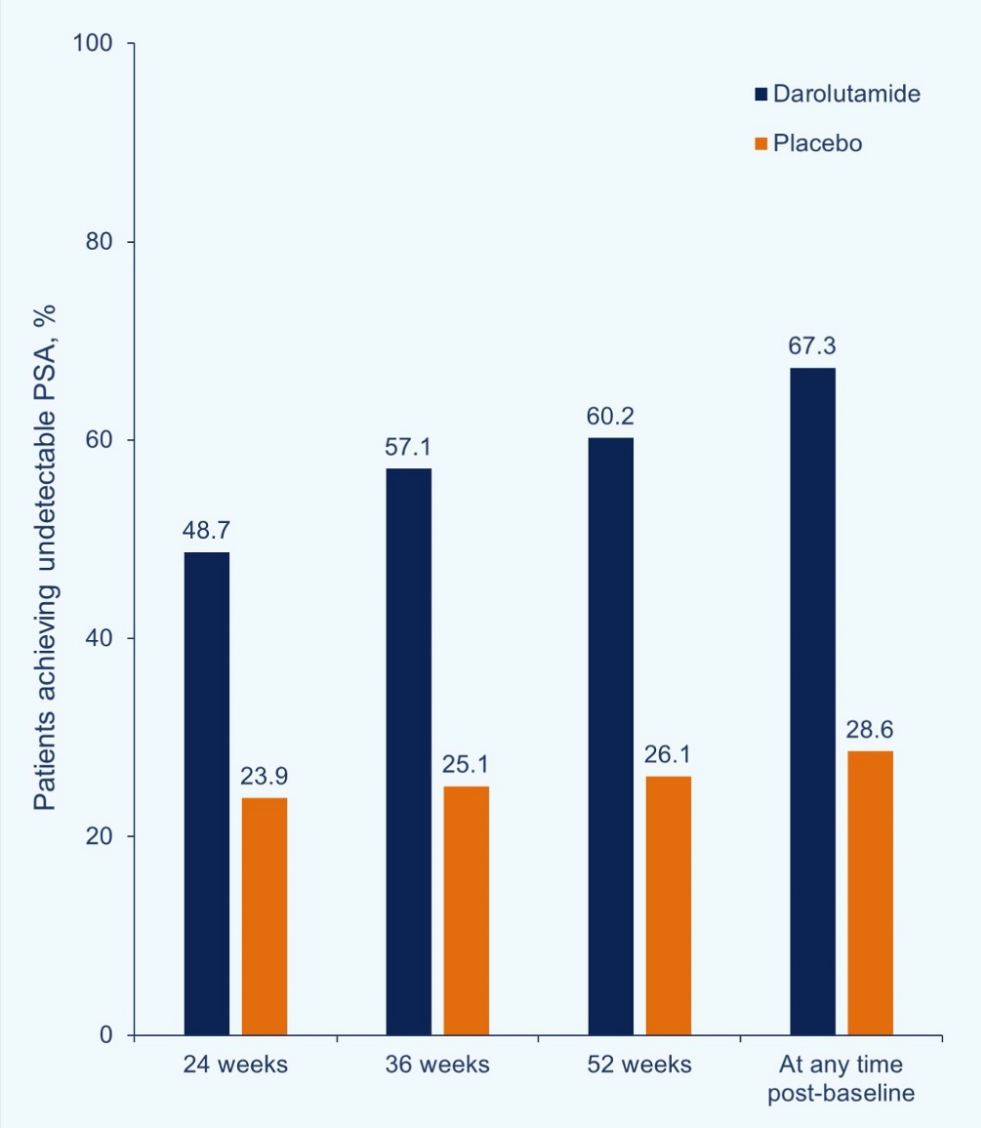
RTP RESEARCH TO PRACTICE

Association of Prostate-Specific Antigen (PSA) Response and Overall Survival (OS) in Patients with Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) from the Phase 3 ARASENS Trial

Saad F et al.

ASCO 2022;Abstract 5078.

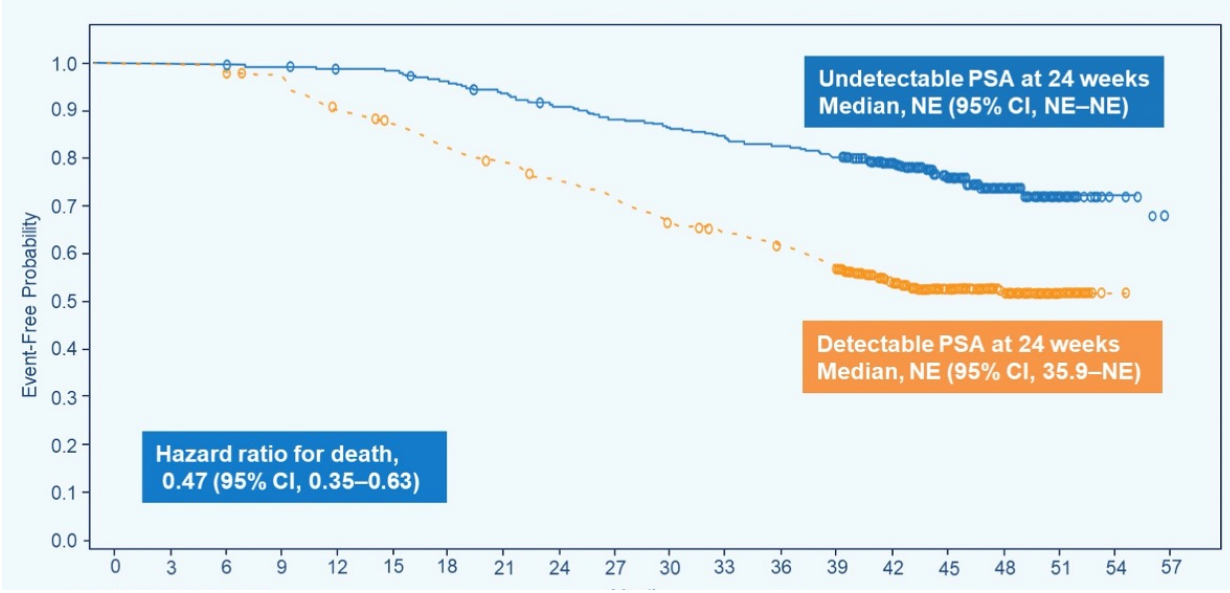
Undetectable PSA (<0.2 ng/mL) Achieved in More than Twice the Number of Patients Receiving Darolutamide versus Placebo



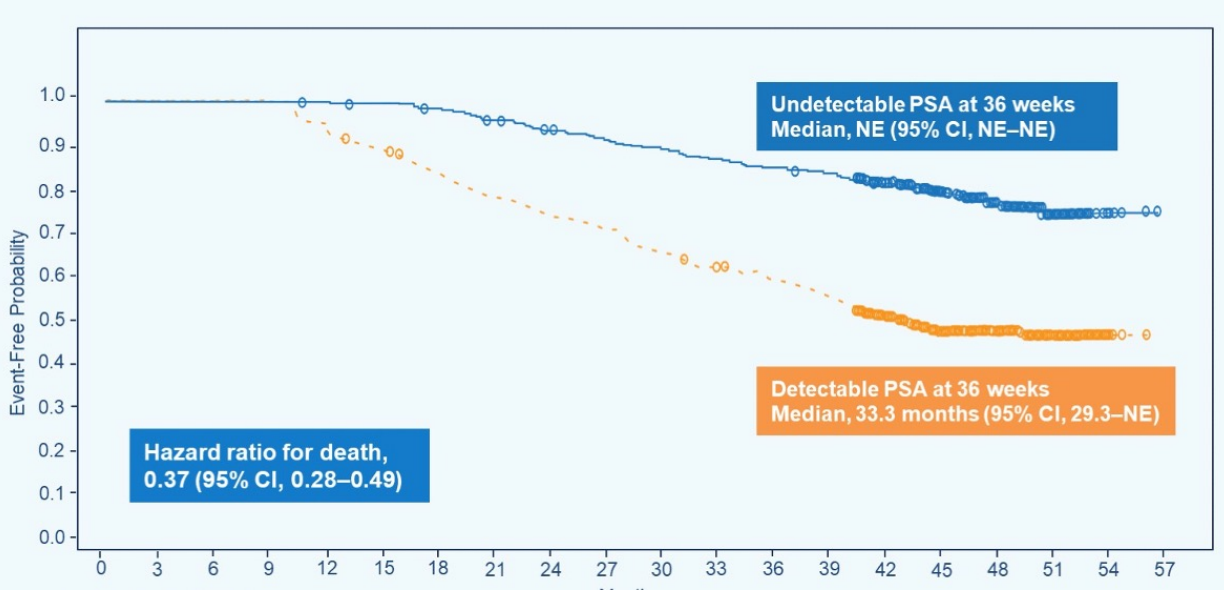
Saad F et al. ASCO 2022;Abstract 5078.

Overall Survival (OS) Improved for Patients Who Achieved Undetectable PSA

OS: PSA at 24 weeks



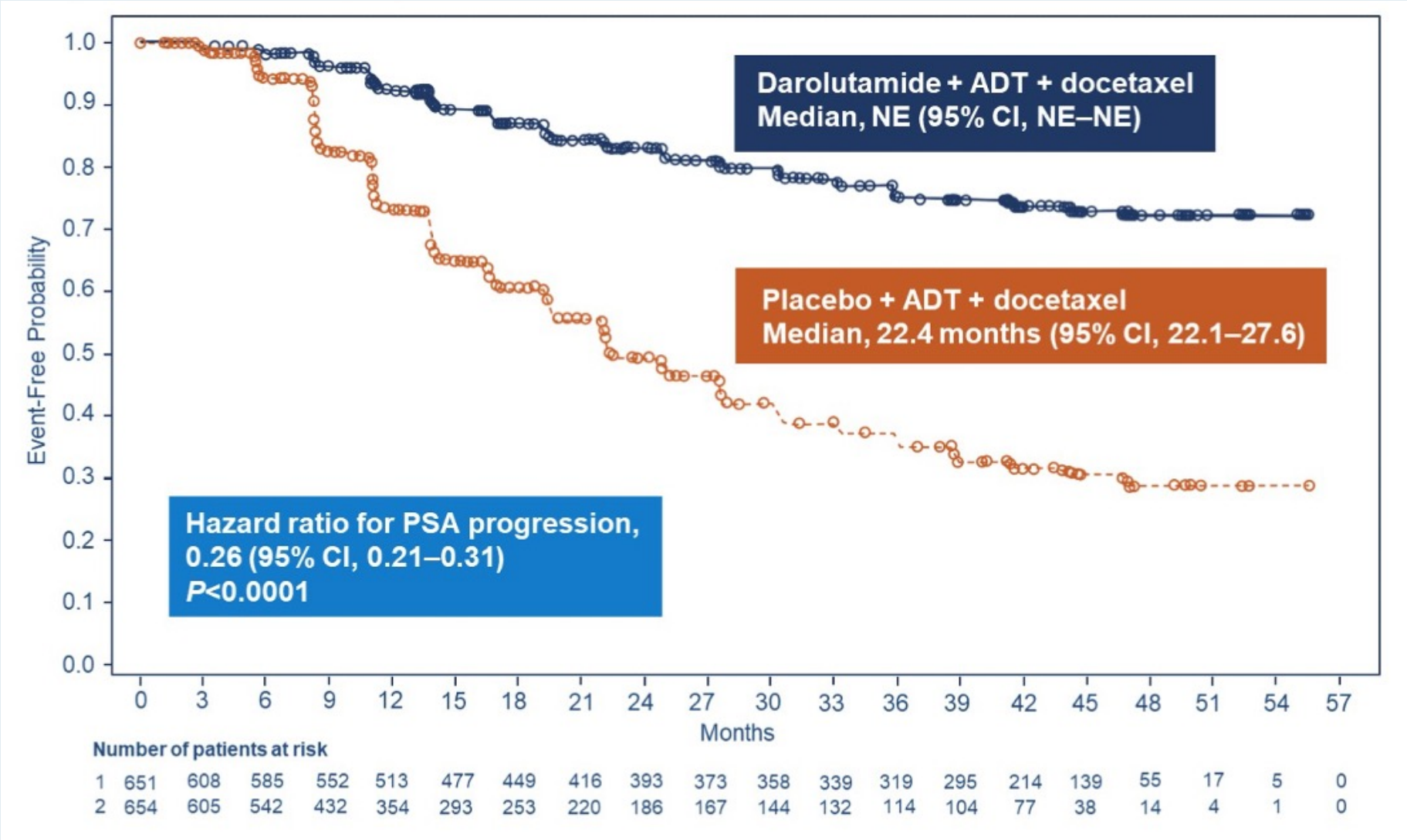
OS: PSA at 36 weeks



Darolutamide + ADT + Docetaxel

Saad F et al. ASCO 2022;Abstract 5078.

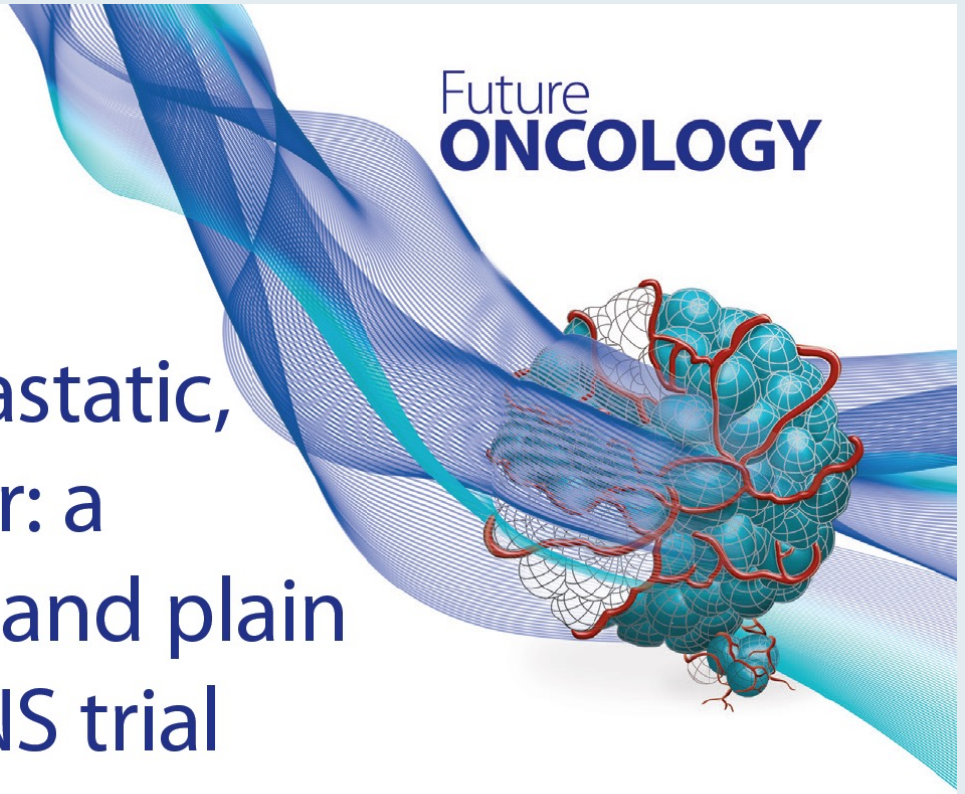
Time to PSA Progression



Saad F et al. ASCO 2022;Abstract 5078.

Future Oncol 2022;18(21):2585-97.

Plain Language Summary of Publication

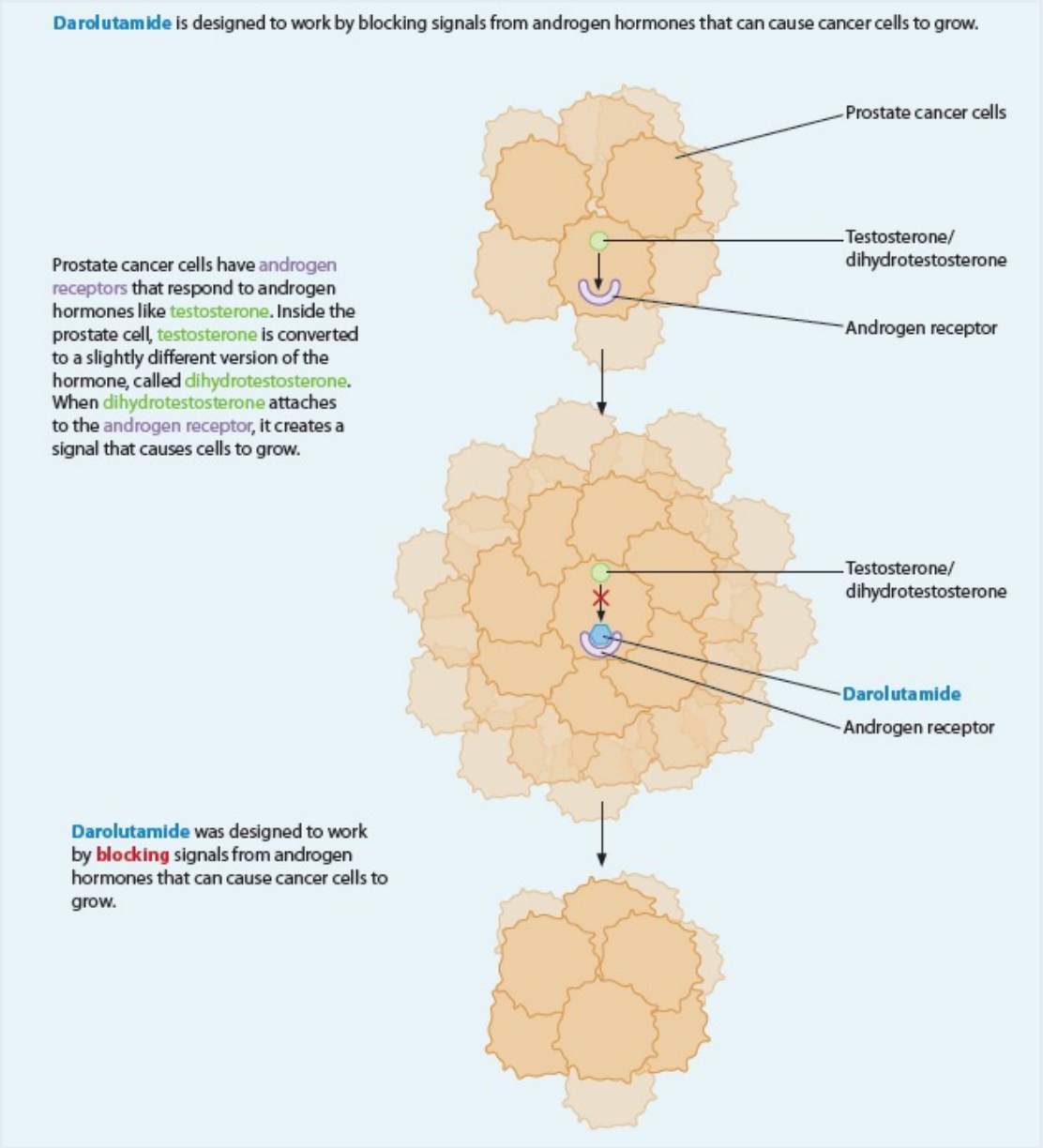


Darolutamide and survival in metastatic, hormone-sensitive prostate cancer: a patient and caregiver perspective and plain language summary of the ARASENS trial

Matthew R Smith*[,1], Maha Hussain[2], Fred Saad[3], Karim Fizazi[4], Cora N Sternberg[5], David Crawford[6], Jan Manarite[7,8], David Muslin[9], Thomas Farrington[9,10] & Bertrand Tombal[11]

[1]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [2]Northwestern University, Feinberg School of Medicine, Chicago, IL, USA; [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, USA; [6]UC San Diego School of Medicine, San Diego, CA, USA; [7]Caregiver Author; [8]Cancer ABCs, Brooklyn, NY, USA; [9]Patient Author; [10]Prostate Health Education Network, Quincy, MA, USA; [11]Division of Urology, IREC, Cliniques Universitaires Saint Luc, UCLouvain, Brussels, Belgium

How Is Darolutamide Designed to Work?



Smith MR et al. *Future Oncol* 2022;18(21):2585-97.

About the ARASENS trial

started in November 2016 and is still ongoing as of April 2022.

Placebo-controlled
A placebo looks like a trial treatment but does not have any medicine in it. Researchers use a **placebo** to make sure the effects of the trial treatment are actually caused by the trial treatment. In this trial, in addition to **ADT** and **docetaxel**, about half of trial patients received a placebo and the other half received **darolutamide**.

includes 1,306 patients with mHSPC.

Double-blinded
None of the trial patients, researchers, or doctors knew what treatment each patient received. This means they were "blind" to this information.

Randomized
Random chance was used by a computer to place trial patients into different equally sized groups. This is similar to flipping a coin.

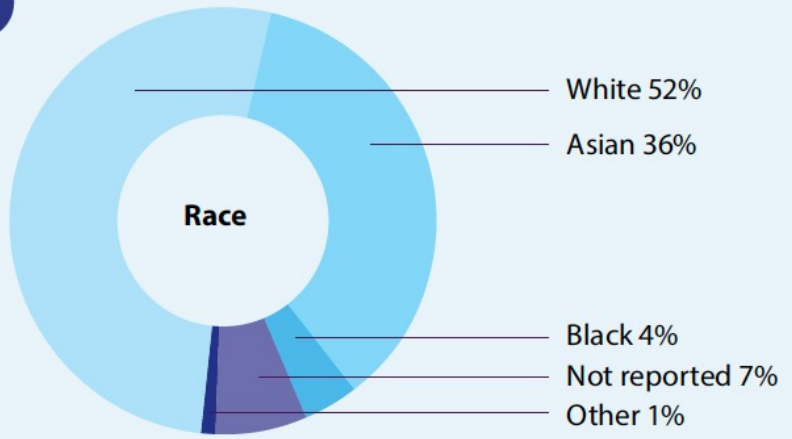
Smith MR et al. *Future Oncol* 2022;18(21):2585-97.

