Second Opinion: Investigators Discuss How They and Their Colleagues Apply Available Clinical Research in the Care of Patients with Prostate Cancer

A CME Symposium Held in Conjunction with the 2023 ASCO® Annual Meeting

Saturday, June 3, 2023

7:00 PM – 9:00 PM CT

Faculty

Emmanuel S Antonarakis, MD

Prof Karim Fizazi, MD, PhD

Rana R McKay, MD

Alicia K Morgans, MD, MPH

A Oliver Sartor, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Faculty

Emmanuel S Antonarakis, MD
Clark Endowed Professor of Medicine
Division of Hematology, Oncology and Transplantation
University of Minnesota
Minneapolis, Minnesota

Alicia K Morgans, MD, MPH
Associate Professor of Medicine
Harvard Medical School
Medical Director, Survivorship Program
Dana-Farber Cancer Institute
Boston, Massachusetts

Prof Karim Fizazi, MD, PhD
Head of Service and Full Professor
Institut Gustave Roussy
University of Paris Saclay
Villejuif, France

A Oliver Sartor, MD
Director of Radiopharmaceutical Clinical Trials
Professor, Department of Oncology
Mayo Clinic in Rochester, Minnesota
Rochester, Minnesota

Rana R McKay, MD
Associate Professor of Medicine and Urology
Associate Director, Translational Sciences
Co-Lead, Genitourinary Oncology Program
University of California San Diego
Moores Cancer Center
La Jolla, California

Moderator
Neil Love, MD
Research To Practice
Miami, Florida

RTP
RESEARCH
TO PRACTICE

Dr Antonarakis — Disclosures

Advisory Committee	Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Janssen Biotech Inc, Merck, Sanofi, Tempus
Consulting Agreements	Aadi Bioscience, AIkido Pharma Inc, Blue Earth Diagnostics, CM Propel, Corcept Therapeutics, EcoR1 Capital LLC, Foundation Medicine, HOOKIPA Pharma Inc, KeyQuest Health, MacroGenics Inc, Menarini Silicon Biosystems, z-Alpha
Contracted Research	Astellas, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Constellation Pharmaceuticals, Merck, Orion Corporation, Sanofi
Patent Holder	QIAGEN
Nonrelevant Financial Relationship	European Association of Urology (UROwebinar), Ismar Healthcare NV

Prof Fizazi — Disclosures

Advisory Committee	Arvinas, CureVac, Orion Corporation
Data and Safety Monitoring Board/Committee	Lilly
Consulting Agreements (with My Institution)	Advanced Accelerator Applications, Amgen Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Clovis Oncology, Daiichi Sankyo Inc, Janssen Biotech Inc, Merck Sharp & Dohme LLC, Novartis, Pfizer Inc, Sanofi

Dr McKay — Disclosures

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Bristol Myers Squibb, Caris Life Sciences, Dendreon Pharmaceuticals Inc, Exelixis Inc, Johnson & Johnson Pharmaceuticals, Lilly, Merck, Myovant Sciences, Novartis, Pfizer Inc, Sanofi, Seagen Inc, Sorrento Therapeutics, Telix Pharmaceuticals Limited, Tempus
Contracted Research	AstraZeneca Pharmaceuticals LP, Exelixis Inc, Oncternal Therapeutics, Tempus

RTP
RESEARCH
TO PRACTICE

Dr Morgans — Disclosures

Consulting Agreements	Advanced Accelerator Applications, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Exelixis Inc, Foundation Medicine, Janssen Biotech Inc, Lantheus, Merck, Myovant Sciences, Novartis, Pfizer Inc, Sanofi, Telix Pharmaceuticals Limited
Contracted Research	Bayer HealthCare Pharmaceuticals, Myovant Sciences, Pfizer Inc
Data and Safety Monitoring Board/Committee	Gilead Sciences Inc

RTP
RESEARCH
TO PRACTICE

Dr Sartor — Disclosures

Consultant	Advanced Accelerator Applications, Amgen Inc, ARTbio, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Blue Earth Diagnostics, Clarity Pharmaceuticals, Clovis Oncology, Constellation Pharmaceuticals, Convergent Therapeutics Inc, Dendreon Pharmaceuticals Inc, EMD Serono Inc, Foundation Medicine, Fusion Pharmaceuticals, Genzyme Corporation, Hengrui Therapeutics Inc, ITM Isotopen Technologien München AG, Janssen Biotech Inc, Merck, Morphimmune, Myovant Sciences, Myriad Genetic Laboratories Inc, Noria Therapeutics Inc, NorthStar Rx LLC, Novartis, Noxopharm, Pfizer Inc, POINT Biopharma, Progenics Pharmaceuticals Inc, Ratio Therapeutics, Sanofi, Telix Pharmaceuticals Limited, TeneoBio, Tessa Therapeutics, Theragnostics, z-Alpha
Equity Interests	Telix Pharmaceuticals Limited
Grant/Research Support	Advanced Accelerator Applications, Amgen Inc, Arvinas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Constellation Pharmaceuticals, Invitae, Janssen Biotech Inc, Lantheus, Merck, Novartis, Progenics Pharmaceuticals Inc, TeneoBio
Nonrelevant Financial Relationship	Ratio Therapeutics

RTP RESEARCH TO PRACTICE

Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Lilly, Merck, and Sanofi.

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.

Friday June 2	**Gastroesophageal Cancers** 11:45 AM – 12:45 PM CT (12:45 PM – 1:45 PM ET)
	Non-Small Cell Lung Cancer 6:30 PM – 9:00 PM CT (7:30 PM – 10:00 PM ET)
Saturday June 3	**Hepatobiliary Cancers** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Prostate Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Sunday June 4	**Ovarian Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Lymphoma, Chronic Lymphocytic Leukemia and Multiple Myeloma 7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)
Monday June 5	**Urothelial Bladder Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Breast Cancer 7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)
Tuesday June 6	**Renal Cell Carcinoma (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

RTP
RESEARCH TO PRACTICE

Exciting CME Events in Chicago You Do Not Want to Miss

A CME Hybrid Symposium Series Held in Conjunction with the 2023 ASCO® Annual Meeting

Ovarian Cancer

Sunday, June 4, 2023
6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty
Philipp Harter, MD, PhD
David M O'Malley, MD
Shannon N Westin, MD, MPH

Urothelial Bladder Cancer

Monday, June 5, 2023
6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty
Matthew D Galsky, MD
Andrea Necchi, MD
Scott T Tagawa, MD, MS

Lymphoma, Chronic Lymphocytic Leukemia and Multiple Myeloma

Sunday, June 4, 2023
7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)

Faculty
John N Allan, MD
Shaji K Kumar, MD
Ann S LaCasce, MD, MMSc
Sagar Lonial, MD
Loretta J Nastoupil, MD
Susan O'Brien, MD

Breast Cancer

Monday, June 5, 2023
7:00 PM – 9:30 PM CT (8:00 PM – 10:30 PM ET)

Faculty
Komal Jhaveri, MD
Kevin Kalinsky, MD, MS
Ian E Krop, MD, PhD
Joyce O'Shaughnessy, MD
Hope S Rugo, MD
Professor Peter Schmid, FRCP, MD, PhD

Exciting CME Events in Chicago You Do Not Want to Miss

A CME Hybrid Symposium Series Held in Conjunction with the 2023 ASCO® Annual Meeting

Renal Cell Carcinoma Webinar

Tuesday, June 6, 2023

7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

Faculty

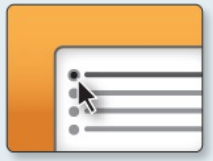
David F McDermott, MD

Sumanta Kumar Pal, MD

Clinicians in the Meeting Room

Networked iPads are available.

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



Answer Survey Questions: Complete the pre- and postmeeting surveys.

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

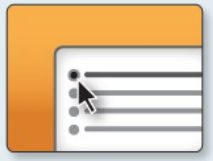
Complete Your Evaluation: Tap the CME Evaluation button to complete your evaluation electronically to receive credit for your participation.

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

RTP RESEARCH TO PRACTICE

Clinicians Attending via Zoom

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



Answer Survey Questions: Complete the pre- and postmeeting surveys.

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

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

RTP
RESEARCH
TO PRACTICE

PREMEETING SURVEY – Available Now

Clinicians in Attendance: If you have not already done so, please take a moment to complete the premeeting survey on the iPads for attendees in the room and on Zoom for those attending virtually. Your input on this survey will be integral to the program today.

A postmeeting survey will be posted toward the end of the session.

Thank you for your input.

RTP
RESEARCH
TO PRACTICE

About the Enduring Program

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

RTP
RESEARCH
TO PRACTICE

Second Opinion: Investigators Discuss How They and Their Colleagues Apply Available Clinical Research in the Care of Patients with Prostate Cancer

A CME Symposium Held in Conjunction with the 2023 ASCO® Annual Meeting

Saturday, June 3, 2023

7:00 PM – 9:00 PM CT

Faculty

Emmanuel S Antonarakis, MD

Prof Karim Fizazi, MD, PhD

Rana R McKay, MD

Alicia K Morgans, MD, MPH

A Oliver Sartor, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

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

David S Morris, MD
President and Co-Director of Advanced Therapeutics Center
Urology Associates
Nashville, Tennessee

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

Agenda

Module 1 – Current Management of Nonmetastatic Prostate Cancer — Dr Morgans

Module 2 – New Considerations in Treatment Intensification for Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) — Prof Fizazi

Module 3 – Available and Emerging Strategies for Newly Diagnosed Metastatic Castration-Resistant Prostate Cancer (mCRPC) — Dr McKay

Module 4 – Identification and Management of mCRPC with a Homologous Recombination Repair (HRR) Gene Abnormality — Dr Antonarakis

Module 5 – Management of Progressive mCRPC — Dr Sartor

ASCO 2023 Oral Abstracts — Prostate Cancer

- Bossi A et al. **Prostate irradiation in men with de novo, low-volume, metastatic, castration-sensitive prostate cancer (mCSPC): Results of PEACE-1, a phase 3 randomized trial with a 2x2 design**. ASCO 2023;Abstract LBA5000.
- Armstrong AJ et al. **Development and validation of an AI-derived digital pathology-based biomarker to predict benefit of long-term androgen deprivation therapy with radiotherapy in men with localized high-risk prostate cancer across multiple phase III NRG/RTOG trials.** ASCO 2023;Abstract 5001.
- Ravi P et al. **Prognostic impact of PSA nadir (n) ≥0.1 ng/mL within 6 months (m) after completion of radiotherapy (RT) for localized prostate cancer (PCa): An individual patient-data (IPD) analysis of randomized trials from the ICECAP collaborative.** ASCO 2023;Abstract 5002.
- Olmos D et al. **Presence of somatic/germline homologous recombination repair (HRR) mutations and outcomes in metastatic castration-resistant prostate cancer (mCRPC) patients (pts) receiving first-line (1L) treatment stratified by BRCA status.** ASCO 2023;Abstract 5003.

ASCO 2023 Oral Abstracts — Prostate Cancer

- Fizazi K et al. **TALAPRO-2: Phase 3 study of talazoparib (TALA) + enzalutamide (ENZA) versus placebo (PBO) + ENZA as first-line (1L) treatment for patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) harboring homologous recombination repair (HRR) gene alterations.** ASCO 2023;Abstract 5004.
- Sandhu S et al. **LuPARP: Phase 1 trial of 177Lu-PSMA-617 and olaparib in patients with metastatic castration resistant prostate cancer (mCRPC).** ASCO 2023;Abstract 5005.

Agenda

Module 1 – Current Management of Nonmetastatic Prostate Cancer — Dr Morgans

Module 2 – New Considerations in Treatment Intensification for Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) — Prof Fizazi

Module 3 – Available and Emerging Strategies for Newly Diagnosed Metastatic Castration-Resistant Prostate Cancer (mCRPC) — Dr McKay

Module 4 – Identification and Management of mCRPC with a Homologous Recombination Repair (HRR) Gene Abnormality — Dr Antonarakis

Module 5 – Management of Progressive mCRPC — Dr Sartor

RTP
RESEARCH TO PRACTICE

Case Presentation: 71-year-old man diagnosed with localized prostate cancer who underwent a radical prostatectomy in 2010 experiences rising PSA from 0.18 to 0.4 – PSA doubling time 7 months, PSMA PET negative for other sites of disease

Dr David Morris (Nashville, Tennessee)

RTP RESEARCH TO PRACTICE

Case Presentation: 73-year-old man with M0 HSPC with PSA persistence after radical prostatectomy received ADT intensification with abiraterone/prednisone and went to the ER with hypertension, palpitations, headache and abnormal LFTs

Dr Sandy Srinivas (Stanford, California)

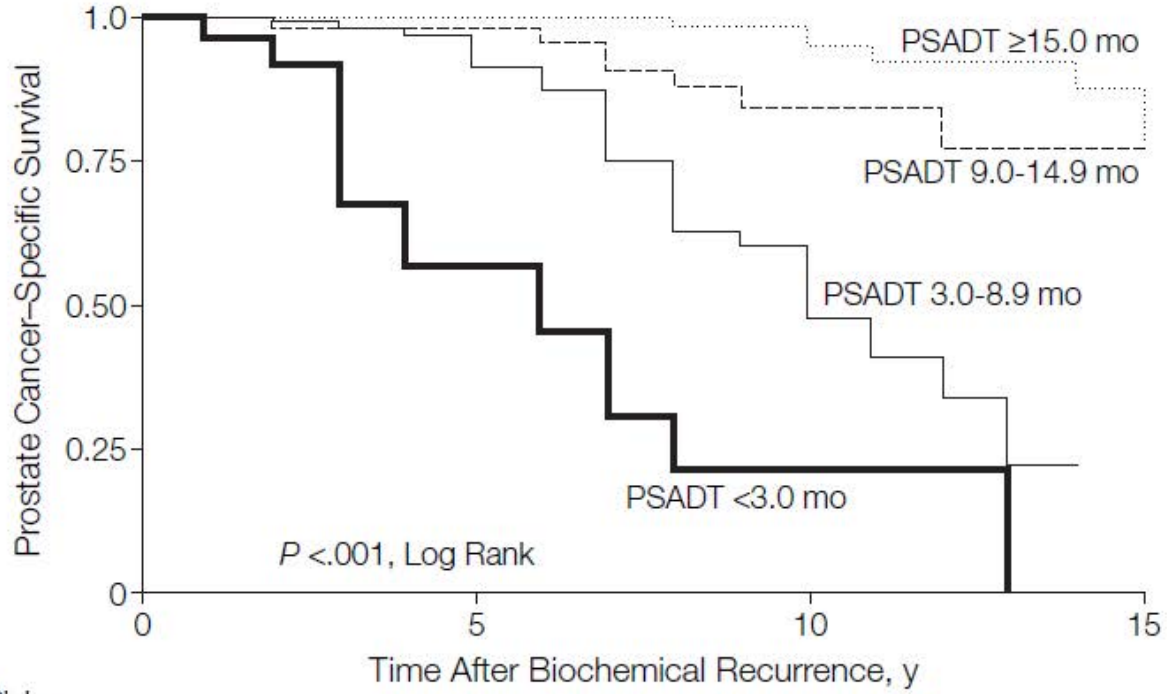
RTP RESEARCH TO PRACTICE

Current Management of Non-metastatic Prostate Cancer

Alicia Morgans, MD, MPH
Medical Director, Survivorship Program
Dana-Farber Cancer Institute

Dana-Farber
Cancer Institute

PSA Doubling Time Influences Risk of Recurrence

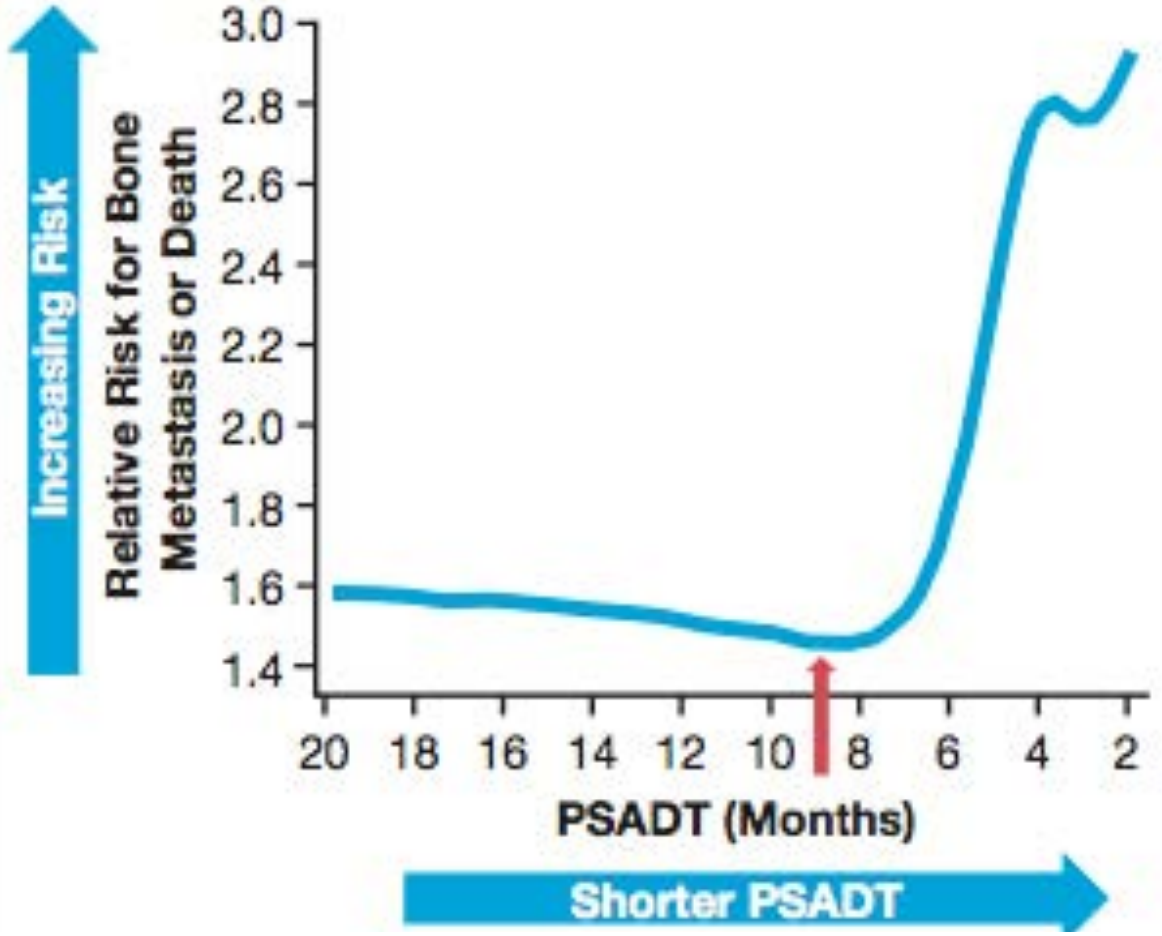


No. at Risk PSADT, mo				
<3.0	23	10	2	0
3.0-8.9	119	85	19	0
9.0-14.9	79	51	19	3
≤15	158	113	52	9

Biochemical recurrence segregated by prostate-specific antigen doubling time among patients who experienced a biochemical recurrence. PSADT indicates prostate-specific antigen doubling time.

Freedland SJ, et al. JAMA. 2005.

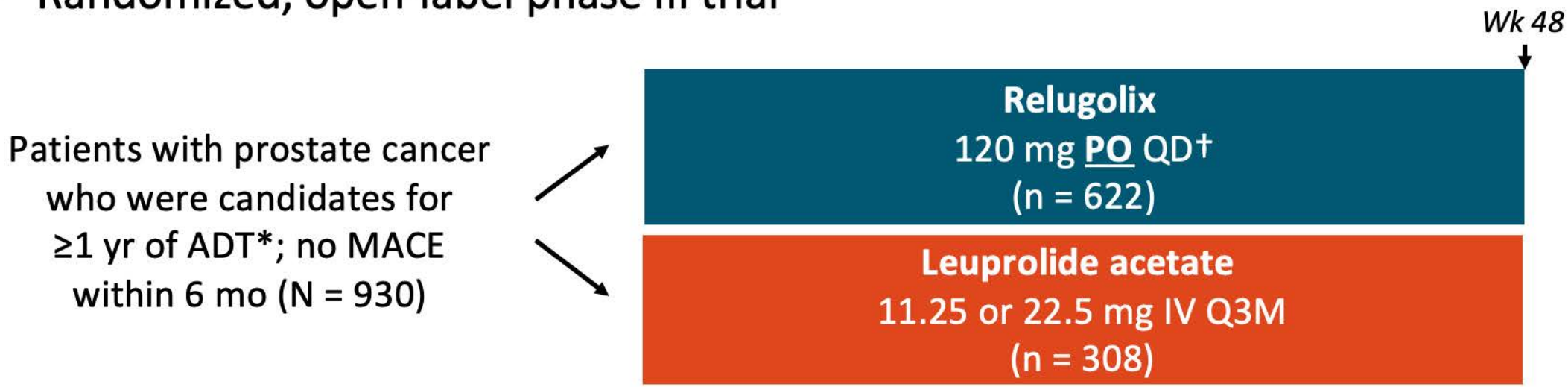
Risk of Metastases Increases as PSADT Falls in nmCRPC



Smith MR, et al. J Clin Oncol. 2013.
Small EJ, et al. Poster 161. GU ASCO 2018.

HERO: Relugolix vs Leuprolide for Prostate Cancer

- Randomized, open-label phase III trial

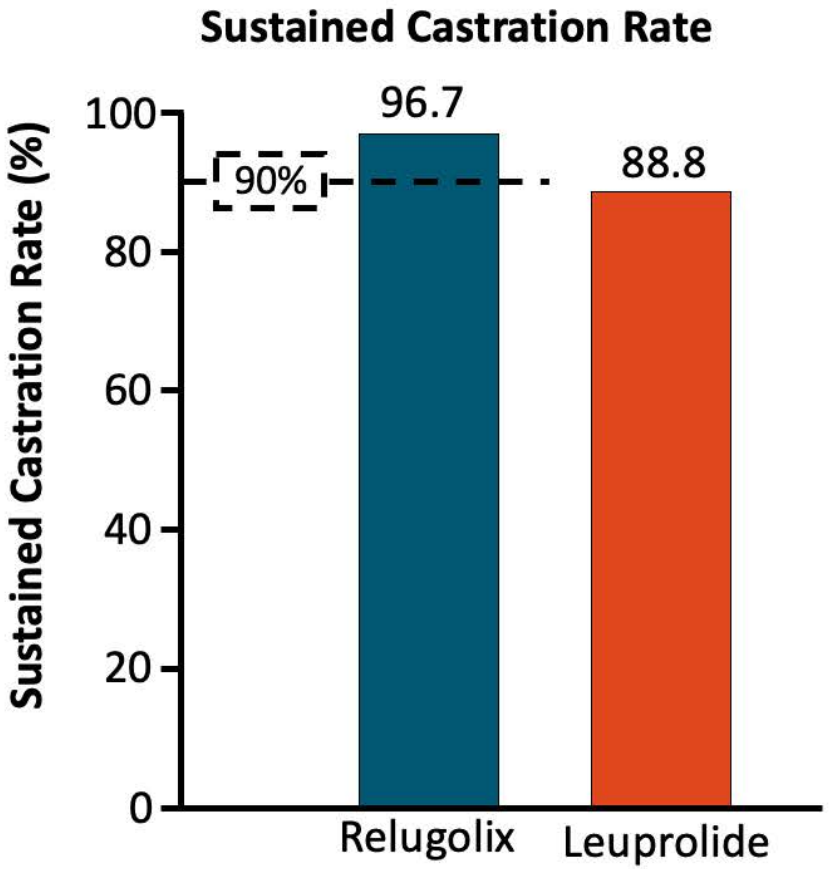


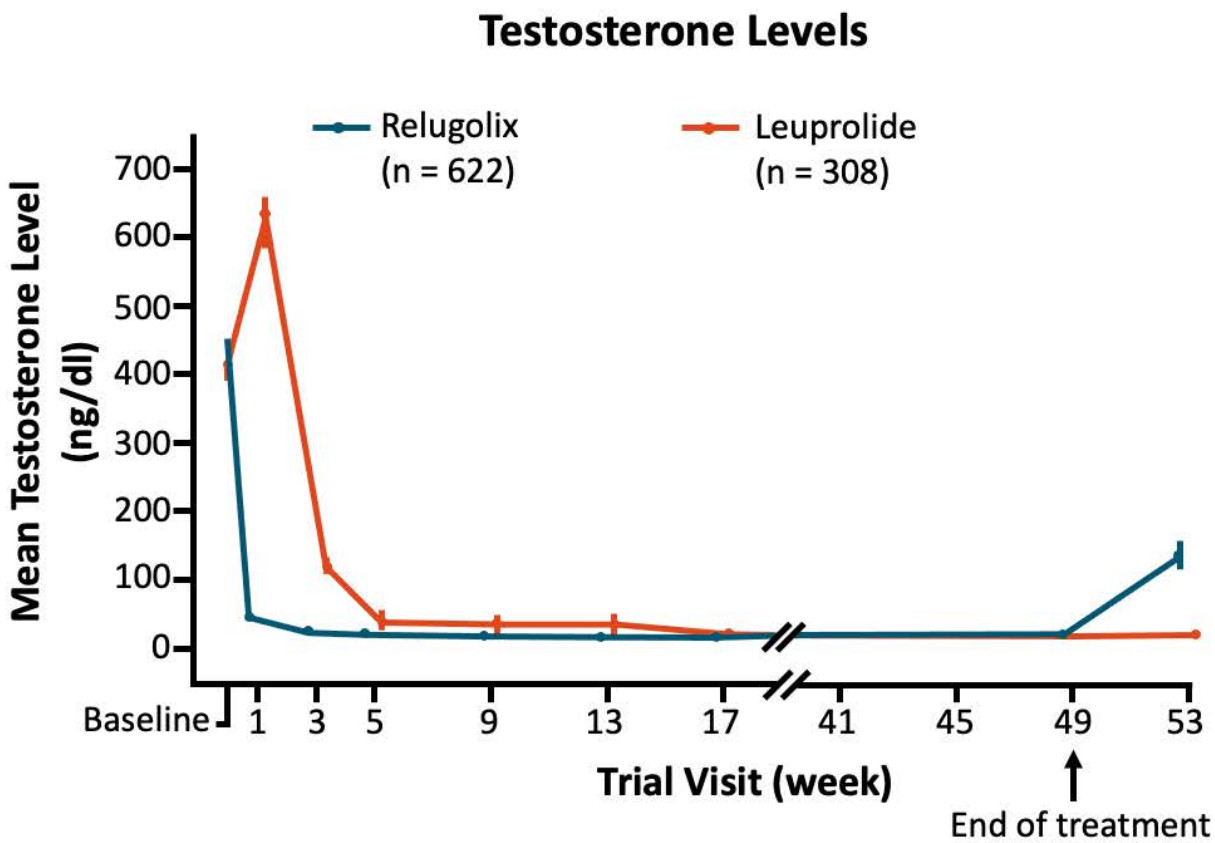
- Primary endpoint: sustained castration rate (cumulative probability of testosterone suppression to <50 ng/dL from Day 29 through Wk 48)
- Baseline: 32% with metastatic disease, 93% with CV risk factors, mean testosterone 428 ng/mL

*PSA or clinical relapse after local primary intervention (curative intent), newly diagnosed mHSPC, or uncurable advanced localized disease.
†After a single loading dose of 360 mg PO.

Shore et al. NEJM 2020 382(23):2187-2196.

HERO: Efficacy

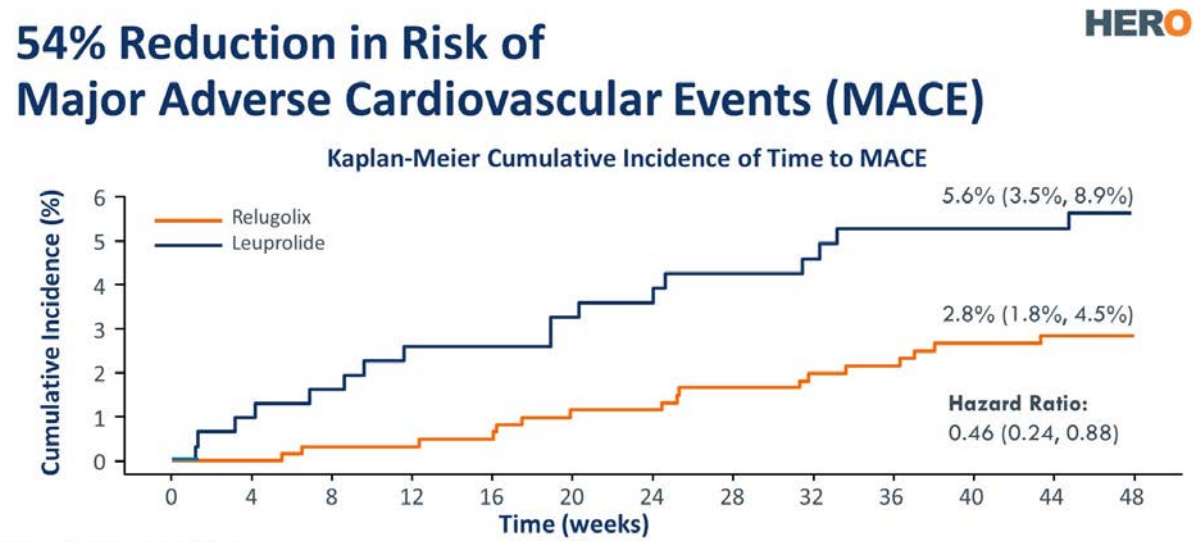




- Relugolix noninferiority/superiority demonstrated

Shore et al. NEJM 2020 382(23):2187-2196.

Cardiovascular events in the HERO trial



History of MACE	Yes		No	
N (%)	Relugolix 84 (13.5%)	Leuprolide 45 (14.6%)	Relugolix 538 (86.5%)	Leuprolide 263 (85.4%)
MACE	3.6%	17.8%	2.8%	4.2%
Odds Ratio Leuprolide vs Relugolix (95% confidence interval)	5.8 (1.5, 23.3)		1.5 (0.7, 3.4)	

MACE = non-fatal myocardial infarction + non-fatal stroke + all-cause mortality

Shore et al. NEJM 2020 382(23):2187-2196.