About the patients in the ARASENS trial

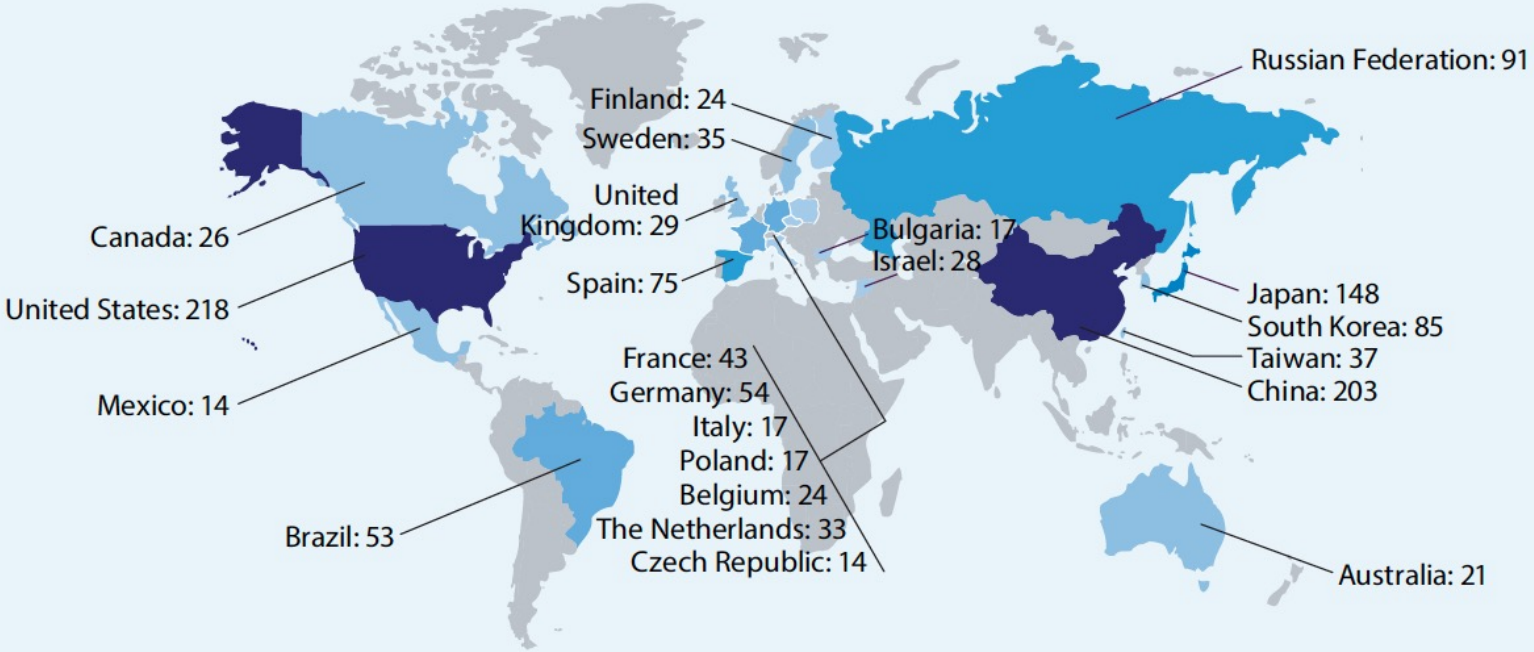
41–89 years
age range

67 years
median age

The median is the middle number in a list of numbers organized from lowest to highest.



Number of patients from 23 countries



Smith MR et al. *Future Oncol* 2022;18(21):2585-97.

What happened in the ARASENS trial?

1,306
patients were split into
2 groups

651
patients were put into the
darolutamide group
and received these treatments:

655
patients were put into the
placebo group
and received these treatments:

Docetaxel
6 cycles of 75 mg per 1 square meter of body-surface area on day 1 and every 21 days

ADT
As prescribed, throughout the entire trial

Darolutamide
600 mg taken twice a day, throughout the entire trial

Docetaxel
6 cycles of 75 mg per 1 square meter of body-surface area on day 1 and every 21 days

ADT
As prescribed, throughout the entire trial

Placebo
Taken twice a day, throughout the entire trial

The patients received **darolutamide** or the **placebo**, in addition to **ADT** and **docetaxel,** until any of the following happened:

- Their cancer got worse
- They had a change in chemotherapy
- They had treatment effects that were too toxic
- They or their doctor decided to stop treatment for a different reason

Smith MR et al. *Future Oncol* 2022;18(21):2585-97.

What were the results?

The purpose of the ARASENS trial was to learn if combining **darolutamide** with **ADT** and **docetaxel** could help treat patients with mHSPC better than **placebo** with **ADT** and **docetaxel**.

The researchers wanted to learn the answers to several questions to determine if combining **darolutamide** was working better than the **placebo**. To answer these questions, the researchers collected data from the trial patients until October 2021.

They compared the results of the patients who received **darolutamide** to the patients who received the **placebo**. The results below were similar in all race groups.

Below are the answers to these questions.

Compared to the **placebo**, did adding **darolutamide** to **ADT** and **docetaxel** help…

		Risk reduction	After 4 years of receiving trial treatment
trial patients live longer?	Yes	Overall, treatment with **darolutamide** increased the chance of survival and reduced the risk of dying by **32.5%** compared to the **placebo**.	**62.7%** of patients in the **darolutamide group** were still alive **50.4%** of patients in the **placebo group** were still alive

As of October 2021

delay castration-resistant cancer? When prostate cancer becomes castration-resistant, it means it is no longer responding to treatment with ADT and the growth of cancer cells may increase.	Yes	Overall, treatment with **darolutamide** increased the length of time patients continued to respond to ADT and didn't require treatment change. It also reduced the risk of cancer becoming castration-resistant by **64%** compared to the **placebo**.	**35%** of patients in the **darolutamide group** had castration-resistant cancer **60%** of patients in the **placebo group** had castration-resistant cancer
delay worsening pain? Severity of pain was measured using a survey called the Brief Pain Inventory (Short Form) that was completed by trial patients.	Yes	Overall, treatment with **darolutamide** increased the length of time patients remained alive without worsening of pain and reduced the risk of pain becoming worse by **21%** compared to the **placebo**.	**34%** of patients in the **darolutamide group** had worsening pain **38%** of patients in the **placebo group** had worsening pain

Smith MR et al. *Future Oncol* 2022;18(21):2585-97.

Intermediate Clinical Endpoints (ICE) as Potential Surrogates for Overall Survival (OS) in Men with Metastatic Hormone-Sensitive Prostate Cancer (mHSPC)

Halabi S et al.

ESMO 2022;Abstract 1375P.

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

N Engl J Med 2022 Mar 24;386(12):1132-42.

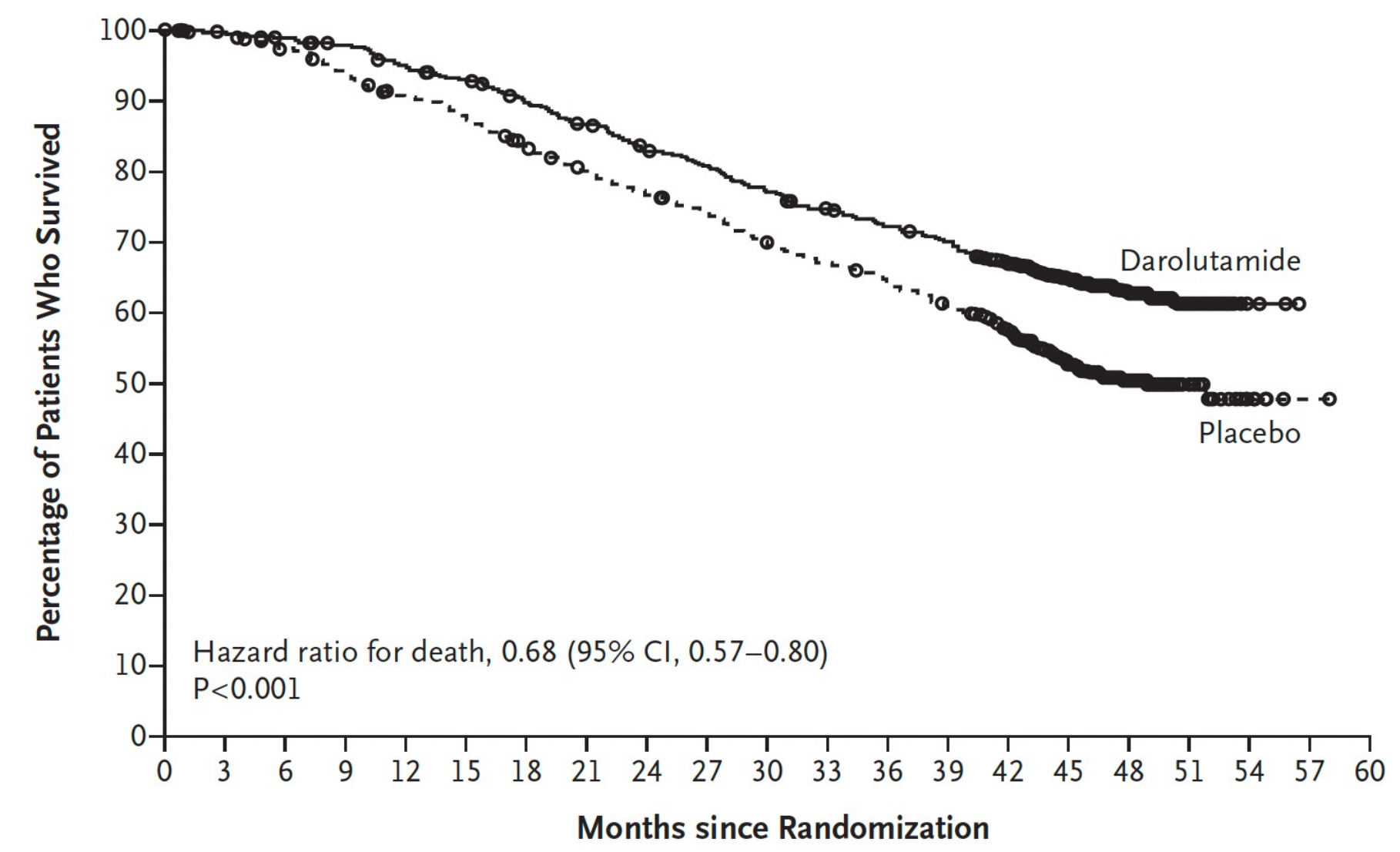
ORIGINAL ARTICLE

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*

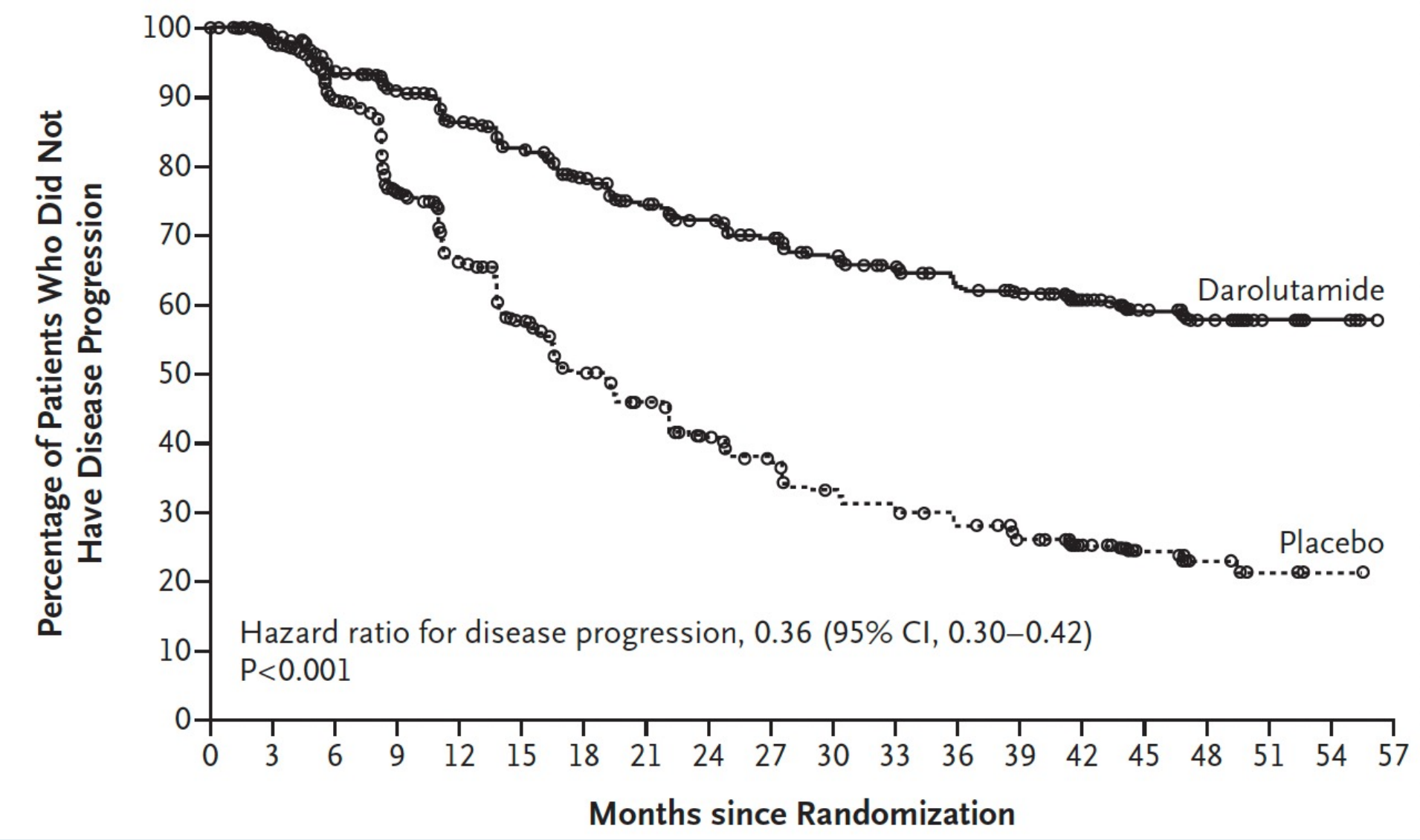
RTP RESEARCH TO PRACTICE

ARASENS: Overall Survival (Primary Endpoint)



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

ARASENS: Progression-Free Survival



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

ARASENS: Adverse Events

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

*EAIR is the number of patients with a given AE divided by the total darolutamide/placebo treatment duration of all patients in years and expressed in 100 PY. †This category combines the following MedDRA terms: rash, maculopapular rash, drug eruption, pruritic rash, erythematous rash, macular rash, papular rash, follicular rash, pustular rash, and vesicular rash. ‡This category is a MedDRA High-Level Group Term. EAIR, exposure-adjusted incidence rate; PY, patient year.

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

2022;386(24):2345.

The NEW ENGLAND JOURNAL of MEDICINE

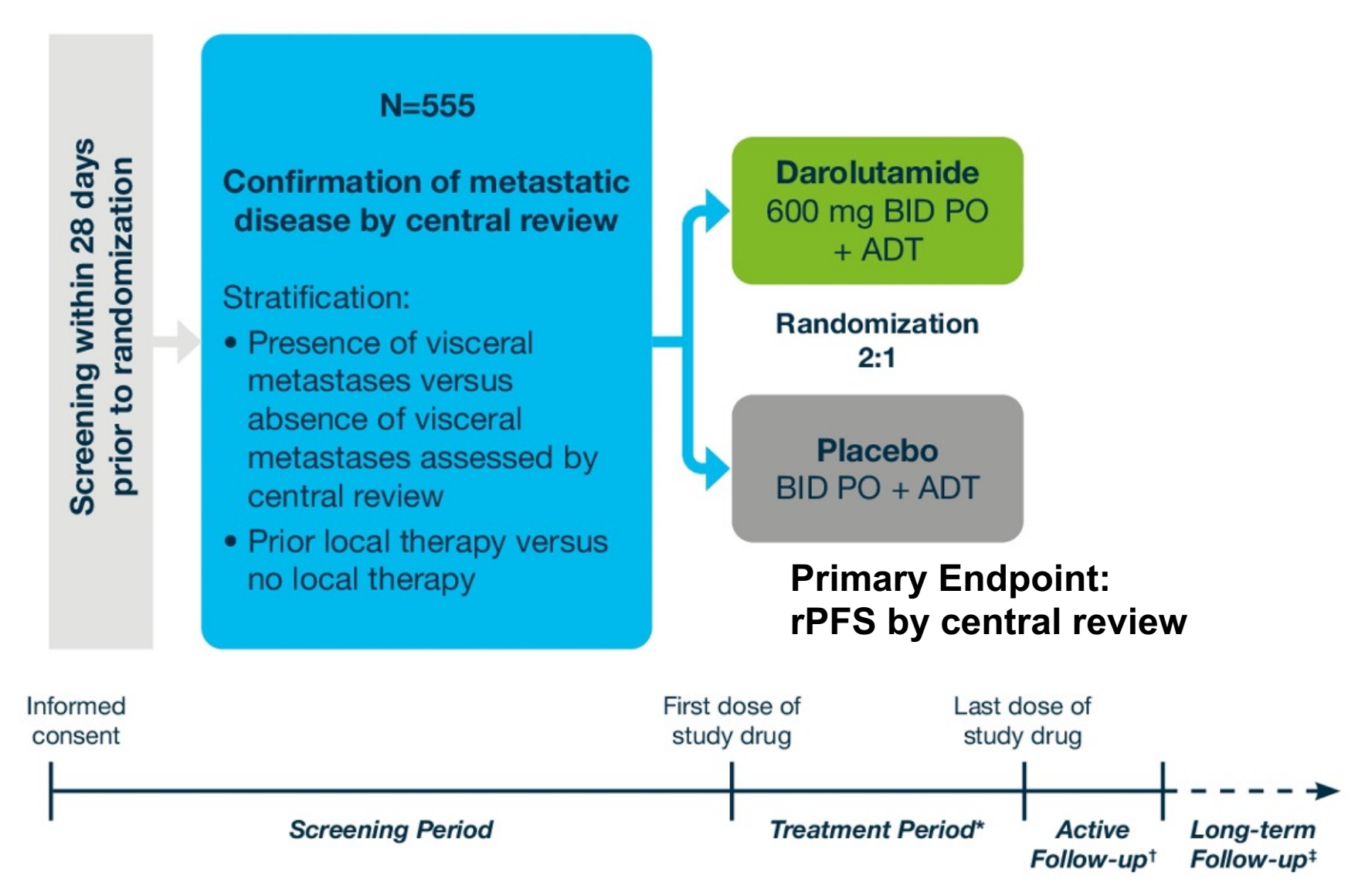
Darolutamide in Metastatic Prostate Cancer

THE AUTHOR REPLIES:

Matthew R. Smith, M.D., Ph.D.

Massachusetts General Hospital
Boston, MA
mrsmith@mgh.harvard.edu

ARANOTE Phase III Study Design



Haresh KP et al. ASCO 2022;Abstract TPS200.

ARANOTE Phase III Study: Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
Men aged ≥18 years with histologically or cytologically confirmed adenocarcinoma of the prostate	Prior treatment with: • LHRH agonist/antagonist started ≥12 weeks before study treatment starts except neoadjuvant and/or adjuvant therapy for a duration of ≤24 months and completed ≥12 months prior to randomization • Second-generation ARIs or other investigational ARIs • CYP17 enzyme inhibitors as antineoplastic treatment • Chemotherapy including docetaxel or immunotherapy for prostate cancer • Systemic corticosteroids with a dose greater than the equivalent 10 mg of prednisone per day within 28 days prior to randomization
Documented metastatic disease*	Radiotherapy in the 2 weeks prior to randomization
Started ADT (LHRH agonist/antagonist or orchiectomy) with or without first-generation anti-androgen (not longer than 12 weeks before randomization)	Prior malignancy, other than treated basal or squamous cell skin cancer, superficial bladder cancer, or any other cancer *in situ* currently in complete remission, within 5 years prior to randomization
ECOG performance status 0, 1, or 2	Known leptomeningeal metastases
Adequate bone marrow, liver, and renal function	Inability to swallow oral medications
	Stroke, myocardial infarction, severe or unstable angina pectoris, coronary or peripheral artery bypass graft, or congestive heart failure (New York Heart Association Class III or IV) in the 6 months prior to randomization
	A gastrointestinal disorder or procedure that may interfere with absorption of the study drug

Haresh KP et al. ASCO 2022;Abstract TPS200.

Prostate Cancer and Prostatic Diseases www.nature.com/pcan

Prostate Cancer Prostatic Dis 2022 October 8;[Online ahead of print].

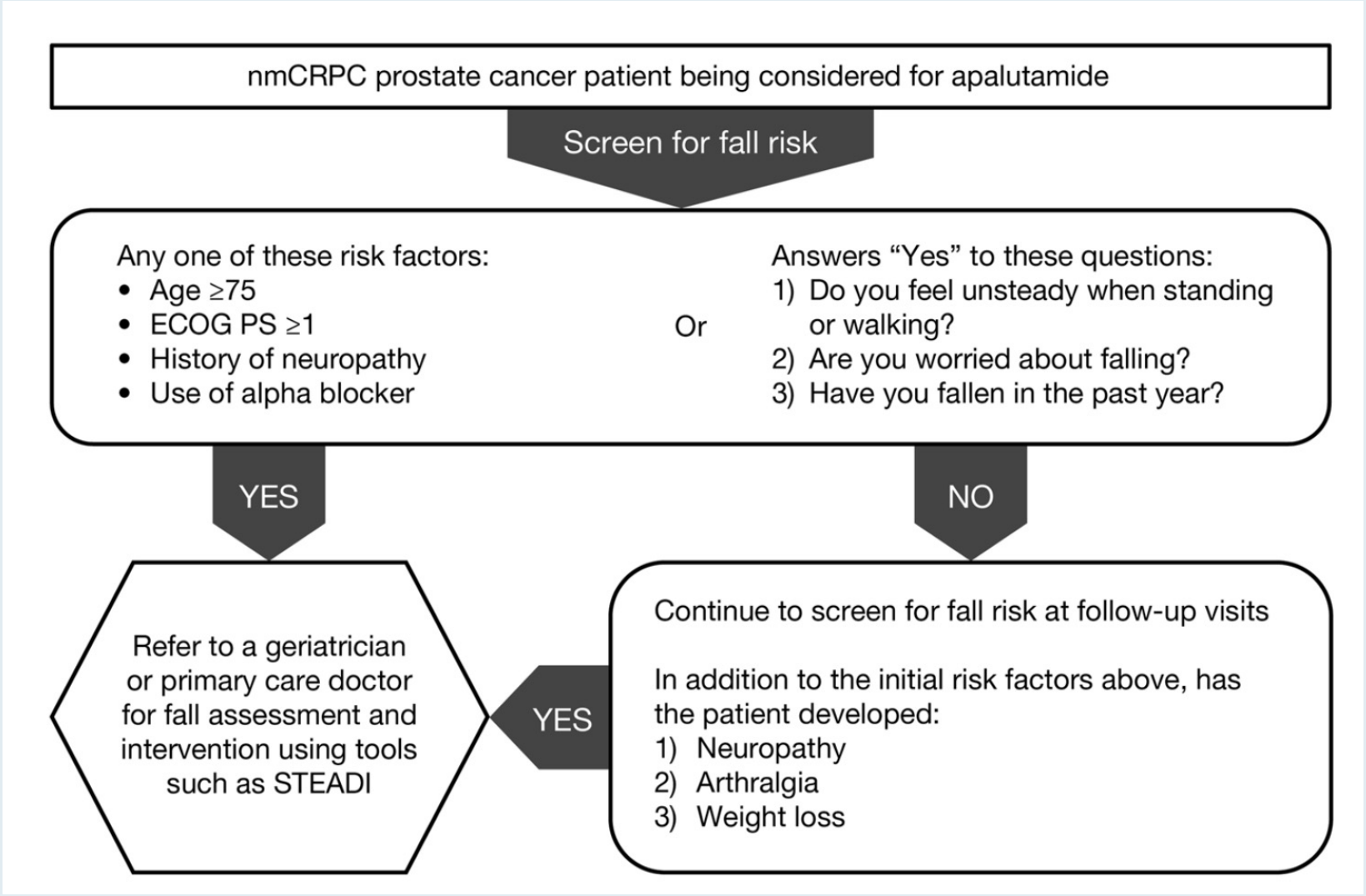
ARTICLE

Clinical Research

Clinical characteristics associated with falls in patients with non-metastatic castration-resistant prostate cancer treated with apalutamide

YaoYao Pollock[1,16]✉, Matthew R. Smith[2], Fred Saad[3], Simon Chowdhury[4], Stéphane Oudard[5], Boris Hadaschik[6], David Olmos[7], Ji Youl Lee[8], Hiroji Uemura[9], Amitabha Bhaumik[10], Anil Londhe[10], Brendan Rooney[11], Sabine D. Brookman-May[12,13], Peter De Porre[14], Suneel D. Mundle[15] and Eric J. Small[1]

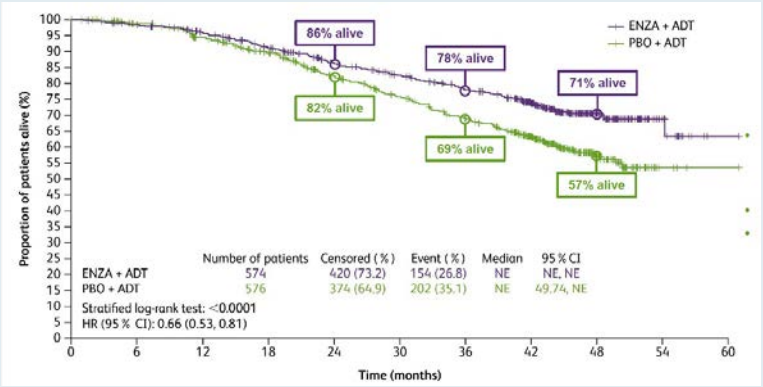
Fall Risk Screening Diagram



Pollock YY et al. *Prostate Cancer Prostatic Dis* 2022 October 8;[Online ahead of print].

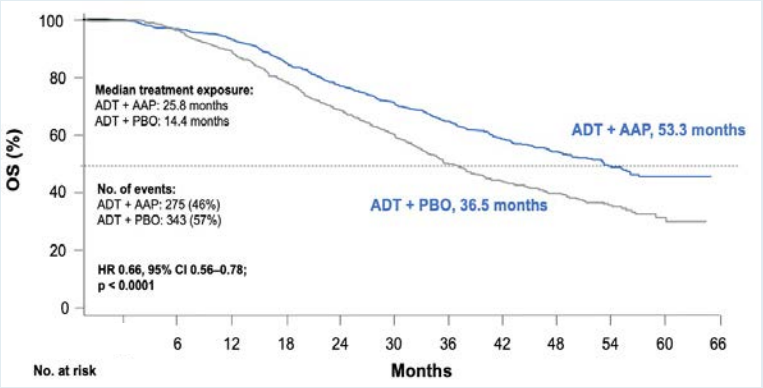
Final Overall Survival (OS) Analyses: Enzalutamide, Abiraterone and Apalutamide for mHSPC

ARCHES[1] enzalutamide + androgen deprivation therapy (ADT)



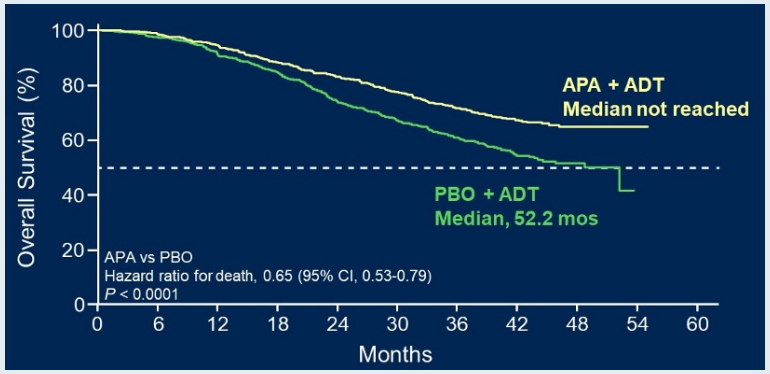
- 34% reduction in risk of death
- Median follow-up of 44.6 months
- Median OS was significantly longer for enzalutamide + ADT vs placebo + ADT
  - **40.2 months vs 13.8 months**
  - **HR = 0.66; *p* < 0.001**

LATITUDE[2] abiraterone + 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 + 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. *J Clin Oncol* 2022 May 20;40(15):1616-22. 2. Fizazi K et al. *Lancet Oncol* 2019;20(5):686-700;. 3. Chi KN et al. *J Clin Oncol* 2021;39(20):2294-303.

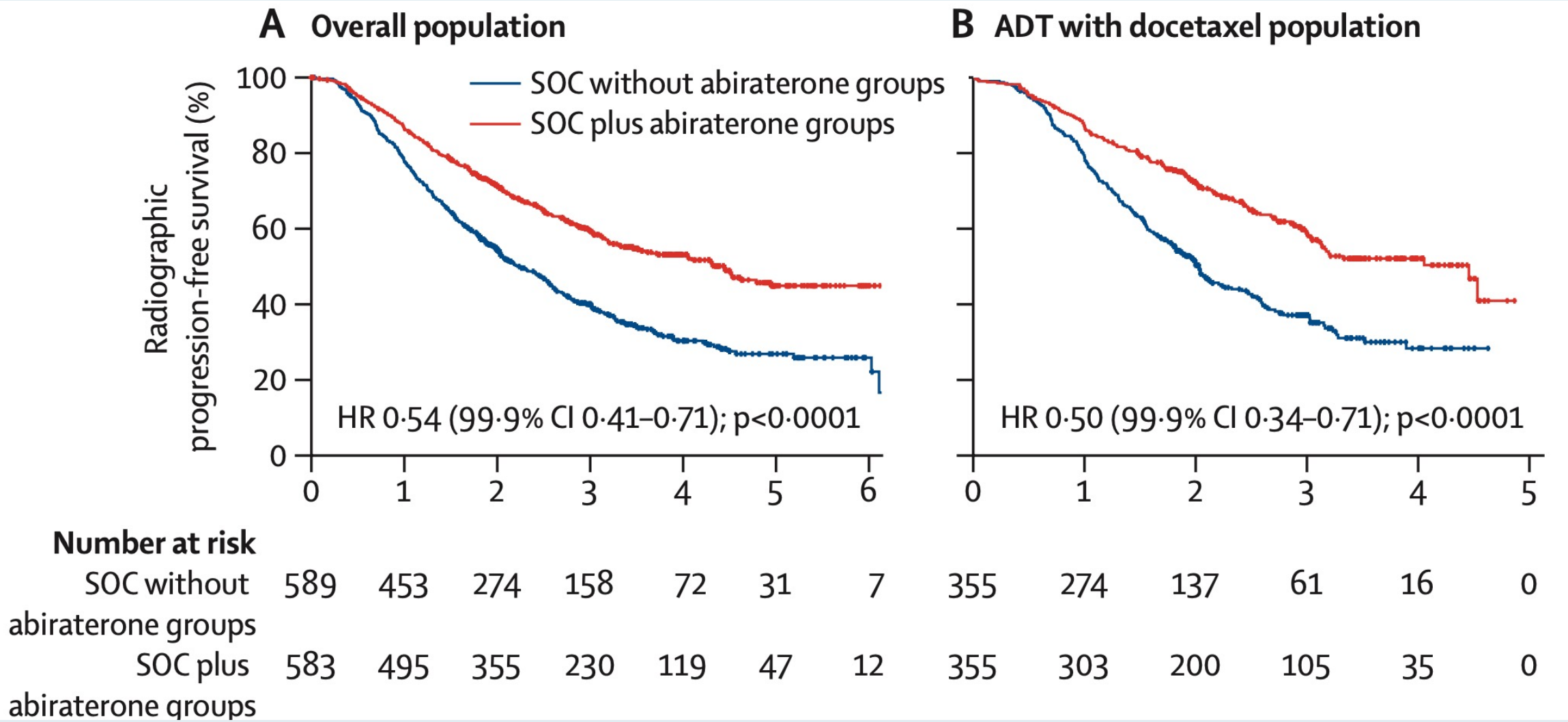
RTP RESEARCH TO PRACTICE

Lancet 2022 April 30;399(10336):1695-707.

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**

PEACE-1: Radiographic Progression-Free Survival (rPFS)



ADT = androgen deprivation therapy

Fizazi K et al. *Lancet* 2022;399(10336):1695-707.

RTP RESEARCH TO PRACTICE

PEACE-1: Grade 3 to 5 Adverse Events (ADT with Docetaxel in the Safety Population)

Toxicity, n (%)	SOC (+/- RXT) + Abiraterone (n=346)	SOC (+/- RXT) (n=350)
Neutropenia	34 (10)	32 (9)
Febrile neutropenia	18 (5)	19 (5)
Liver	20 (6)	2 (1)
Hypertension	76 (22)	45 (13)
Hypokalemia	11 (3)	1 (0)
Cardiac	6 (2)	5 (1)
Fatigue	10 (3)	15 (4)
Gastro-intestinal	14 (4)	18 (5)
Grade 5	7 (2)	3 (1)

Fizazi K et al. ESMO 2021;Abstract LBA5.

Current and Future Application of Hormonal Therapy for Metastatic CRPC (mCRPC)

Darolutamide maintenance in metastatic castration resistant prostate cancer (mCRPC) previously treated with novel hormonal agents (NHA) and non-progressive disease after subsequent treatment with a taxane: A randomized double-blind placebo-controlled phase II trial (SAKK 08/16)

Richard Cathomas, Giuseppe Procopio, Stefanie Hayoz, Eloïse Kremer, Dirk Kienle, Orazio Caffo, David Lorente, Augusto Pedrazzini, Guilhem Roubaud, Soazig Nenan, Aurelius Omlin, Consuelo Buttigliero, Ricardo Pereira Mestre, Karin Ribi, Silke Gillessen

For the Swiss Group of Clinical Cancer Research SAKK

SAKK
WE BRING PROGRESS TO CANCER CARE

ESMO Annual Meeting, Paris, 18.09.2021 – LBA26

2021 ESMO congress

16-21 SEPTEMBER 2021

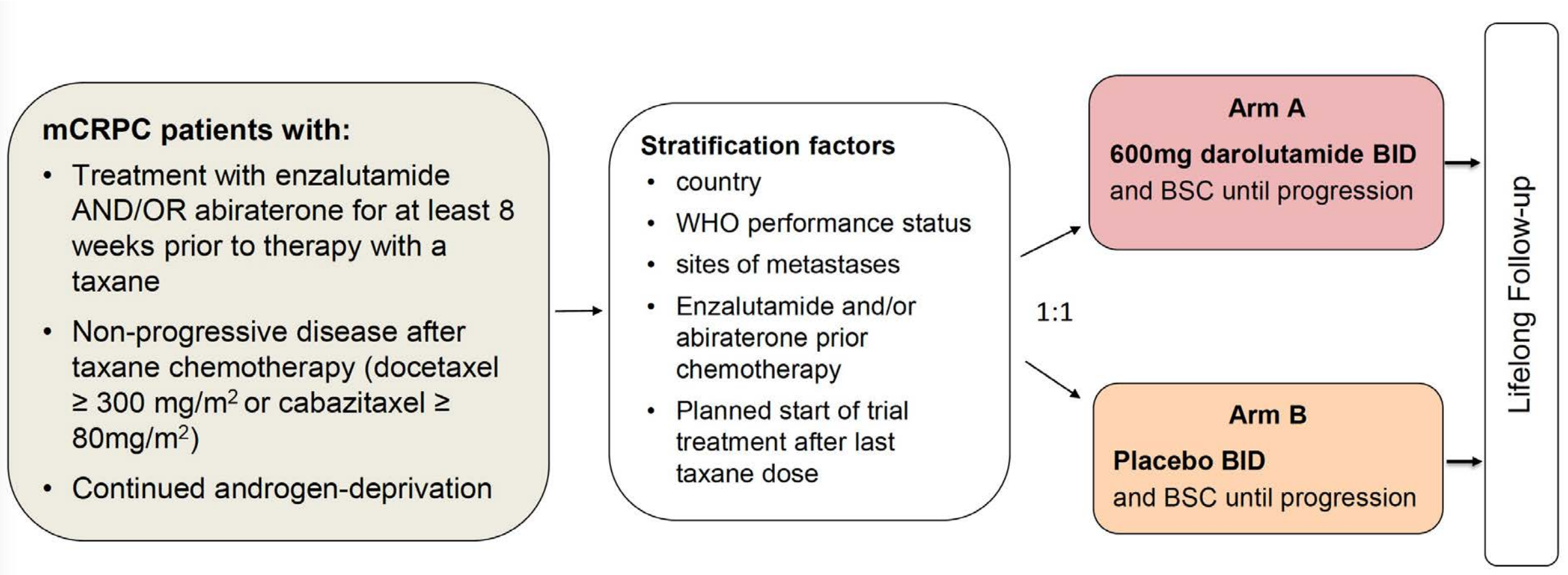
SAKK 08/16: Baseline Characteristics

	Arm A (N=45): Darolutamide	Arm B (N=45): Placebo
Age (years)	71 (56-81)	72 (55-87)
WHO PS 0/1	100%/0%	98%/2%
Metastases		
- Bone	87%	89%
- Lymph node	51%	51%
- Liver/Lung	2%/2%	2%/4%
Gleason score		
- Gleason 6-7/8-10	40%/53%	47%/53%
- Missing	7%	0%
End taxane to trial start		
- < 35 days/ ≥ 35 days	49%/51%	47%/53%

	Arm A (N=45): Darolutamide	Arm B (N=45): Placebo
Previous NHA		
- Abiraterone/Enzalutamide	60%/31%	60%/31%
- both	9%	9%
Best response to latest NHA		
- CR/PR	2%/24%	4%/33%
- SD/PD	36%/38%	38%/24%
Previous taxane		
- Docetaxel/Cabazitaxel	96%/4%	87%/13%
Best response to latest taxane		
- CR/PR	2%29%	4%/42%
- SD	69%	53%

Cathomas R et al. ESMO 2021;Abstract LBA26.

SAKK 08/16 Phase II Study Design



Initiation of trial treatment within 2-8 weeks after last taxane dose

Cathomas R et al. ESMO 2021;Abstract LBA26.

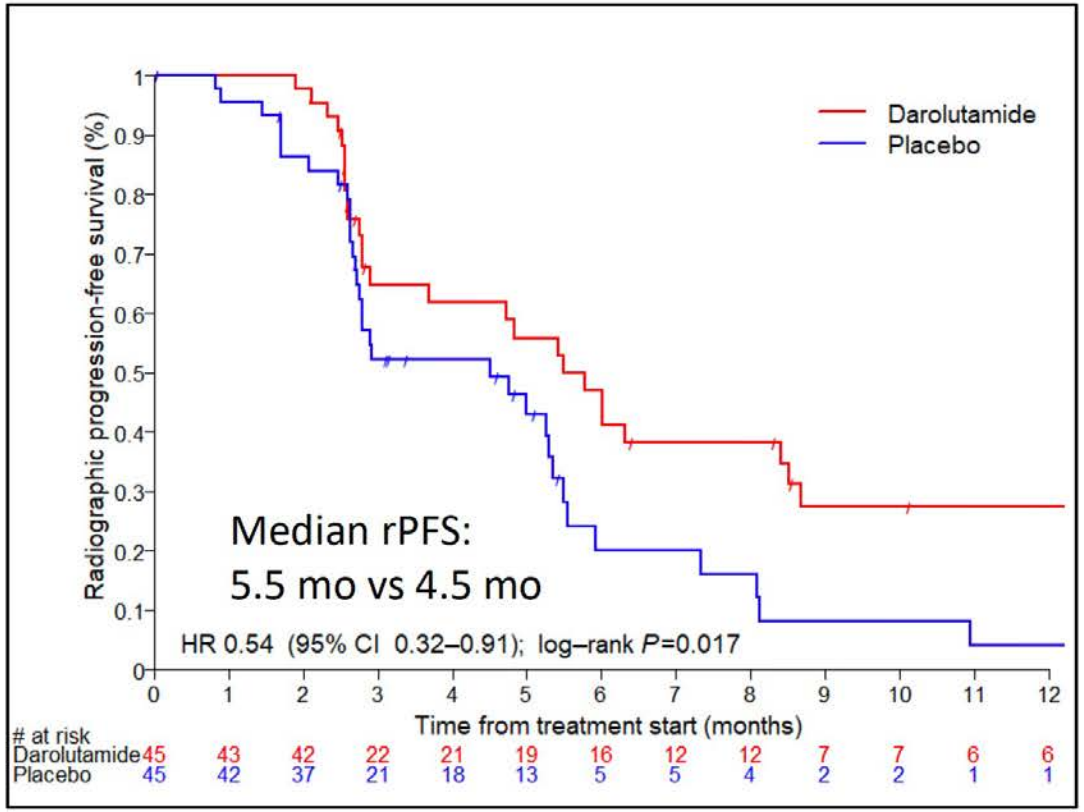
SAKK 08/16: Primary and Secondary rPFS Endpoints

Primary endpoint: rPFS at 12 weeks

	Arm A (N=45): Darolutamide	Arm B (N=45): Placebo
rPFS at 12 weeks	64.7%	52.2%
95% CI	47.6%, 77.5%	36.1%, 66.1%

	Result
Est. difference in rPFS at 12 weeks	12.5%
One-sided 85% CI (lower bound)	1.1%
P-value (one-sided)	0.127

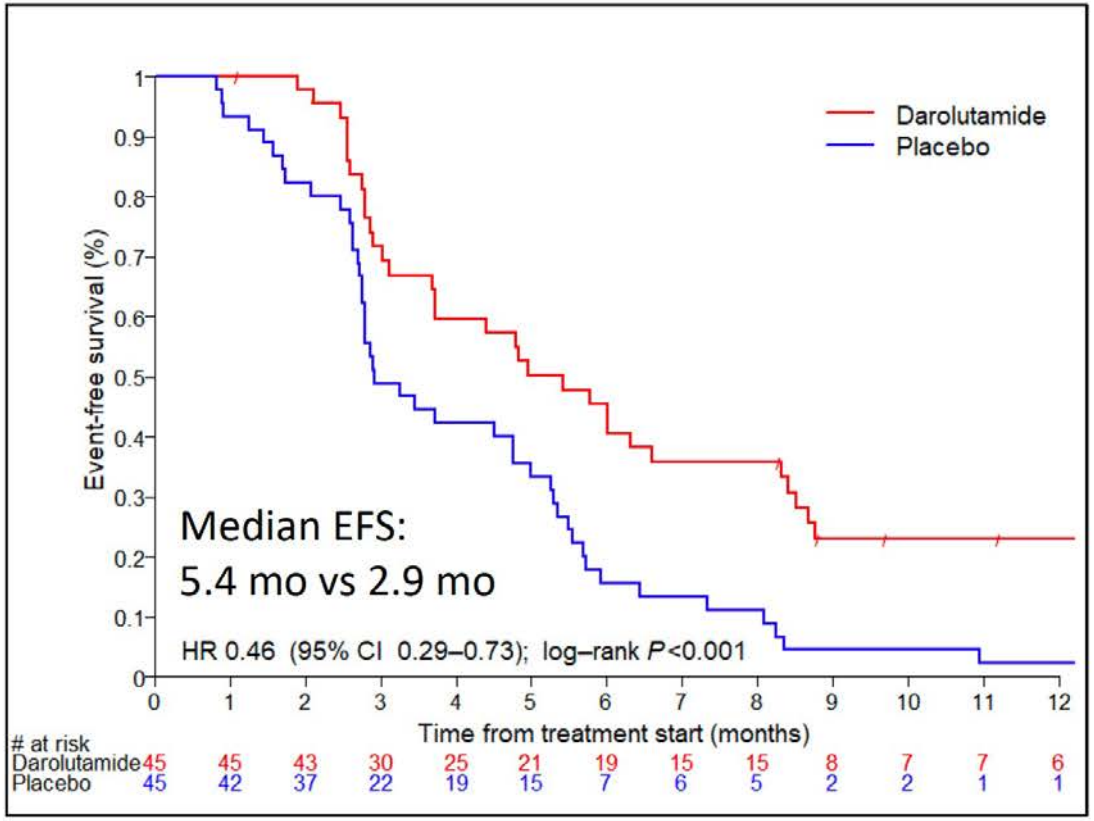
Secondary endpoint: rPFS



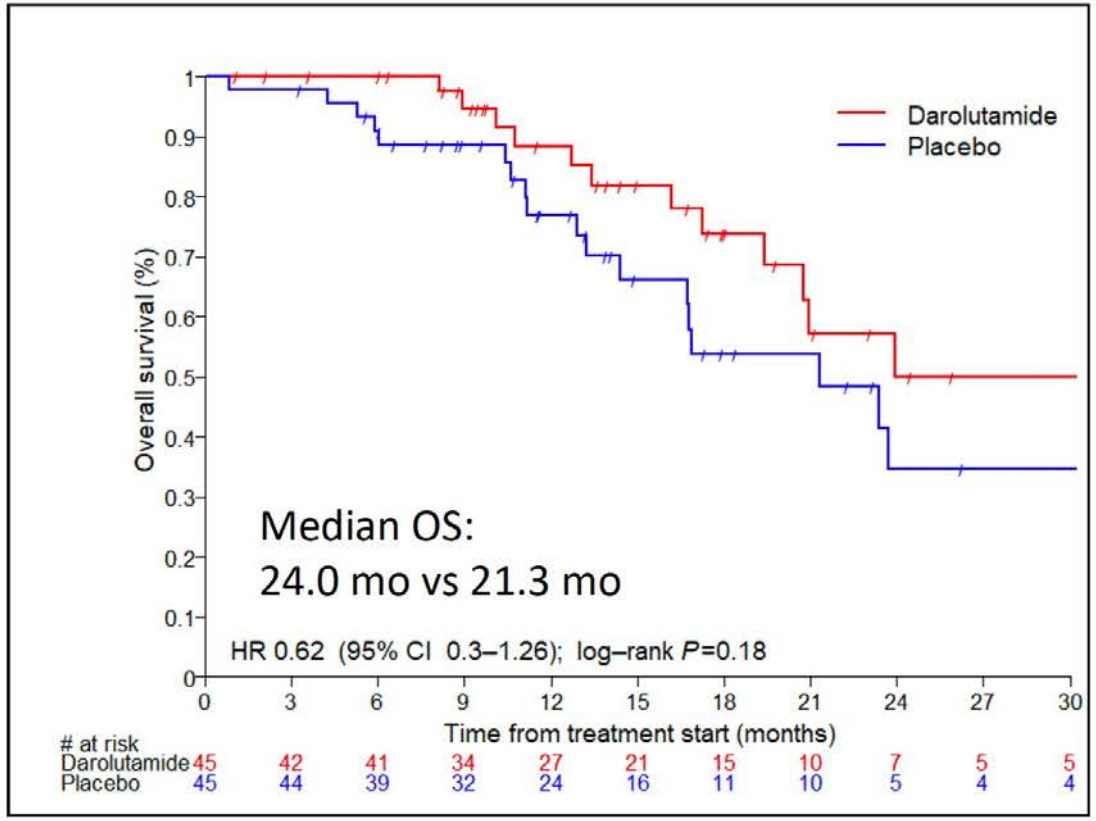
Cathomas R et al. ESMO 2021;Abstract LBA26.