Abiraterone acetate plus prednisolone with or without enzalutamide added to androgen deprivation therapy compared to ADT alone for men with high-risk nonmetastatic prostate cancer: primary combined analysis from two comparisons in the STAMPEDE platform protocol

M0
No evidence of metastases on bone and CT scan of pelvis, abdo, chest
(pre-defined stratification criterion)

Newly-diagnosed
Any of:
- Node-Positive
- ≥2 of: Stage T3 or T4
  PSA≥40ng/ml
  Gleason 8, 9 or 10

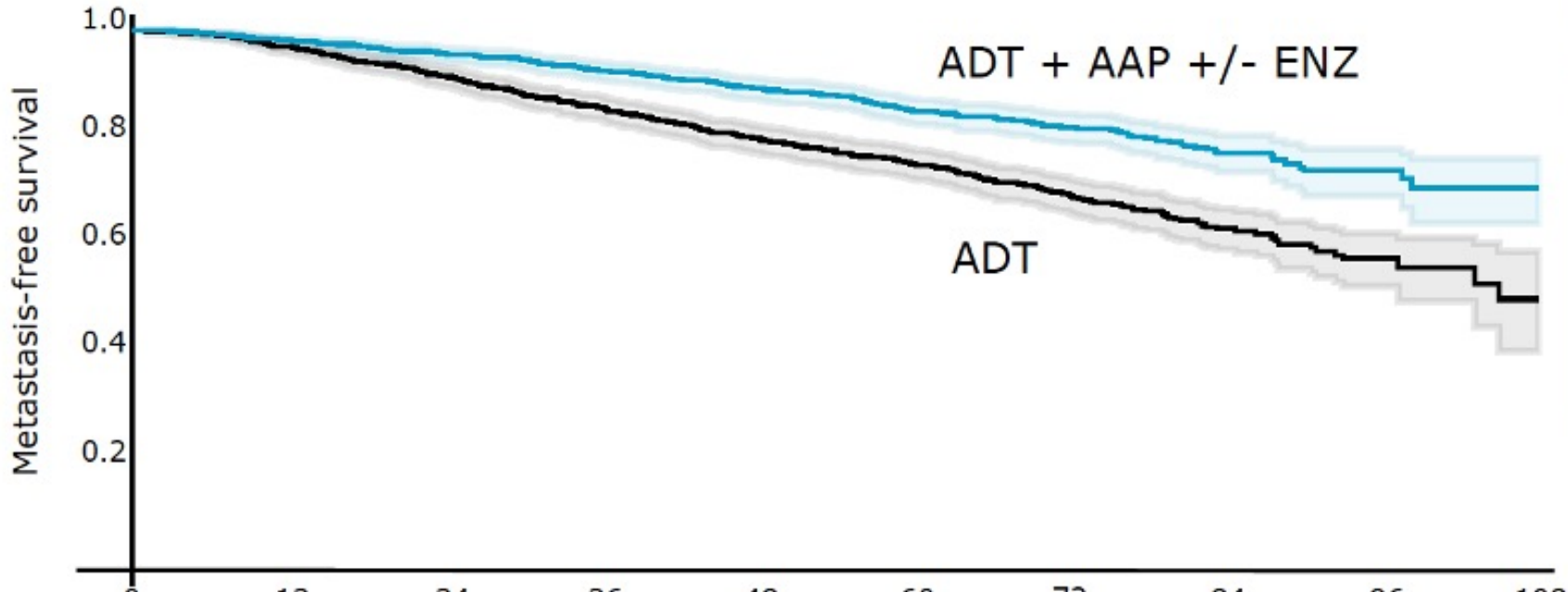
Relapsing after previous RP or RT
Any of:
- Node-positive
- PSA≥4ng/ml, rising & doubling time <6m
- PSA≥20ng/ml

All patients
Written informed consent
Fit for all protocol treatment
Fit for follow-up

Full criteria: www.stampedetrial.org

Attard G, et al. ESMO 2021.

STAMPEDE non-metastatic cohort: MFS



ADT										
At-risk	988	950	894	836	767	550	329	172	53	9
Censored	0	8	11	14	26	201	387	522	632	673
Event	0	30	83	138	195	237	272	294	303	306
ADT+AAP+/-ENZ										
At-risk	986	948	917	884	839	622	369	198	71	14
Censored	0	21	28	31	45	225	460	615	737	792
Event	0	17	41	71	102	139	157	173	178	180

Kaplan-Meier estimates with 95% CI in lighter shade

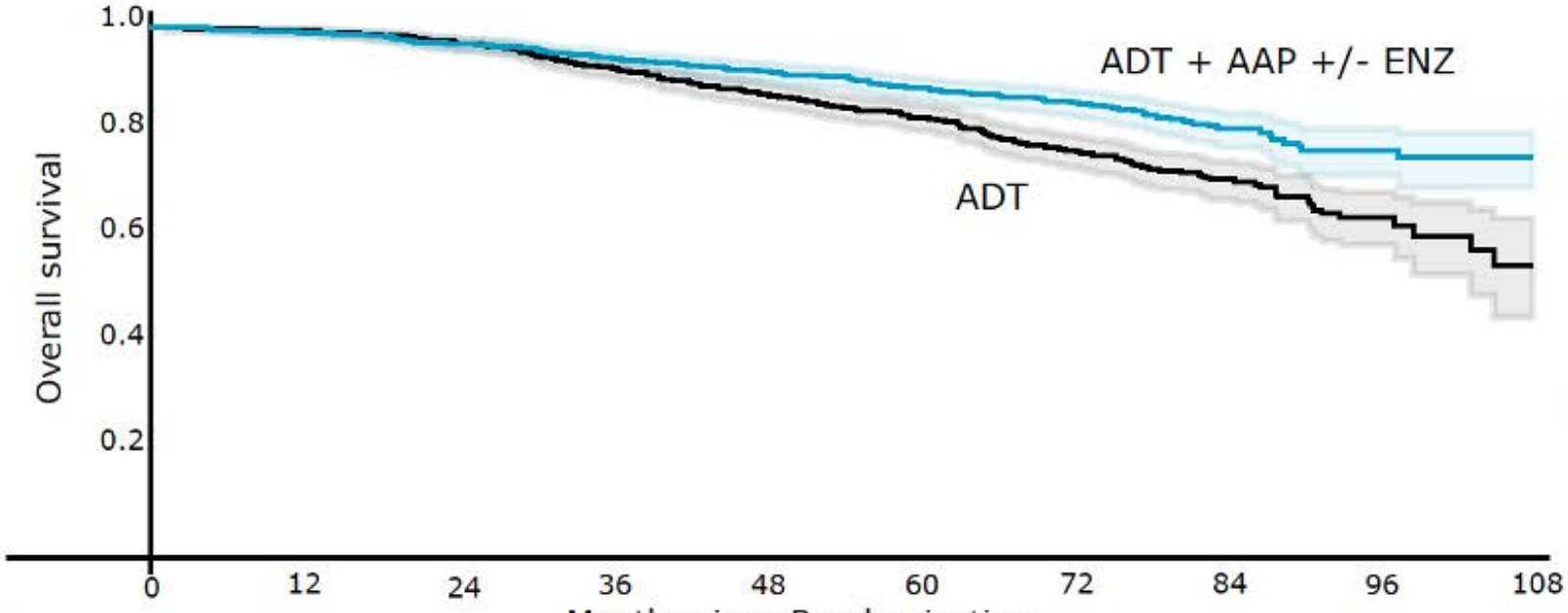
Events
180 ADT+ AAP +/- ENZ
306 ADT

HR:	**0.53**
95% CI:	0.44-0.64
P value	2.9×10^{-11}

6-year MFS improved from 69% to 82%

Attard G, et al. ESMO 2021.; Attard G, et al. Lancet, 2022.

STAMPEDE non-metastatic cohort: OS



Events
147 ADT+AAP +/- ENZ
236 ADT

HR: 0.60
95% CI 0.48 to 0.73
P value 9.3×10^{-7}

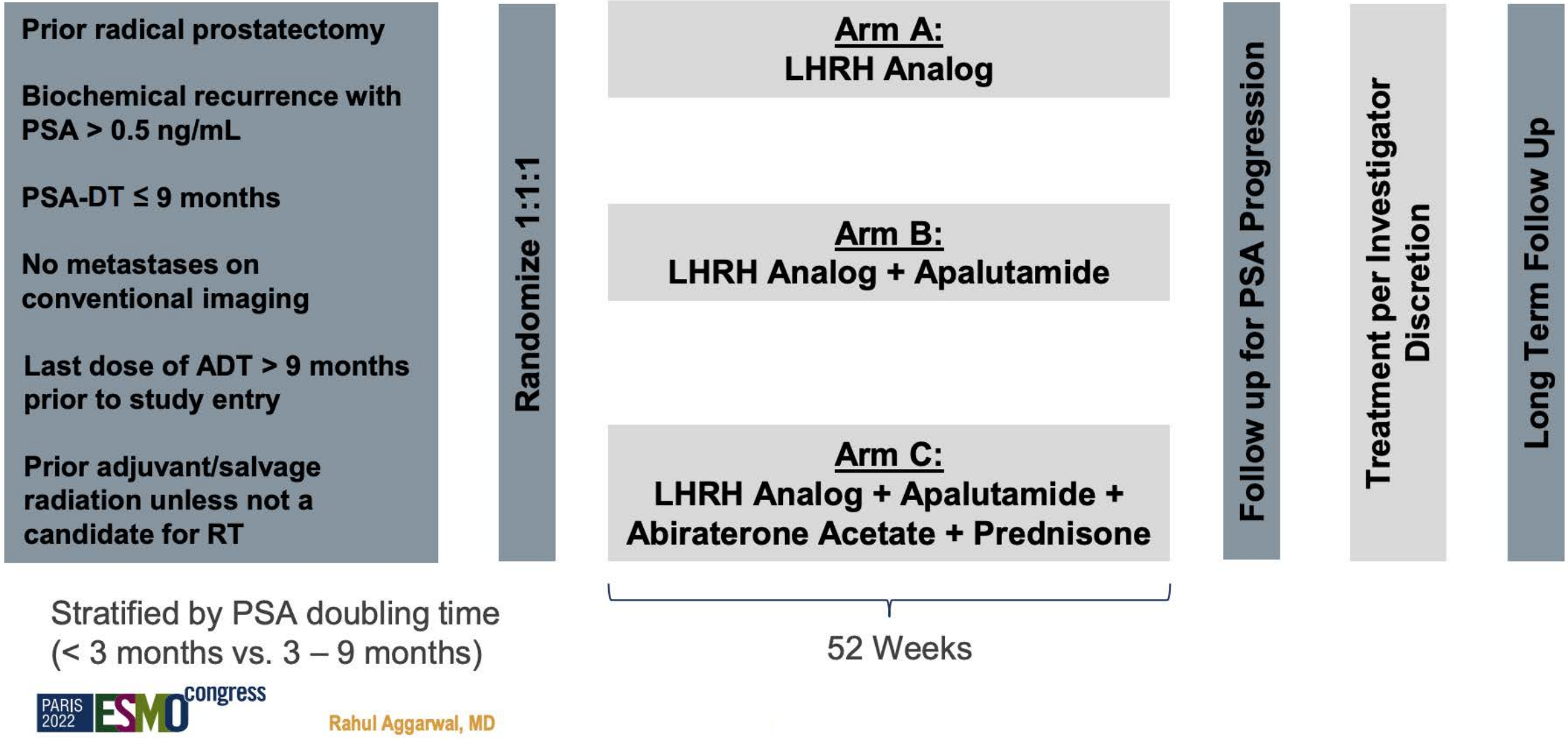
6-year survival improved from 77% to 86%

ADT										
At-risk	988	974	947	901	837	610	368	200	63	10
Censored	0	8	11	14	28	216	421	568	693	742
Event	0	6	30	73	123	162	199	220	232	236
ADT+AAP+/-ENZ										
At-risk	986	956	928	899	861	645	386	205	74	16
Censored	0	21	29	32	46	234	477	641	766	823
Event	0	9	29	55	79	107	123	140	146	147

Kaplan-Meier estimates with 95% CI in lighter shade

Attard G, et al. ESMO 2021.; Attard G, et al. Lancet, 2022.

PRESTO Study Schema

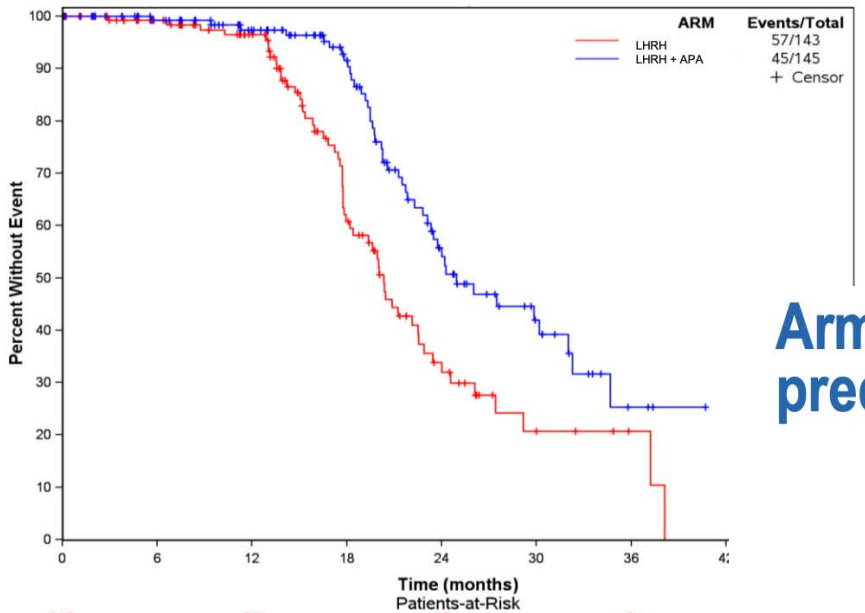


PARIS 2022 ESMO congress

Rahul Aggarwal, MD

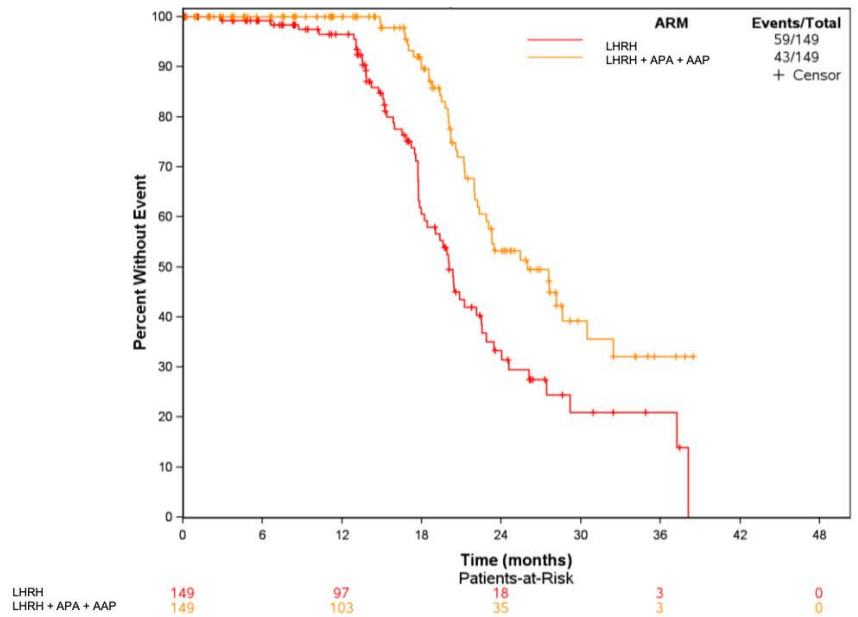
Aggarwal R et al. ESMO 2022;Abstract LBA63.

ADT + Apalutamide Prolongs PSA Progression-Free Survival



- Median follow up 21.5 months
- 102 PSA PFS events
- Median PSA progression-free survival

Arm C: ADT + apalutamide + abiraterone acetate + prednisone vs. ADT monotherapy



- Median follow up 21.3 months
- 102 PSA PFS events
- Median PSA progression-free survival
  - ADT + APA + AAP = 26.0 months (95% CI: 22.9 – 32.5)
  - ADT alone = 20.0 months (95% CI: 18.2 – 22.5)
  - **Hazard ratio = 0.48 (95% CI: 0.32 – 0.71)**
  - One-sided p-value = 0.00008

PARIS 2022 ESMO congress

Rahul Aggarwal, MD

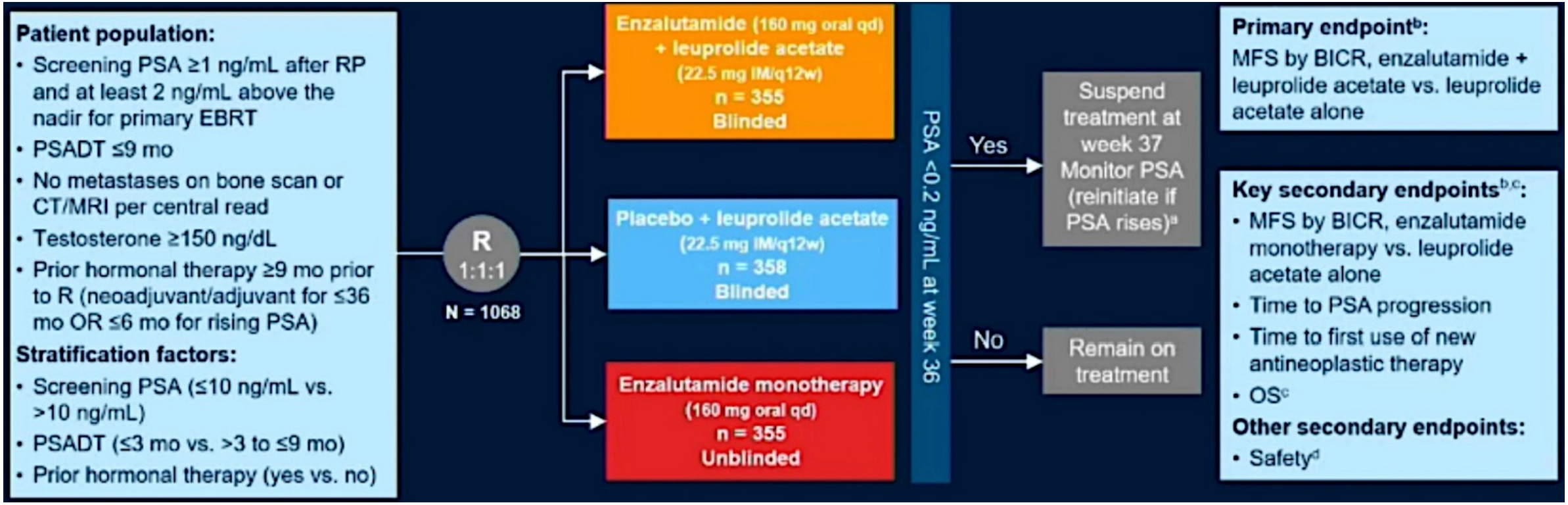
Content o

PARIS 2022 ESMO congress

Rahul Aggarwal, MD

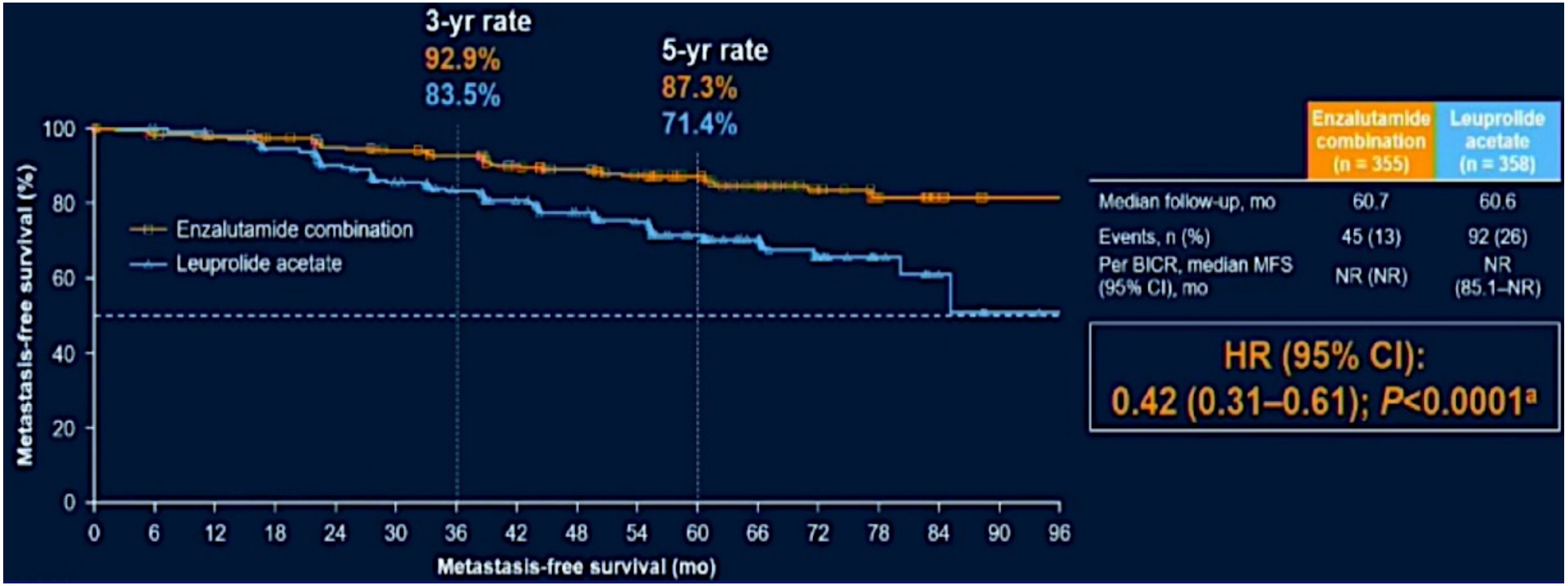
Aggarwal R et al. ESMO 2022;Abstract LBA63.

EMBARK: Enzalutamide for high-risk BCR



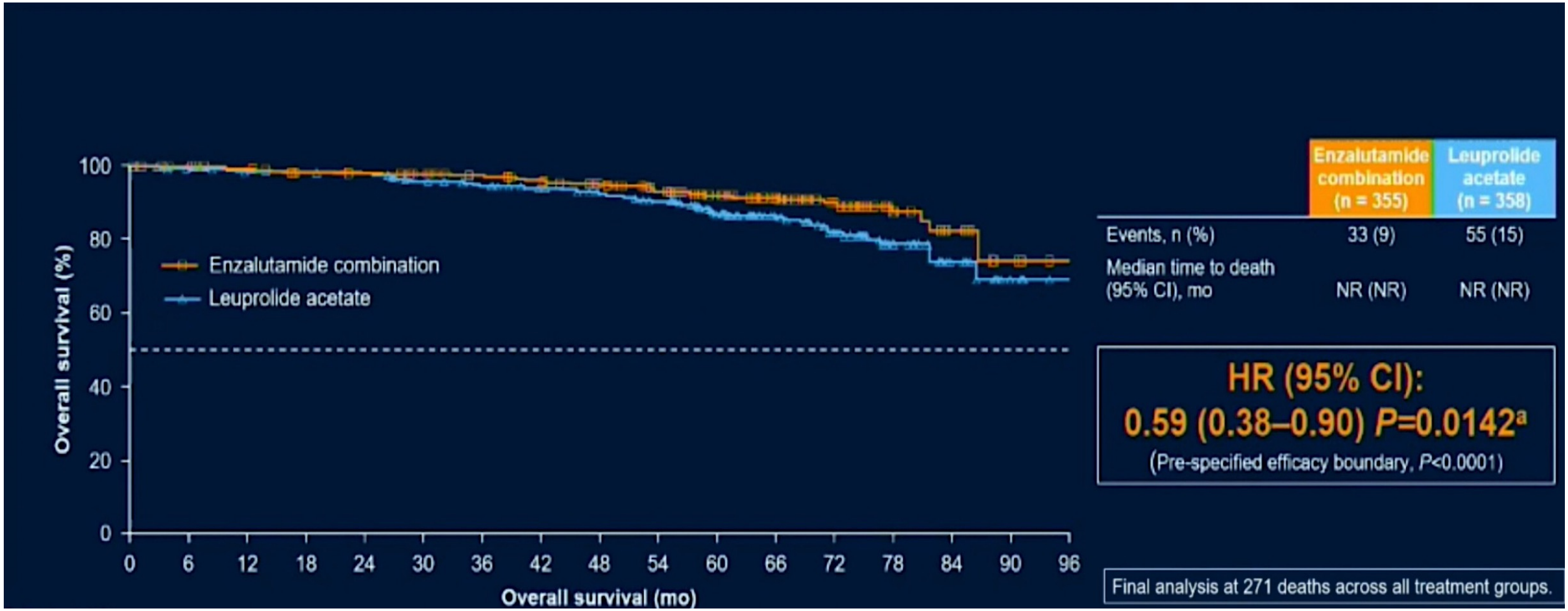
Shore N, et al. AUA, 2023.

EMBARK MFS: Enzalutamide + ADT vs ADT



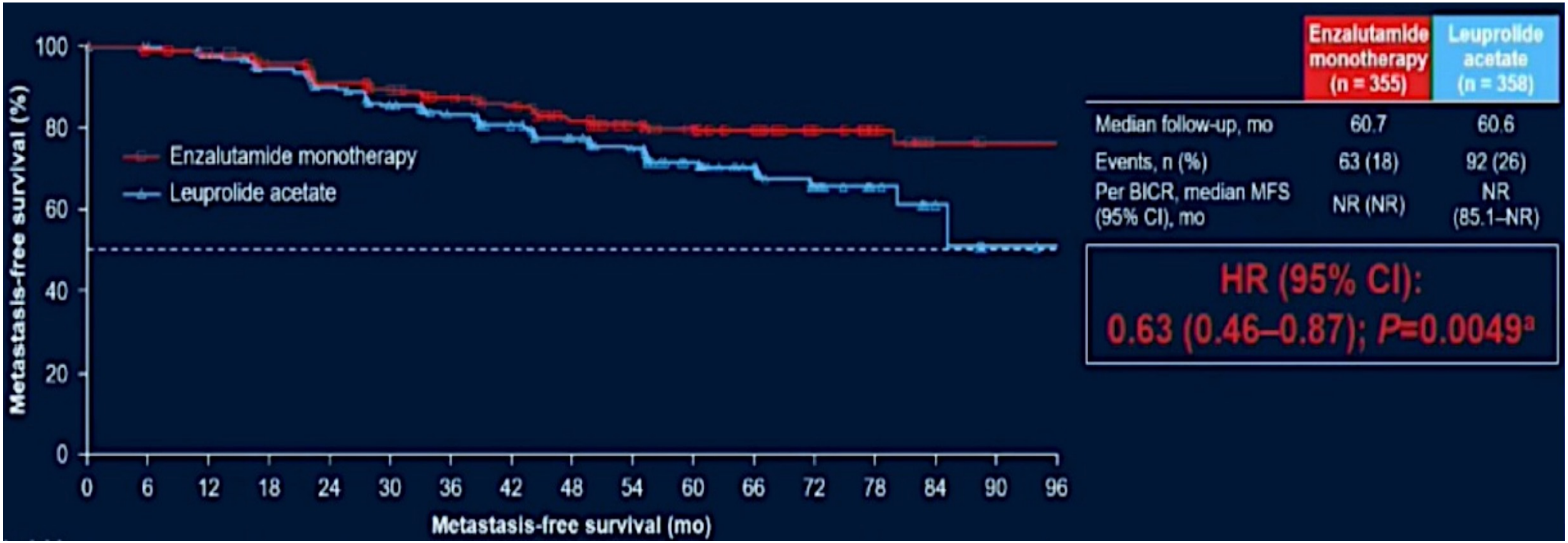
Shore N, et al. AUA, 2023.

EMBARK OS: Enzalutamide + ADT vs ADT



Shore N, et al. AUA, 2023.

EMBARK MFS: Enzalutamide vs ADT



	Enzalutamide monotherapy (n = 355)	Leuprolide acetate (n = 358)
Median follow-up, mo	60.7	60.6
Events, n (%)	63 (18)	92 (26)
Per BICR, median MFS (95% CI), mo	NR (NR)	NR (85.1–NR)

HR (95% CI): 0.63 (0.46–0.87); *P*=0.0049[a]

Shore N, et al. AUA, 2023.

EMBARK: Treatment Emergent AEs

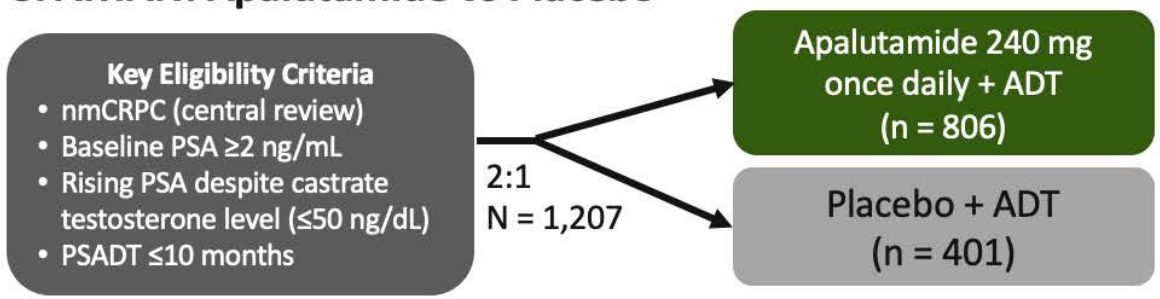
Most common TEAEs (>15% of patients), n (%)[a]	Enzalutamide combination (n = 353)		Leuprolide acetate (n = 354)		Enzalutamide monotherapy (n = 354)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Hot flash	243 (68.8)	2 (0.6)	203 (57.3)	3 (0.8)	77 (21.8)	1 (0.3)
Fatigue	151 (42.8)	12 (3.4)	116 (32.8)	5 (1.4)	165 (46.6)	14 (4.0)
Arthralgia	97 (27.5)	5 (1.4)	75 (21.2)	1 (0.3)	81 (22.9)	1 (0.3)
Hypertension	82 (23.2)	2 (0.6)	69 (19.5)	0	67 (18.9)	0
Fall	74 (21.0)	3 (0.8)	51 (14.4)	2 (0.6)	56 (15.8)	5 (1.4)
Back pain	60 (17.0)	1 (0.3)	54 (15.3)	0	62 (17.5)	1 (0.3)
Nausea	42 (11.9)	0	29 (8.2)	0	54 (15.3)	1 (0.3)
Gynecomastia	29 (8.2)	0	32 (9.0)	0	159 (44.9)	1 (0.3)
Nipple pain	11 (3.1)	0	4 (1.1)	0	54 (15.3)	0

- The most common AEs (>15% of patients) for all treatment cohorts were hot flash, fatigue; plus gynecomastia in the enzalutamide monotherapy cohort; most were grade <3.

Shore N, et al. AUA, 2023.

nmCRPC: SPARTAN, PROSPER, ARAMIS

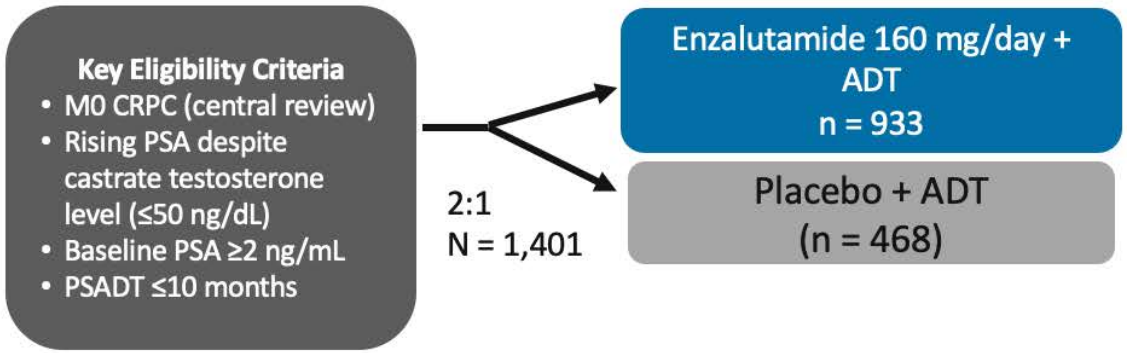
SPARTAN: Apalutamide vs Placebo



Primary endpoint: MFS

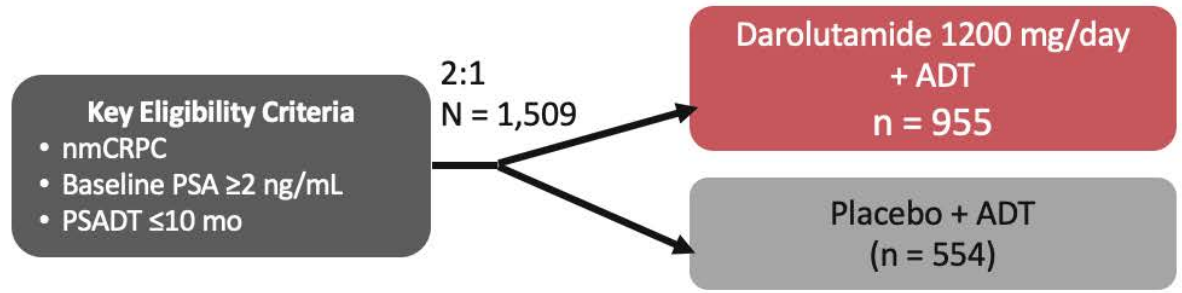
Secondary endpoints: Safety, time to PSA progression, time to symptomatic progression, OS, PSA response, QOL

PROSPER: Enzalutamide vs Placebo



Primary endpoint: MFS
Secondary endpoints: Safety, time to PSA progression, time to use of new antineoplastic therapy, OS, PSA response, and QOL

ARAMIS: Darolutamide vs Placebo

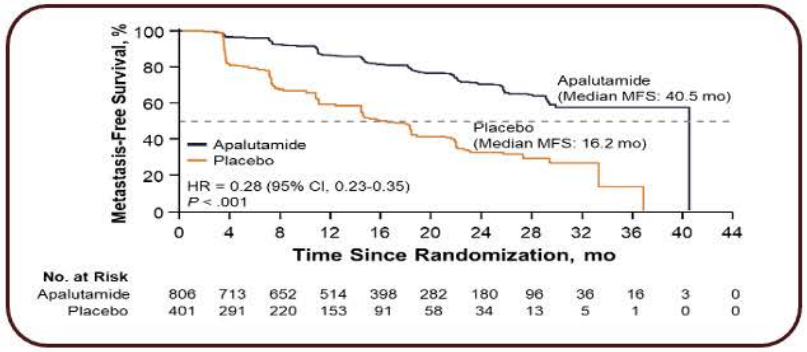


Primary endpoint: MFS
Secondary endpoints: OS, time to first symptomatic skeletal event, time to initiation of first cytotoxic chemotherapeutic, time to pain progression, safety, and tolerability

Smith MR, et al. *N Engl J Med*. 2018;378:1408-1418; Hussain M, et al. N Engl J Med. 2018;378:2465-2474. Fizazi K, et al. NEJM.2019;1235-1246.

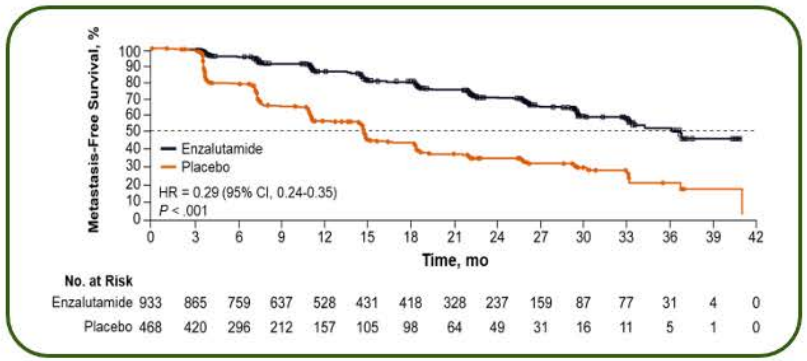
Primary Endpoint: Metastasis Free Survival

SPARTAN
Apalutamide



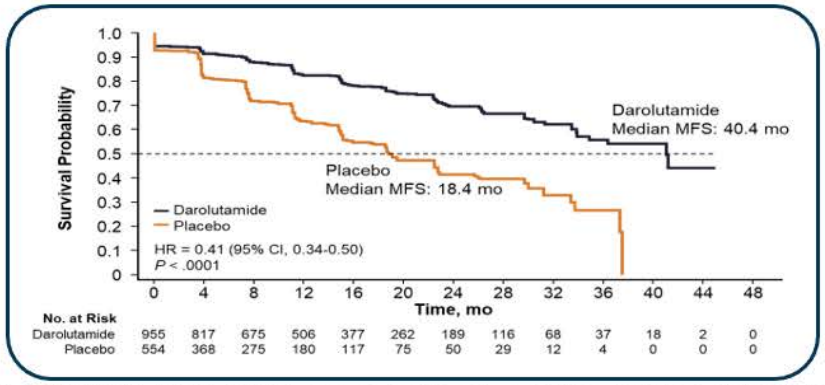
- 72% reduction of distant progression or death
- Median MFS: APA 40.5 vs PBO 16.2 months
- 24-month MFS benefit

PROSPER
Enzalutamide



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

ARAMIS
Darolutamide

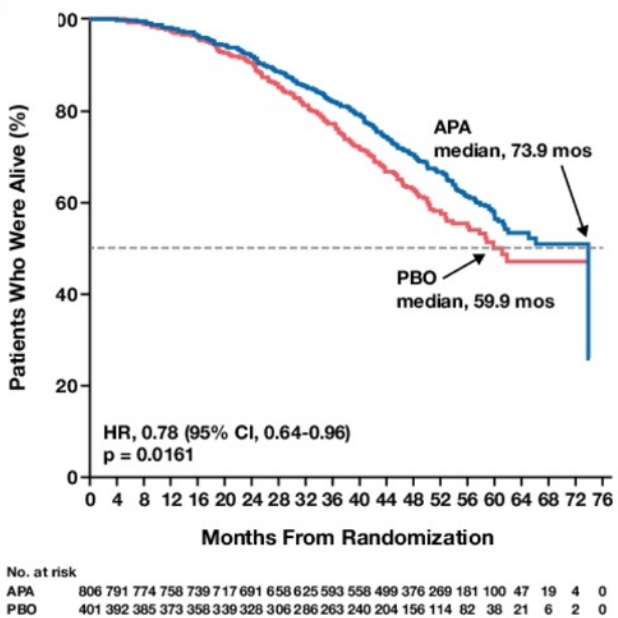


- 59% reduction of distant progression or death
- Median MFS: DARO 40.4 vs PBO 18.4 months
- 22-month MFS benefit

Smith M, et al. *N Engl J Med*. 2018;378:1408-1418. Hussain M, et al. N Engl J Med. 2018;378:2465-2474. Fizazi K, et al. N Engl J Med. 2019;380:1235-1246.

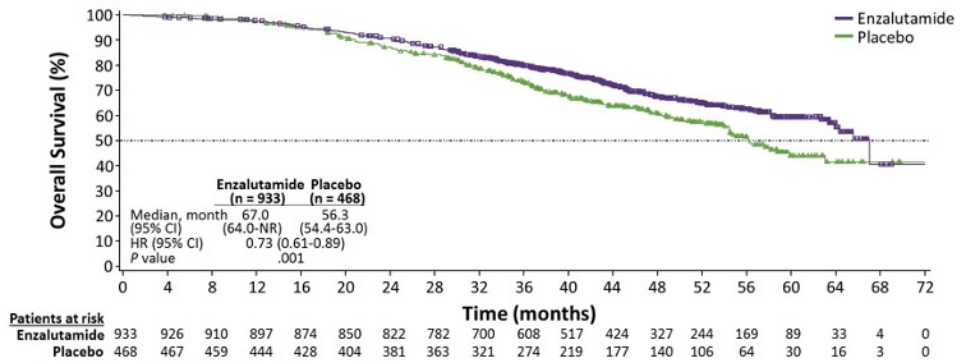
Secondary Endpoint: Updated Overall Survival

SPARTAN
Apalutamide



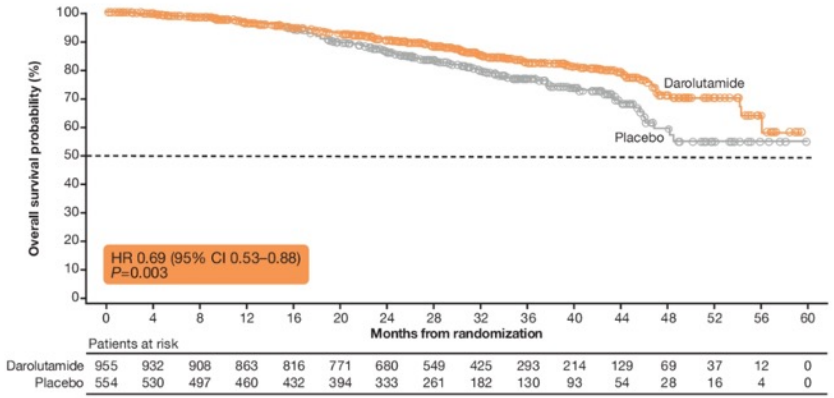
- 22% reduction in risk of death
- HR = 0.78 (95% CI, 0.64-0.96)
- *P* = .0161

PROSPER
Enzalutamide



- 27% reduction in risk of death
- HR = 0.73 (95% CI 0.61-0.89)
- *P* = .001

ARAMIS
Darolutamide



- 31% reduction in risk of death
- HR = 0.69 (95% CI, 0.53-0.88);
- *P* = .003

Smith MR, et al. Eur Urol 2021. Sternberg CN, et al. NEJM 2020. Fizazi K, et al. NEJM 2020.

Summary

- Patient selection for intensified treatment is critical in balancing risks and benefits of treatment.
- Abiraterone in addition to ADT in combination with EBRT prolongs OS in high risk, locally advanced prostate cancer
- Intensified treatment with ADT+ apalutamide prolongs PFS in high risk BCR
- Intensified treatment with ADT + enzalutamide prolongs MFS in high risk BCR
- Intensified treatment with ADT and enzalutamide, apalutamide, or darolutamide prolongs MFS and OS in nmCRPC

Agenda

Module 1 – Current Management of Nonmetastatic Prostate Cancer — Dr Morgans

Module 2 – New Considerations in Treatment Intensification for Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) — Prof Fizazi

Module 3 – Available and Emerging Strategies for Newly Diagnosed Metastatic Castration-Resistant Prostate Cancer (mCRPC) — Dr McKay

Module 4 – Identification and Management of mCRPC with a Homologous Recombination Repair (HRR) Gene Abnormality — Dr Antonarakis

Module 5 – Management of Progressive mCRPC — Dr Sartor

RTP
RESEARCH
TO PRACTICE

Case Presentation: 64-year-old man with localized prostate cancer and biochemical recurrence 5 years after neoadjuvant and adjuvant leuprolide and IMRT to the whole pelvis

Dr Neeraj Agarwal (Salt Lake City, Utah)

RTP
RESEARCH
TO PRACTICE

Case Presentation: 82-year-old man who underwent radical prostatectomy 15 years ago and received RT and ADT for biochemical recurrences is now diagnosed with M0 CRPC with quickly rising PSA levels

Dr David Morris (Nashville, Tennessee)

RTP
RESEARCH
TO PRACTICE

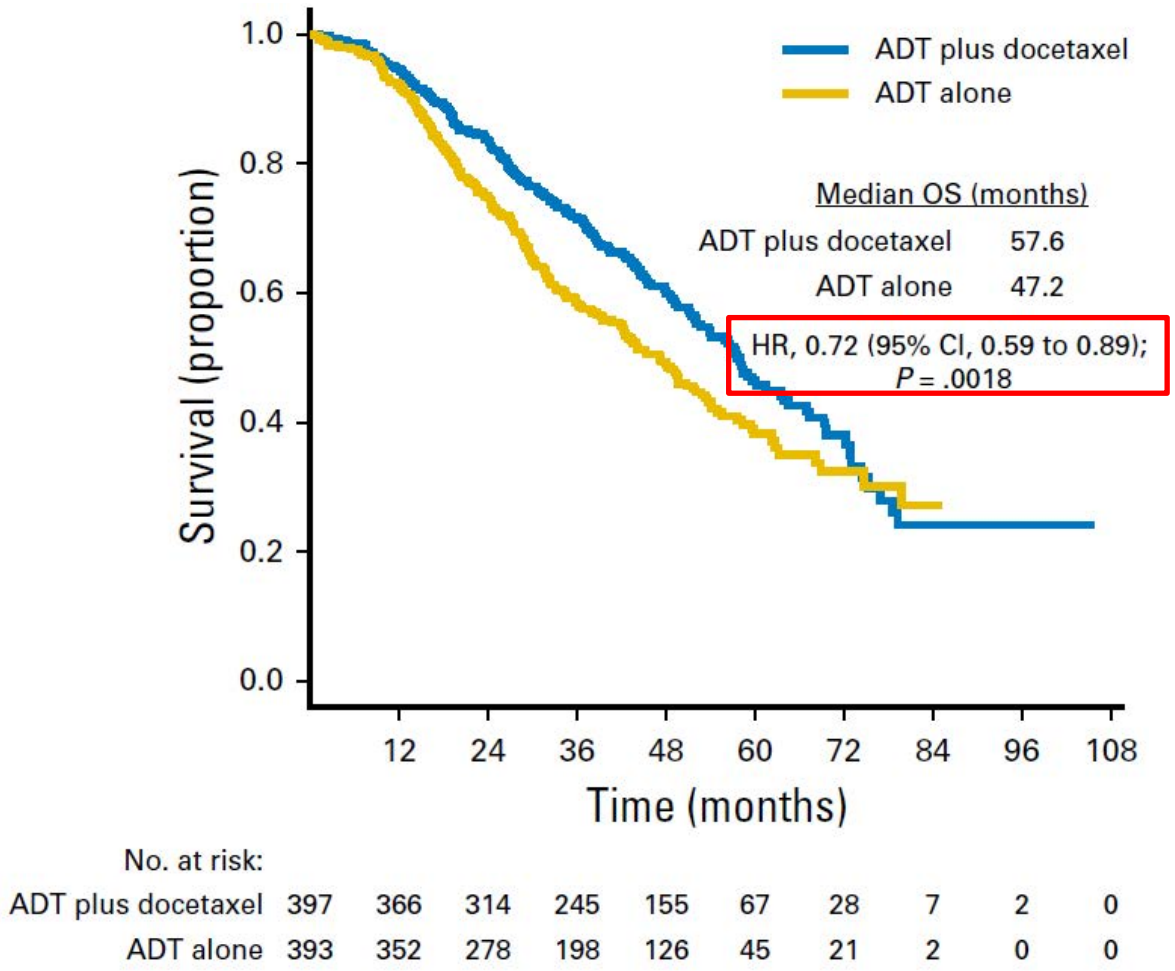
Treatment Intensification in M1 Prostate Cancer

Karim Fizazi, MD, PhD

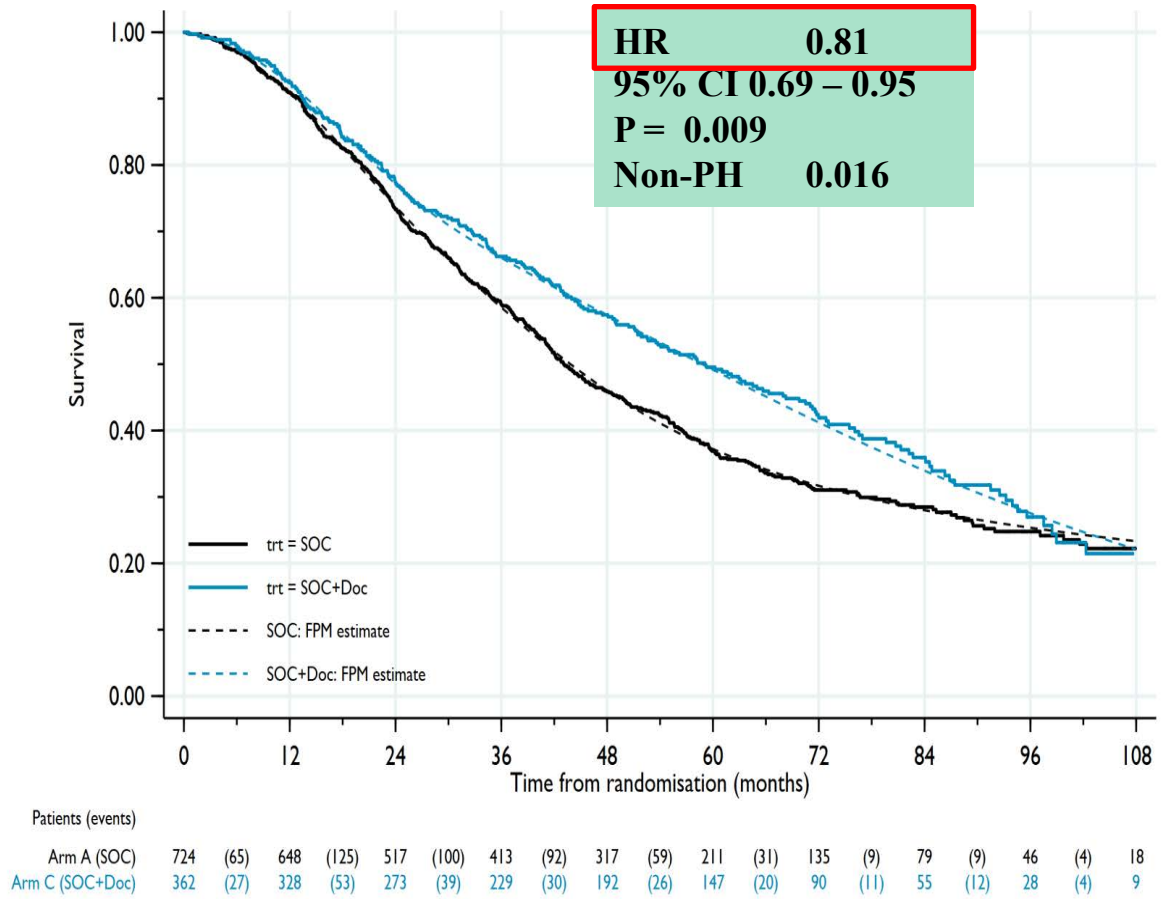
Institut Gustave Roussy

Villejuif, France

CHAARTED and STAMPEDE: Lower OS benefit of docetaxel in long-term analysis



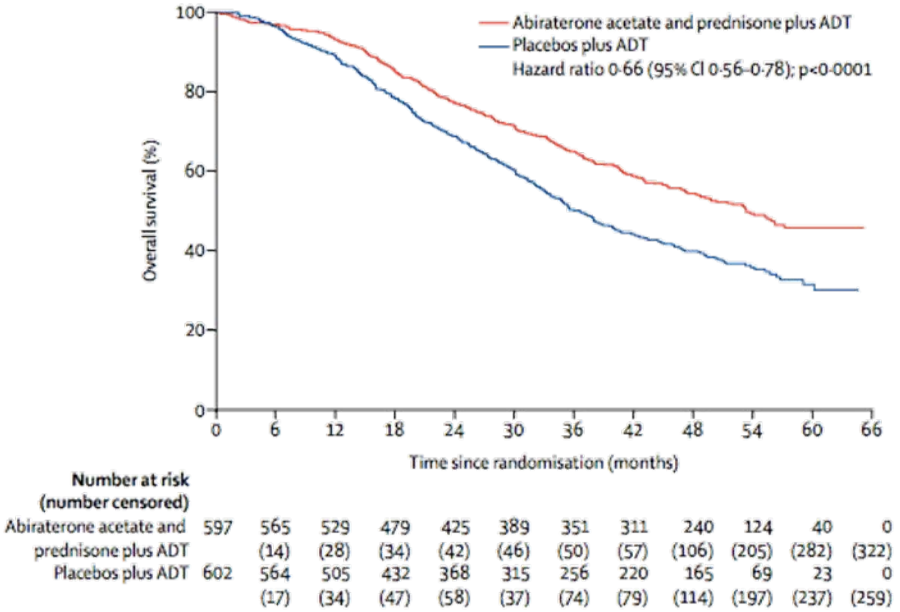
Kyriakopoulos CE, J Clin Oncol 2018



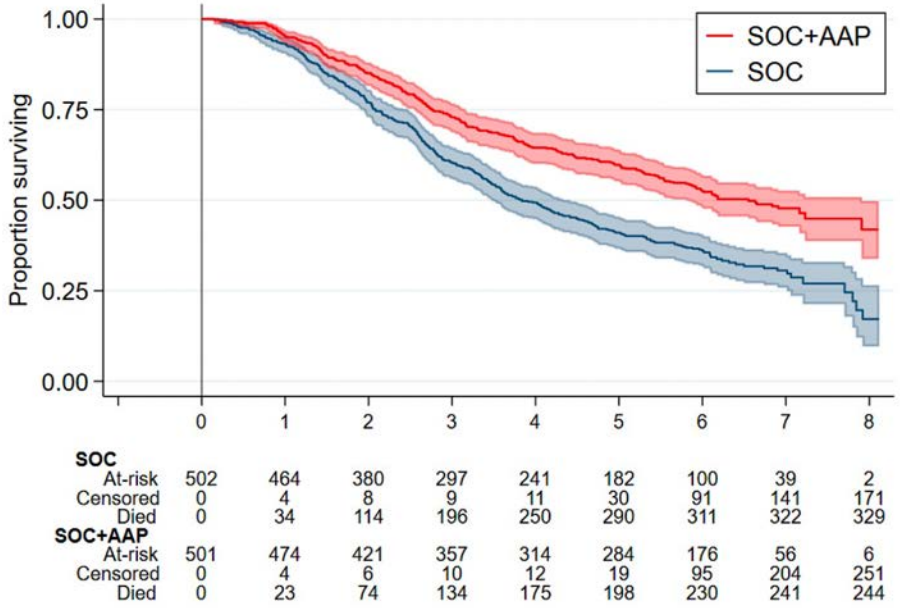
Clarke N, Ann Oncol. 2019

Long-term follow-up confirms OS benefit with Abiraterone in mCSPC

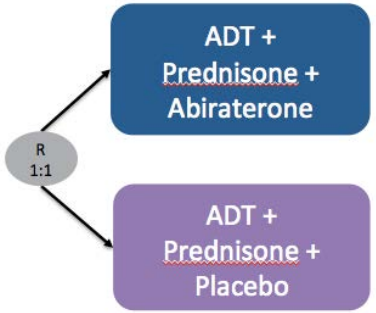
LATITUDE



STAMPEDE



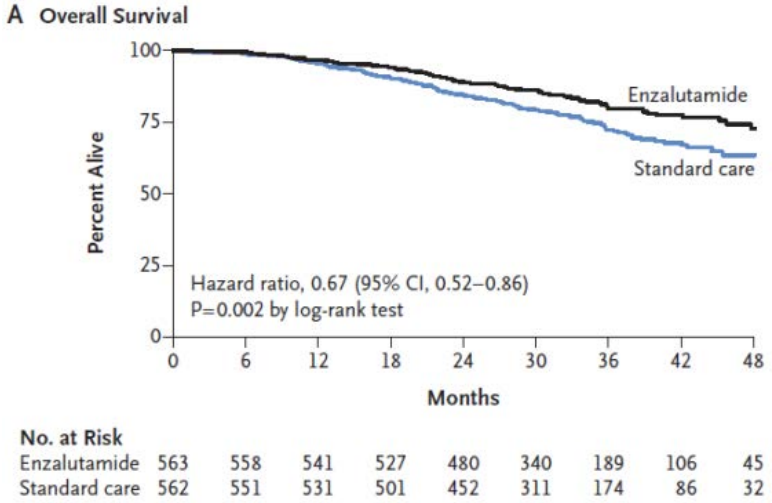
Study	N	Follow up	OS abiraterone	HR OS	95% CI
LATITUDE	1199	52 mo	53.3 mo	0.66	0.56-0.78
STAMPEDE	1003	72 mo	79 mo	0.60	0.50-0.71



Fizazi K, et al. Lancet Oncol 2019; 20: 686-700
James ND, et al. Ann Oncol 2020; 31 (suppl_4): S507-S549

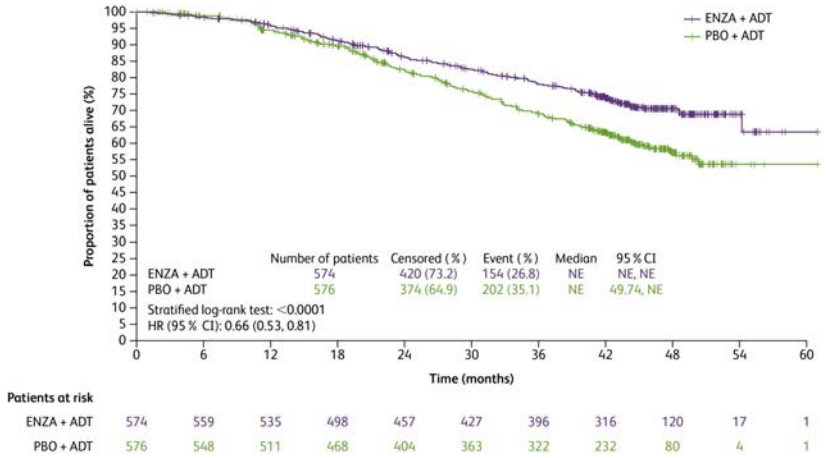
ADT + ARPI > ADT in M1 CSPC

ENZAMET (Enzalutamide)



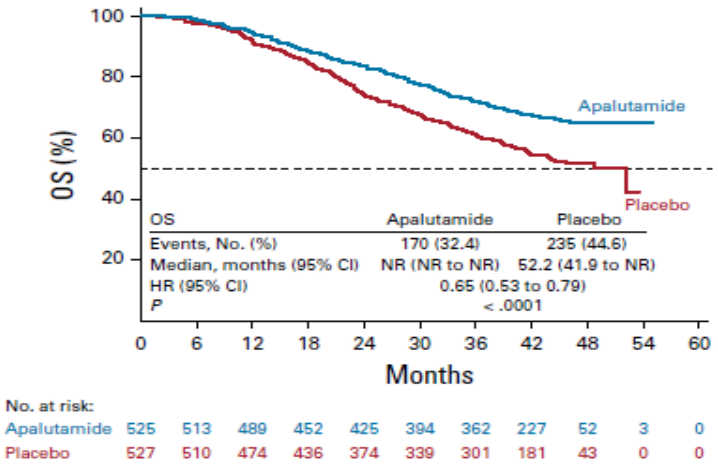
Davis I, NEJM 2019

ARCHES (Enzalutamide)



Armstrong A, ESMO 2021

TITAN (Apalutamide)



Chi K, J Clin Oncol 2021

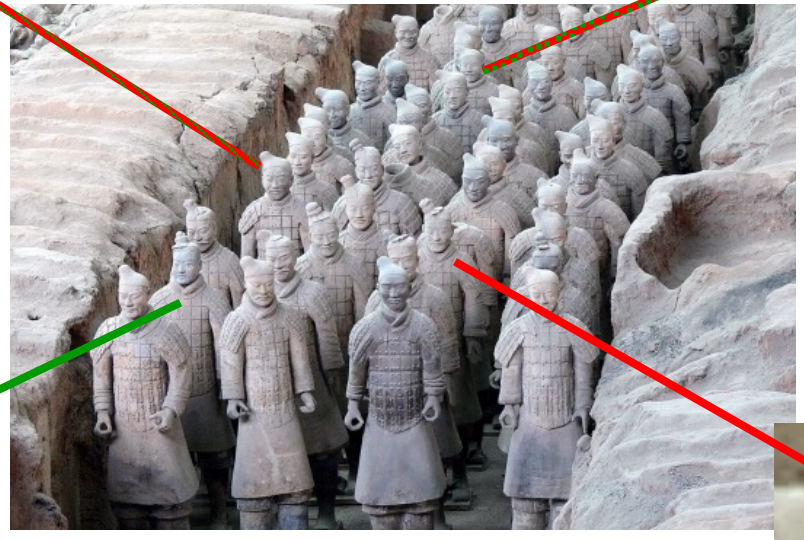
Should the systemic treatment differ according to timing and metastatic burden?