SAKK 08/16: EFS and OS

Secondary endpoint: event-free survival



Secondary endpoint: overall survival

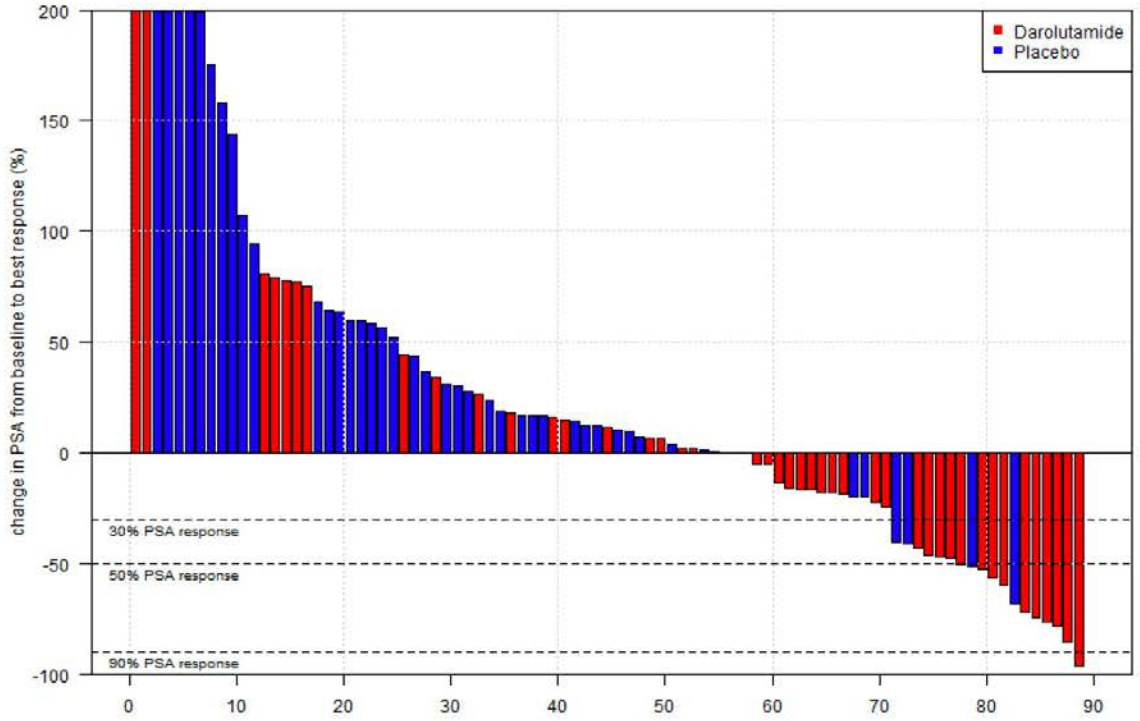


Cathomas R et al. ESMO 2021;Abstract LBA26.

RTP RESEARCH TO PRACTICE

SAKK 08/16: PSA Response

Secondary endpoint: PSA reponse



	Arm A (N=45): Darolutamide	Arm B (N=45): Placebo
30% PSA response	31%	9%
50% PSA response	22%	4%
90% PSA response	2%	0%
Median duration of PSA 50% response	7.7 mo	2.8 mo

Cathomas R et al. ESMO 2021;Abstract LBA26.

RTP RESEARCH TO PRACTICE

SAKK 08/16: Treatment-Related Adverse Events

	Arm A (N=46): Darolutamide			Arm B (N=46): Placebo		
CTC AE v.4.03	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 1**	**Grade 2**	**Grade 3**
Overall TRAE (% of pts)	26%	13%	2%	22%	15%	2%
Most common TRAE (≥4%)						
- Fatigue	9%	2%	-	13%	7%	-
- Anorexia	2%	4%	-	4%	2%	-
- Nausea	7%	-	-	4%	2%	-
- Bone pain and arthralgia	11%	2%	-	2%	-	-
- Peripheral edema	2%	-	2%	7%	-	-
- Hot flushes	7%	-	-	2%	-	-
- Pruritus	4%	-	-	-	-	-

Cathomas R et al. ESMO 2021;Abstract LBA26.

SAKK 08/16: Conclusions

- Proof of concept study has met primary endpoint
- Statistically significant but clinically modest improvement of rPFS
- Significant improvement of EFS and numerical improvement of OS
- Prior response to NHA might predict benefit from maintenance treatment after NHA and taxane
  - Hypothesis generating for phase 3 trial
- Favorable side effect profile compared to placebo

Cathomas R et al. ESMO 2021;Abstract LBA26.

ASCO Genitourinary Cancers Symposium

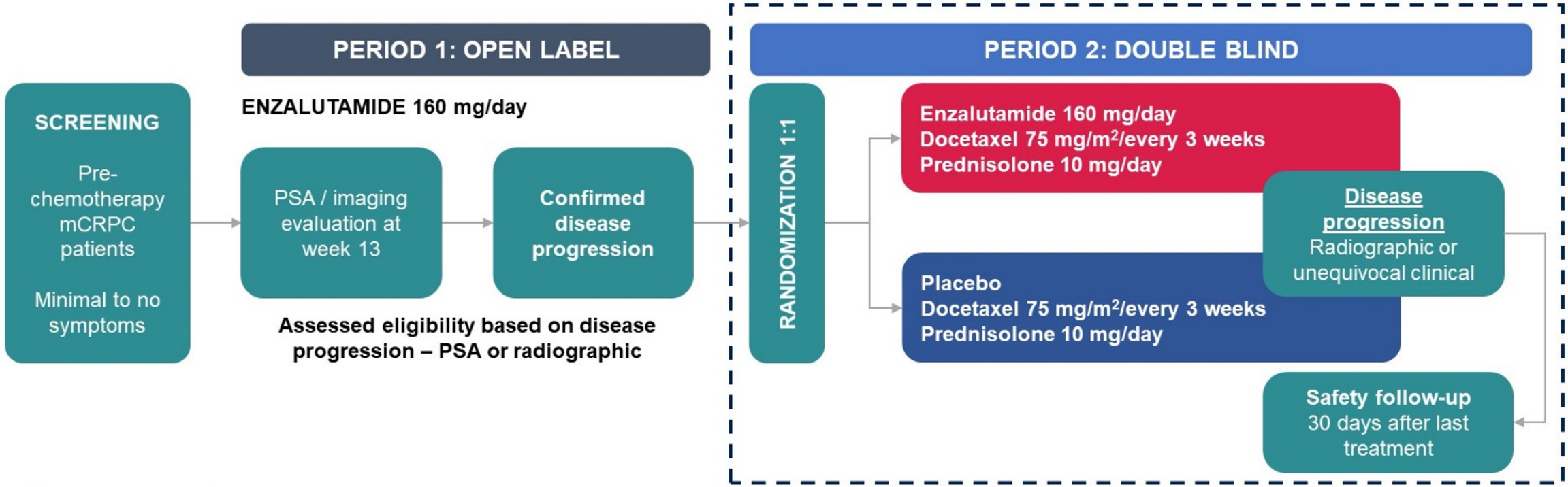
Abstract 15

A Randomized, Double-Blind, Placebo-Controlled, Phase 3b Study of the Efficacy and Safety of Continuing Enzalutamide in Chemotherapy-Naïve Metastatic Castration-Resistant Prostate Cancer Patients Treated With Docetaxel Plus Prednisolone Who Have Progressed on Enzalutamide Alone – PRESIDE

Axel S. Merseburger,[1] Gert Attard,[2] Gunther Boysen,[3] Georgia Gourgioti,[3] Karla Martins,[3] Simon Chowdhury,[4] on behalf of the PRESIDE investigators

[1]Universitätsklinikum Schleswig-Holstein - Campus Lübeck, Lubeck, Germany; [2]UCL Cancer Institute, London, UK; [3]Astellas Pharma Europe Ltd., Addlestone, UK; [4]Guy's, King's and St. Thomas' Hospitals, London, UK

PRESIDE Phase IIIb Study Design



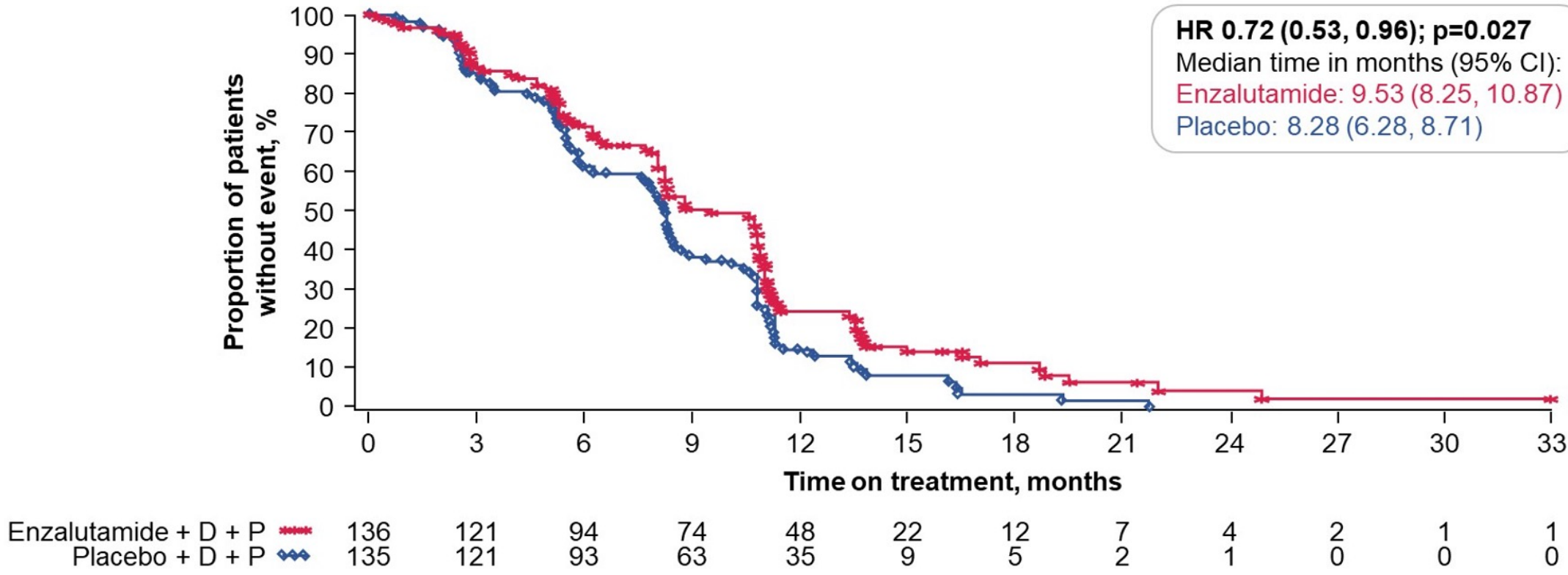
Endpoints

- **Primary endpoint:** PFS
  - Progression in Period 2 was defined as radiographic progression, unequivocal clinical progression, or death on study
- **Secondary endpoints:** time to PSA progression, PSA response, and ORR
- Safety

ORR=objective response rate; PFS=progression-free survival; PSA=prostate-specific antigen.

Merseburger AS et al. Genitourinary Cancers Symposium 2022;Abstract 15.

PRESIDE Primary Endpoint: Radiographic Progression-Free Survival

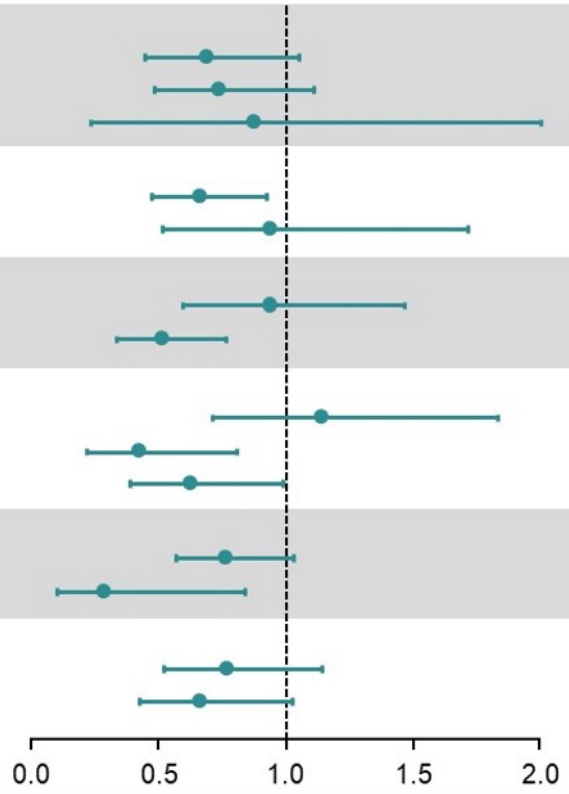


The study met its primary endpoint and enzalutamide plus docetaxel and prednisolone demonstrated a statistically significant reduction in the risk of progression compared with placebo plus docetaxel and prednisolone

Merseburger AS et al. Genitourinary Cancers Symposium 2022;Abstract 15.

PRESIDE: PFS Subgroup Analyses

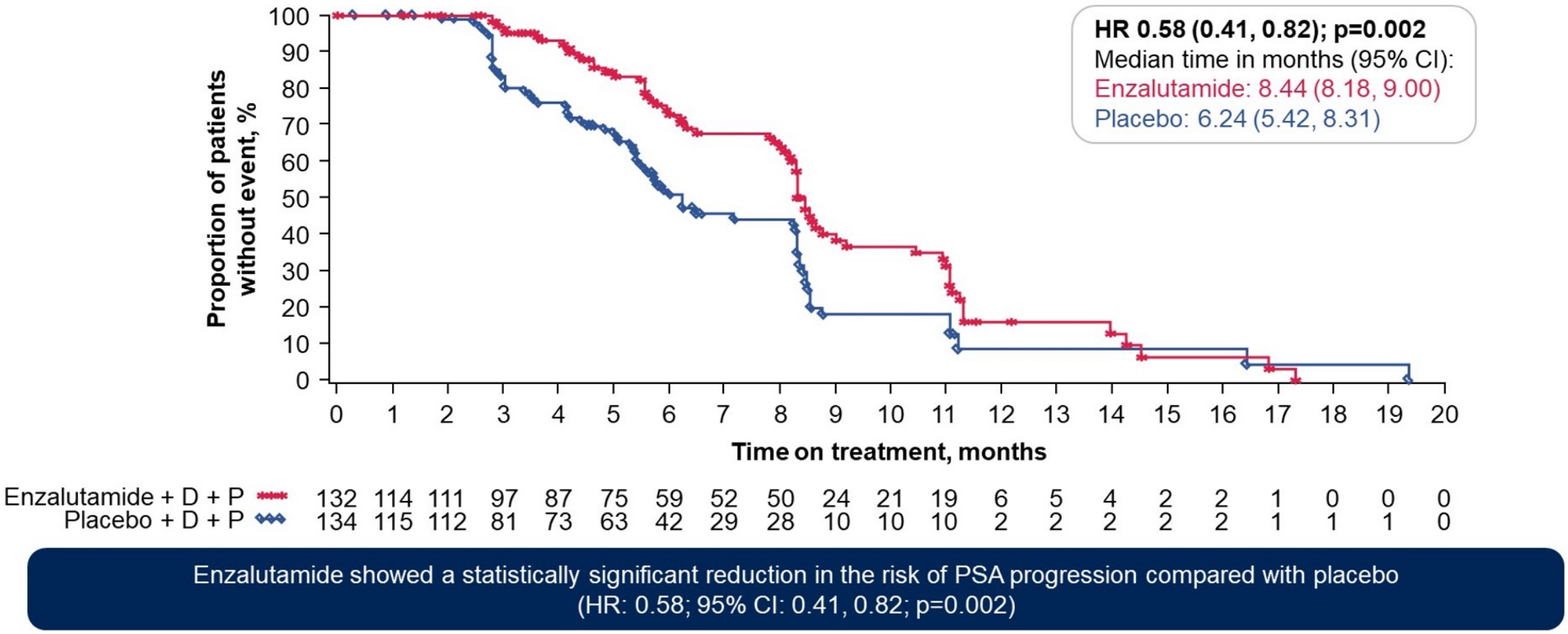
Analysis	Enzalutamide + D + P *Number of events (%) / number of censored*	Placebo + D + P *Number of events (%) / number of censored*	Hazard ratio (95% CI)[b]	P-value[c]
ECOG score				**0.8484**
0	41 (70.7) / 17	45 (72.6) / 17	0.69 (0.45, 1.06)	
1	47 (77.0) / 14	44 (77.2) / 13	0.73 (0.48, 1.11)	
2	5 (83.3) / 1	4 (100.0) / 0	0.88 (0.23, 3.38)	
Age				**0.8396**
<75 years	69 (76.7) / 21	74 (74.7) / 25	0.67 (0.47, 0.93)	
≥75 years	24 (68.6) / 11	19 (79.2) / 5	0.94 (0.51, 1.73)	
Gleason score				**0.0015**
<8	39 (76.5) / 12	39 (76.5) / 12	0.93 (0.59, 1.47)	
≥8	49 (72.1) / 19	51 (73.9) / 18	0.51 (0.34, 0.77)	
Disease location				**0.0097**
Bone only	41 (78.8) / 11	30 (66.7) / 15	1.14 (0.71, 1.84)	
Tissue only	20 (71.4) / 8	18 (90.0) / 2	0.42 (0.22, 0.81)	
Bone and tissue	32 (71.1) / 13	45 (77.6) / 13	0.63 (0.39, 1.00)	
Visceral disease				**0.0237**
No	87 (76.3) / 27	85 (73.9) / 30	0.77 (0.56, 1.04)	
Yes	6 (54.5) / 5	8 (100.0) / 0	0.29 (0.10, 0.85)	
Baseline median PSA				**0.0693**
≤36.6 ug/L	50 (76.9) / 15	51 (77.3) / 15	0.77 (0.52, 1.15)	
>36.6 ug/L	43 (71.7) / 17	42 (73.7) / 15	0.66 (0.43, 1.03)	



PFS subgroup analyses illustrated consistent results with those observed in the overall group

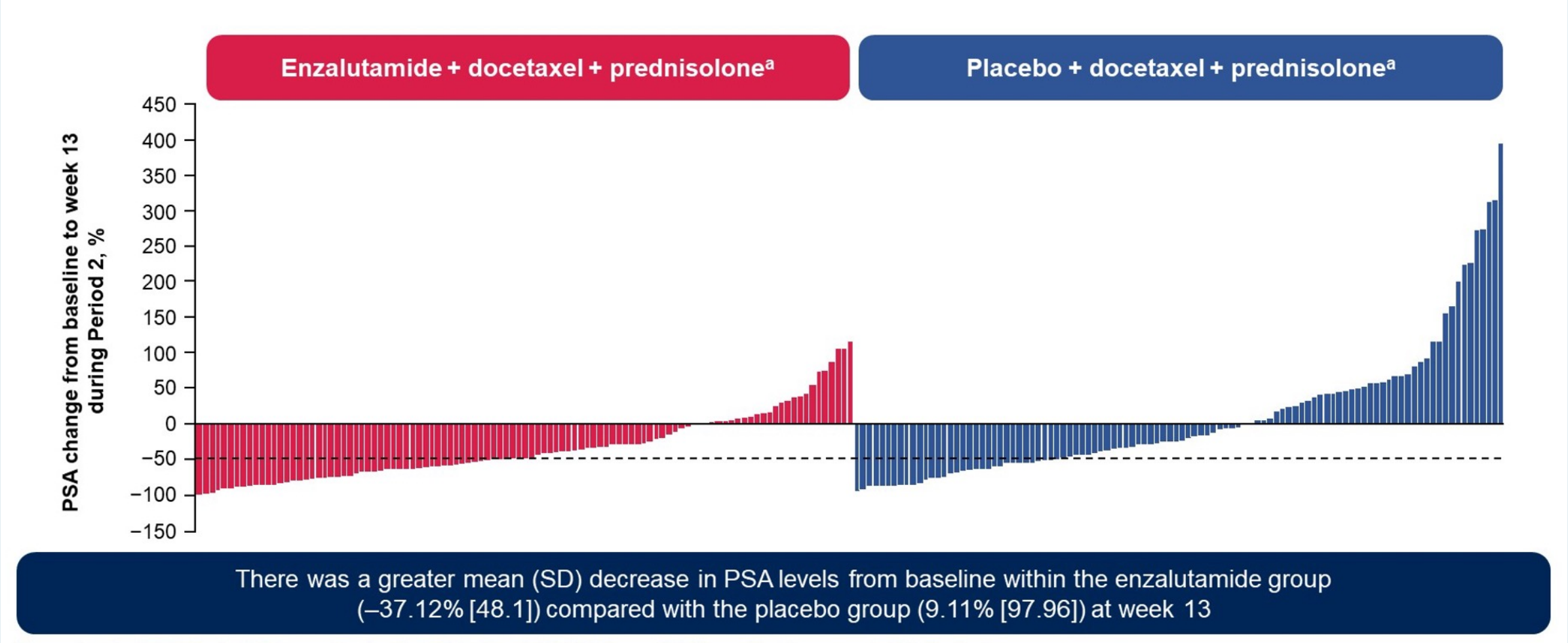
Merseburger AS et al. Genitourinary Cancers Symposium 2022;Abstract 15.