Timing and burden of metastases in M1 CSPC

De novo
Low burden

De novo
High burden

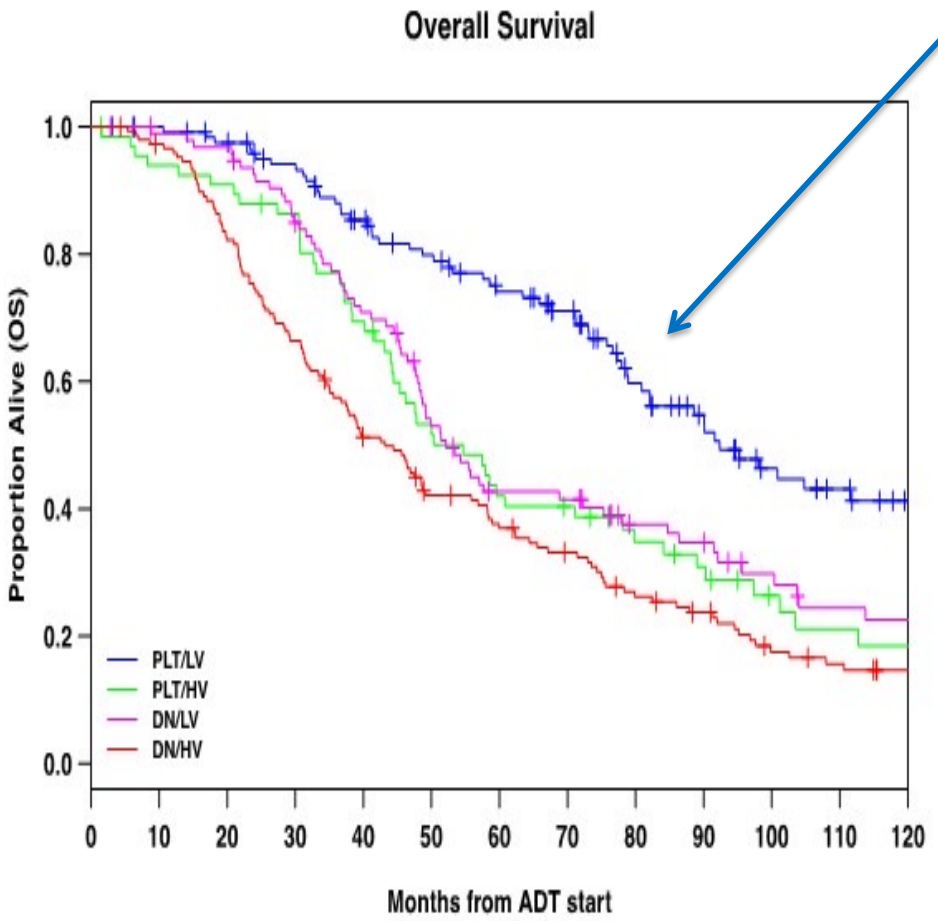
M1 Castrate-Sensitive Prostate Cancer (mCSPC)



Recurrence
Low burden

Recurrence
High burden

The outlier: M1 relapse and oligo



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

Gravis G, Eur Urol 2018

Francini E, Prostate 2018

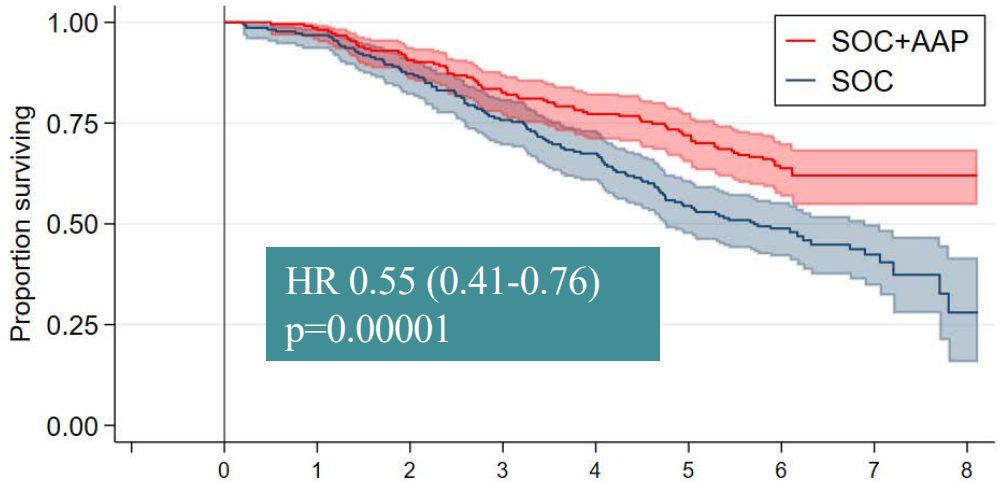
Docetaxel effect in mCSPC: Timing of metastases is more important than « Volume »

Subgroup	Progression free survival			Overall survival		
	Number of events/ patients	% difference (95% CI)	Change from baseline	Number of events/ patients	% difference (95% CI)	Change from baseline
Disease volume x timing of diagnosis						
Low volume, metachronous	**107/229**	**-1% (-15 to 12%)**	**48% to 47%**	**70/229**	**0% (-10 to 12%)**	**72% to 72%**
Low volume, synchronous	346/582	8% (1 to 15%)	37% to 45%	267/582	8% (0 to 16%)	52% to 60%
High volume, metachronous	92/132	11% (-2 to 24%)	14% to 25%	78/132	10% (-1 to 26%)	28% to 38%
High volume, synchronous	856/1044	12% (7 to 16%)	11% to 23%	736/1044	12% (7 to 18%)	26% to 39%
Disease volume x clinical T stage						
Low volume, cT-stage 1-3	302/569	5% (-2 to 12%)	41% to 46%	225/569	4% (-3 to 11%)	58% to 62%
Low volume, cT-stage 4	61/85	12% (-6 to 29%)	24% to 36%	51/85	16% (-3 to 36%)	38% to 54%
High volume, cT-stage 1-3	562/709	8% (4 to 13%)	14% to 22%	484/709	6% (0 to 12%)	29% to 35%
High volume, cT-stage 4	**157/192**	**27% (17 to 37%)**	**8% to 35%**	**136/192**	**35% (24 to 47%)**	**20% to 55%**

Vale C, ASCO 2022 (Abst 5070)

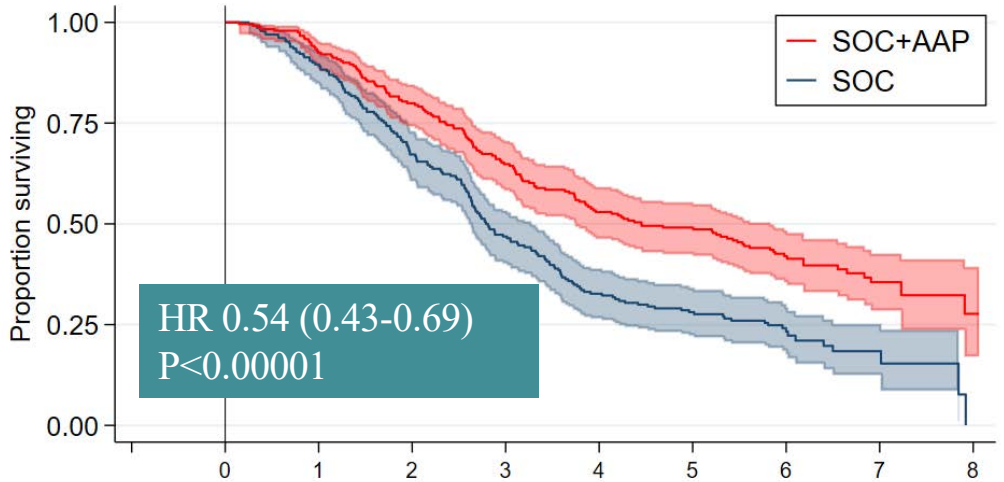
Second generation ARPI active regardless of M1 burden (mostly *de novo* pts)

Low risk



HR 0.66 (0.44-0.98)
p=0.041

High risk



HR 0.54 (0.41-0.70)
P<0.001

James N, ESMO 2020

Should we intensify even more systemic treatment for men with mCSPC?

Taxanes and Second generation AR pathway inhibitors playing together?

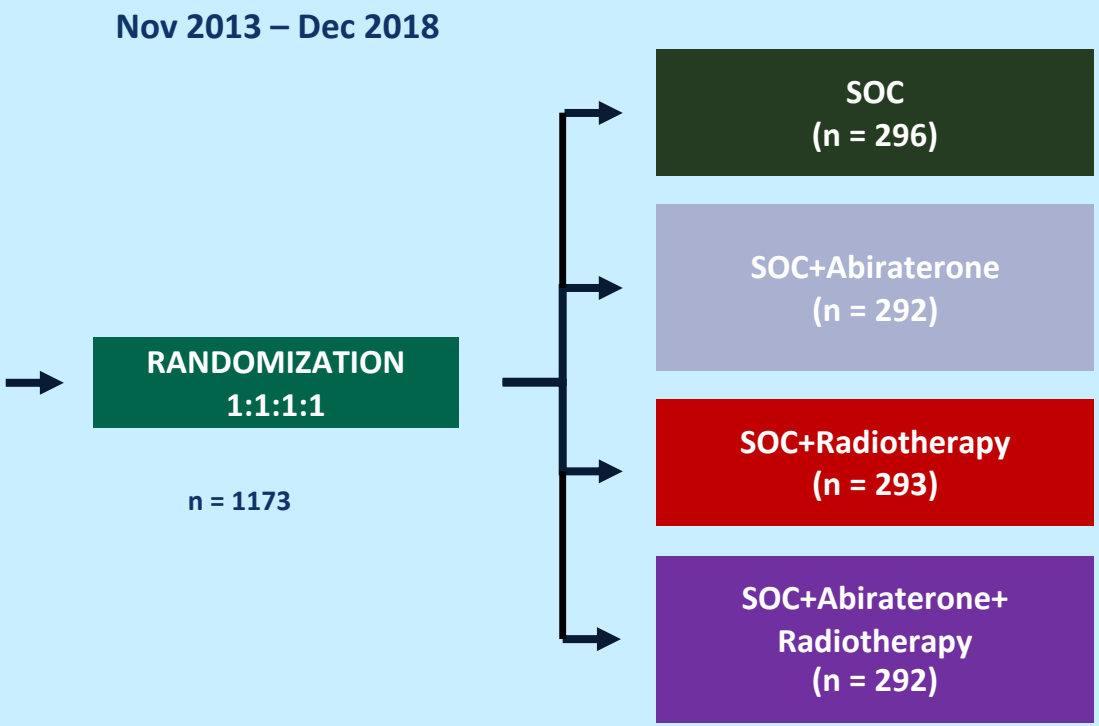
Design of PEACE-1 (2x2)

Key Eligibility Criteria
De novo mCSPC
Distant metastatic disease by ≥ 1 lesion on bone scan and/or CT scan
ECOG PS 0 -2

On-Study Requirement
Continuous ADT

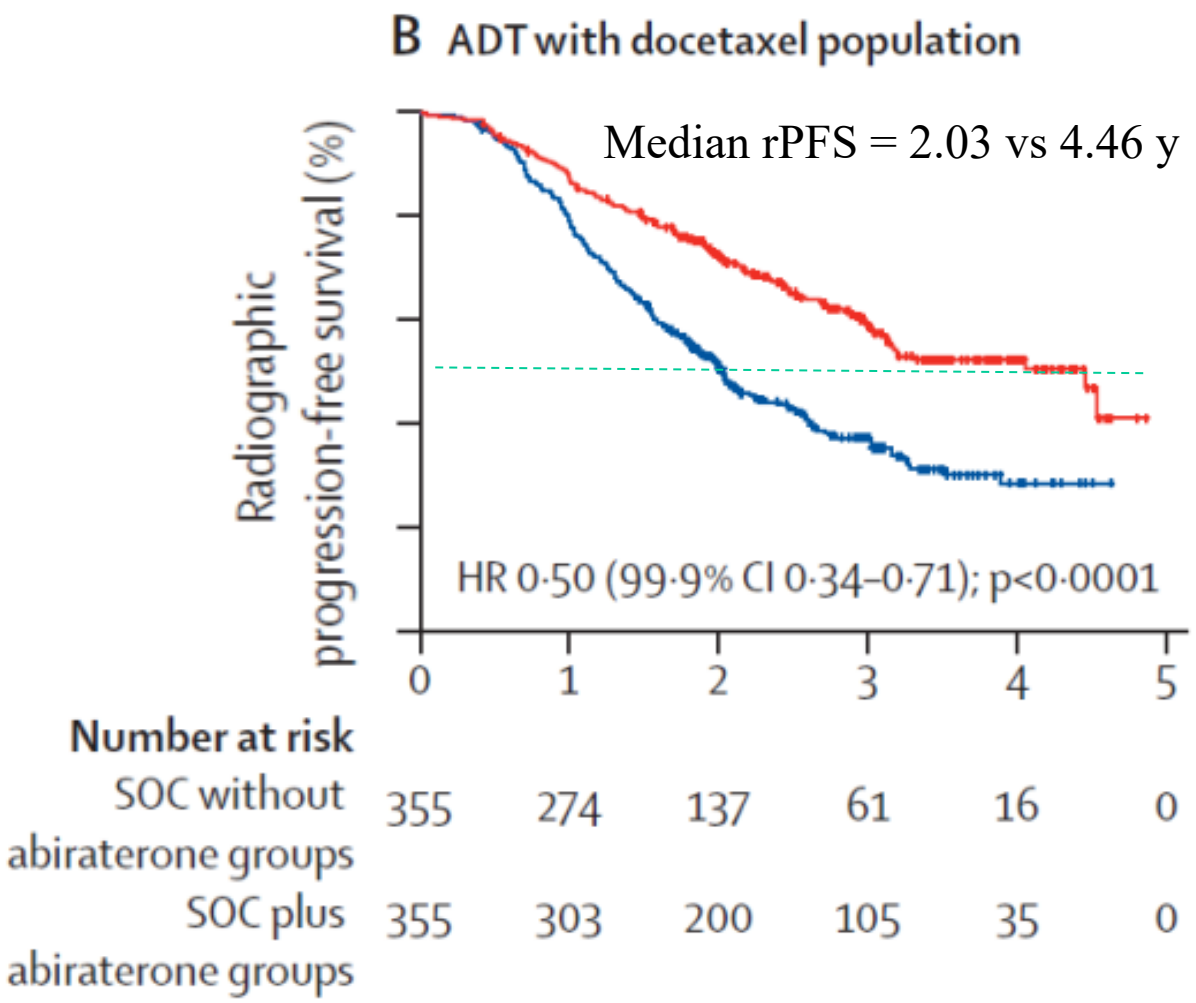
Permitted
ADT ≤ 3 months

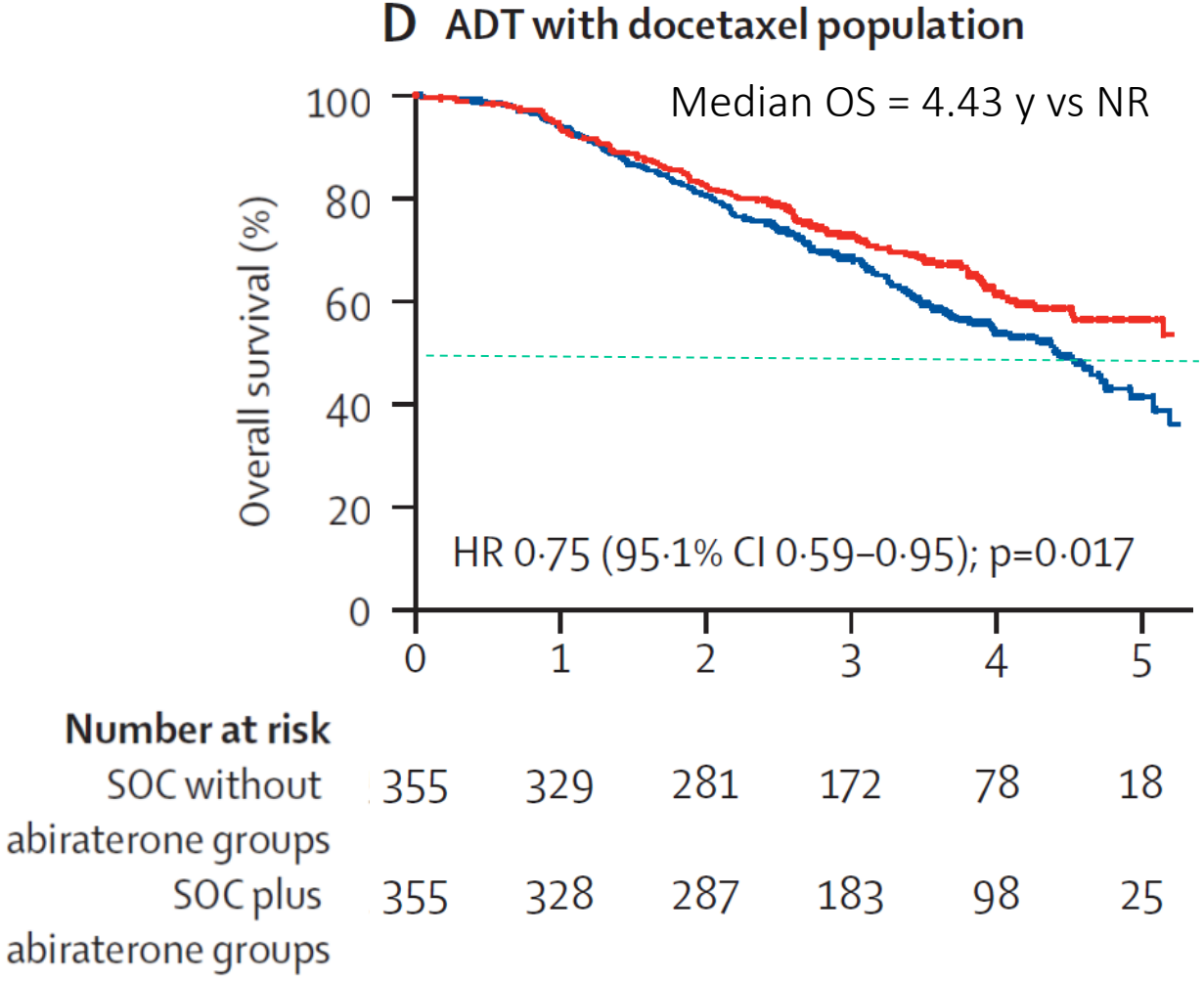
Stratification
ECOG PS (0 vs 1-2)
Metastatic sites (LN vs bone vs visceral)
Type of castration (orchidectomy vs LHRH agonist vs LHRH antagonist)
Docetaxel (yes vs no)



ECOG PS, Eastern Cooperative Oncology Group performance status

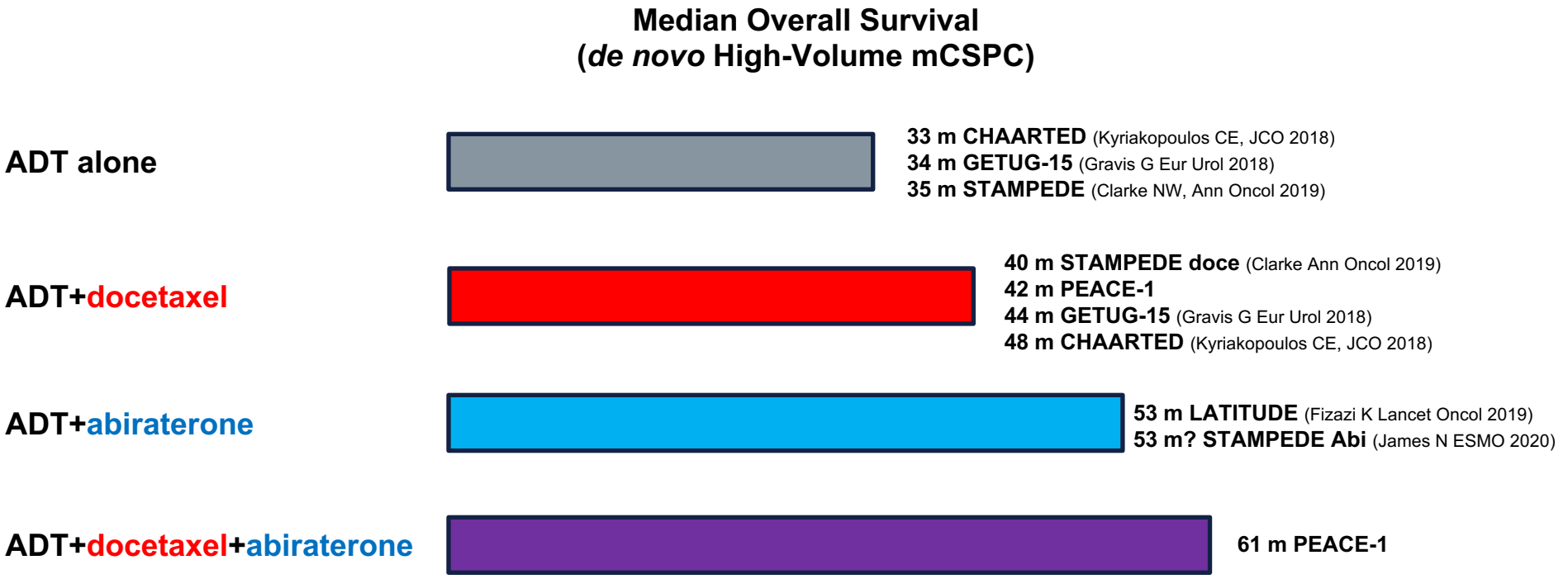
PEACE-1: ADT+Docetaxel+Abiraterone > ADT+Docetaxel





Fizazi K, Lancet 2022

Triplet PEACE-1 OS results in the context of recent data



PEACE-1: Grade 3-5 Toxicity on study treatments (ADT+docetaxel 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, Lancet 2022

ARASENS Study Design

Global, randomized, double-blind, placebo-controlled phase III study (NCT02799602)

Patients (N=1306)
- mHSPC
- ECOG PS 0 or 1
- Candidates for ADT and docetaxel

Stratification
- Extent of disease: M1a vs M1b vs M1c
- ALP < vs ≥ ULN

1:1 randomization (N=1305*)

Darolutamide 600 mg twice daily + ADT + **Docetaxel × 6**

Placebo twice daily + ADT + **Docetaxel × 6**

Primary analysis

Data cut-off Oct 25, 2021

FPFV: Nov 2016
LPFV: Jun 2018

Endpoints

Primary: OS

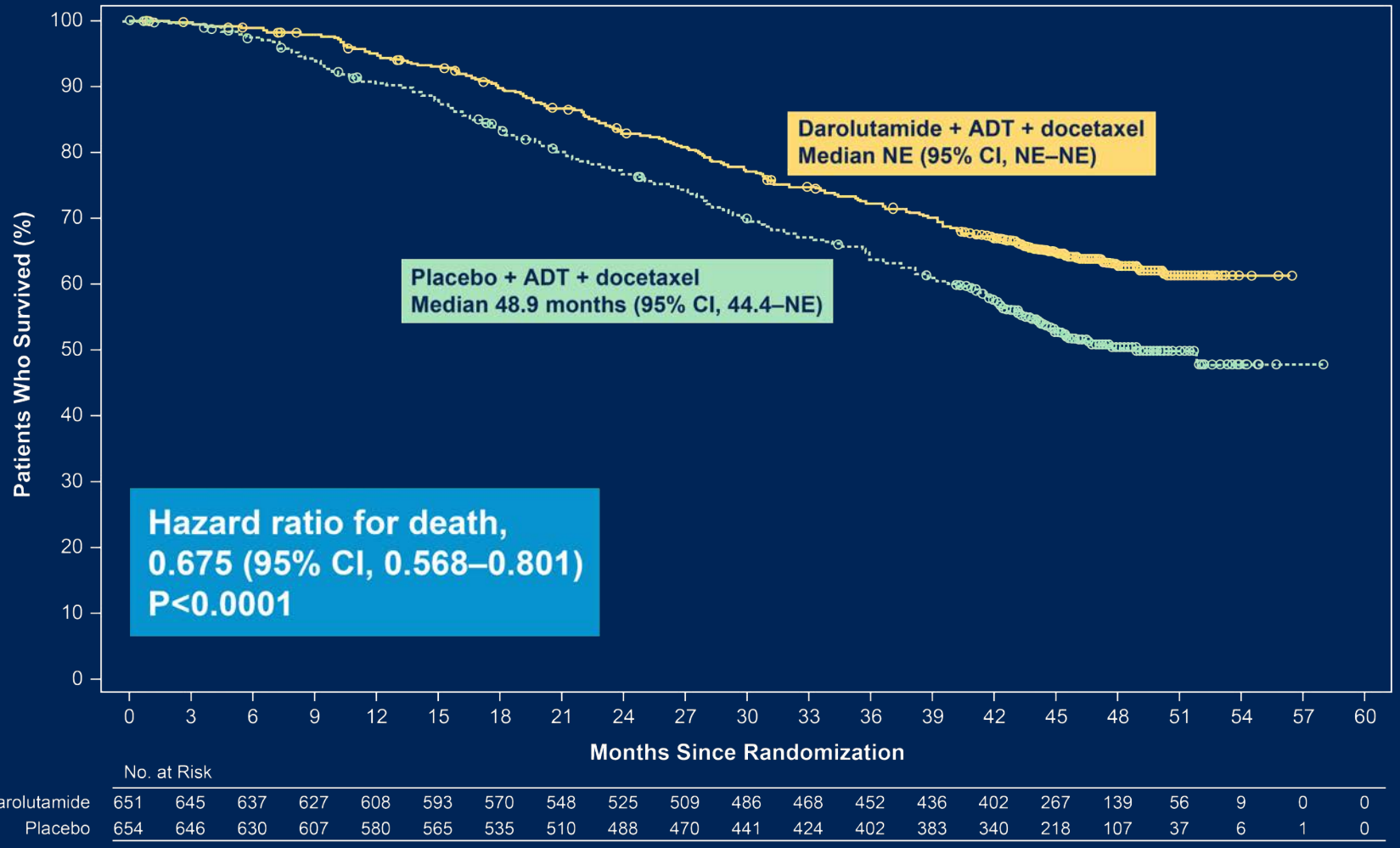
Secondary
- Time to CRPC
- Time to pain progression
- SSE-free survival
- Time to first SSE
- Time to initiation of subsequent systemic antineoplastic therapy
- Time to worsening of disease-related physical symptoms
- Time to initiation of opioid use for ≥7 consecutive days
- Safety

- The primary analysis was planned to occur after ~509 deaths
- Secondary efficacy endpoints were tested hierarchically

*One enrolled patient was excluded from all analysis sets because of Good Clinical Practice violations.-ALP, alkaline phosphatase; CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; FPFV, first patient first visit; LPFV, last patient first visit; M1a, nonregional lymph node metastases only; M1b, bone metastases ± lymph node metastases; M1c, visceral metastases ± lymph node or bone metastases; Q3W, every 3 weeks; SSE, symptomatic skeletal event; ULN, upper limit of normal.

ARASENS Primary Endpoint*: Overall Survival

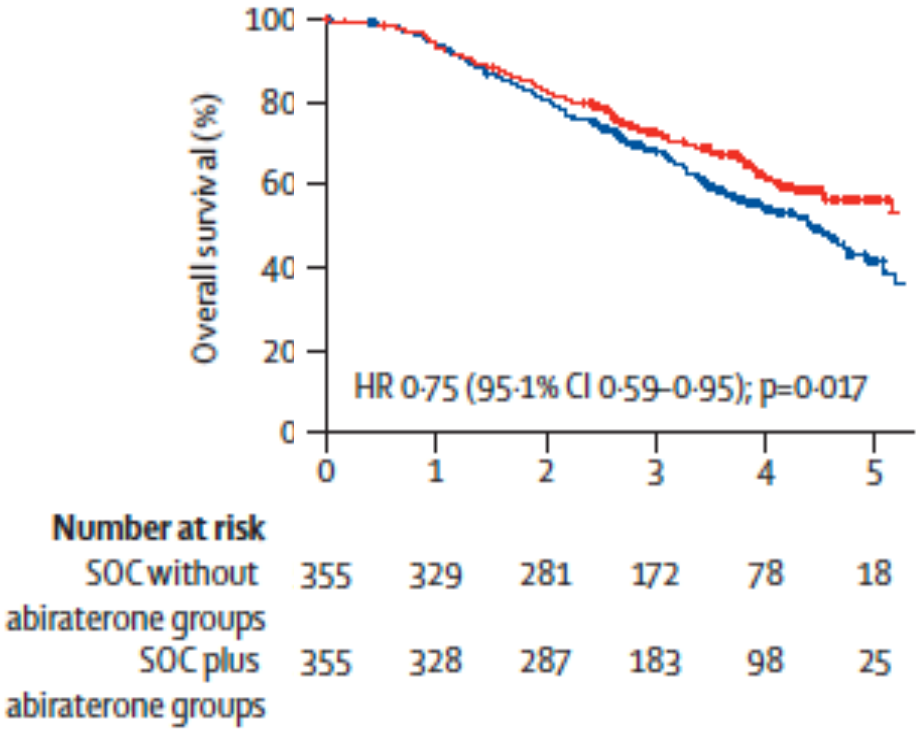
Darolutamide significantly reduced the risk of death by 32.5%



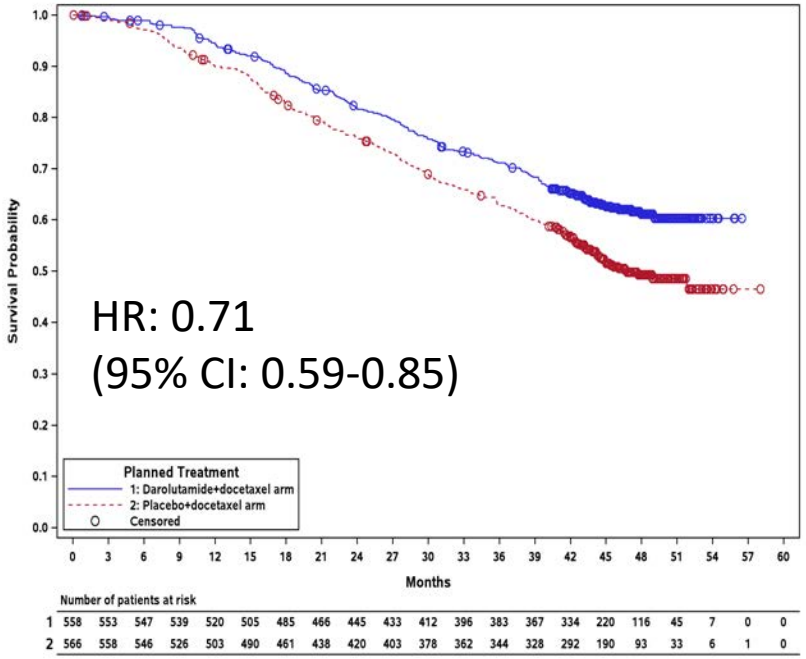
*Primary analysis occurred after 533 deaths (darolutamide, 229; placebo, 304). CI, confidence interval; NE, not estimable.

Consistent OS benefit with Triplet treatment in men with de novo mCSPC

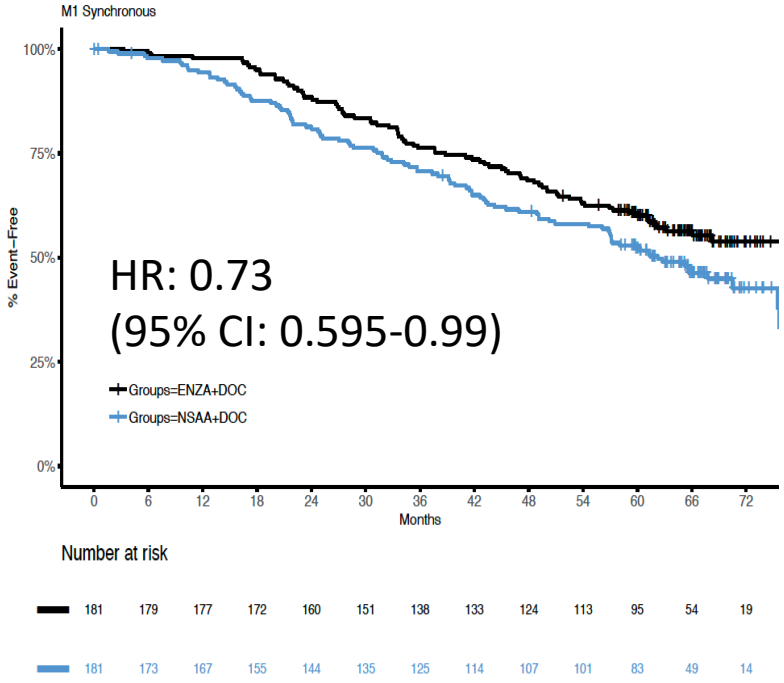
ADT + Doc + Abi > ADT + Doc
PEACE-1 (All De novo)



ADT + Doc + Daro > ADT + Doc
ARASENS (All De novo)



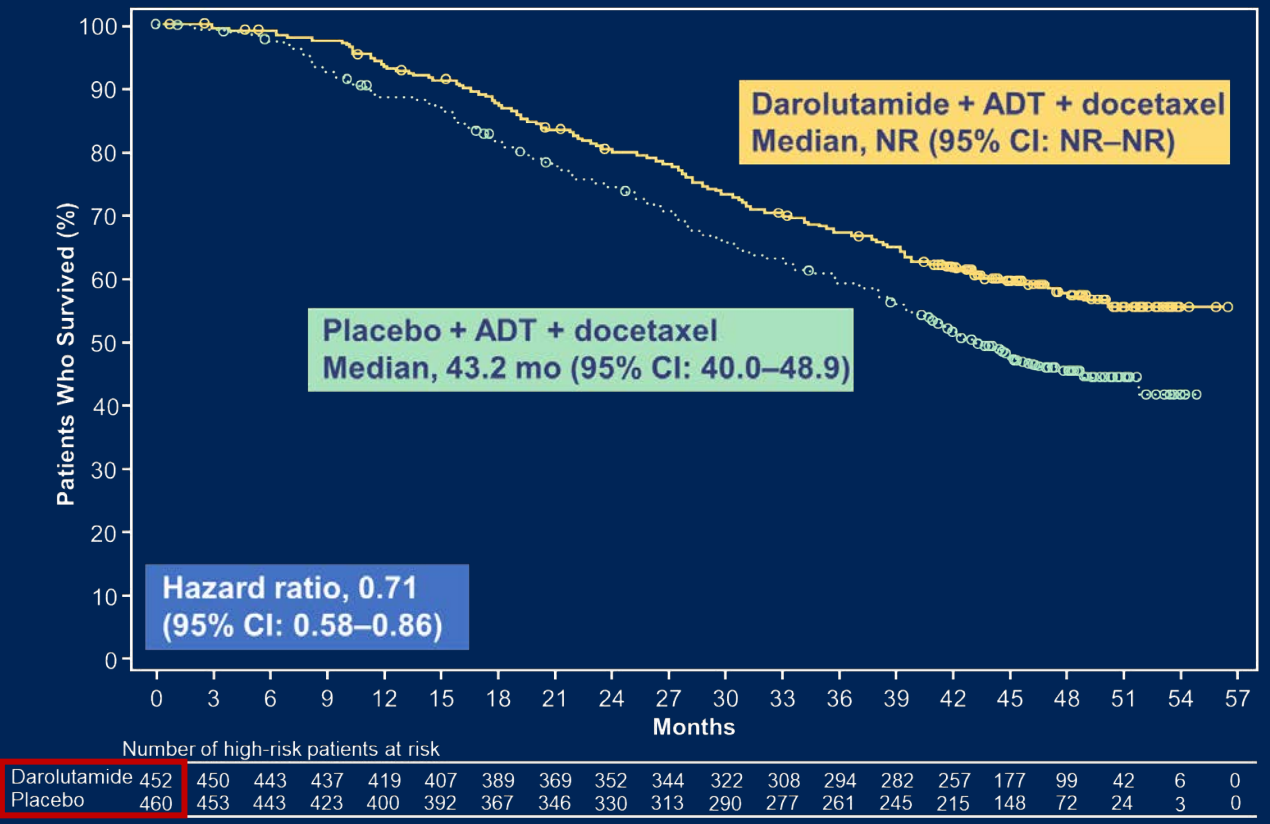
ADT + Doc + Enza > ADT + Doc
ENZAMET



Fizazi K Lancet 2022; Smith M NEJM 2022; Davis I ASCO 2022

ARASENS RISK Subgroups: Overall Survival

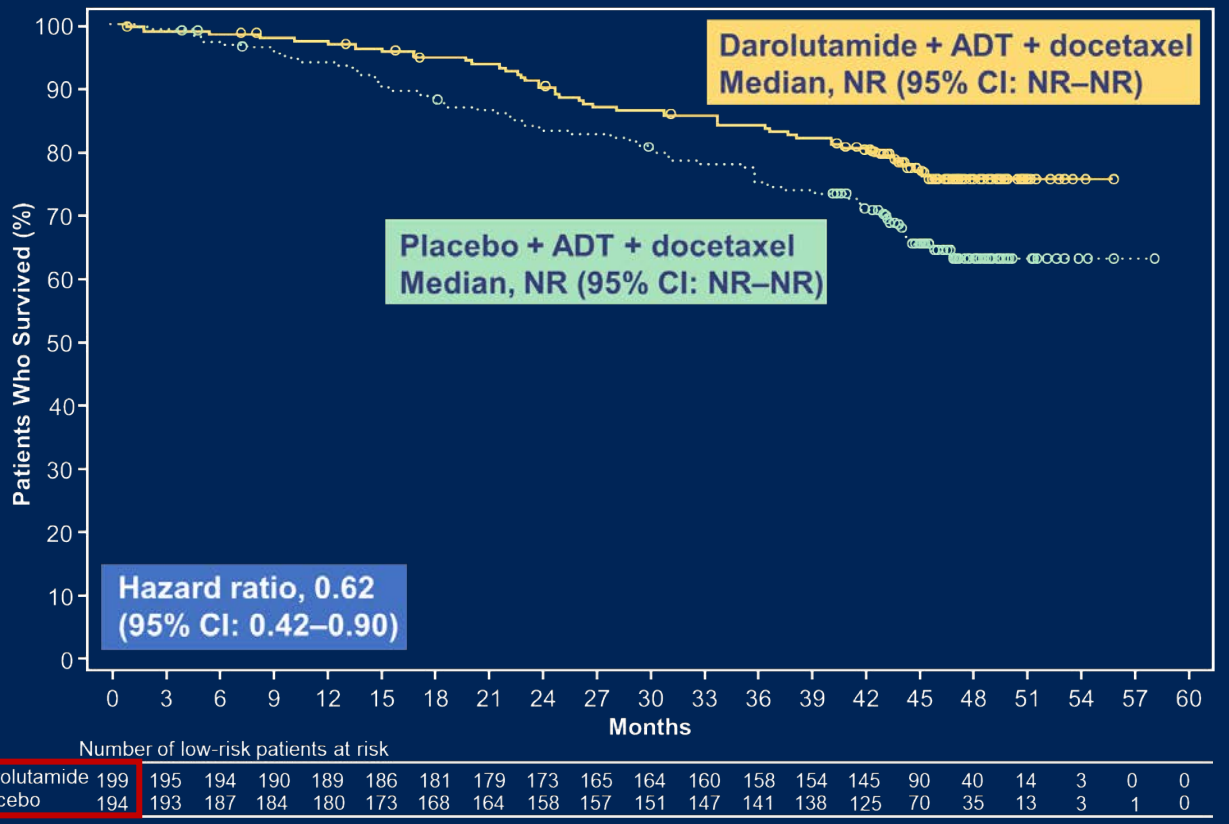
High-risk mHSPC



Number of high-risk patients at risk

Darolutamide	452	450	443	437	419	407	389	369	352	344	322	308	294	282	257	177	99	42	6	0
Placebo	460	453	443	423	400	392	367	346	330	313	290	277	261	245	215	148	72	24	3	0

Low-risk mHSPC



Number of low-risk patients at risk

Darolutamide	199	195	194	190	189	186	181	179	173	165	164	160	158	154	145	90	40	14	3	0	0
Placebo	194	193	187	184	180	173	168	164	158	157	151	147	141	138	125	70	35	13	3	1	0

Many reasons to choose a Triplet (in fit mCSPC men)?

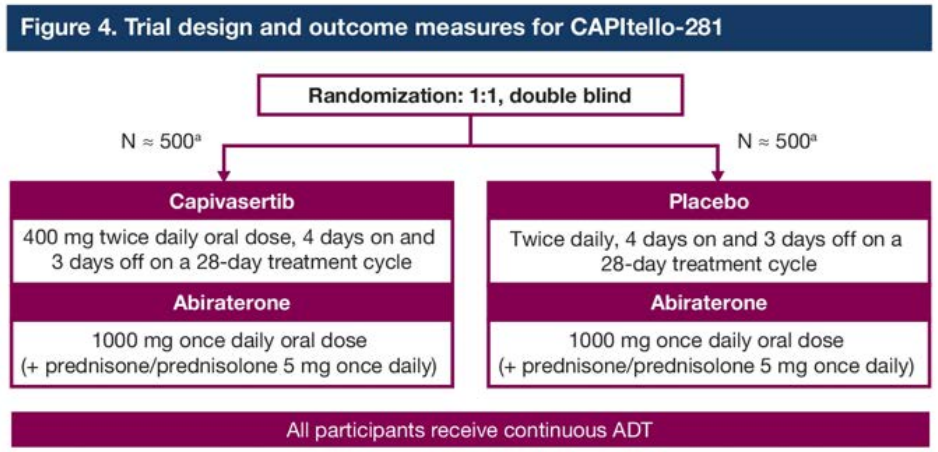
- The triplet efficacy makes sense: both ARSI and Taxanes active after one has failed:
  - COU 301/AFFIRM (ARSI post-taxane)
  - CARD (Taxane post-ARSI)
- Poly-therapy needed to target heterogeneity (less resistant cells)
- If an ADT-ARSI doublet is used for CSPC, then docetaxel will be used anyway when mCRPC occurs! Why not use it earlier (mCSPC) with more efficacy and less toxicity?
- At the end of the day, 6 cycles of docetaxel is short and mostly well tolerated with G-CSF support

Take-Home Message: M1 CSPC

- Current standard (2023):
  - **De novo, High Volume:**
    - **Fit: ADT+docetaxel+abiraterone/pred or Darolutamide (or Enza)**
    - **Unfit for Docetaxel: ADT+NHT**
  - **De novo, Low Volume:**
    - **At least ADT+NHT (PEACE-1 RT data: tomorrow!)**
    - **Discuss systemic triplet on a one by one basis (young, fit, bone)?**
  - **Relapse (LV or HV): ADT+NHT ? (scarce data)**
  - **Frail/very elderly patients: ADT alone ?**
- Next-generation trial stratified on clinical/molecular biomarkers (PEACE-6 and others)

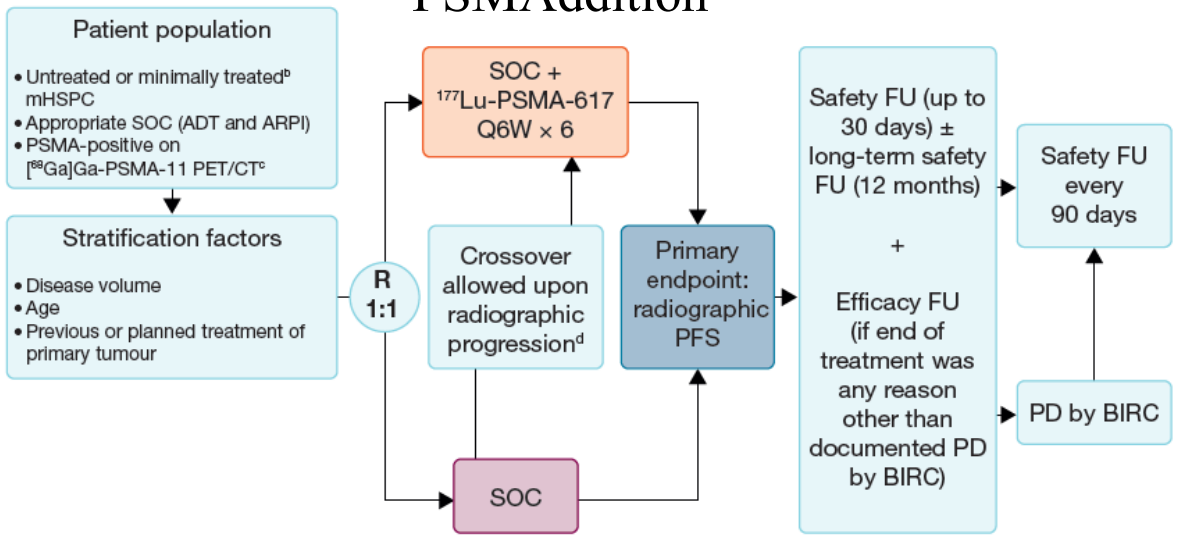
Examples of ongoing trials in mCSPC

Capivasertib: Akt inhibitor (PTEN loss)



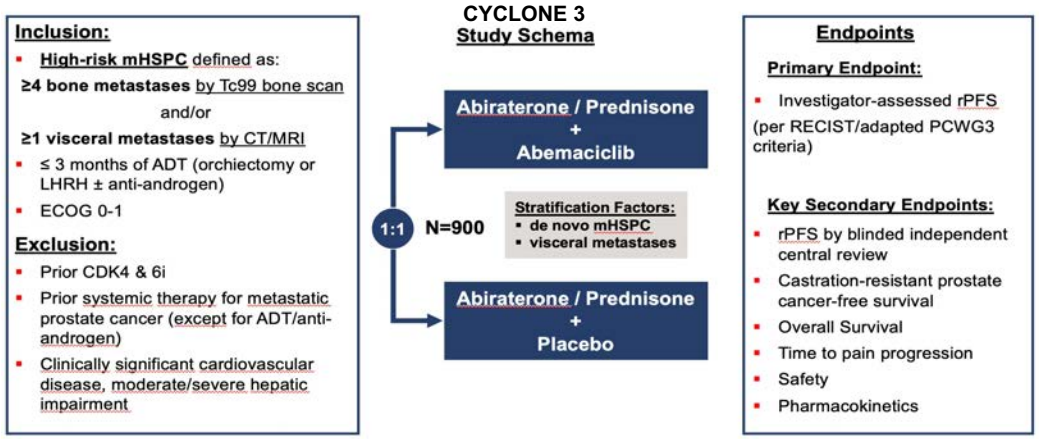
Crabb et al. JCO 2020; Crabb et al. ASCO GU 2022

PSMAddition



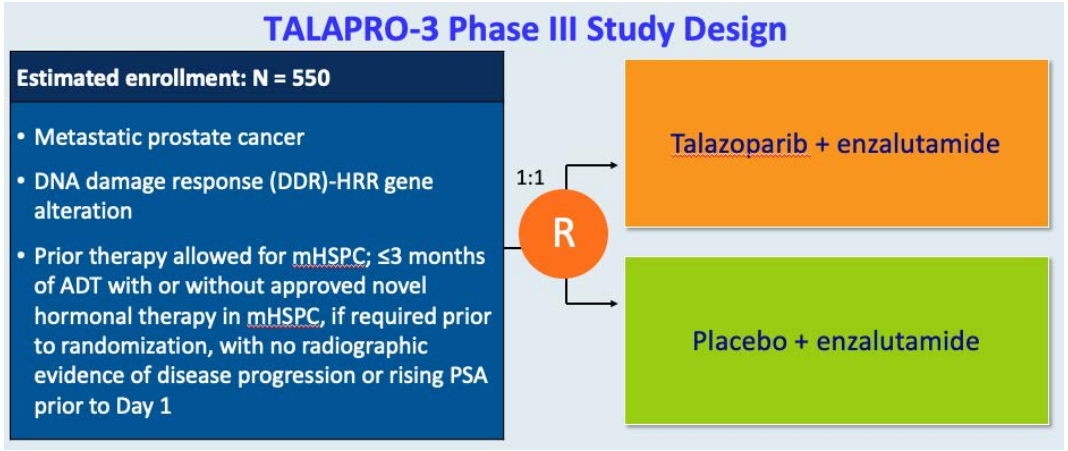
Sartor O et al. ASCO GU 2023

Abemaciclib: CDK4/6 inhibitor



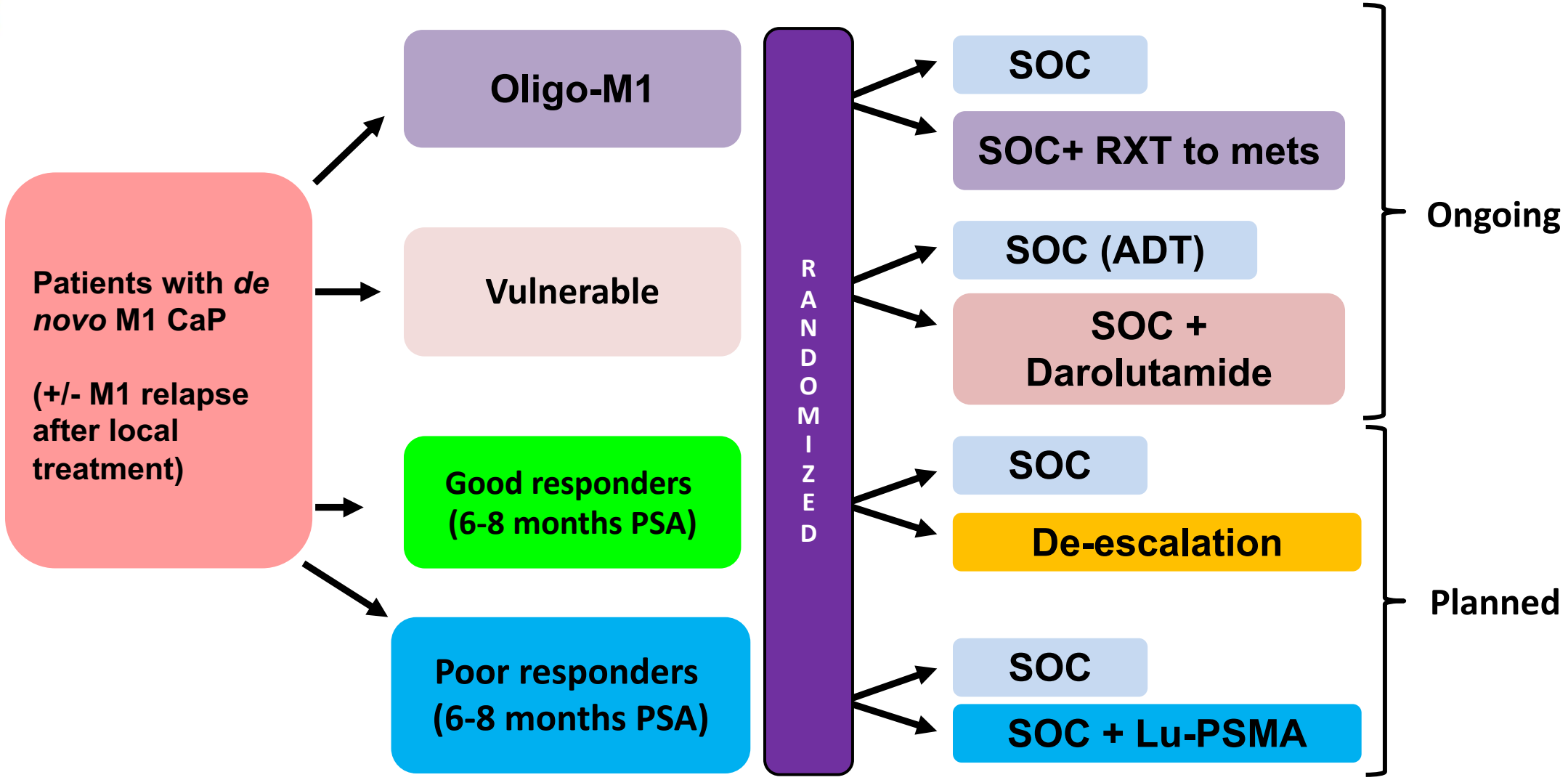
Smith MR et al. ASCO GU 2023

Talazoparib: PARP inhibitor



Agarwal N et al. ASCO 2022

The PEACE-6 program: Current European trials in M1 CSPC



Agenda

Module 1 – Current Management of Nonmetastatic Prostate Cancer — Dr Morgans

Module 2 – New Considerations in Treatment Intensification for Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) — Prof Fizazi

Module 3 – Available and Emerging Strategies for Newly Diagnosed Metastatic Castration-Resistant Prostate Cancer (mCRPC) — Dr McKay

Module 4 – Identification and Management of mCRPC with a Homologous Recombination Repair (HRR) Gene Abnormality — Dr Antonarakis

Module 5 – Management of Progressive mCRPC — Dr Sartor

Case Presentation: 64-year-old man diagnosed with metastatic HSPC and PSMA positivity in the pubic ramus, bilateral external iliac nodes and lungs

Dr Sandy Srinivas (Stanford, California)

RTP
RESEARCH
TO PRACTICE

UC San Diego Health

Available and Emerging Strategies for Newly Diagnosed Metastatic CRPC (mCRPC)

Rana R. McKay, MD

Associate Professor of Medicine and Urology

Moores Cancer Center

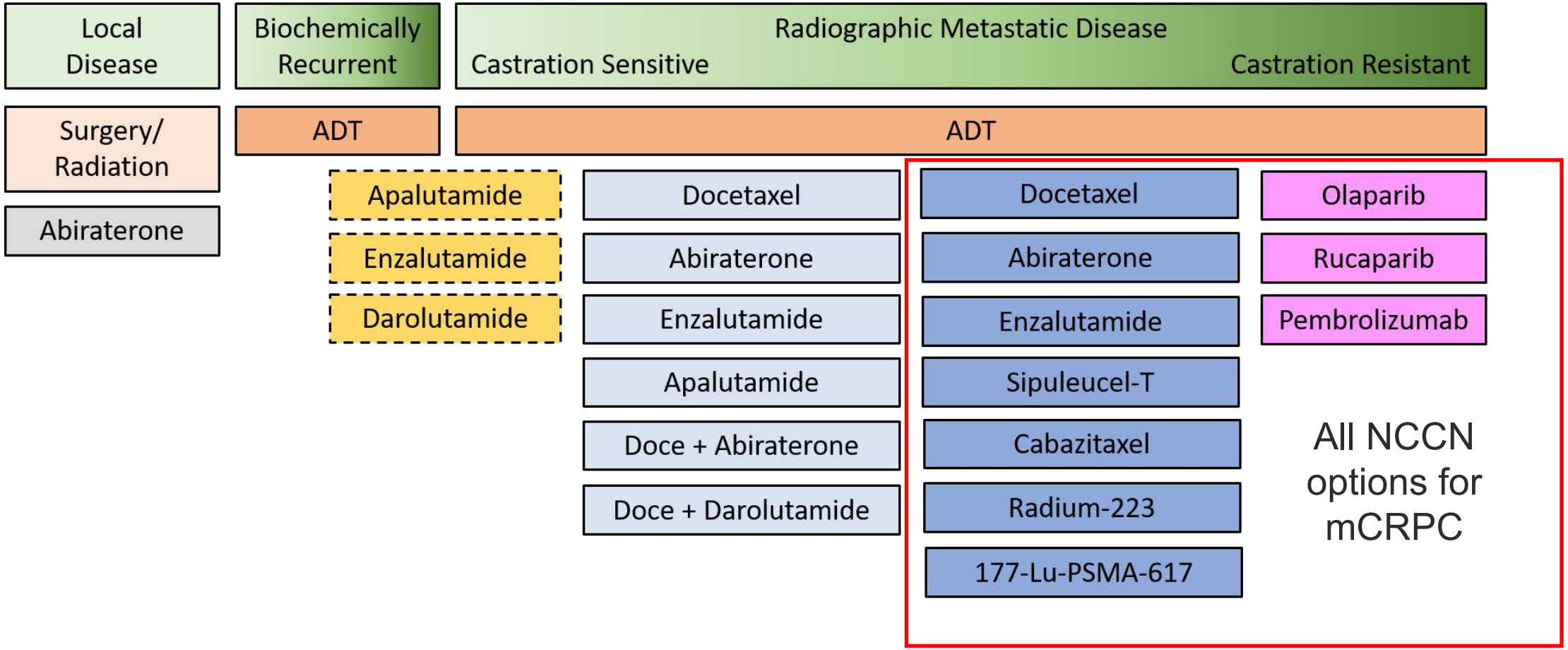
University of California San Diego

@DrRanaMcKay

Objectives

- Clinical and biologic factors impacting the selection of therapy for newly diagnosed mCRPC
- Findings from clinical trial and real-world data sets exploring the efficacy and safety of sipuleucel-T for mCRPC
- Data sets defining the role of secondary hormonal therapies for patients with mCRPC, including among those who have received one of these agents in an earlier disease setting
- Role of the CDK4/6 pathway in prostate cancer proliferation and resistance to AR-targeted therapy
- Available efficacy and safety findings with CDK4/6 inhibitors for mCRPC
- Design, eligibility criteria and primary and secondary endpoints of the Phase II/III CYCLONE 2 trial evaluating first-line abiraterone and prednisone with or without abemaciclib for mCRPC

Treatment Landscape for Advanced Prostate Cancer



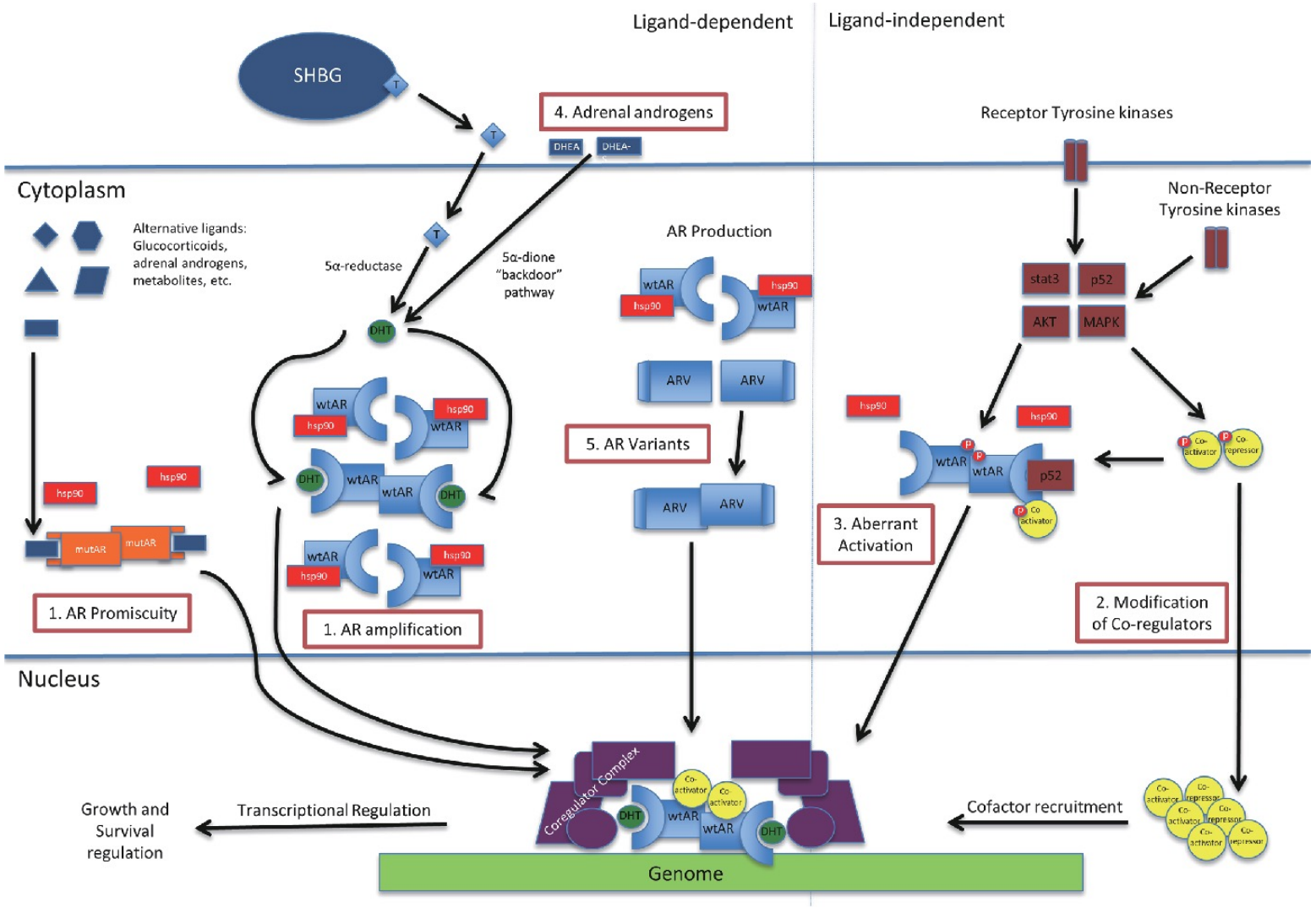
ADT is still the mainstay of therapy…but treatments have evolved for different disease states