PRESIDE Secondary Endpoint: Time to PSA Progression



Merseburger AS et al. Genitourinary Cancers Symposium 2022;Abstract 15.

PRESIDE Secondary Endpoint: PSA Change from Baseline to Week 13



Merseburger AS et al. Genitourinary Cancers Symposium 2022;Abstract 15.

RTP RESEARCH TO PRACTICE

PRESIDE Secondary Endpoint: Objective Response Rate (ORR)

Parameter, n (%)	Enzalutamide + docetaxel + prednisolone (n=136)	Placebo + docetaxel + prednisolone (n=135)
PR rate	17 (12.5)	18 (13.3)
95% CI	7.5, 19.3	8.1, 20.3
CR rate	**26 (19.1)**	**17 (12.6)**
95% CI	12.9, 26.7	7.5, 19.4
ORR (CR + PR)	**43 (31.6)**	**35 (25.9)**
95% CI	23.9, 40.1	18.8, 34.2
p-value	0.142	

The ORR was numerically higher in the enzalutamide group compared with the placebo group (31.6% vs. 25.9%)

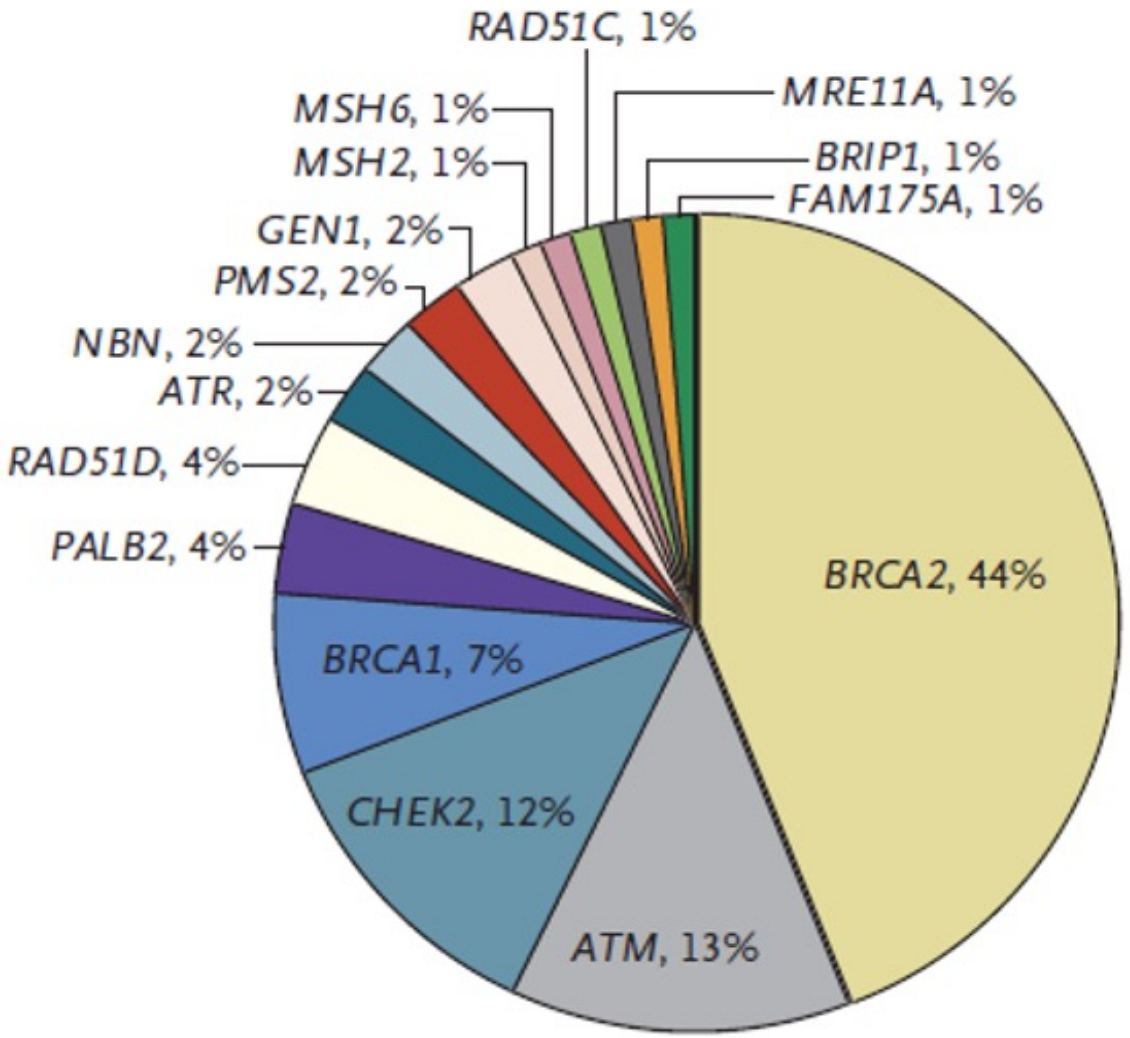
Merseburger AS et al. Genitourinary Cancers Symposium 2022;Abstract 15.

PRESIDE: Safety and Treatment Duration

Event, n (%)	Enzalutamide + docetaxel + prednisolone (n=136)	Placebo + docetaxel + prednisolone (n=135)
TEAEs	133 (97.8)	131 (97.0)
Related TEAEs	63 (46.3)	56 (41.5)
Docetaxel-related TEAEs	123 (90.4)	122 (90.4)
Serious TEAEs	67 (49.3)	52 (38.5)
Related serious TEAEs	7 (5.1)	10 (7.4)
TEAEs leading to permanent discontinuation of study drug	12 (8.8)	9 (6.7)
Deaths	13 (9.6)	7 (5.2)
Most common TEAEs ≥15%		
Asthenia	47 (34.6)	35 (25.9)
Neutropenia	46 (33.8)	45 (33.3)
Alopecia	44 (32.4)	37 (27.4)
Fatigue	40 (29.4)	28 (20.7)
Diarrhea	37 (27.2)	44 (32.6)
Anemia	28 (20.6)	16 (11.9)
Nausea	26 (19.1)	26 (19.3)
Arthralgia	25 (18.4)	10 (7.4)
Lacrimation increased	25 (18.4)	6 (4.4)
Decreased appetite	23 (16.9)	17 (12.6)
Neuropathy, peripheral	22 (16.2)	12 (8.9)
Treatment duration		
Median study drug exposure, weeks[a]	36.1	30.1
Median docetaxel exposure, weeks	19.1	19.1
Median number of docetaxel cycles	6.9	7.0

Merseburger AS et al. Genitourinary Cancers Symposium 2022;Abstract 15.

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

Recent FDA Approvals of PARP Inhibitors for mCRPC

PARP inhibitor	Approval date	Pivotal study
Olaparib	May 19, 2020	PROfound
Rucaparib	May 15, 2020	TRITON2

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

RTP RESEARCH TO PRACTICE

TRITON3 Meets Primary Endpoint for Patients with mCRPC with BRCA or ATM Mutations

Press Release: October 3, 2022

"[The manufacturer] today announced positive top-line data from the Phase 3, open-label, multicenter, randomized TRITON3 trial demonstrating that rucaparib monotherapy treatment achieved the primary endpoint of significantly improved radiographic progression-free survival (rPFS) by independent radiology review (IRR) compared with the control group, which consisted of physician's choice of docetaxel, abiraterone acetate, or enzalutamide.

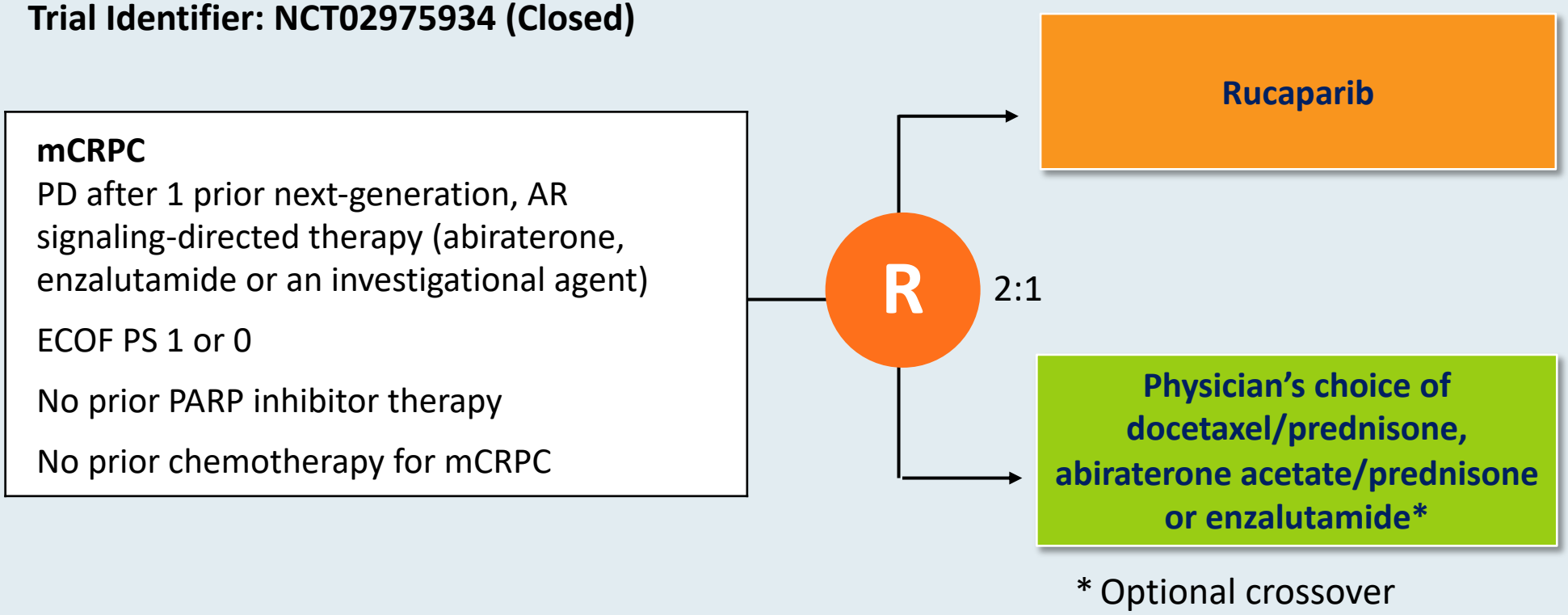
Benefit was observed in both primary efficacy analyses of patients with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC): first, those who had mutations in BRCA, as well as all patients randomized in the trial, inclusive of mutations in BRCA or ATM (the overall intent-to-treat population (ITT)). The safety profile of rucaparib observed in the TRITON3 study was consistent with rucaparib labelling."

https://www.businesswire.com/news/home/20221003005303/en

RTP RESEARCH TO PRACTICE

TRITON3: Phase III Study of Rucaparib versus Physician's Choice of Therapy for Patients with mCRPC and Homologous Recombination Gene Deficiency

Trial Identifier: NCT02975934 (Closed)



Primary endpoint: Radiographic PFS by independent radiology review
Key secondary endpoints include objective response rate and DoR by modified RECIST, OS and clinical benefit rate

Ryan CJ et al. Genitourinary Cancers Symposium 2018;Abstract TPS389; www.clinicaltrials.gov. NCT02975934. Accessed October 2022.

Phase III TALAPRO-2 Trial Meets Primary Endpoint for Patients with mCRPC with or without HRR Gene Mutations

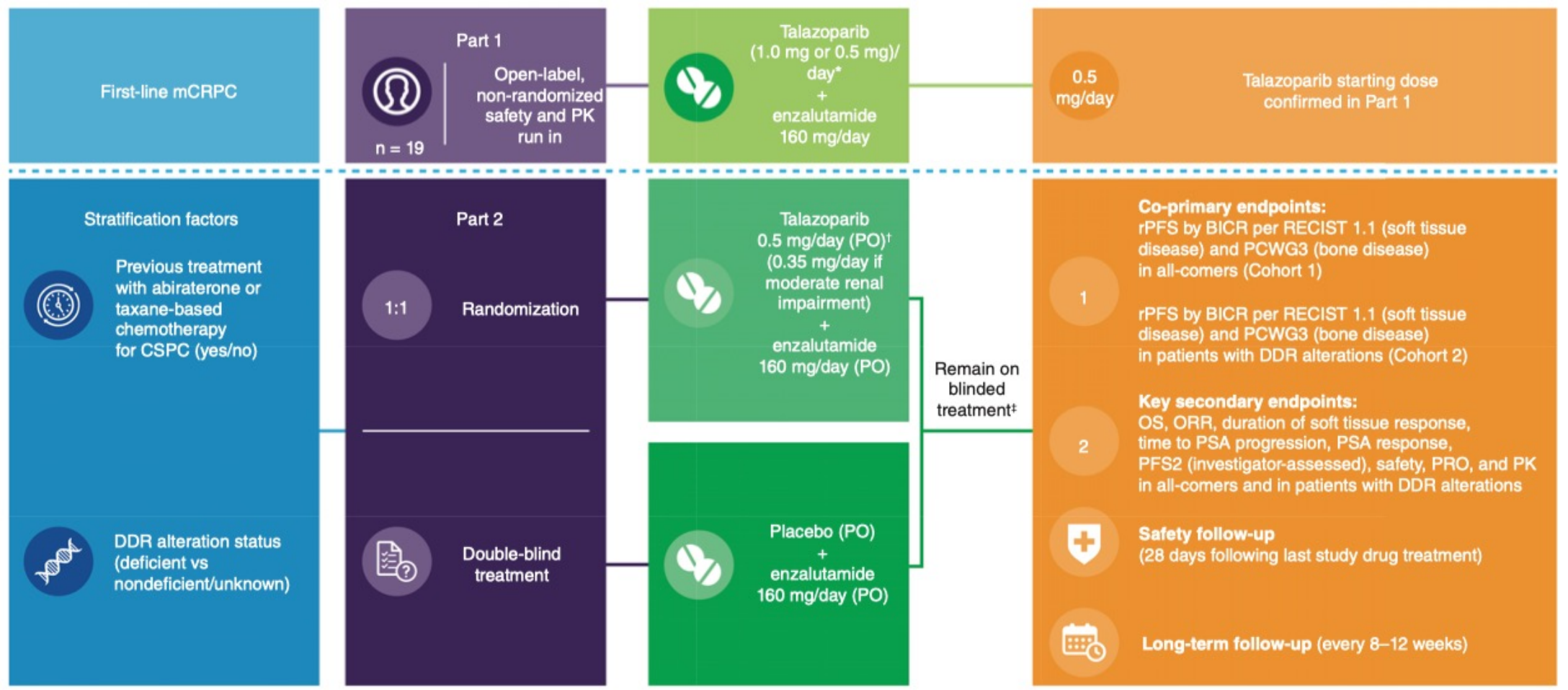
Press Release: October 4, 2022

"[The manufacturer] today announced positive topline results from the Phase 3 TALAPRO-2 study of talazoparib, an oral poly ADP-ribose polymerase (PARP) inhibitor, in combination with enzalutamide compared to placebo plus enzalutamide in men with metastatic castration-resistant prostate cancer (mCRPC), with or without homologous recombination repair (HRR) gene mutations. The study met its primary endpoint with a statistically significant and clinically meaningful improvement in radiographic progression-free survival (rPFS) compared with placebo plus enzalutamide. The results of the primary endpoint exceeded the pre-specified hazard ratio of 0.696.

Results showed a trend toward improved overall survival, a key secondary endpoint, at the time of the analysis, but these data are not yet mature. Benefits were also observed in other secondary endpoints, including investigator assessed rPFS, prostate specific antigen (PSA) response, time to PSA progression, and overall response rate. Other secondary endpoints are being analyzed. At the time of topline analysis, the safety of talazoparib plus enzalutamide were generally consistent with the known safety profile of each medicine."

https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-positive-topline-results-phase-3-talapro-2

TALAPRO-2: Phase III Trial of Talazoparib/Enzalutamide vs Placebo/Enzalutamide for 1L mHRPC ± DNA Damage Repair Mutations



Agarwal N et al. *Future Oncol* 2022;18:425.

NEJM Evidence

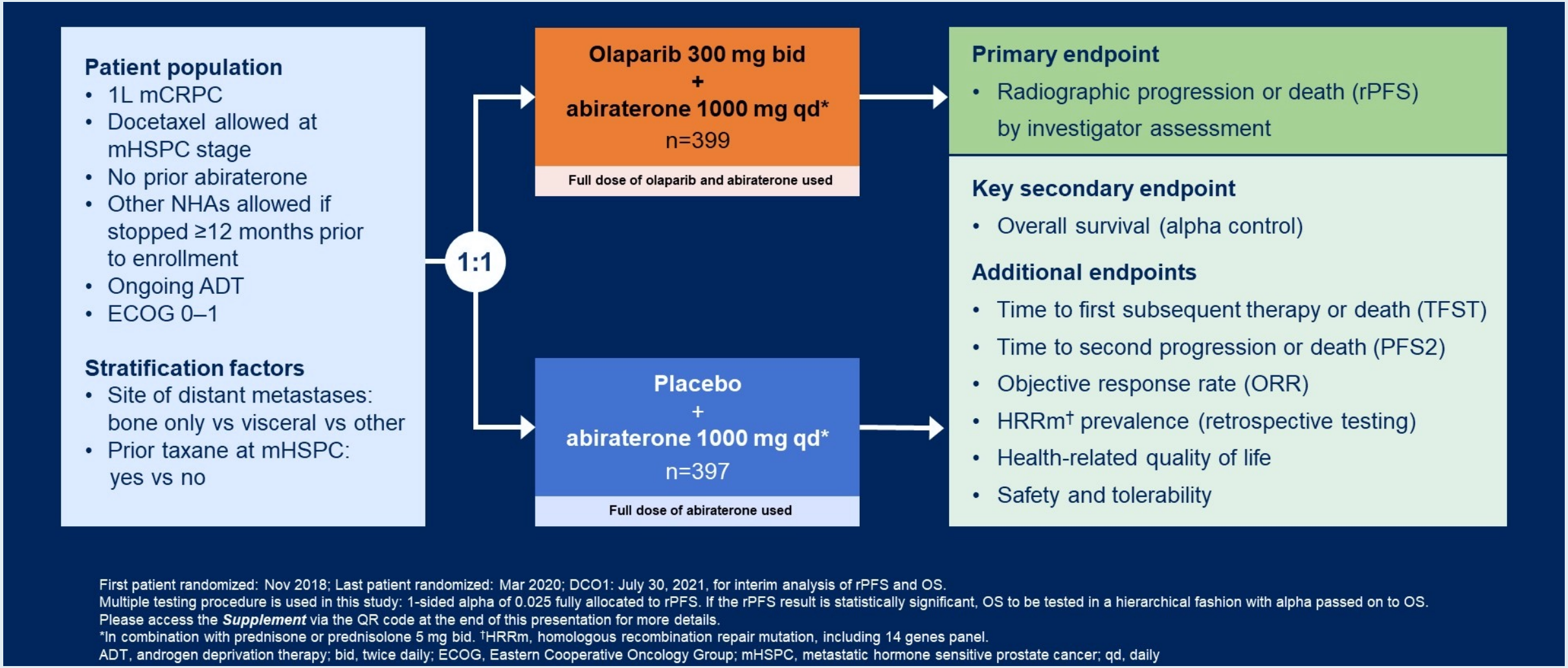
Published June 3, 2022
NEJM Evid 2022; 1 (9)
DOI: 10.1056/EVIDoa2200043

ORIGINAL ARTICLE

Abiraterone and Olaparib for Metastatic Castration-Resistant Prostate Cancer

Noel W. Clarke, M.B.B.S., Ch.M., F.R.C.S.,[1] Andrew J. Armstrong, Sc.M., M.D.,[2] Antoine Thiery-Vuillemin, M.D., Ph.D.,[3] Mototsugu Oya, M.D.,[4] Neal Shore, M.D.,[5] Eugenia Loredo, M.D.,[6] Giuseppe Procopio, M.D.,[7] Juliana de Menezes, M.D.,[8] Gustavo Girotto, M.D.,[9] Cagatay Arslan, M.D.,[10] Niven Mehra, M.D., Ph.D.,[11] Francis Parnis, F.R.A.C.P.,[12] Emma Brown, M.D.,[13] Friederike Schlürmann, M.D.,[14] Jae Y. Joung, M.D., Ph.D.,[15] Mikio Sugimoto, M.D., Ph.D.,[16] Juan A. Virizuela, M.D., Ph.D.,[17] Urban Emmenegger, M.D.,[18] Jiri Navratil, M.D.,[19] Gary L. Buchschacher, Jr., M.D., Ph.D.,[20] Christian Poehlein, M.D.,[21] Elizabeth A. Harrington, Ph.D.,[22] Chintu Desai, Ph.D.,[23] Jinyu Kang, M.D.,[24] Fred Saad, M.D., F.R.C.S.,[25] for the PROpel Investigators*

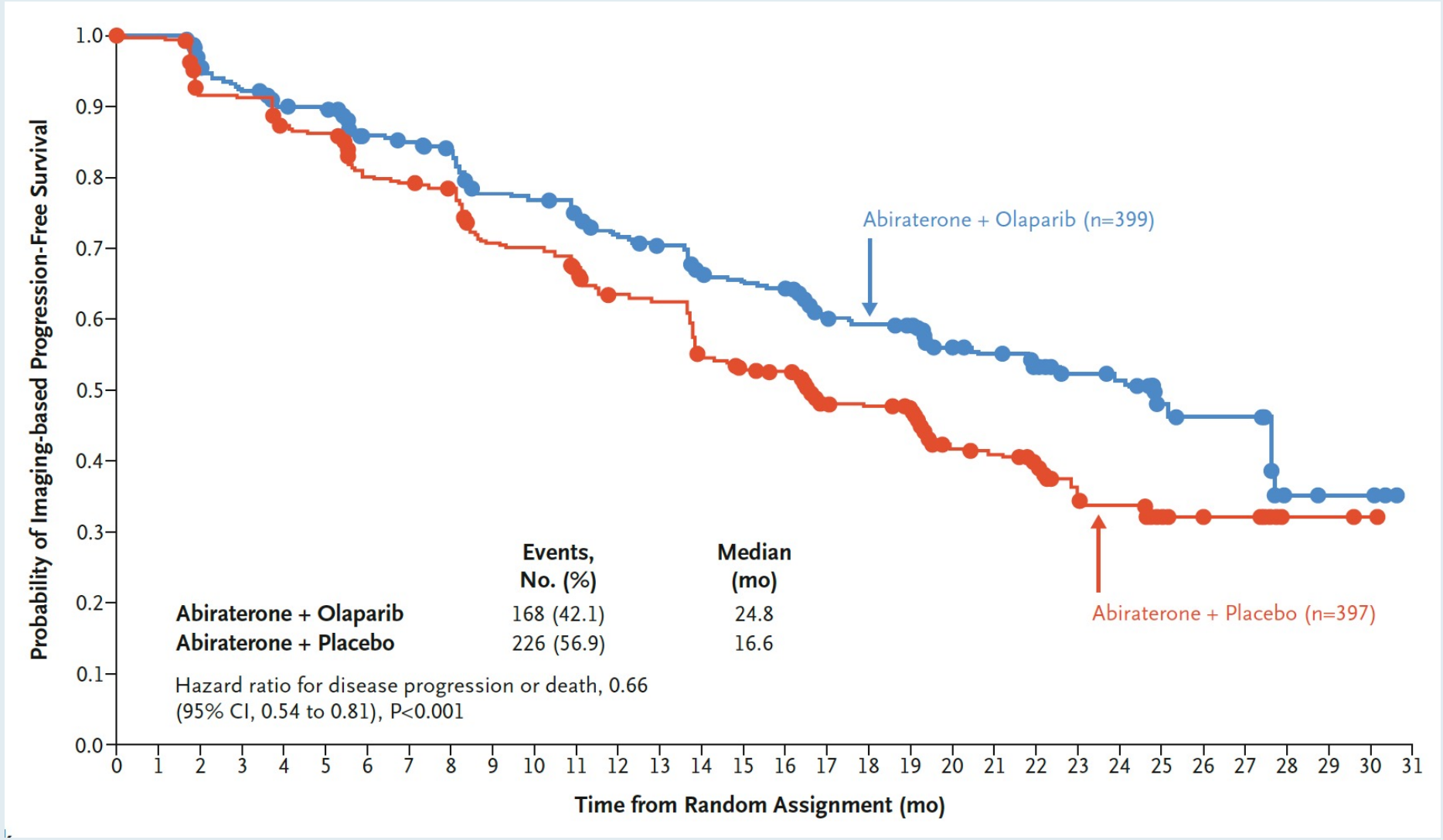
PROpel: Study Design



First patient randomized: Nov 2018; Last patient randomized: Mar 2020; DCO1: July 30, 2021, for interim analysis of rPFS and OS.
Multiple testing procedure is used in this study: 1-sided alpha of 0.025 fully allocated to rPFS. If the rPFS result is statistically significant, OS to be tested in a hierarchical fashion with alpha passed on to OS.
Please access the ***Supplement*** via the QR code at the end of this presentation for more details.
*In combination with prednisone or prednisolone 5 mg bid. †HRRm, homologous recombination repair mutation, including 14 genes panel.
ADT, androgen deprivation therapy; bid, twice daily; ECOG, Eastern Cooperative Oncology Group; mHSPC, metastatic hormone sensitive prostate cancer; qd, daily

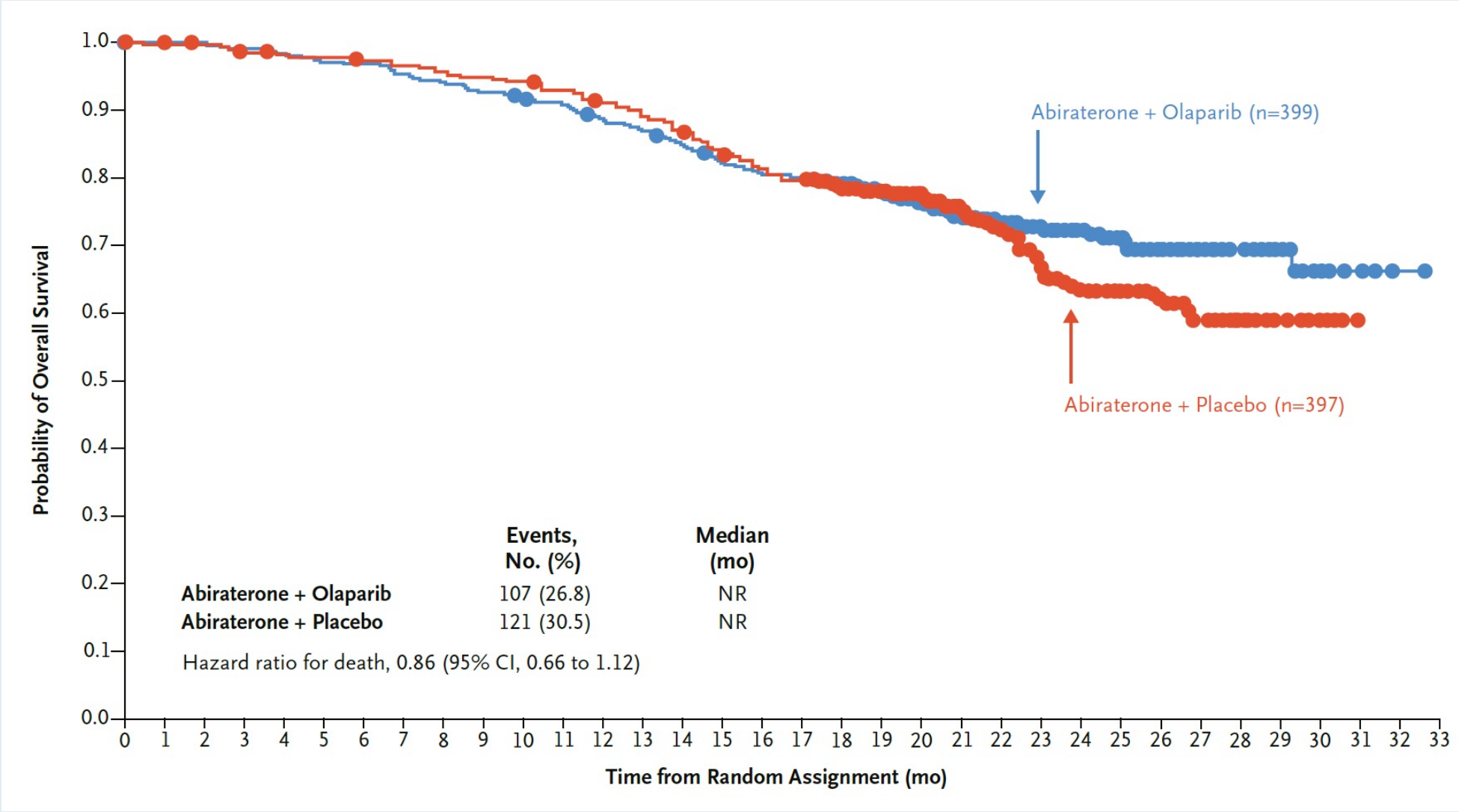
Saad F et al. Genitourinary Cancers Symposium 2022;Abstract 11.

PROpel Primary Endpoint: Imaging-Based Progression-Free Survival by Investigator Assessment



Clarke NW et al. *NEJM Evidence* 2022;1(9).

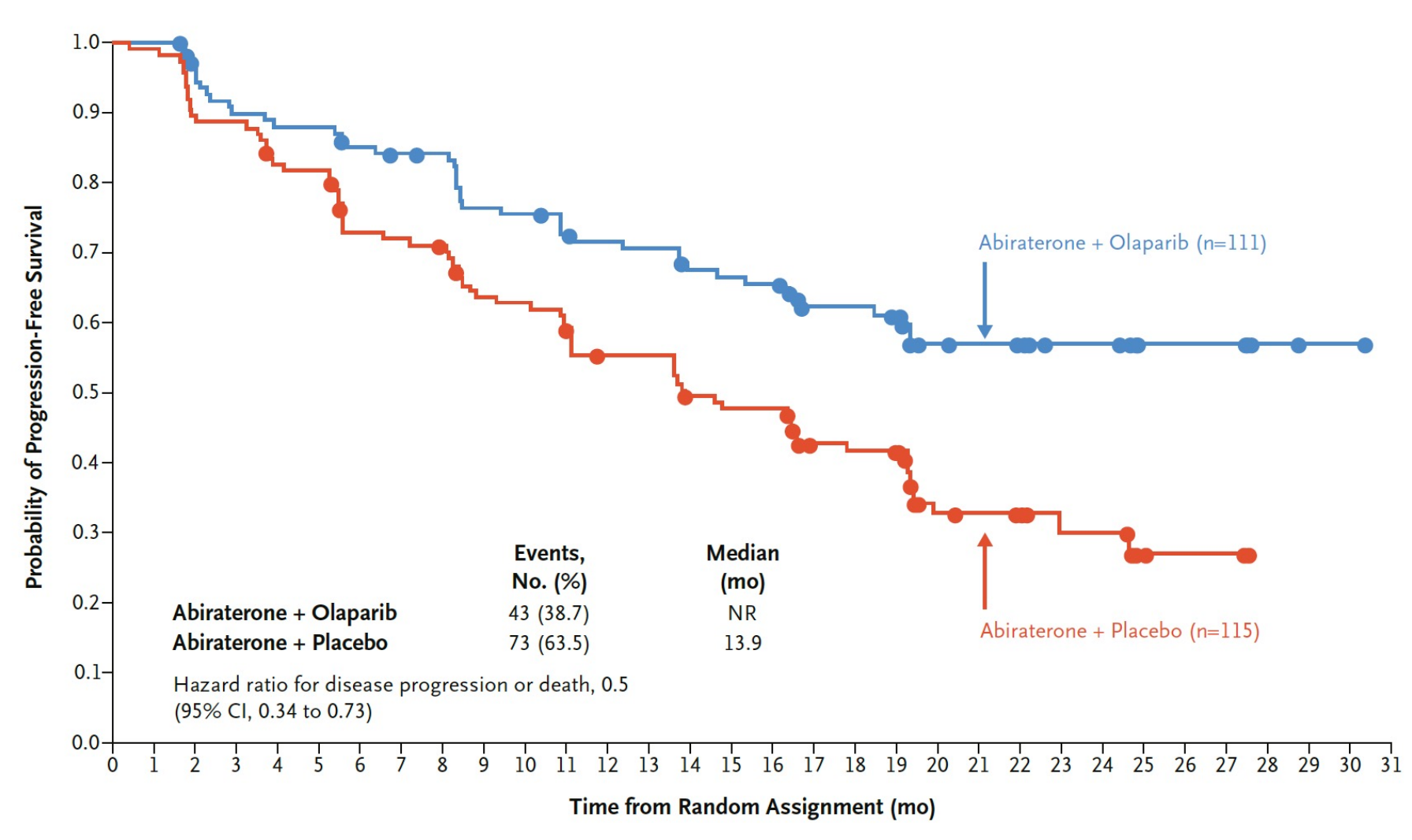
PROpel Key Secondary Endpoint: Overall Survival by Investigator Assessment



Clarke NW et al. *NEJM Evidence* 2022;1(9).

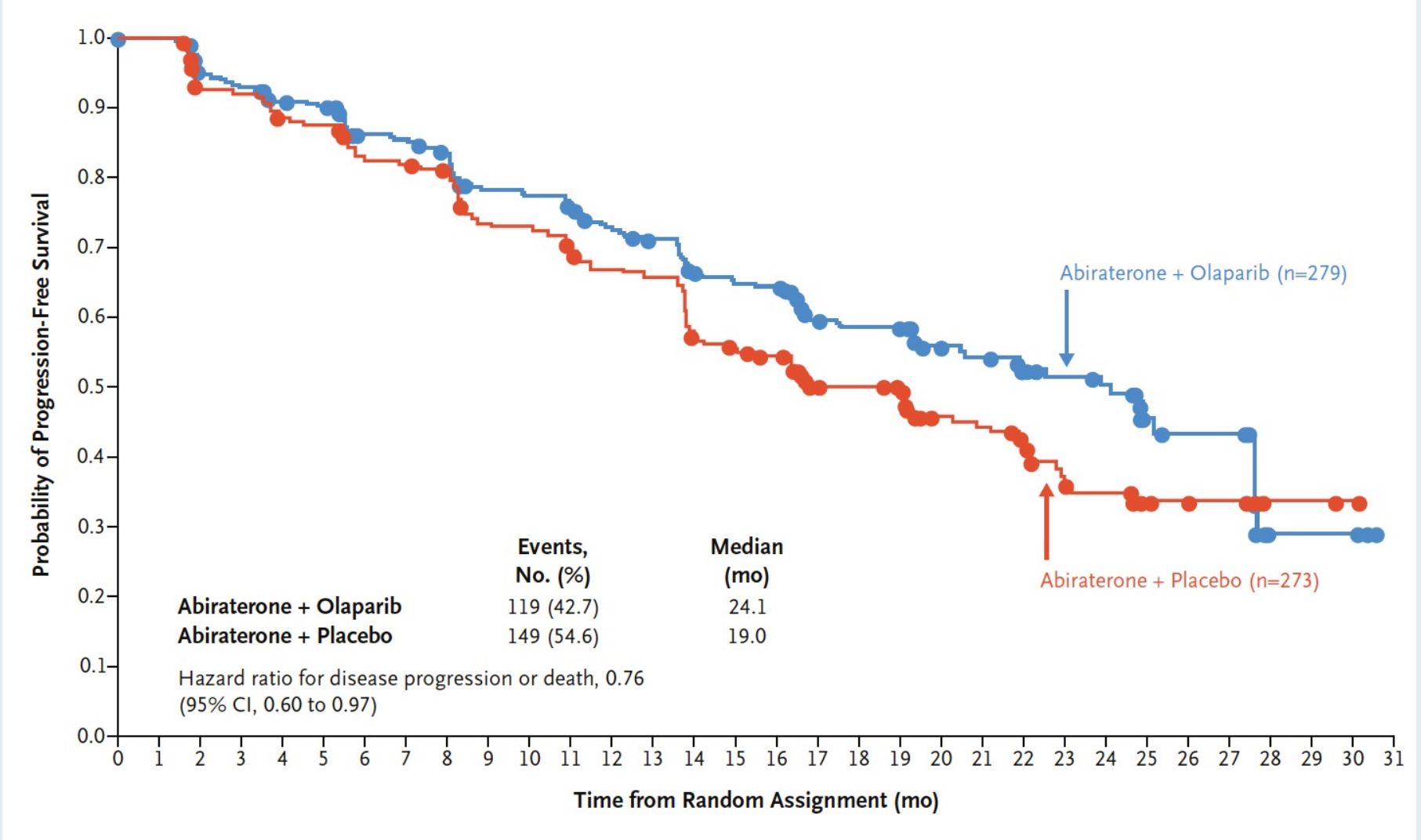
RTP RESEARCH TO PRACTICE

PROpel: Progression-Free Survival for Patients in the HRR Gene Mutation Subgroup



Clarke NW et al. *NEJM Evidence* 2022;1(9).

PROpel: Progression-Free Survival for Patients in the Non-HRR Gene Mutation Subgroup



Clarke NW et al. *NEJM Evidence* 2022;1(9).

PROpel: Safety Summary

	Abiraterone and Olaparib (n=398)		Abiraterone and Placebo (n=396)	
Adverse Event	**All Grades**	**Grade ≥3**	**All Grades**	**Grade ≥3**
Any	387 (97.2)	188 (47.2)	376 (94.9)	152 (38.4)
Any serious	135 (33.9)	NA	107 (27.0)	NA
Interruption due to adverse event				
Olaparib or placebo	178 (44.7)	NA	100 (25.3)	NA
Abiraterone	131 (32.9)	NA	87 (22.0)	NA
Dose reduction due to adverse event				
Olaparib or placebo	80 (20.1)	NA	22 (5.6)	NA
Abiraterone	10 (2.5)	NA	17 (4.3)	NA
Discontinuation due to adverse event				
Olaparib or placebo	55 (13.8)	NA	31 (7.8)	NA
Abiraterone	34 (8.5)	NA	35 (8.8)	NA
Death due to adverse event	16 (4.0)	NA	17 (4.3)	NA

Clarke NW et al. *NEJM Evidence* 2022;1(9).

RTP RESEARCH TO PRACTICE

PROpel: Treatment-Emergent Adverse Events

Adverse Event	Abiraterone and Olaparib (n=398)		Abiraterone and Placebo (n=396)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Anemia†	183 (46.0)	60 (15.1)	65 (16.4)	13 (3.3)
Fatigue or asthenia	148 (37.2)	9 (2.3)	112 (28.3)	6 (1.5)
Nausea	112 (28.1)	1 (0.3)	50 (12.6)	1 (0.3)
Diarrhea	69 (17.3)	3 (0.8)	37 (9.3)	1 (0.3)
Constipation	69 (17.3)	0	55 (13.9)	1 (0.3)
Back pain	68 (17.1)	3 (0.8)	73 (18.4)	4 (1.0)
Decreased appetite	58 (14.6)	4 (1.0)	23 (5.8)	0
Vomiting	52 (13.1)	4 (1.0)	36 (9.1)	1 (0.3)
Arthralgia	51 (12.8)	0	70 (17.7)	2 (0.5)
Hypertension	50 (12.6)	14 (3.5)	65 (16.4)	13 (3.3)
Dizziness	43 (10.8)	0	25 (6.3)	0
Peripheral edema	41 (10.3)	0	45 (11.4)	1 (0.3)
Urinary tract infection	41 (10.3)	8 (2.0)	31 (7.8)	4 (1.0)
Other				
Cardiac failure‡	6 (1.5)	4 (1.0)	5 (1.3)	1 (0.3)
Embolic and thrombotic events				
Arterial‡	8 (2.0)	6 (1.5)	10 (2.5)	8 (2.0)
Venous‡	29 (7.3)	27 (6.8)	13 (3.3)	8 (2.0)

Clarke NW et al. *NEJM Evidence* 2022;1(9).

ASCO Genitourinary Cancers Symposium

Abstract 12

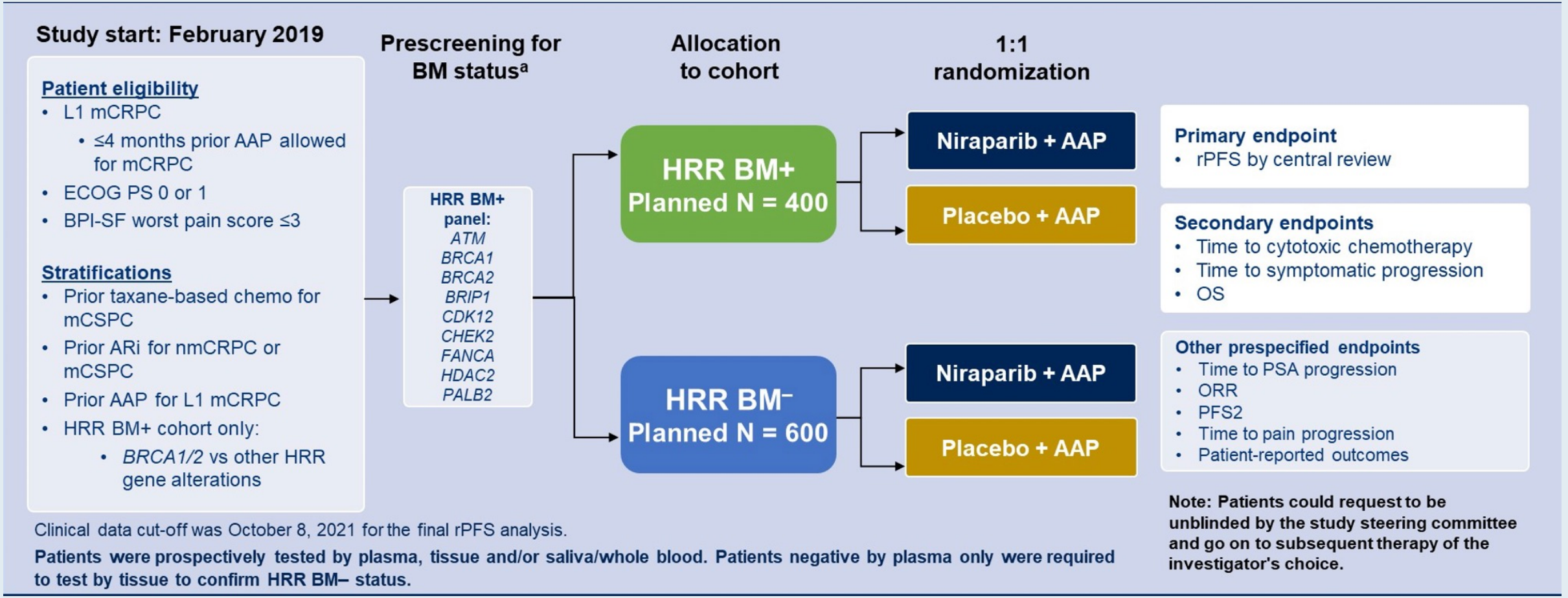
Phase 3 MAGNITUDE study: First results of niraparib (NIRA) with abiraterone acetate and prednisone (AAP) as first-line therapy in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) with and without homologous recombination repair (HRR) gene alterations