NCCN Guidelines Version 1.2023

Factors that Impact Treatment Decision

Disease Factors

Mechanisms of Resistance in Castration Resistant Prostate Cancer



Chandrasekar et al, Transl Androl Urol, 2015

NCCN Guidelines – Systemic Therapy for M1 CRPC

National Comprehensive Cancer Network®

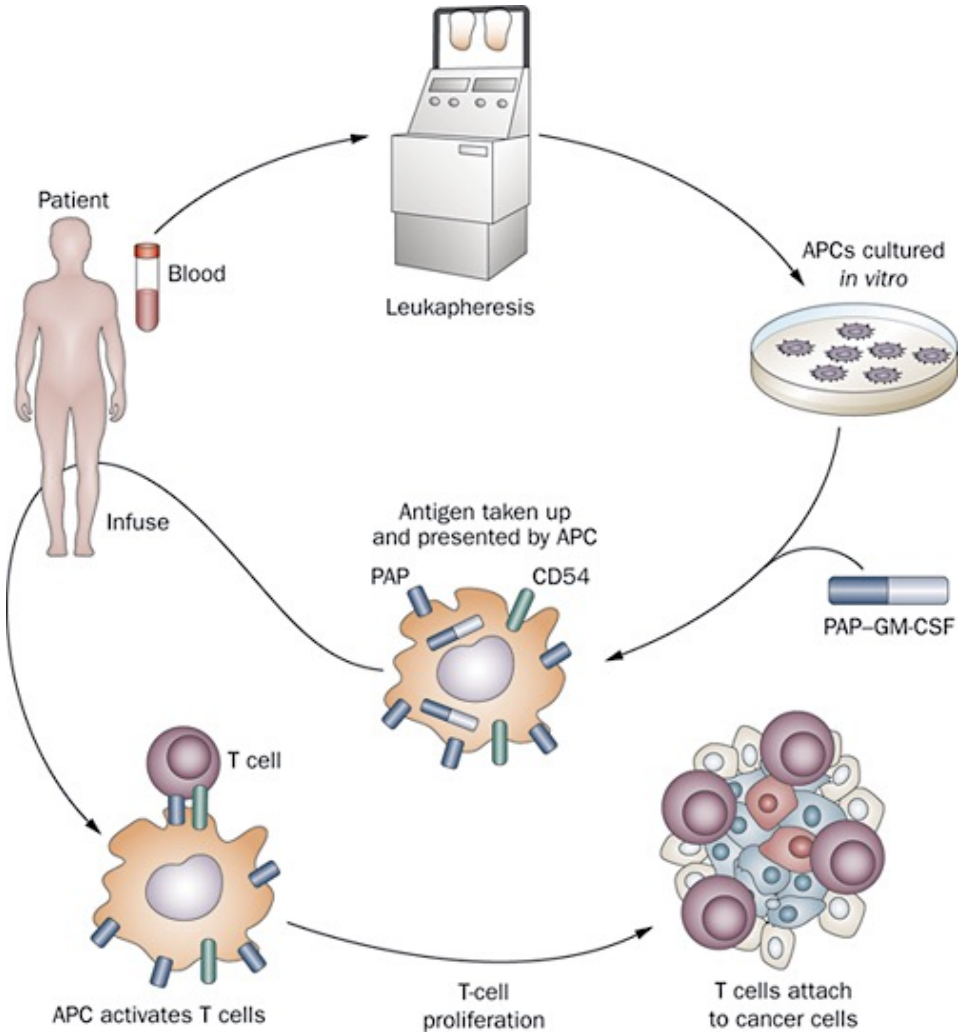
NCCN Guidelines Version 1.2023
Prostate Cancer

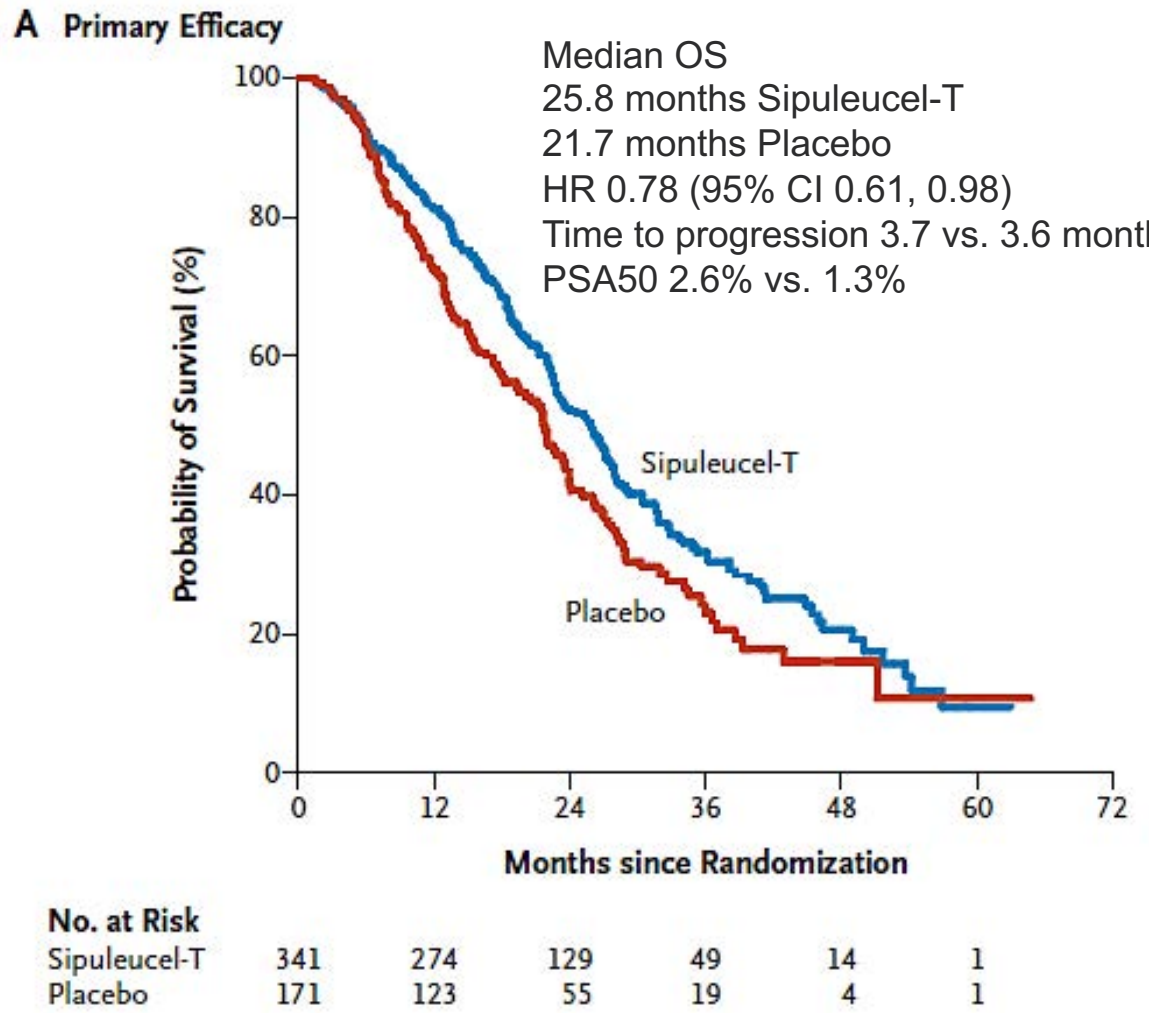
NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[iii,kkk,lll]

No prior docetaxel/no prior novel hormone therapy[mmm]	Prior novel hormone therapy/no prior docetaxel[mmm,sss]
• Preferred regimens ▸ Abiraterone[u,nnn] (category 1[ooo]) ▸ Docetaxel[fff,ppp] (category 1) ▸ Enzalutamide[u] (category 1) • Useful in certain circumstances ▸ Radium-223[rrr] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[fff,qqq] (category 1) • Other recommended regimens ▸ Other secondary hormone therapy[u]	• Preferred regimens ▸ Docetaxel (category 1)[fff] • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[fff,jjj] ▸ Olaparib for HRRm (category 1)[ttt] ▸ Radium-223[rrr] for symptomatic bone metastases (category 1) ▸ Rucaparib for BRCA mutation[uuu] ▸ Sipuleucel-T[fff,qqq] • Other recommended regimens ▸ Abiraterone[u,nnn] ▸ Abiraterone + dexamethasone[nnn,vvv] ▸ Enzalutamide[u] ▸ Other secondary hormone therapy[u]
Prior docetaxel/no prior novel hormone therapy[mmm]	**Prior docetaxel and prior novel hormone therapy[mmm,sss]**
• Preferred regimens ▸ Abiraterone[u,nnn] (category 1) ▸ Cabazitaxel[fff] ▸ Enzalutamide[u] (category 1) • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[fff,jjj] ▸ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[fff] ▸ Radium-223[rrr] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[fff,qqq] • Other recommended regimens ▸ Other secondary hormone therapy[u]	• Useful in certain circumstances ▸ Lutetium Lu 177 vipivotide tetraxetan (Lu-177–PSMA-617) for PSMA-positive metastases (category 1)[www] (The following systemic therapies are category 2B if visceral metastases are present) • Preferred regimens ▸ Cabazitaxel[fff] (category 1[ooo]) ▸ Docetaxel rechallenge[fff] • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[fff,jjj] ▸ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[fff] ▸ Olaparib for HRRm (category 1[ooo])[ttt] ▸ Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb[fff] ▸ Radium-223[rrr] for symptomatic bone metastases (category 1[ooo]) ▸ Rucaparib for BRCA mutation[uuu] • Other recommended regimens ▸ Abiraterone[u,nnn] ▸ Enzalutamide[u] ▸ Other secondary hormone therapy[u]

Sipuleucel-T

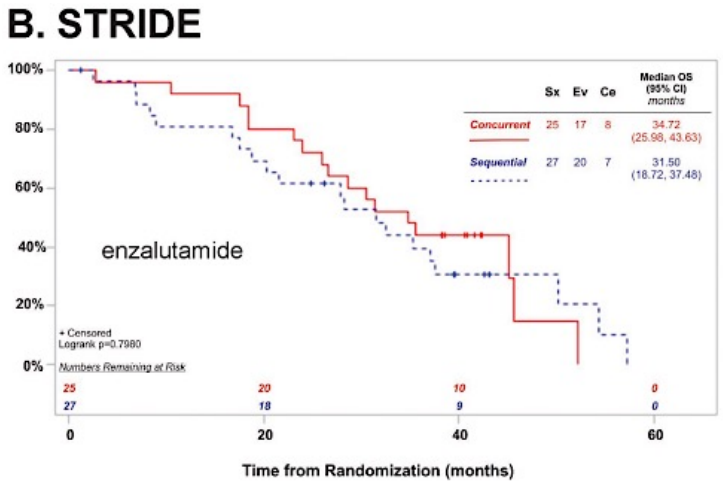


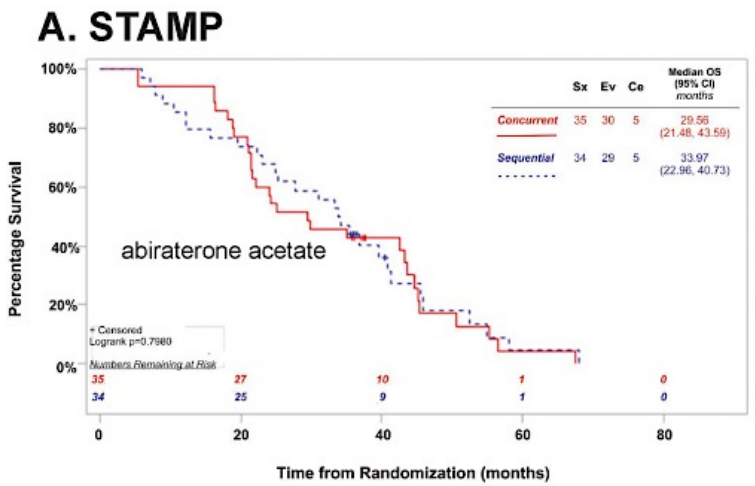


Median OS
25.8 months Sipuleucel-T
21.7 months Placebo
HR 0.78 (95% CI 0.61, 0.98)
Time to progression 3.7 vs. 3.6 months
PSA50 2.6% vs. 1.3%

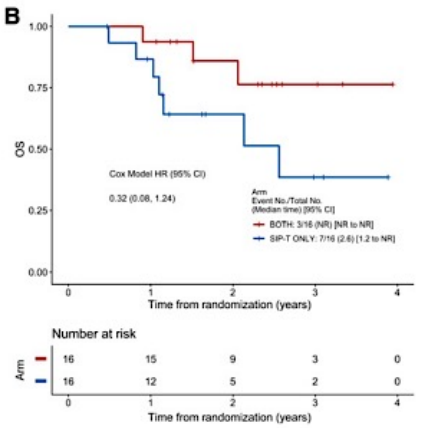
Role of Sipuleucel-T in the Modern Era

Prospective
Concurrent or Sequential ARTA

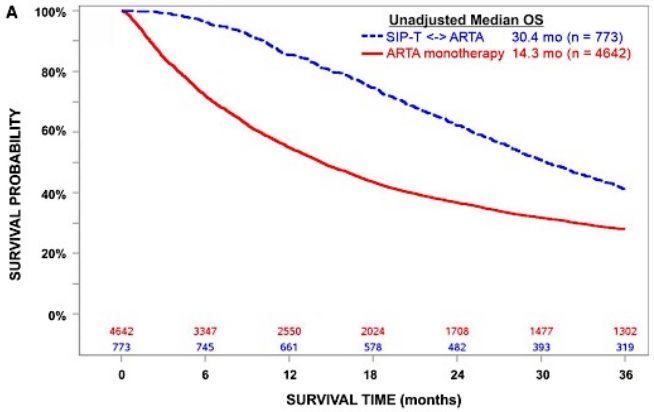




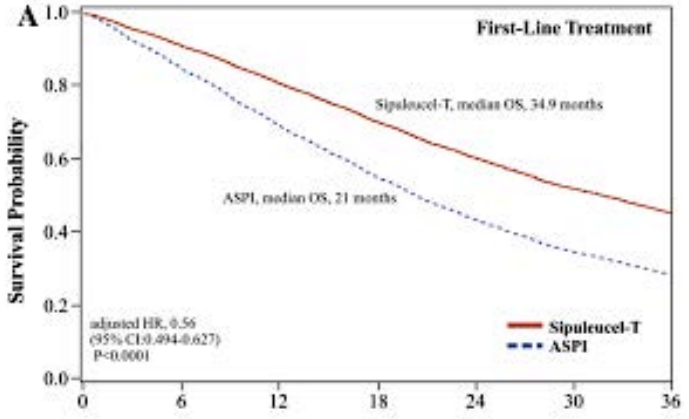
Prospective
Sipuleucel-T +/- Radium-223

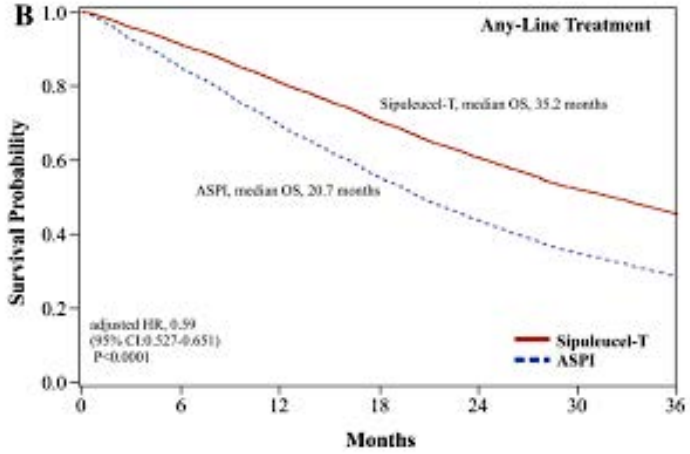


Retrospective
Concurrent/Sequential ARTA



Retrospective
First-Line Any Line





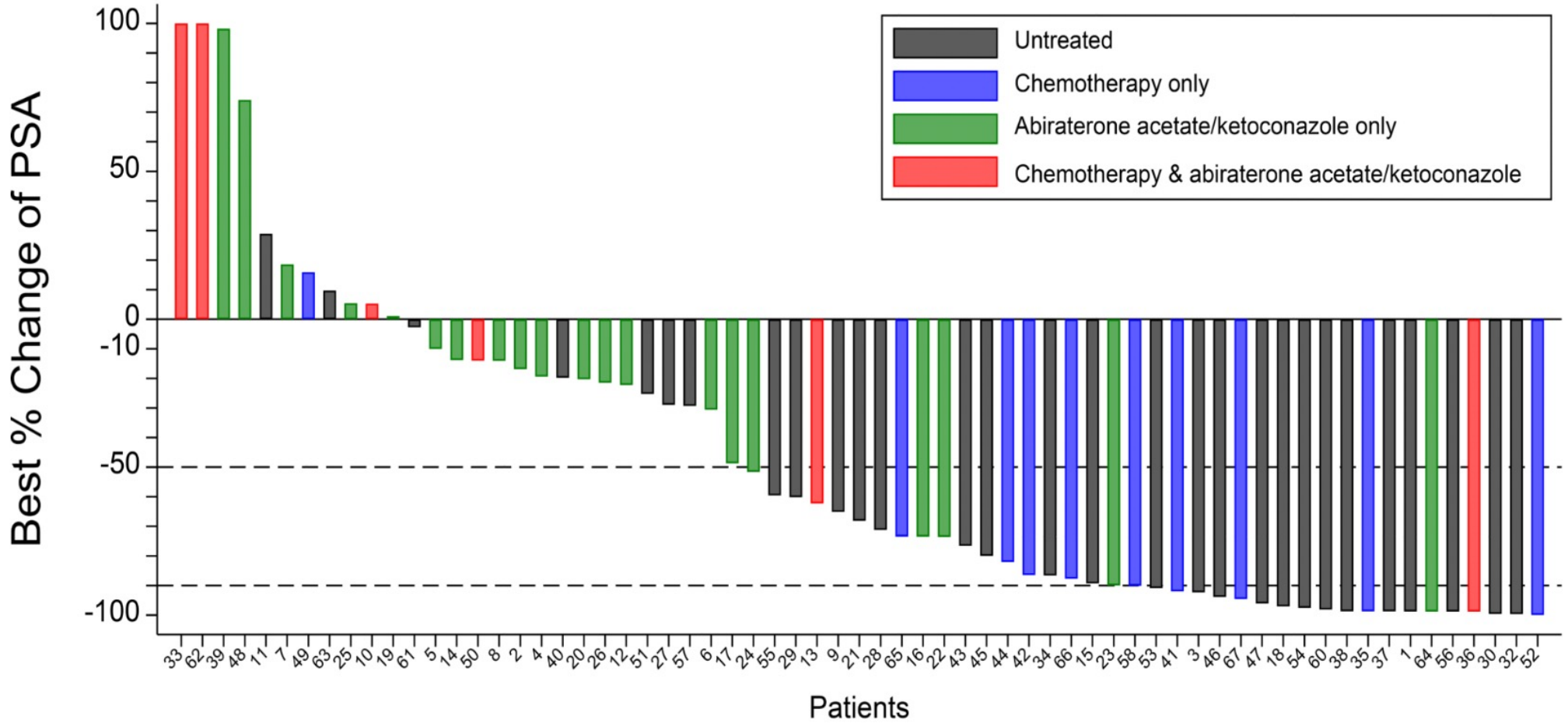
Antonarakis et al, CCR, 2023
Hafron et al, Adv Ther, 2022
McKay et al, Adv Ther, 2020

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

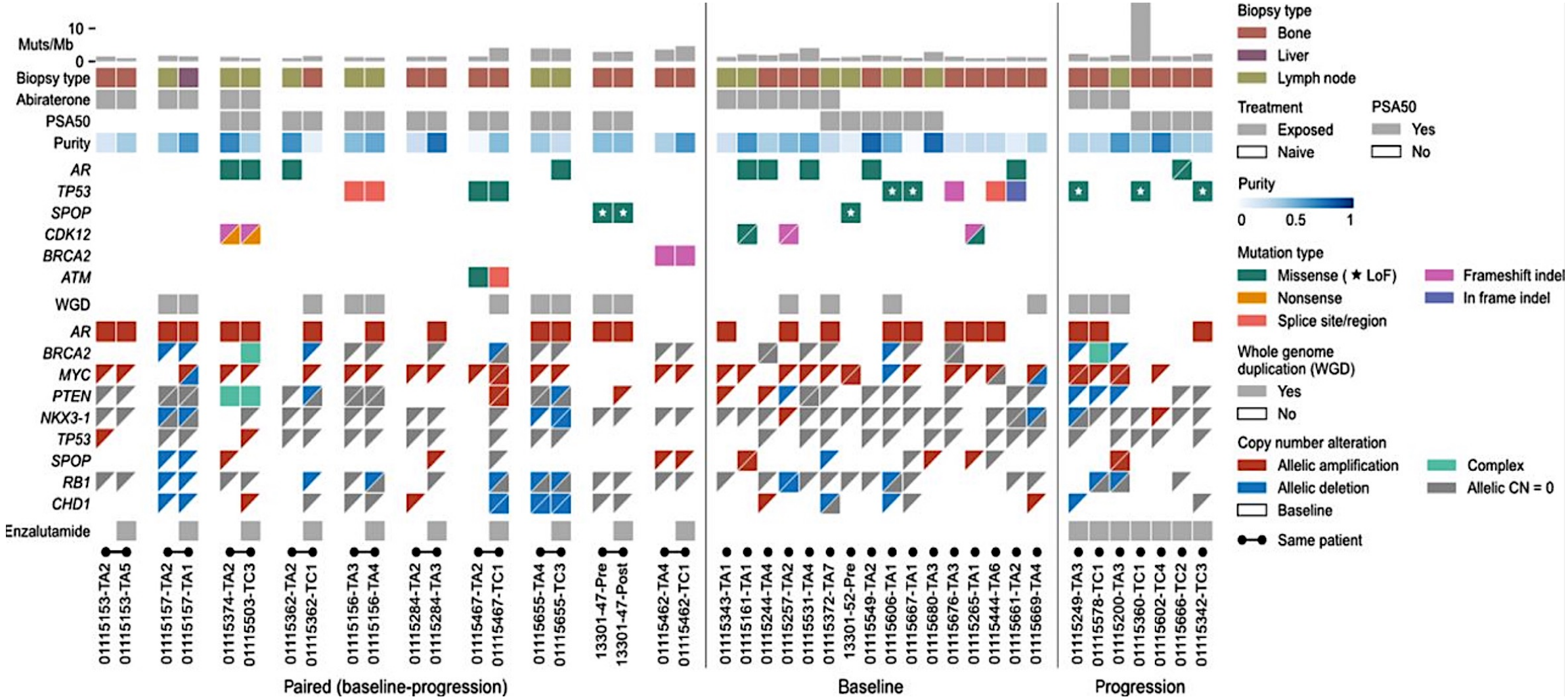
Phase II Multicenter Study of Enzalutamide in Metastatic Castration-Resistant Prostate Cancer to Identify Mechanisms Driving Resistance

Rana R. McKay[1,2], Lucia Kwak[2], Jett P. Crowdis[2], Jamie M. Sperger[3], Shuang G. Zhao[3], Wanling Xie[2], Lillian Werner[2], Rosina T. Lis[2], Zhenwei Zhang[2], Xiao X. Wei[2], Joshua M. Lang[3], Eliezer M. Van Allen[2], Rupal S. Bhatt[4], Evan Y. Yu[5,6], Peter S. Nelson[5,6], Glenn J. Bubley[4], R. Bruce Montgomery[5,6], and Mary-Ellen Taplin[2]

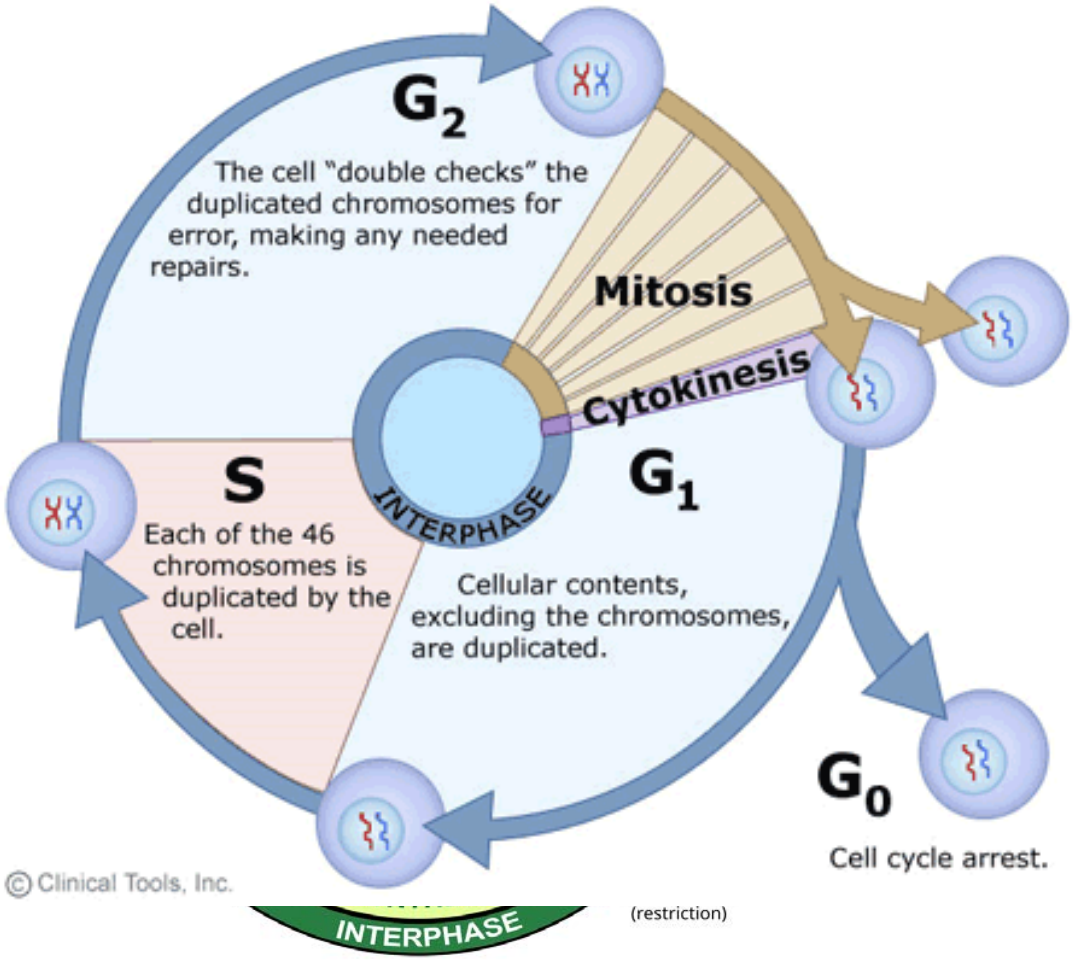
Best PSA Response to Therapy with Enzalutamide in Patients with mCRPC

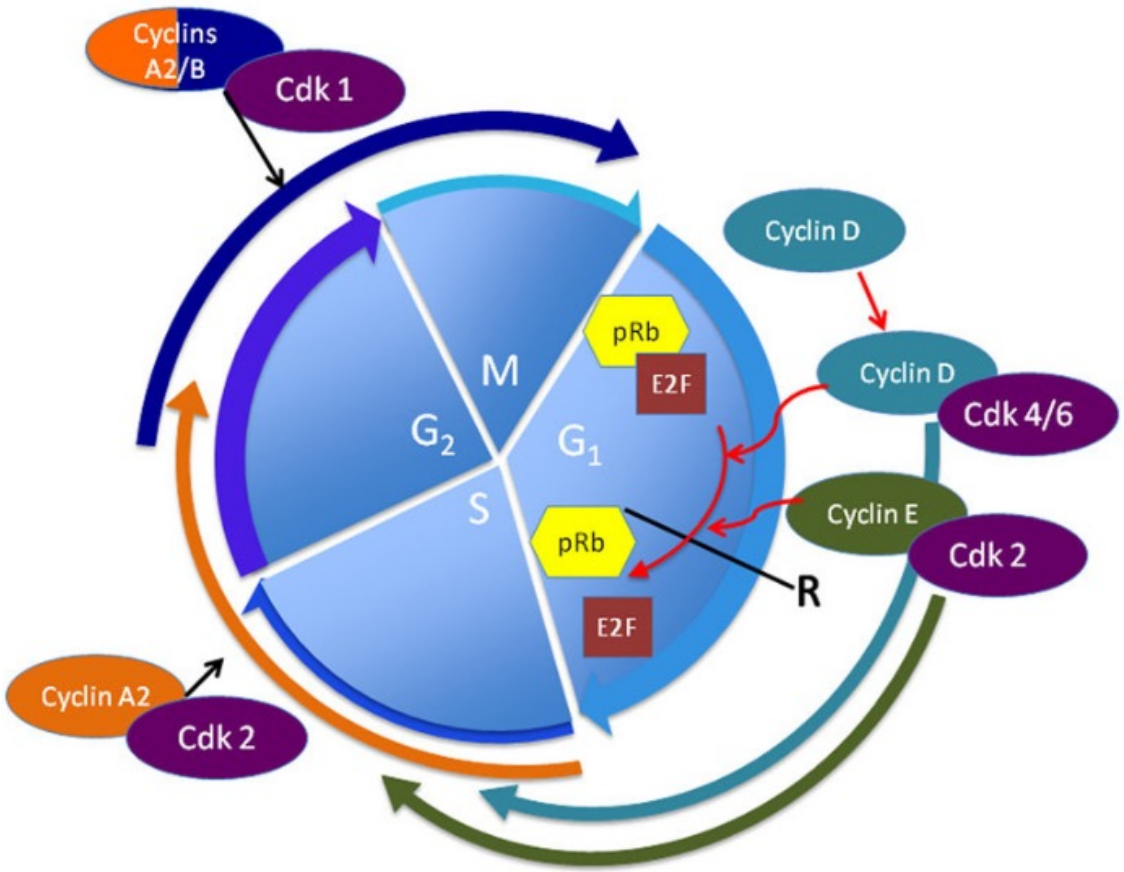


Mechanisms Driving Resistance to Enzalutamide in Patients with mCRPC



Cell Cycle

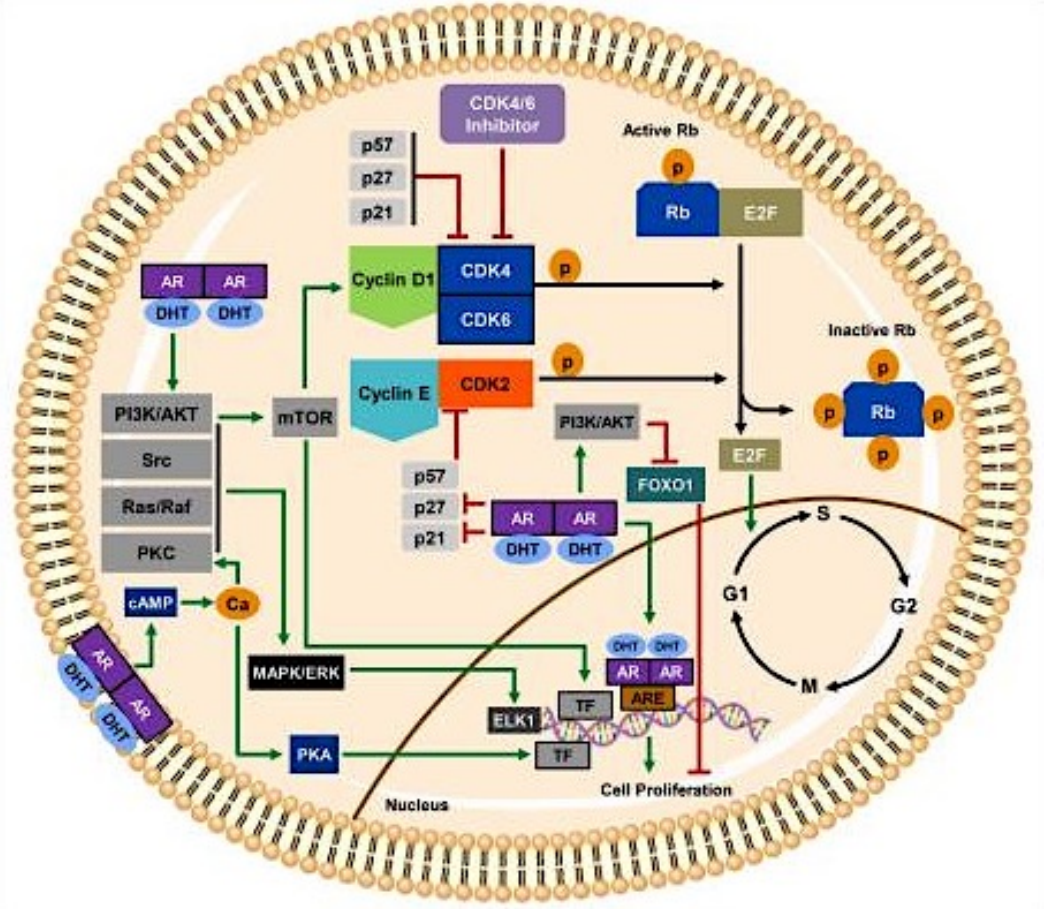




Wolgemuth et al, Journal of Developmental Biology, 2013

Cross Talk Between Cell Cycle and AR Pathway

- Androgen receptors, like the estrogen receptors, are key regulators of cell cycle and instrumental in the regulation of the transcription of genes that allow for G1 to S transition
- Inhibition of CDK4/6 triggers G1 arrest of cell cycle
- Inhibiting both CDK4 and CDK6 essential to effectively impair the G1/S transition
- In prostate cancer, inhibition of both CDK4/6 and AR signaling may disrupt the feed forward loop involving these two pathways



Kase et al, Onco Targets Ther, 2020

Available CDK4/6 Inhibitors

	Abemaciclib[1]	Ribociclib[2]	Palbociclib[3]
Disease state(s) with FDA approval	HR+, HER2- EBC HR+, HER2- MBC	HR+, HER2- MBC	HR+, HER2- MBC
Preliminary/published data in prostate cancer	TBD	Yes[4]	No[5]
CDK4 (IC50, nM)[5]	2	10	11
CDK6 (IC50, nM)[5]	9.9	39	15
CDK9 (IC50, nM)[5]	57	NR	NR

Little or no inhibitory activity for CDK1, 2, 5 and 7

1. Abemaciclib PI. 2. Ribociclib PI. 3. Palbociclib PI. 4. de Kouchkovsky et al, Clin Cancer Res, 2022. 5. Palmbos et al, Clin Cancer Res. 2021. 5. Gelbert et al, Invest New Drugs, 2014.