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

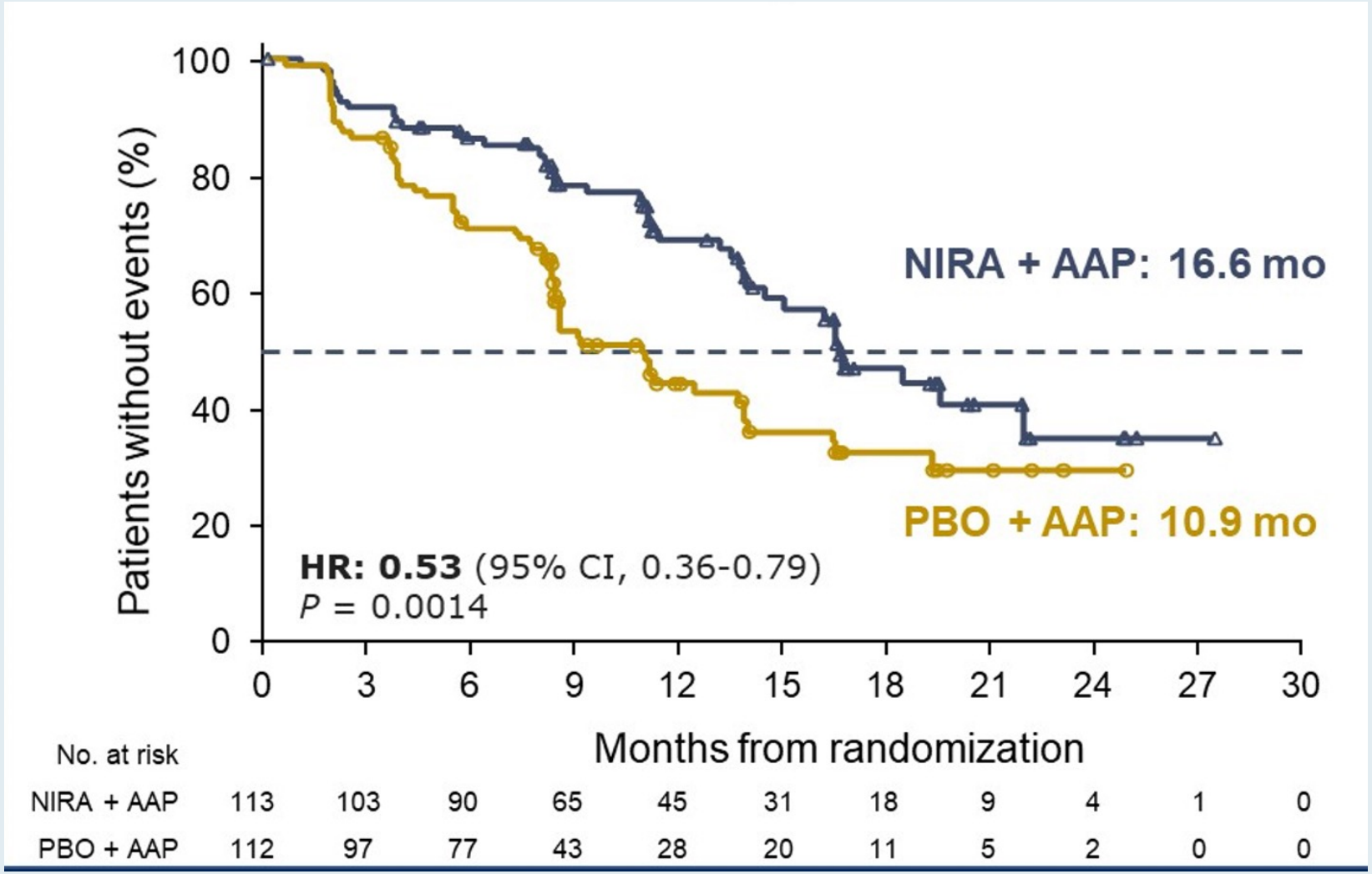
Prospectively selected biomarker cohorts designed to test HRR BM+ and HRR BM-



BM = biomarker

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

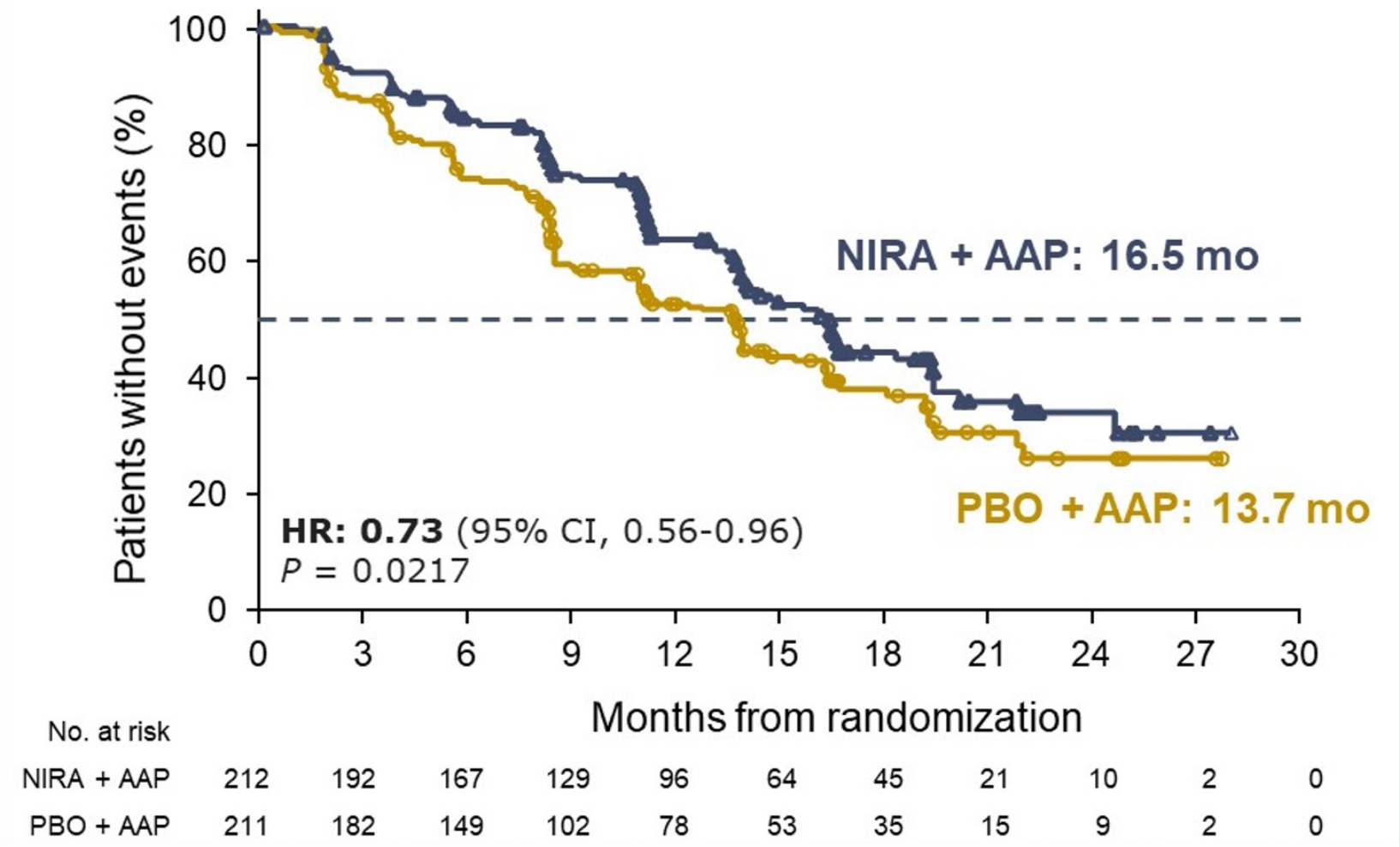
MAGNITUDE BRCA1/2 Mutation Primary Endpoint: Radiographic PFS by Central Review (Median Follow-Up 16.7 Mo)



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

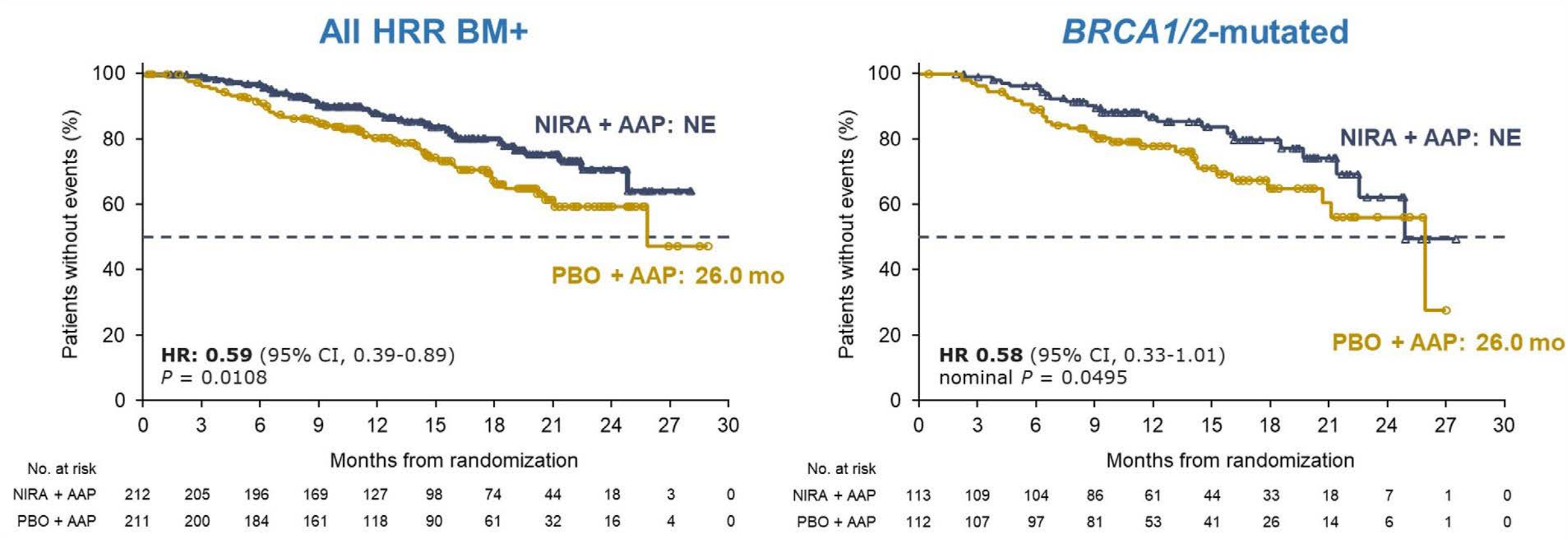
RTP RESEARCH TO PRACTICE

MAGNITUDE All HRR Biomarker-Positive Primary Endpoint: rPFS by Central Review



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

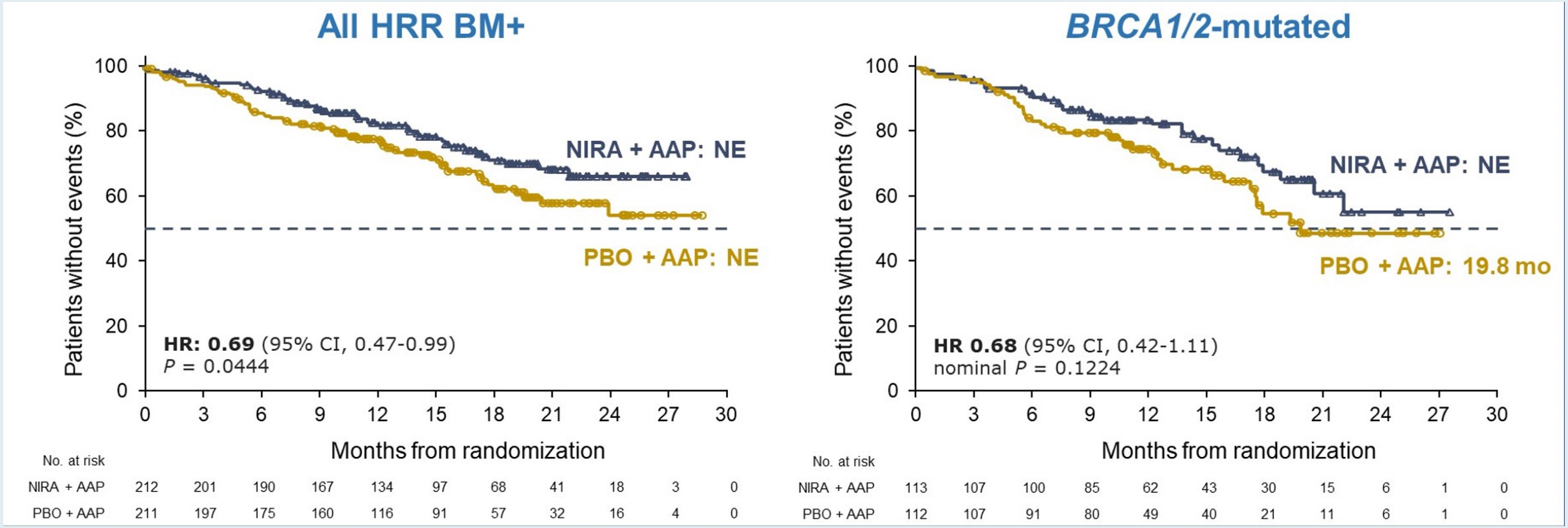
MAGNITUDE Secondary Endpoint: Time to Cytotoxic Chemotherapy Across Gene Alterations



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

RTP RESEARCH TO PRACTICE

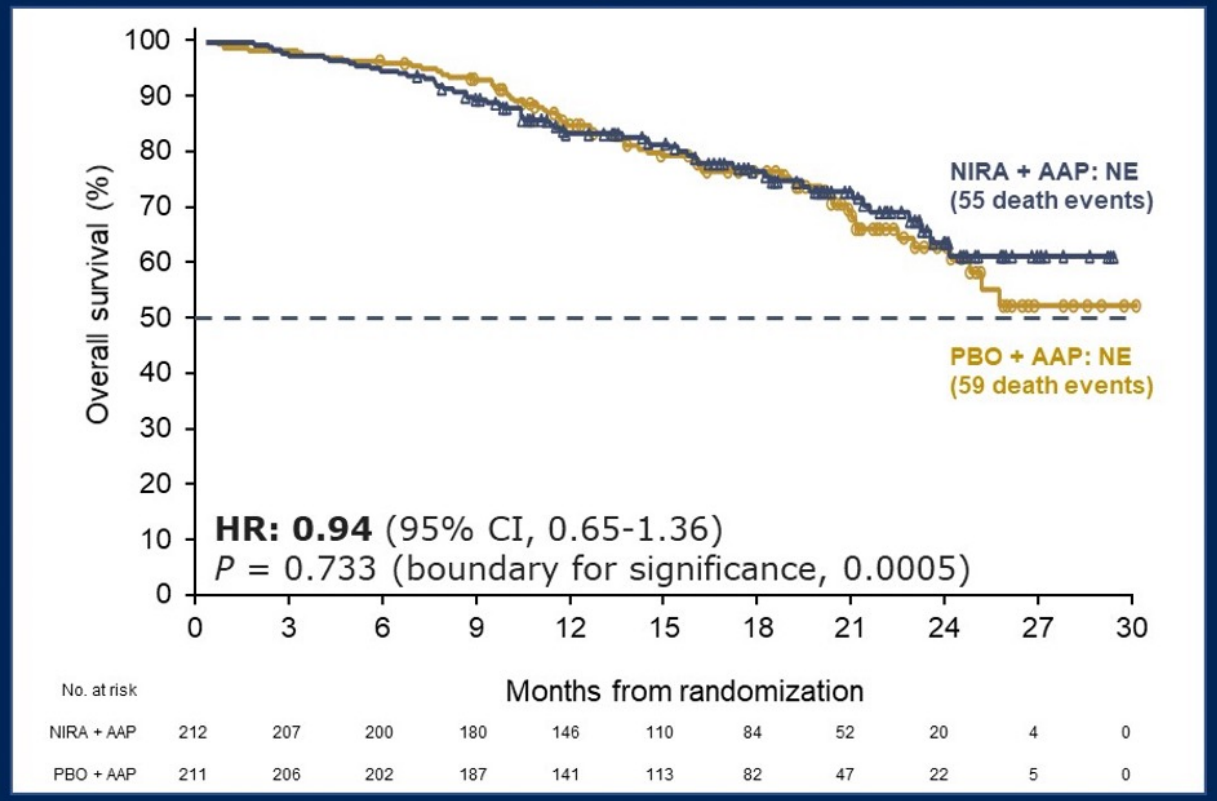
MAGNITUDE Secondary Endpoint: Time to Symptomatic Progression Across Gene Alterations



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

MAGNITUDE All HRR Biomarker-Positive: Overall Survival

First Interim Analysis (Median Follow-Up 18.6 Mo)



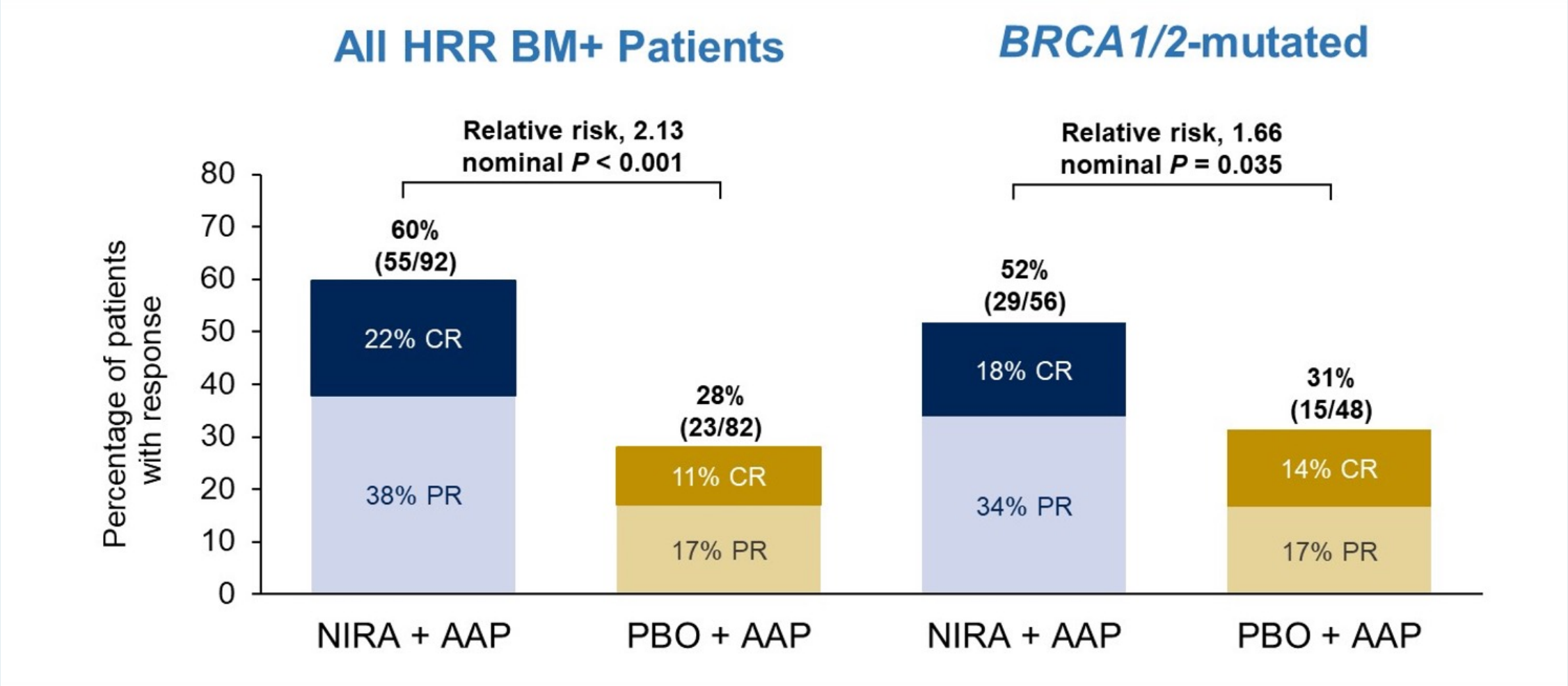
27% of deaths in the study population observed at overall survival interim analysis and thus these data are immature

Pre-specified Overall Survival Multivariate Analysis

- A multivariate analysis accounting for baseline characteristics shows overall survival favors the NIRA + AAP arm
- Overall survival **HR = 0.767** (95% CI, 0.525-1.119; nominal *P* = 0.1682)

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

MAGNITUDE: Overall Response Rates Across Gene Alterations



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

RTP RESEARCH TO PRACTICE

MAGNITUDE HRR Biomarker-Positive: Summary of Treatment-Emergent Adverse Events (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 NIRA + AAP group were anemia (13.2%) and thrombocytopenia (2.8%)
- Median relative dose intensity was 99% in the NIRA + AAP group

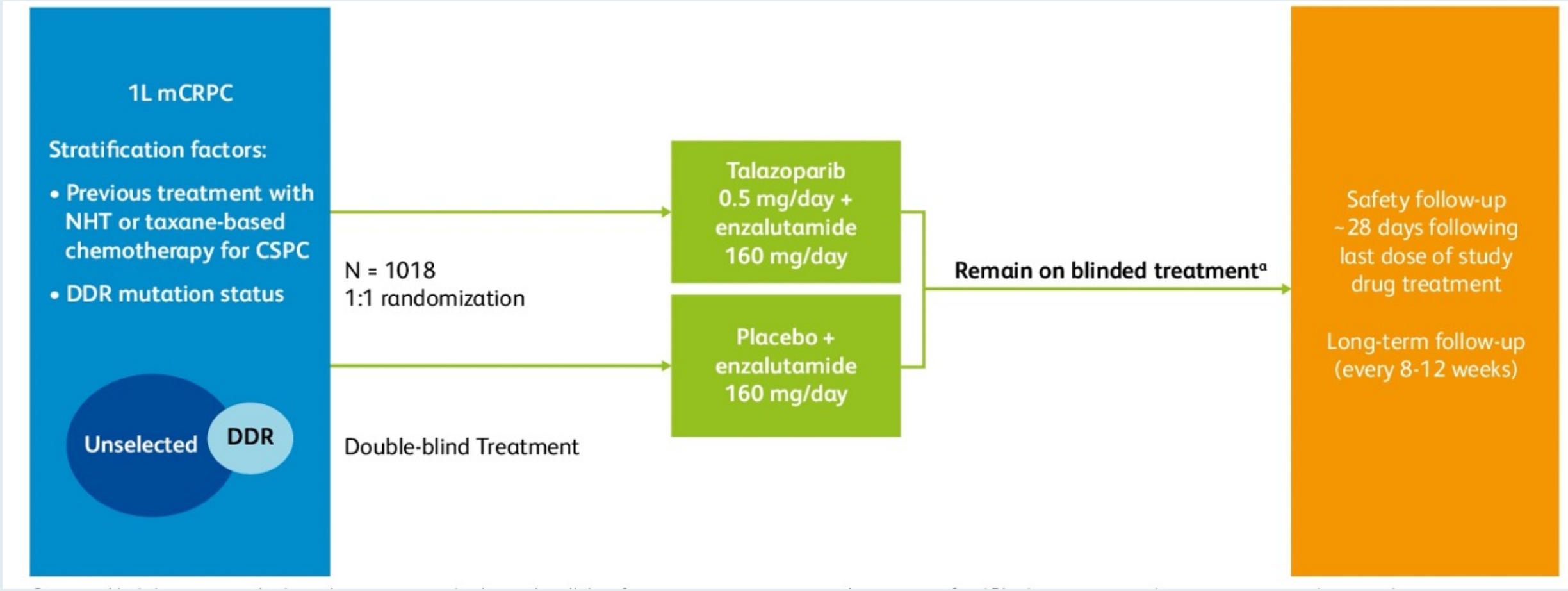
Chi KN et al. Genitourinary Cancers Symposium 2022;Abstract 12.

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]

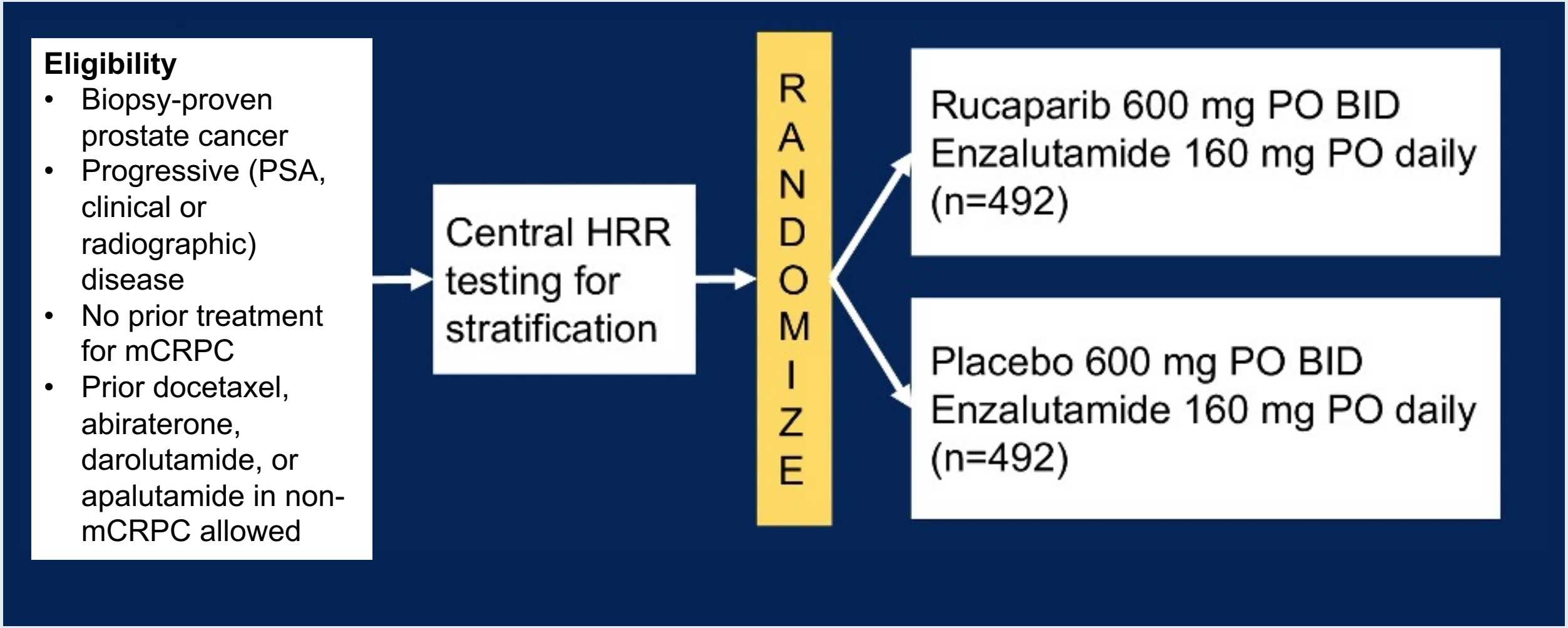
Chi KN et al. Genitourinary Cancers Symposium 2022;Abstract 12.

TALAPRO-2 Phase III Study Design



Agarwal N et al. ASCO 2022;Abstract TPS5598.

Alliance A031902 (CASPAR) Phase III Study Design

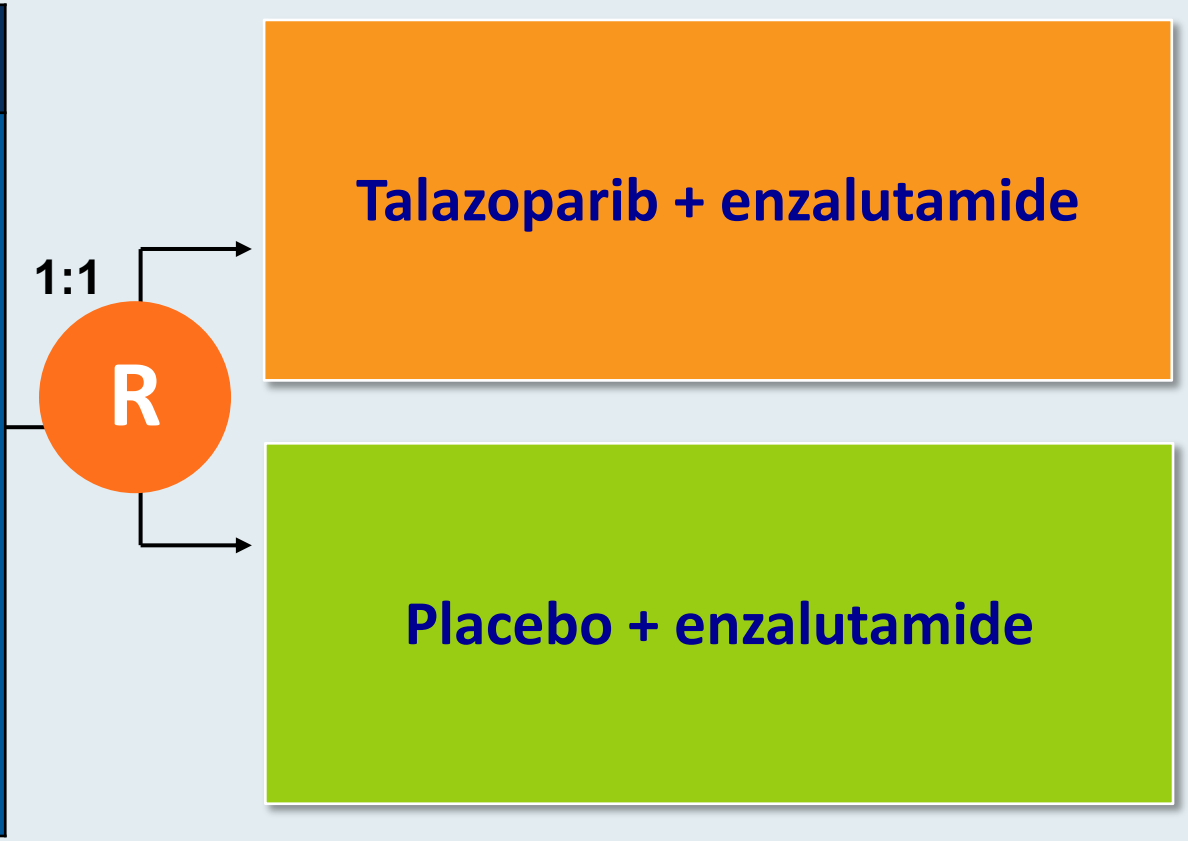


Rao A et al. ASCO 2022;Abstract TPS5107.

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 in mHSPC, if required prior to randomization, with no radiographic evidence of disease progression or rising PSA prior to Day 1

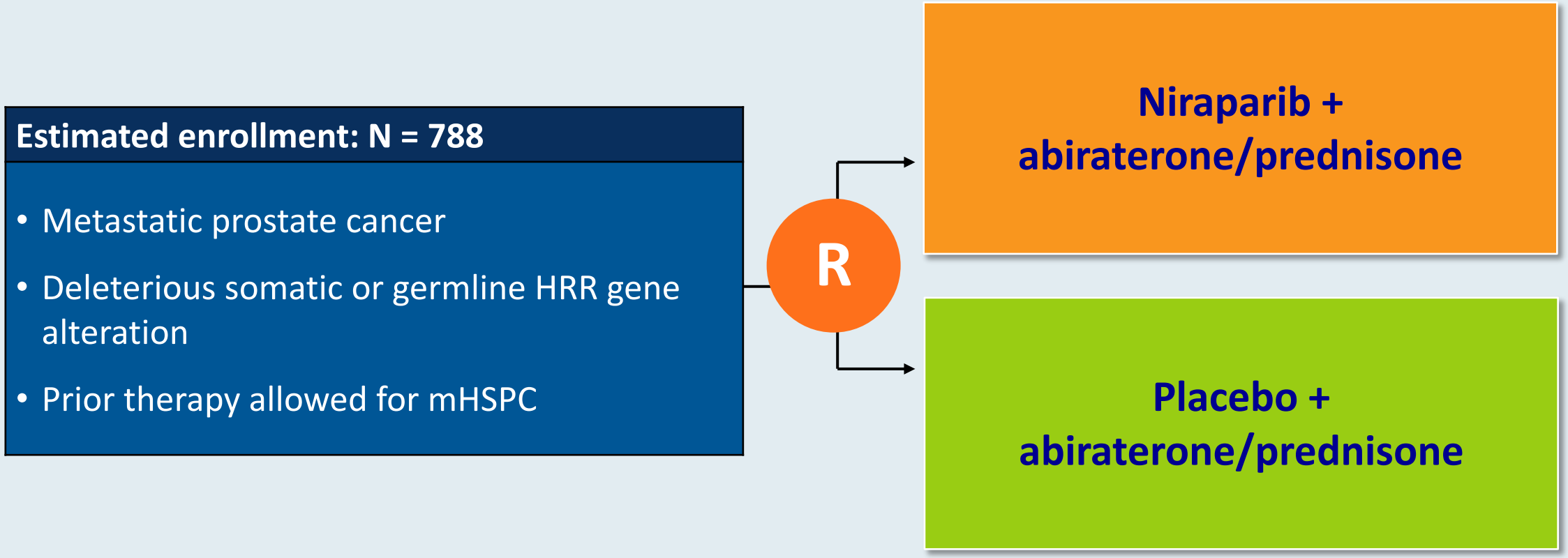


Primary endpoint: rPFS by investigator assessment

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.

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

Side Effects Associated with Hormonal Therapy for Prostate Cancer

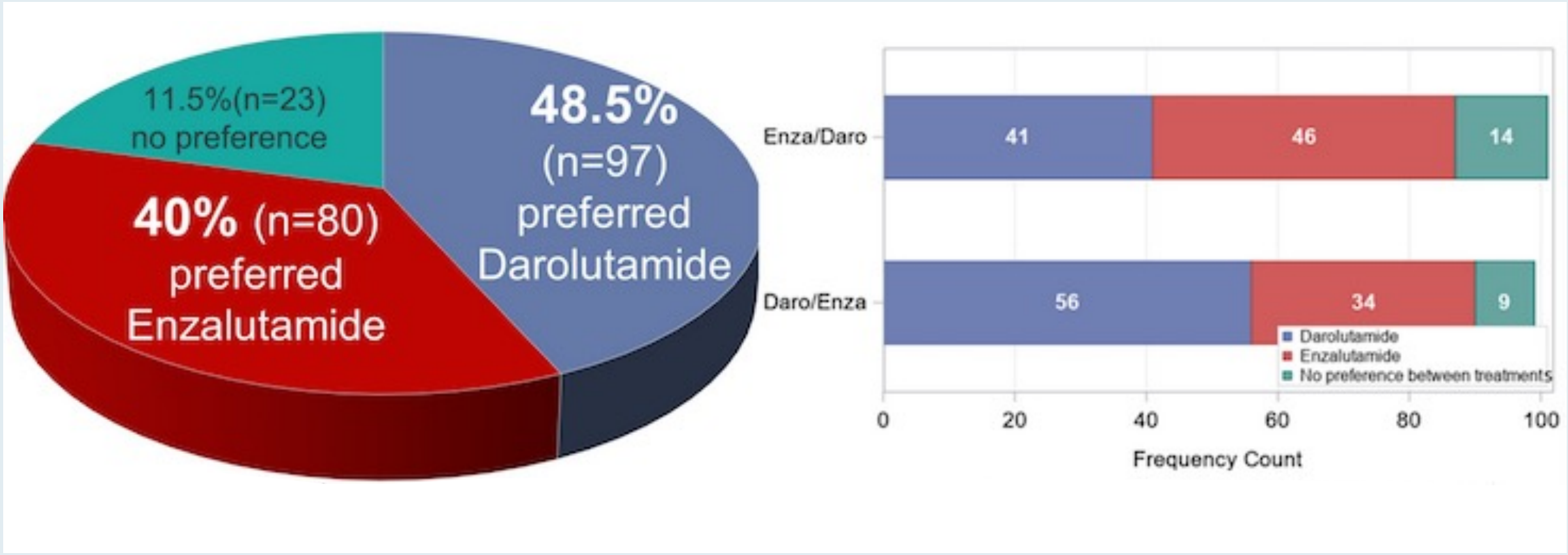
RTP
RESEARCH
TO PRACTICE

ODENZA, A Prospective Randomized, Open-Label, Multicenter, Cross-Over Phase II Trial of Preference Between Darolutamide and Enzalutamide in Men with Asymptomatic or Mildly Symptomatic Metastatic Castrate-Resistant Prostate Cancer (CRPC)

Colomba E et al.

ASCO 2021;Abstract 5046.

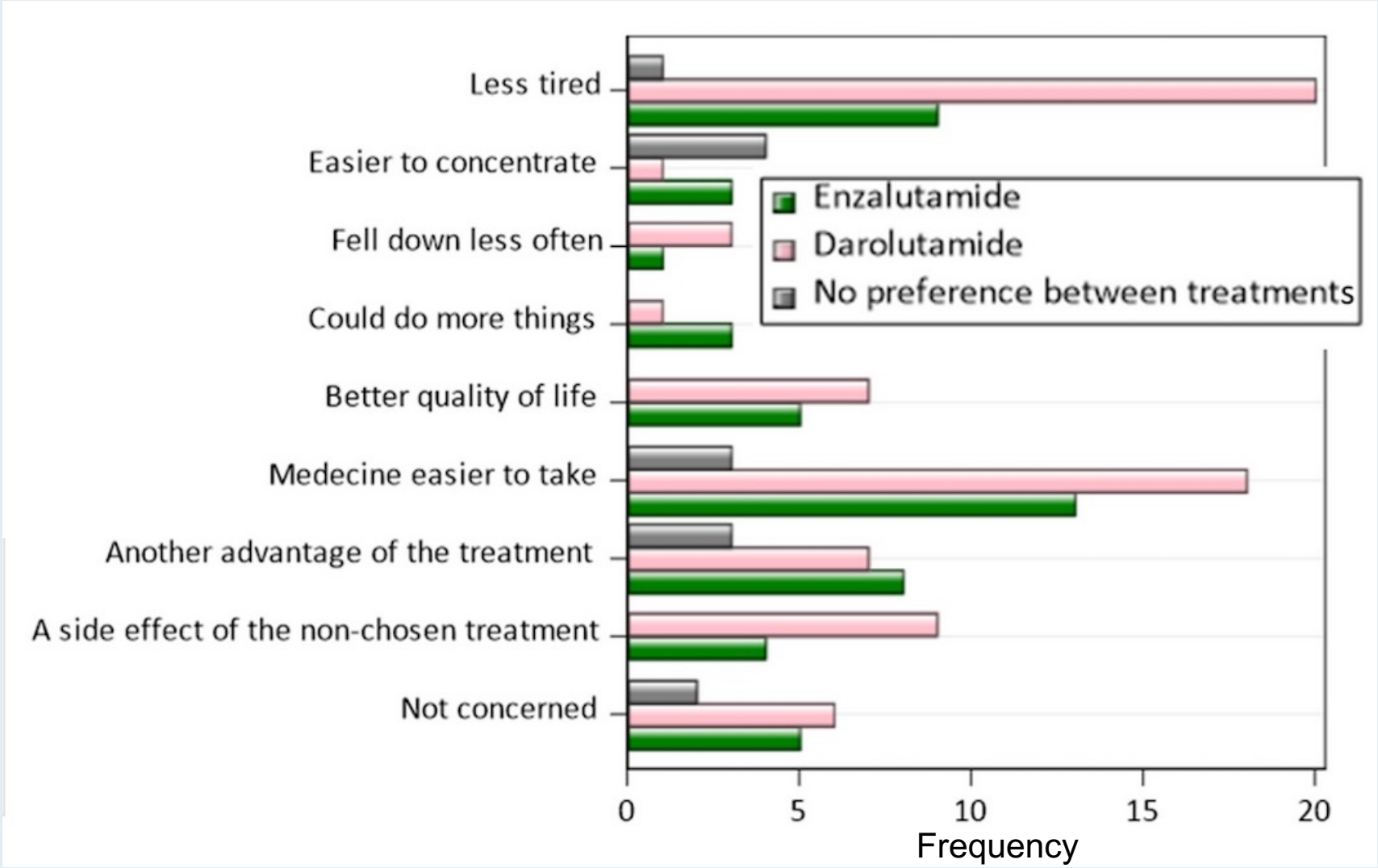
ODENZA Primary Endpoint: Patient Preference



Colomba E et al. ASCO 2021;Abstract 5046.

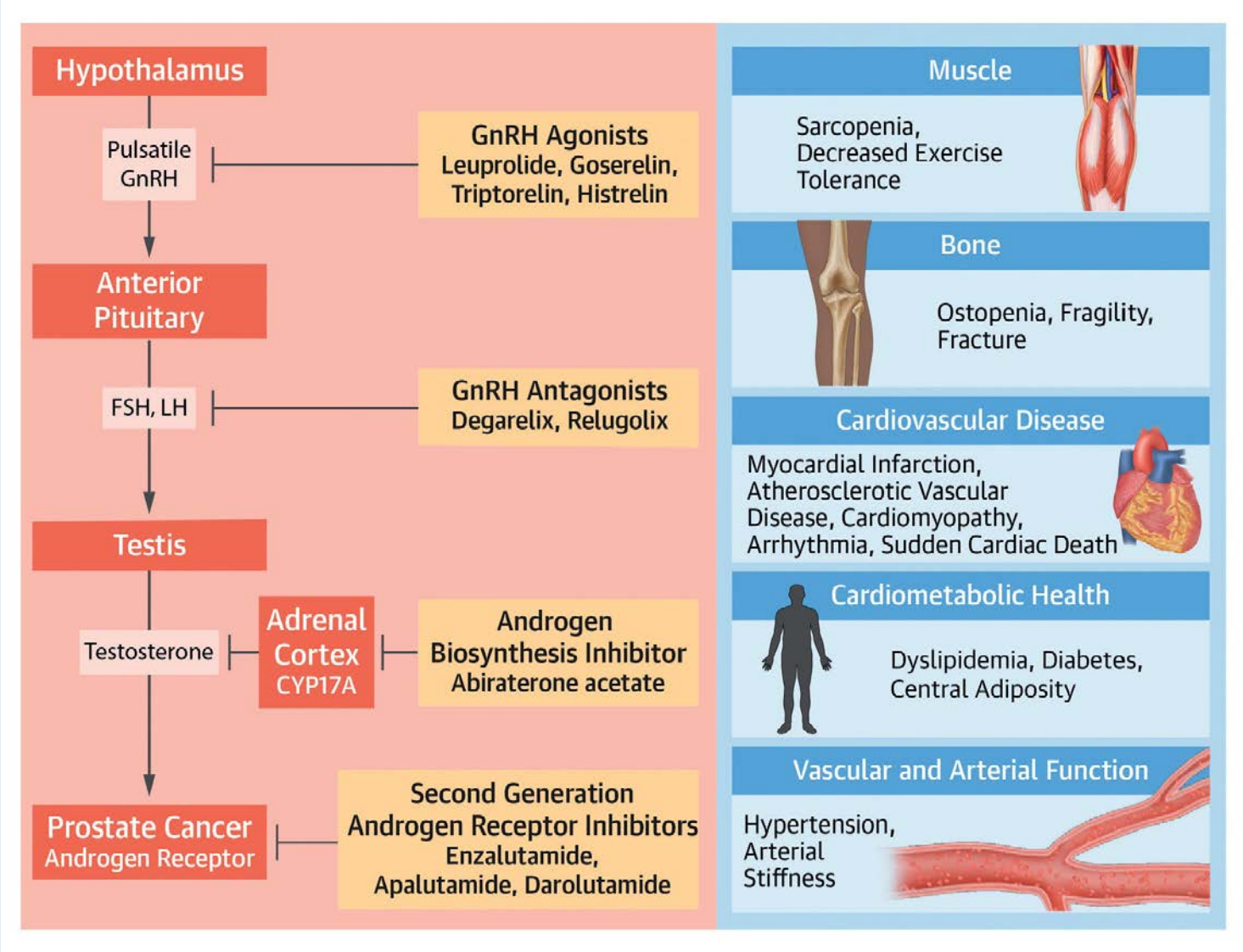
RTP RESEARCH TO PRACTICE

ODENZA: Main Reasons for Patient Preference Between Treatments



Colomba E et al. ASCO 2021;Abstract 5046.

Cardiometabolic Effects of Androgen Suppression Therapies for Prostate Cancer



Narayan V et al. *JACC CardioOncol* 2021;3(5):737-41.

Cardiovascular-Associated Adverse Events in Phase III Trials of Androgen Receptor Inhibitors

Study	Agent	CV-related AE	Androgen receptor inhibitor		Placebo	
			All grades	Grade ≥3	All grades	Grade ≥3
PROSPER[1] N = 1,401	Enzalutamide	Hypertension MACE	12% 5%	5% 4%	5% 3%	2% 2%
SPARTAN[2] N = 1,207	Apalutamide	Hypertension	25%	14%	20%	12%
ARAMIS[3] N = 1,509	Darolutamide	Hypertension CAD Heart failure Cerebral ischemia	7% 3% 2% 1.4%	3% 2% 1% 0.7%	5% 3% 1% 1.4%	2% 0 0 0.7%

AEs = adverse events; MACE = major adverse cardiovascular event

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

BCMA-Directed Therapy in Multiple Myeloma — Expert Opinions and Patient Perspectives

Part 1 of a 2-Part CME/MOC-Accredited Virtual Series

Wednesday, October 26, 2022
5:00 PM – 6:00 PM ET

Faculty

Elizabeth O'Donnell, MD

Moderator

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Thank you for joining us!

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

RTP
RESEARCH
TO PRACTICE