Available CDK4/6 Inhibitors

	Abemaciclib[1]	Ribociclib[2]	Palbociclib[3]
Dose	200 mg BID	600 mg QD	125 mg QD
Route	PO (w or w/o food)	PO (w or w/o food)	PO (w or w/o food)
Dosing schedule	Continuous	3 wks on/1 wk off	3 wks on/1 wk off
Half-life	18.3 hours	32 hours	29 (+/- 5) hours
Primary Metabolism	Liver	Liver	Liver
CNS Penetration	Yes	No	Uncertain
Myelosuppression	+	++	++
GI Toxicity	++	+	+
LFTs	+	+	-
QTc Prolongation	-	+	-
Pneumonitis	+ (rare)	+ (rare)	+ (rare)

1. Abemaciclib PI. 2. Ribociclib PI. 3. Palbociclib PI.

CYCLONE 1: Abemaciclib in Men with Heavily Pretreated Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Agarwal N et al.
AACR 2023;Abstract CT159.

CYCLONE 1: Results of a Phase II Trial of Abemaciclib for Patients with Heavily Pretreated mCRPC

	Abemaciclib monotherapy (n = 44)
Overall response rate without concurrent bone progression	6.8%
Stable disease	40.9%
Disease control rate	47.7%
Median radiographic progression-free survival	2.7 months
Median time to PSA progression	6.5 months
Median overall survival	7.6 months

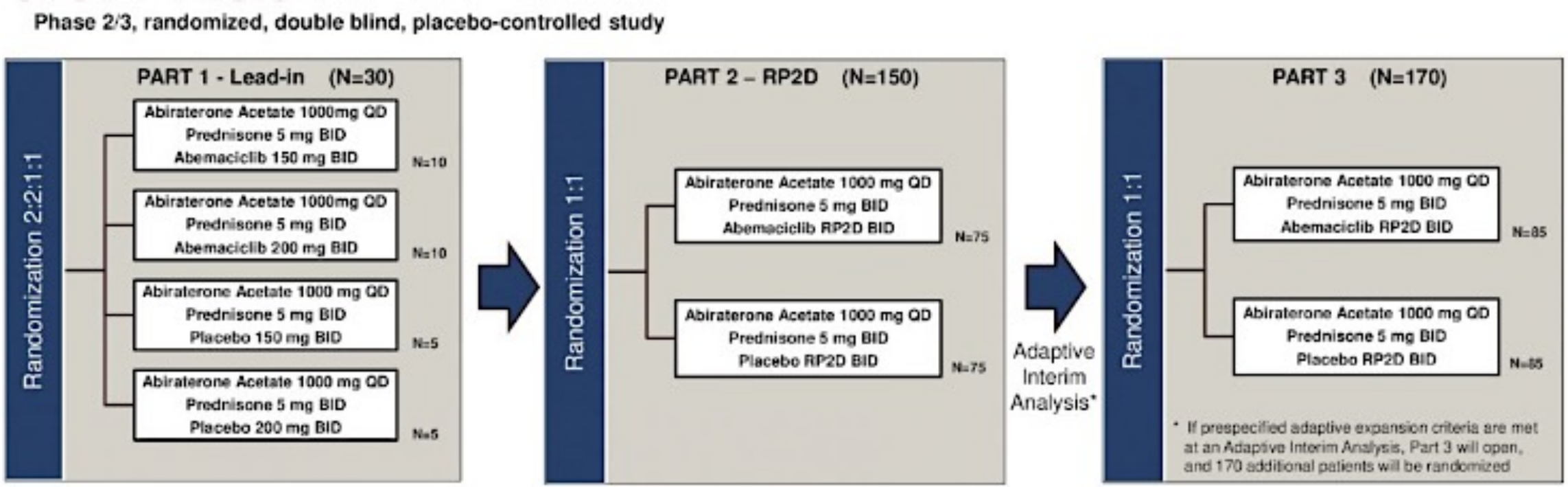
- Treatment-related adverse events (TRAEs) experienced by ≥50% of patients: Diarrhea (79.5%), decreased appetite (52.3%) and fatigue (50%)
- Grade 3 TRAEs in ≥5% of patients: Neutropenia (22.7%), anemia (6.8%), fatigue (6.8%) and diarrhea (6.8%)

Author Conclusions: *Abemaciclib demonstrated modest but objective single-agent clinical activity in heavily pretreated progressive mCRPC. The safety profile of abemaciclib was consistent with the experience in breast cancer. Although the primary endpoint was not formally met, the single agent activity observed in this late line mCRPC setting validates CDK4/6 as a therapeutic target in advanced PC.*

mCRPC: Cyclone 2

Cyclone 2: First Line mCRPC

NCT03706365



Patients who have not undergone bilateral orchiectomy will continue ADT (LHRH agonist/antagonist) throughout the study.
Patients are stratified by radiographic progression at time of study entry, measurable disease and prior docetaxel for mHSCP
Prednisolone may be used in lieu of prednisone per local regulation. For sites in the USA, the fine-particle formulation of abiraterone (500 mg QD) can be used with methylprednisolone (4 mg BID)

Take Home Message

- Many treatment options are available for patients with mCRPC and treatment is dependent on clinical features, prior therapy exposure, and genomics
- Germline and somatic tumor profiling is indicated for all patients with mCRPC
- Sequencing of ARSI is generally not recommended in mCRPC
- Novel therapies including CDK4/6 inhibitors are currently in development in mCRPC

Agenda

Module 1 – Current Management of Nonmetastatic Prostate Cancer — Dr Morgans

Module 2 – New Considerations in Treatment Intensification for Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) — Prof Fizazi

Module 3 – Available and Emerging Strategies for Newly Diagnosed Metastatic Castration-Resistant Prostate Cancer (mCRPC) — Dr McKay

Module 4 – Identification and Management of mCRPC with a Homologous Recombination Repair (HRR) Gene Abnormality — Dr Antonarakis

Module 5 – Management of Progressive mCRPC — Dr Sartor

Case Presentation: 53-year-old man with mCRPC s/p enzalutamide receives olaparib – somatic BRCA2 mutation, TP53 mutation on liquid biopsy

Dr Neeraj Agarwal (Salt Lake City, Utah)

RTP RESEARCH TO PRACTICE

Case Presentation: 72-year-old man with high-grade localized prostate cancer treated with proton beam therapy + ADT for 2 years now has rising PSA and CT scan positive for retroperitoneal node – somatic BRCA2, TP53, FOXA1 and MEN1 mutations, MSS

Dr David Morris (Nashville, Tennessee)

RTP RESEARCH TO PRACTICE

Research To Practice
June 3, 2023

Identification and Management of mCRPC with HRR Abnormalities

Emmanuel S. Antonarakis, M.D.
Clark Endowed Professor of Medicine
Division of Hematology/Oncology & Transplantation, University of Minnesota
Associate Director of Translation, Masonic Cancer Center

Incidence of HRR mutations in PCa, and Indications for testing

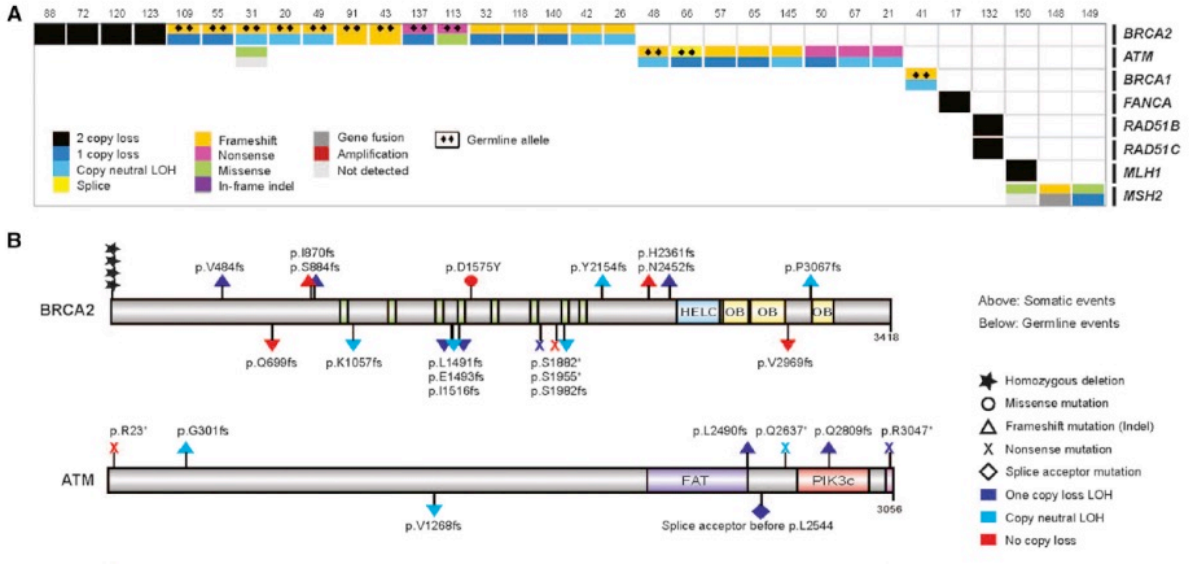
What are the relevant HRR Genes?

"First Tier"	"Second Tier"	"Third Tier"
BRCA2 (6–8%)	***BARD1*** (1%)	***ATM*** (5–7%)
BRCA1 (1–2%)	***BRIP1*** (1–2%)	***CDK12*** (5–7%)
PALB2 (1–2%)	***RAD51C*** (1%)	***CHEK2*** (2–3%)
RAD51B (1%)	***RAD51D*** (1%)	***CHEK1*** (1%)
RAD54L (1%)	***FANCL*** (1–2%)	

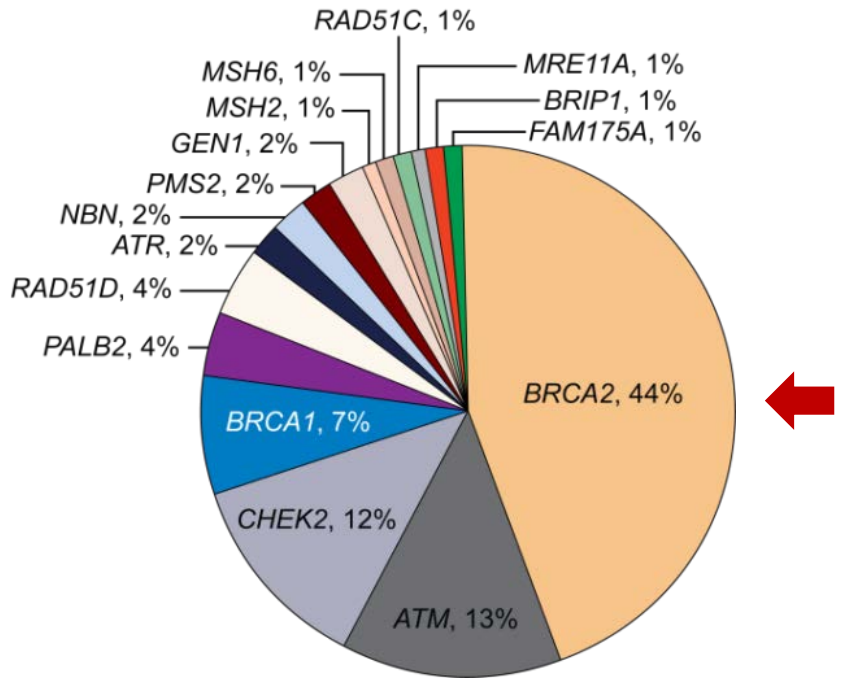
HRR Genes and Metastatic Prostate Cancer

Somatic

- **23%** of metastatic castration-resistant prostate cancers harbor DNA repair alterations
- The frequency of DNA repair alterations **increases in metastatic disease vs. localized disease**



Germline



- **12%** of men with metastatic prostate cancer have a germline DNA repair defect

1. Robinson D, et al. Cell. 2015;161:1215-28. **2.** Pritchard CC, et al. N Engl J Med. 2016;375:443-53.

Prostate NCCN Guidelines v 1.2023

Germline Testing

Germline testing is recommended in patients with a personal history of prostate cancer who:

- Have metastatic, regional (N+), very-high-risk localized, or high-risk localized prostate cancer
- Have family history and/or ancestry with:
  - ≥1 first, second, or third degree relative with
    - Breast cancer at age ≤50 years
    - Colorectal or endometrial cancer at age ≤50 years
    - Male breast cancer at any age
    - Ovarian cancer at any age
    - Pancreatic cancer at any age
    - Metastatic, regional, very-high-risk, or high-risk prostate cancer at any age
  - ≥1 first degree relative with prostate cancer at age ≤60 years
  - ≥2 first, second, or third degree relatives with:
    - Breast cancer at any age
    - Prostate cancer at any age
  - ≥3 first or second degree relatives with:
    - Lynch syndrome-related cancers, especially if diagnosed at age <50 years
    - A known family history of a familial cancer risk mutation
    - Ashkenazi Jewish ancestry
  - Personal history of male breast cancer

Germline testing may be considered in patients with a personal history of PCa who:

- Have intermediate-risk prostate cancer with intraductal/cribriform histology
- Have a personal history of pancreatic, colorectal, gastric, melanoma, upper tract urothelial, glioblastoma, biliary tract, or small intestinal cancer

Germline multigene testing that includes at least BRCA1, BRCA2, ATM, PALB2, CHEK2, HOXB13, MLH1, MSH2, MSH6, and PMS2 is recommended; additional genes may be appropriate based on clinical context

Somatic Tumor Testing

Tumor testing for alterations in HRR DNA repair genes such as ***BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2,*** and ***CDK12*** is recommended in patients with metastatic prostate cancer, and may be considered for patients with regional (N+) prostate cancer

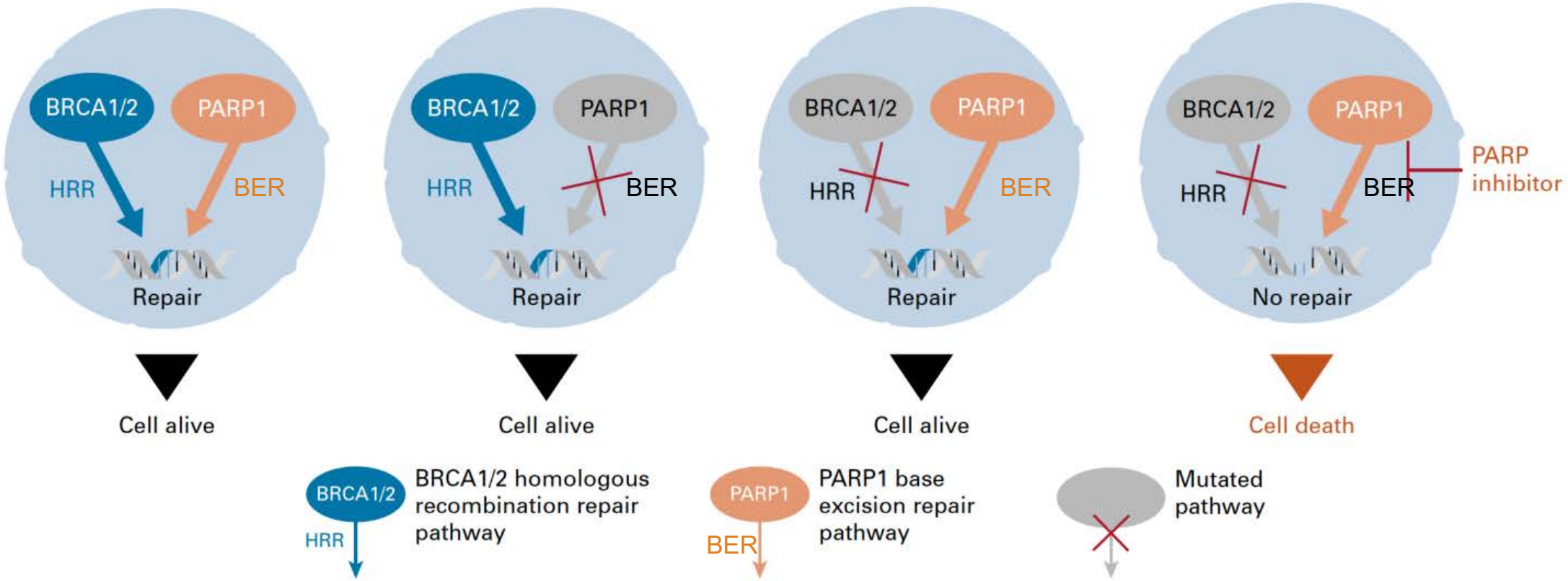
Tumor testing for MSI-H or dMMR is recommended in patients with mCRPC, and may be considered for patients with mCSPC

TMB testing may be considered in patients with mCRPC

NCCN Practice Guidelines: Prostate Cancer. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.

PARP inhibitors for HRR-deficient mCRPC

PARP Inhibition: “Synthetic Lethality”



PARP is required for single-strand break repair (e.g. via BER)

MOA – inhibiting SSB/BER is synthetic lethal with HRD

Different PARP inhibitors tested in PCa

Properties of PARP Inhibitors

	Olaparib	Talazoparib	Niraparib	Rucaparib
Mol. Weight	434.5	380.8	320.4	323.4
PARP1 IC_{50}	5 nM	0.56 nM	3.8 nM	0.65 nM
PARP2 IC_{50}	1 nM	0.15 nM	2.1 nM	0.08 nM
Trapping	++	++++	+++	++

Carney B, et al. *Nat Commun* 2018; 9: 176.

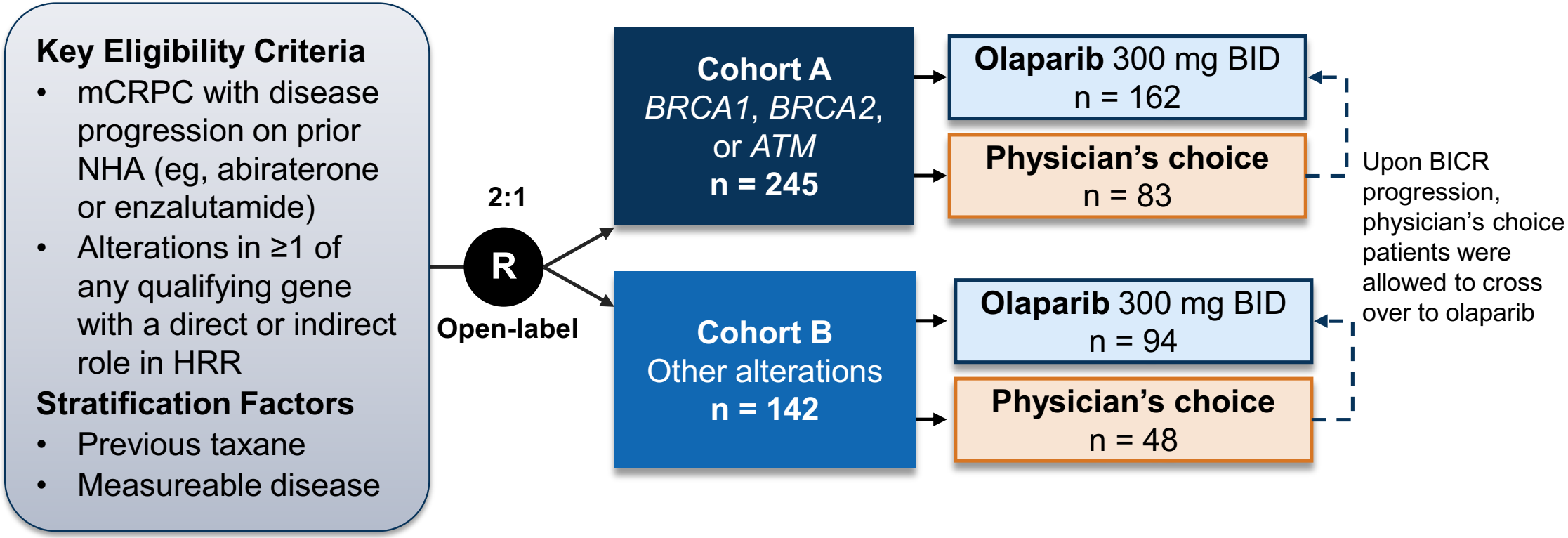
Summary of PARPi *monotherapy* trials in mCRPC

Study and treatment	Prior therapy	HRR status criteria; Sample type	Primary endpoint	Results
TOPARP-A[1] **Olaparib** 400 mg BID (N=50)	1–2 taxane CT regimens; 98% had prior NHT	Deficiency not required; tumor	Composite response rate	**33%** overall; 88% (14 of 16) with DDR gene alterations
TOPARP-B[2] **Olaparib** 300 mg or 400 mg BID, randomized 1:1 (N=98)	1–2 taxane CT regimens; 88%–92% had prior NHT	Deleterious germline or somatic DDR gene alterations; tumor	Composite response rate	**39.1%** 300-mg cohort; **54.3%** 400-mg cohort
TRITON2[3] **Rucaparib** 600 mg BID (N=115)	1 taxane and 1–2 NHT	Deleterious germline or somatic *BRCA1/2* alteration; tumor or plasma	ORR by blinded independent radiology review	**43.5%** (27 of 62)
GALAHAD[4] **Niraparib** 300 mg QD (N=289)	≥1 taxane and ≥1 NHT	Deleterious germline or somatic alteration in ≥1 of 8 prespecified DDR genes; tumor or plasma	ORR in patients with *BRCA* mutation and measurable disease	**34.2%** (26 of 76 measurable *BRCA* cohort) 10.6% (5 of 47 measurable non-*BRCA* cohort)
TALAPRO-1[5] **Talazoparib** 1 mg QD (N=128)	1–2 CT regimens (≥1 taxane) and ≥1 NHT	Deleterious germline or somatic alterations in ≥1 of 11 prespecified DDR-HRR genes; tumor or plasma	ORR by blinded independent review	**29.8%** (31 of 104)

1. Mateo J et al. *N Engl J Med.* 2015;373:1697-708; **2.** Mateo J et al. *Lancet Oncol.* 2020;21:162-174; **3.** Abida W et al. *J Clin Oncol.* 2020;38:3763-3772; **4.** Smith MR et al. *Lancet Oncol.* 2022;23:362-373; **5.** de Bono JS et al. *Lancet Oncol.* 2021;22:1250-1264.

Pivotal trials of PARPi *monotherapy*

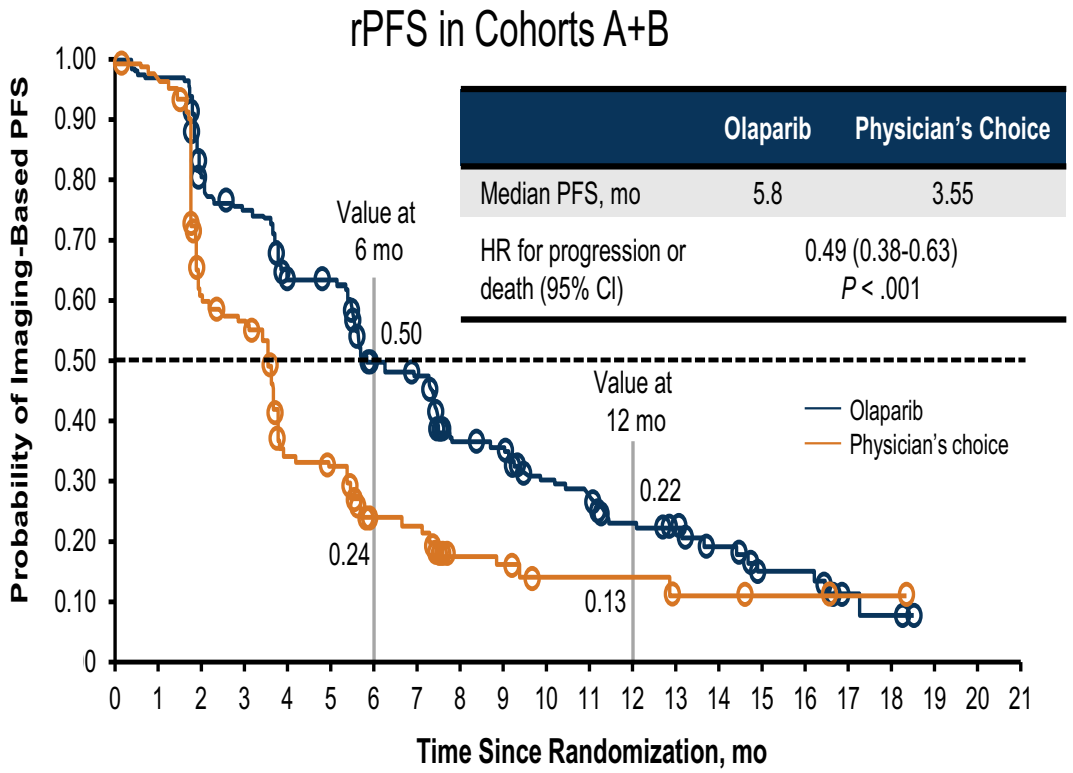
Olaparib: PROfound, Randomized Phase 3 Study



- Primary endpoint: rPFS in cohort A (RECIST 1.1 and PCWG3 by BICR)
- Key secondary endpoints: rPFS (cohorts A+B); confirmed radiographic ORR in cohort A; time to pain progression in cohort A; OS in cohort A

1. de Bono J et al. *N Engl J Med*. 2020;382:2091-2102.

PROfound: rPFS and OS in whole population (A+B)

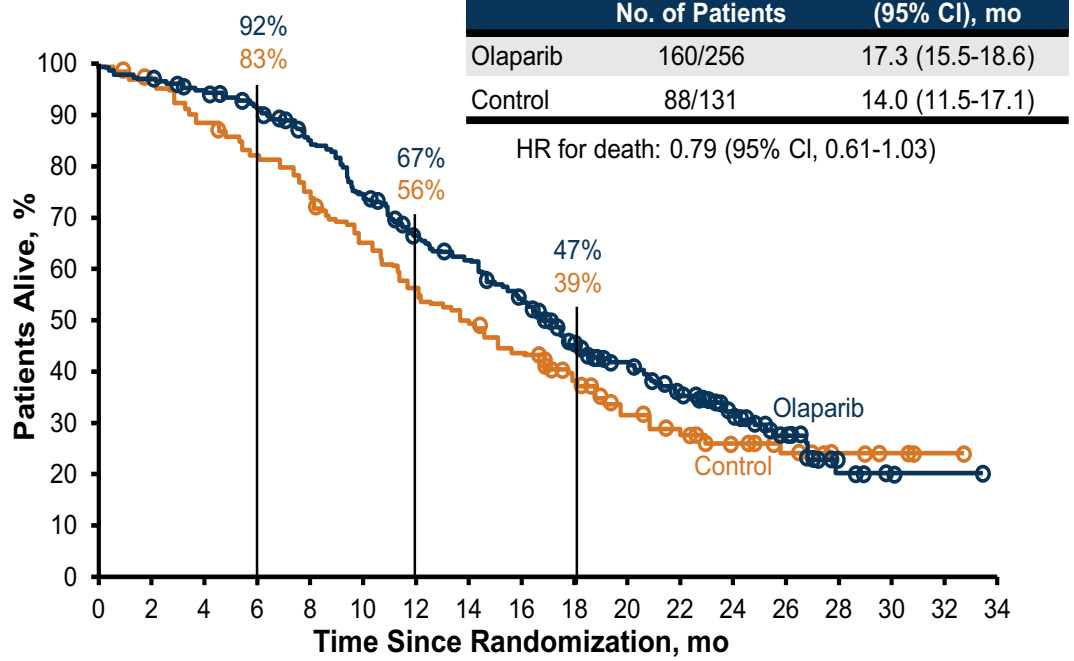


	Olaparib	Physician's Choice
Median PFS, mo	5.8	3.55
HR for progression or death (95% CI)	0.49 (0.38-0.63) $P < .001$	

No. at Risk

Olaparib	256	239	188	176	145	143	106	100	67	63	48	43	31	28	21	11	11	3	2	0	0	0
Control	131	123	73	67	38	35	20	19	9	8	5	5	5	3	3	2	2	1	1	0	0	0

OS in the Overall Population (Cohorts A + B)



	No. of Deaths/ No. of Patients	Median OS (95% CI), mo
Olaparib	160/256	17.3 (15.5-18.6)
Control	88/131	14.0 (11.5-17.1)

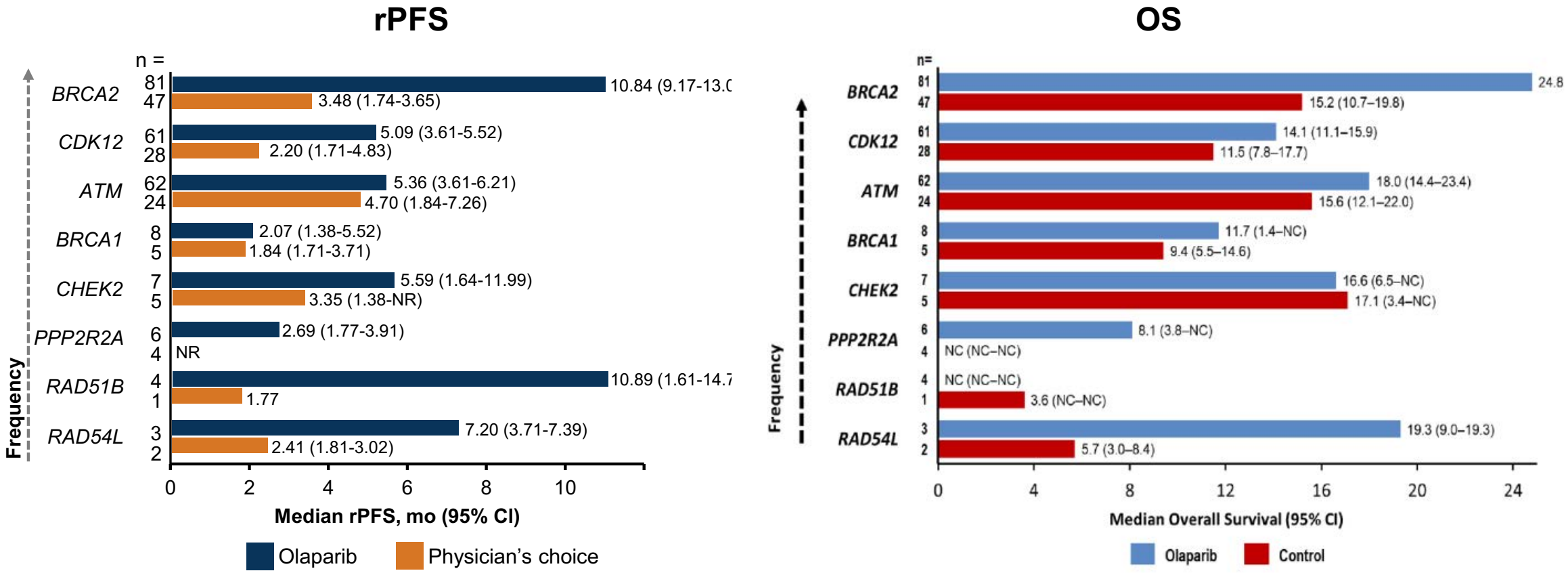
HR for death: 0.79 (95% CI, 0.61-1.03)

No. at Risk

Olaparib	256	249	240	228	209	182	157	146	126	96	73	56	39	22	7	2	1	0			
Control	131	125	115	106	96	83	71	63	55	37	27	22	15	11	6	3	1	0			

1. de Bono J et al. *N Engl J Med*. 2020;382:2091-2102. 2. Hussain M et al. *N Engl J Med*. 2020.

PROfound: Gene-by-gene, rPFS and OS analyses



1. de Bono J et al. *N Engl J Med*. 2020;382:2091-2102. 2. Hussain M et al. *N Engl J Med*. 2020.

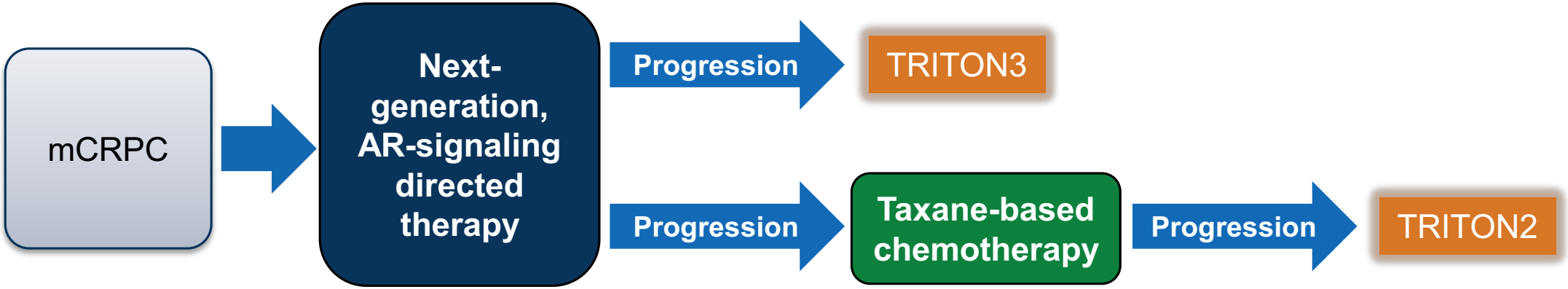
Olaparib for HRR-mutated mCRPC

OLAPARIB: In **May 2020,** based on data from the **PROfound study,** the FDA granted **full approval olaparib** for the treatment of patients with deleterious or suspected **germline or somatic HRR[a] gene-mutated mCRPC, who have progressed following prior treatment with enzalutamide or abiraterone[1,b]**

[a]***BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L***.
[b]Select patients for therapy based on two FDA-approved companion diagnostic tests: BRACAnalysis CDx and FoundationOne CDx.

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

Rucaparib: TRITON2 and TRITON3 studies



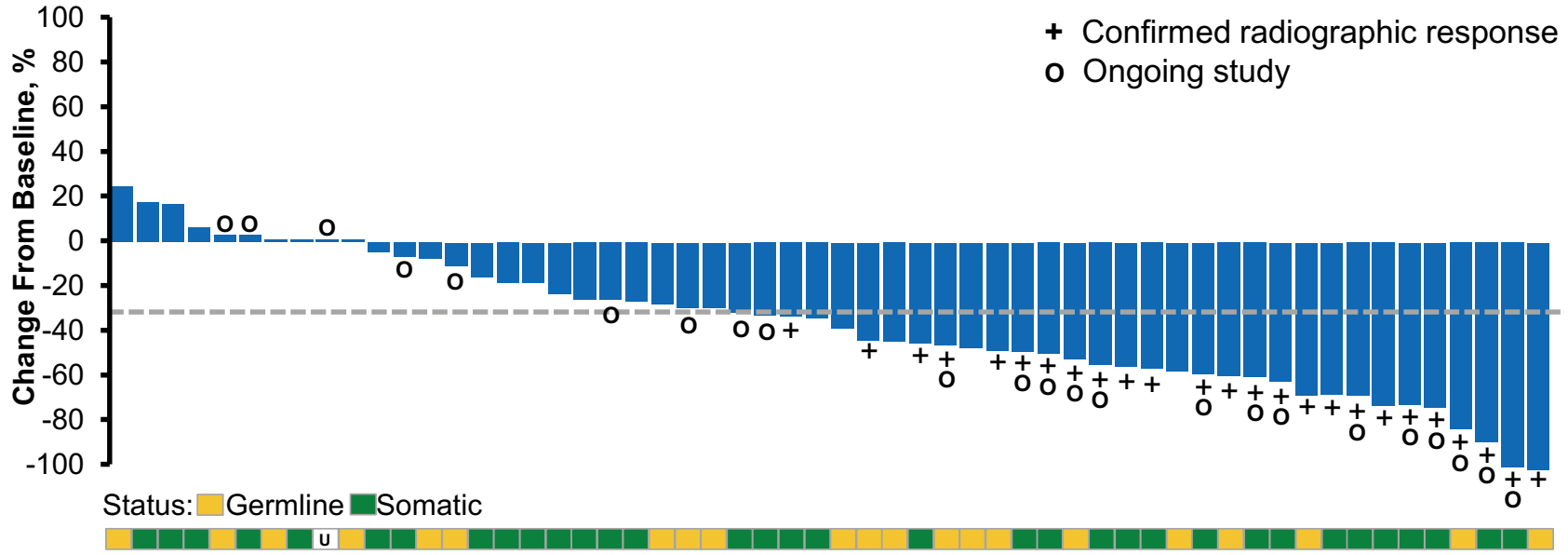
HRR-deficiency is defined by a deleterious alteration in *BRCA1*, *BRCA2*, *ATM*, or 12 other HRR genes (*BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD54L)*

1. Abida W et al. *Annals Onc*. 2018:29(Suppl 8):viii271-viii302.

TRITON2: Objective response rate (ORR)

	DDR Gene				
	BRCA 1/2 (n = 57)	*ATM* (n = 21)	*CDK12* (n = 9)	*CHEK2* (n = 5)	Other (n = 13)
ORR, n (%) [95% CI]	25 (43.9) [30.7-57.6]	2 (9.5) [1.2-30.4]	0 [0.0-33.6]	0 [0.0-52.2]	5 (38.5) [13.9-68.4]
CR, n (%)	3 (5.3)	0	0	0	1 (7.7)
PR, n (%)	22 (38.6)	2 (9.5)	0	0	4 (30.8)
SD, n (%)	26 (45.6)	10 (47.6)	5 (55.6)	3 (60.0)	6 (46.2)
PD, n (%)	5 (8.8)	8 (38.1)	3 (33.3)	2 (40.0)	1 (7.7)
N/E, n (%)	1 (1.8)	1 (4.8)	1 (11.1)	0	1 (7.7)

Best Change From Baseline in Sum of Target Lesion in Patients With *BRCA 1/2* Alteration (N = 56)



1. Abida W et al. ESMO 2019. Abstract 846PD. 2. Abida W et al. *Clin Cancer Res*. 2020 Feb 21

Rucaparib for *BRCA1/2*-mutated mCRPC

RUCAPARIB: In **May 2020,** based on data from the **TRITON2 study,** the FDA granted **accelerated approval to rucaparib** for the treatment of patients with **deleterious *BRCA1/2* (germline and/or somatic)-associated mCRPC, who have been treated with an androgen receptor-directed therapy and a taxane-based chemotherapy.**[1]

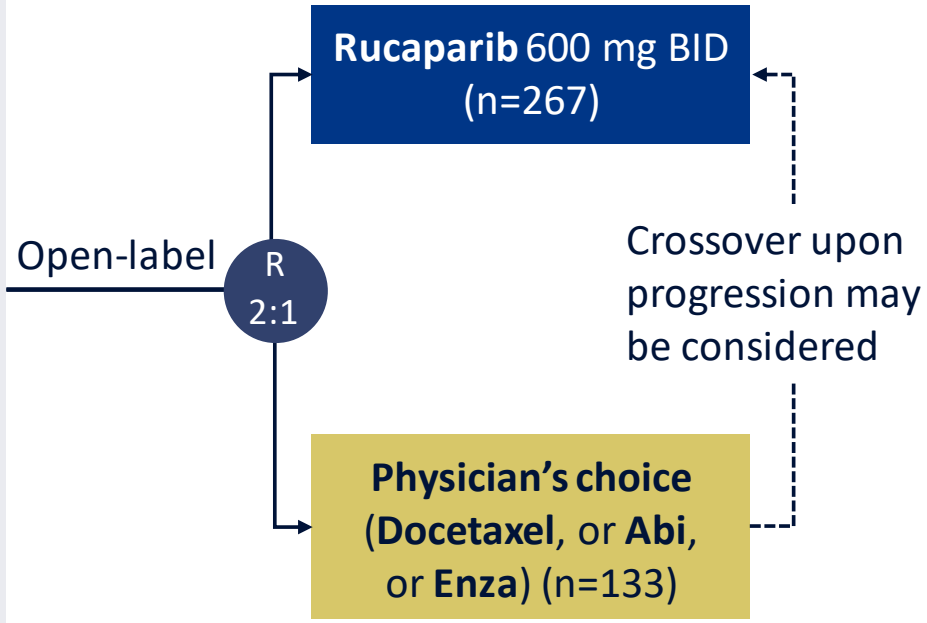
1. https://www.fda.gov/drugs/fda-grants-accelerated-approval-rucaparib-brca-mutated-metastatic-castration-resistant-prostate.

TRITON3: Randomized phase III trial

Patient population

- mCRPC with progression after 1 prior AR signaling-directed therapy (abiraterone, enzalutamide, or investigational agent)
- Deleterious germline or somatic alteration in ***BRCA1, BRCA2,*** or ***ATM****
- No prior PARP inhibitor
- No prior chemotherapy for mCRPC

Planned enrollment: 400



Primary endpoint

rPFS
(RECIST 1.1 and PCWG3 by IRR)

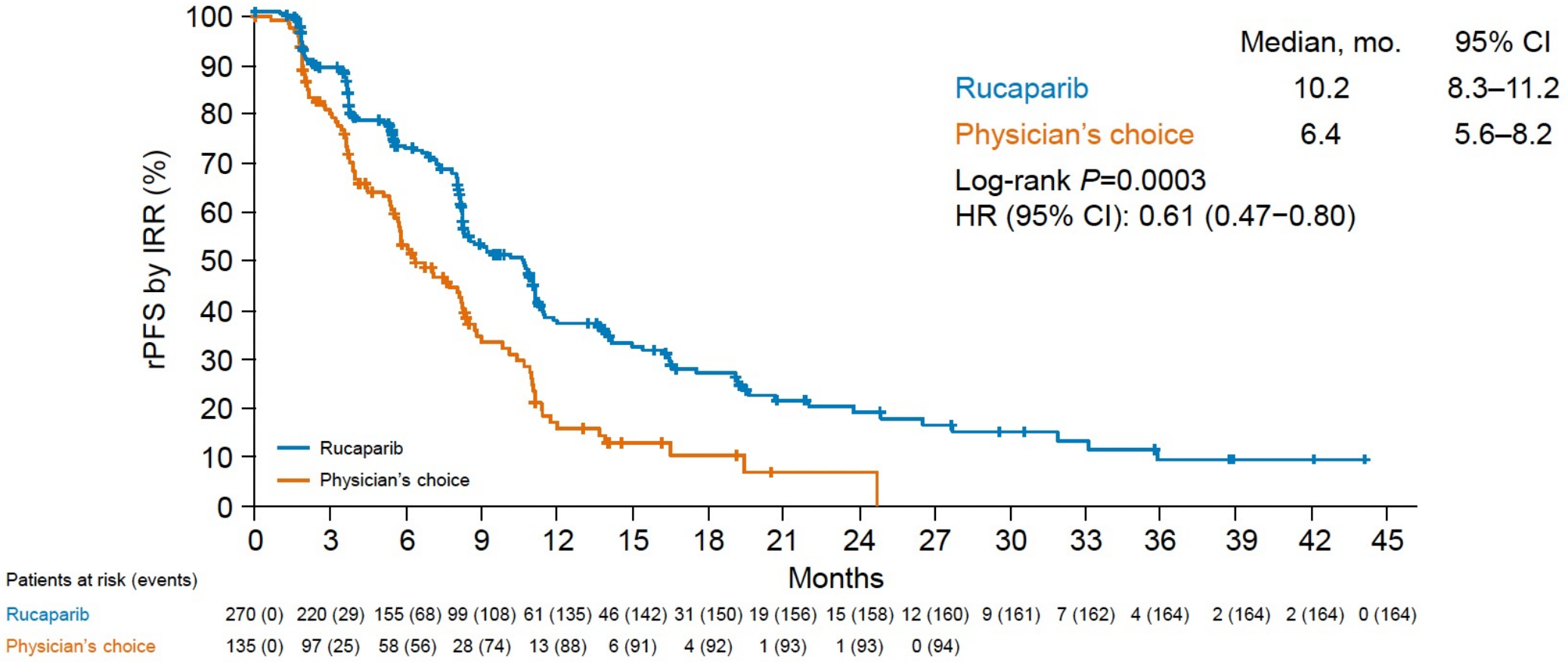
Key secondary endpoints

- ORR and DOR by modified RECIST criteria in patients with measurable nodal/visceral disease
- OS
- Clinical benefit rate
- PSA response of ≥50% and ≥90%
- Time to PSA progression
- Patient-reported outcomes
- Safety and tolerability

*Mutations identified in blood, archival tissue, or screening tumor tissue

Ryan CJ et al. ASCO GU 2019; abst TPS389; NCT02975934.

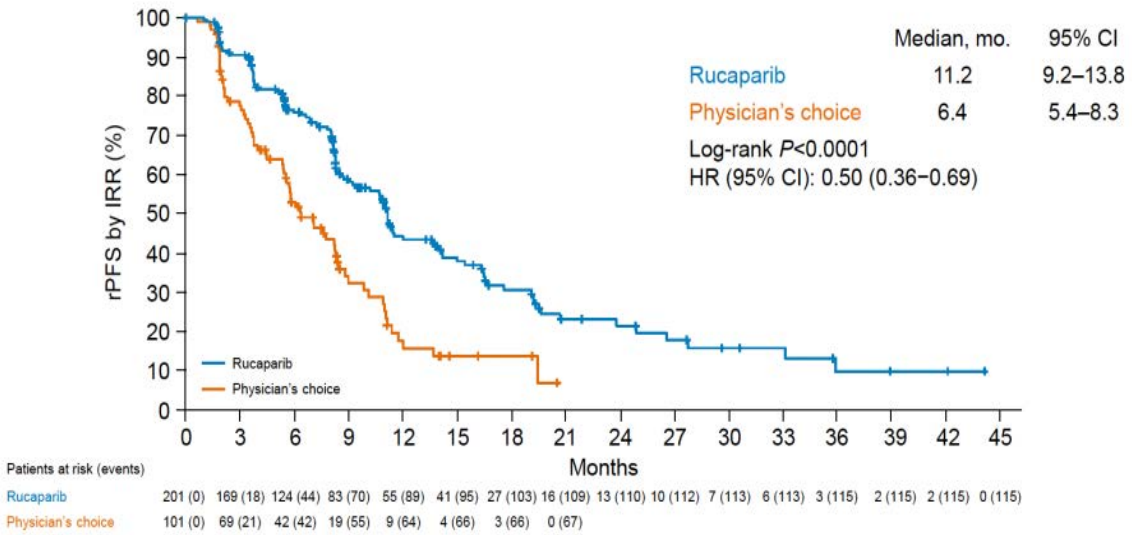
TRITON3: rPFS in ITT population



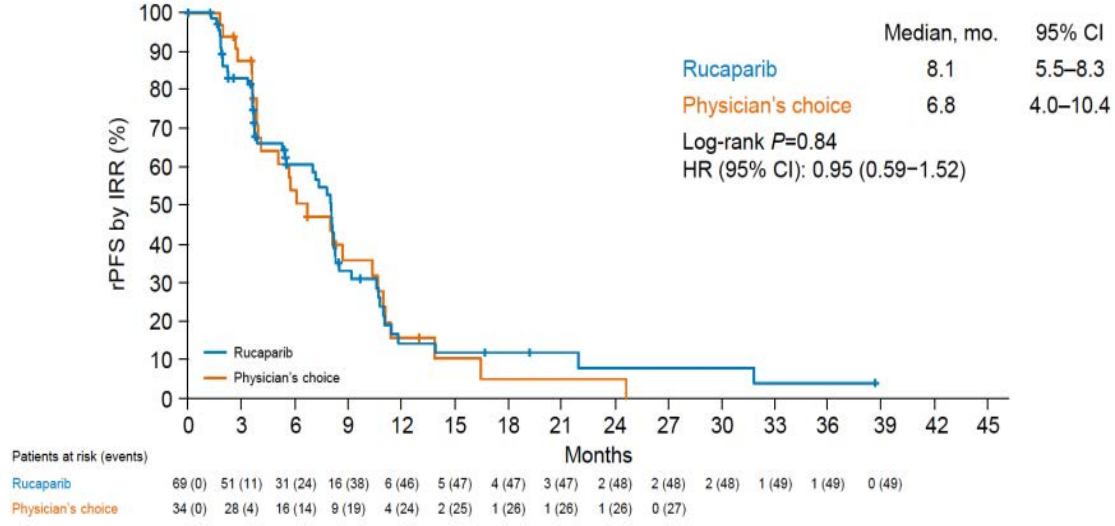
Fizazi K, et al. *NEJM* 2023; 388: 719-32.

TRITON3: rPFS in *BRCA1/2* and *ATM* subgroups

BRCA1/2 Subgroup



ATM Subgroup



Fizazi K, et al. *NEJM* 2023; 388: 719-32.

PARPi–based *combinations*
(PROpel, MAGNITUDE, & TALAPRO-2)

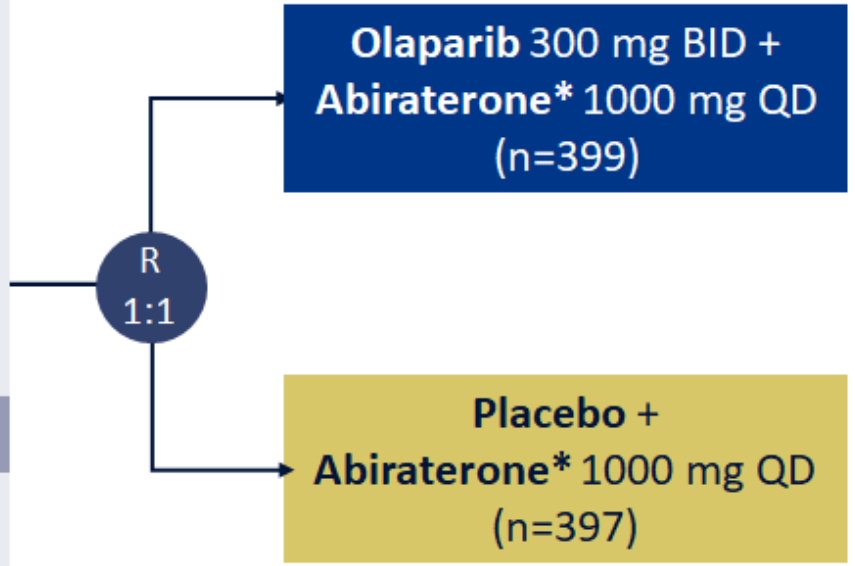
PROpel: Phase III Trial of Abiraterone +/– Olaparib

Patient population

- mCRPC
- Docetaxel for mCSPC allowed
- No prior abiraterone
- Other NHT allowed if stopped ≥12 months prior to enrollment
- Ongoing ADT
- ECOG PS 0–1

Stratification factors

- Site of distant metastases (bone only vs visceral vs other)
- Prior taxane for mCSPC



Primary endpoint

rPFS or death by investigator assessment

Key secondary endpoint

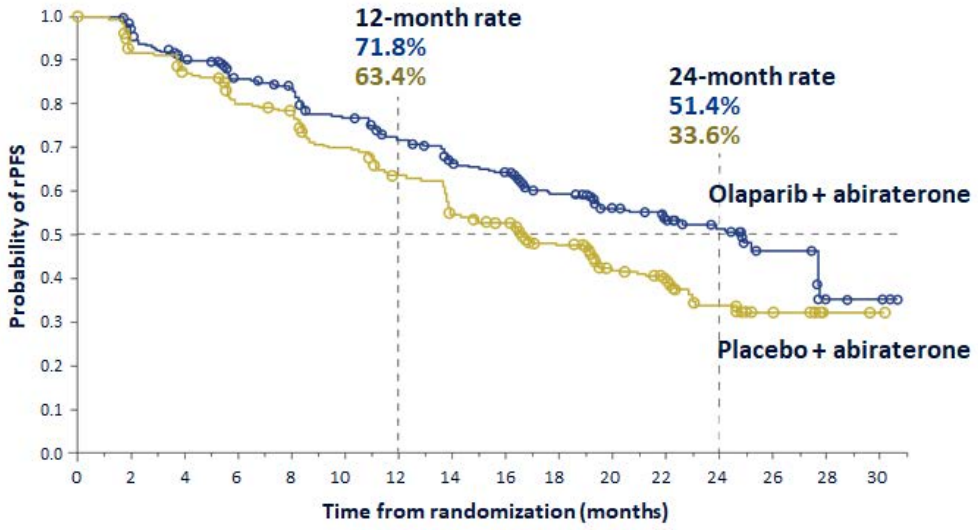
- OS

Additional endpoints

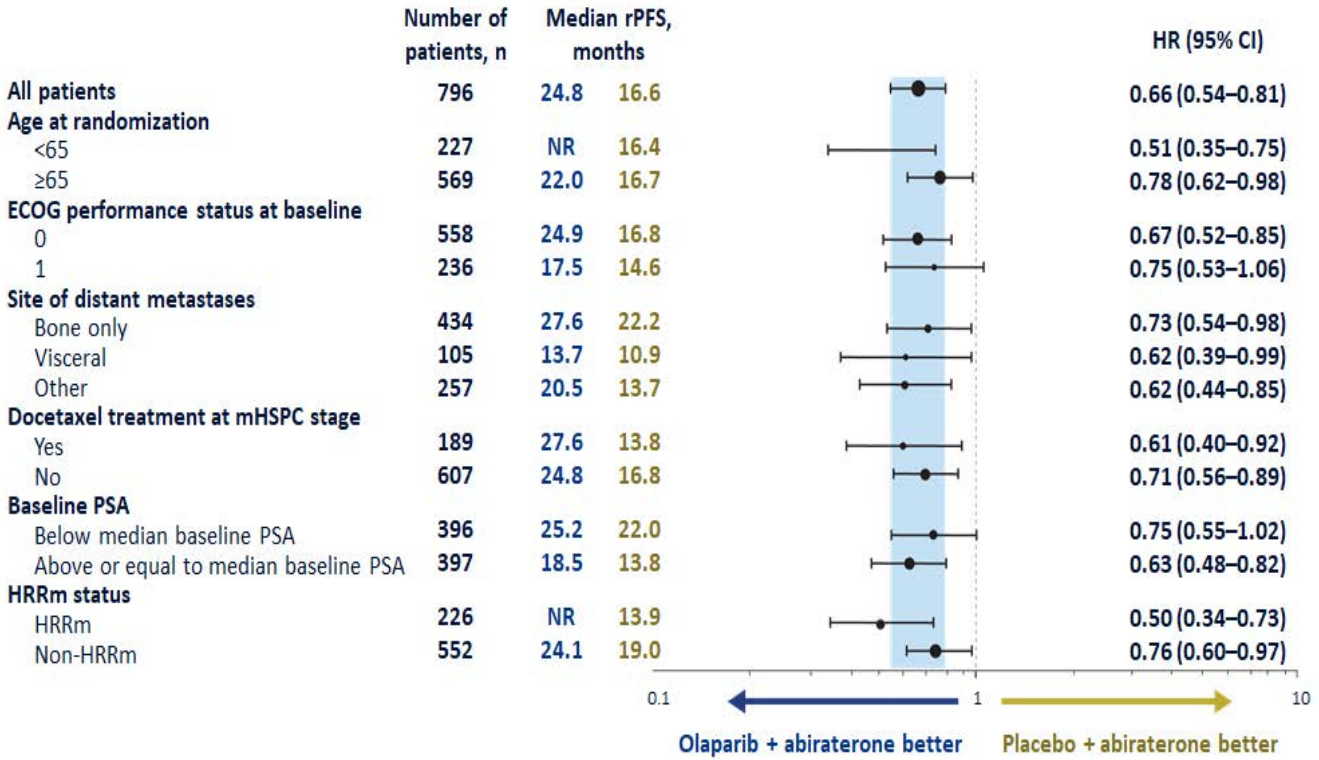
- TFST
- PFS2
- ORR
- HRR mutation prevalence (tested retrospectively)
- HRQOL
- Safety and tolerability

Saad F et al. *ASCO GU 2022*; abstr 11; NCT03732820.

PROpel: Radiographic progression-free survival

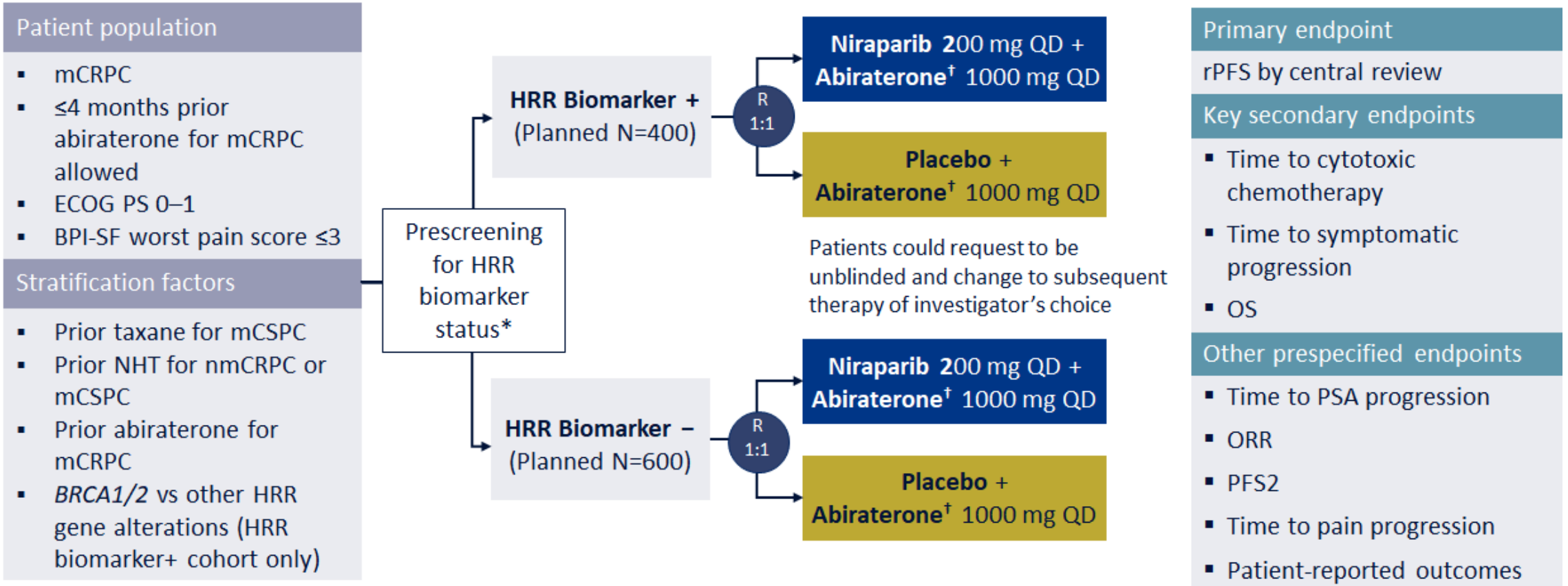


	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
rPFS by investigator assessment		
Events, n (%)	168 (42.1)	226 (56.9)
Median rPFS, months	24.8	16.6
HR (95% CI)	0.66 (0.54–0.81); *P*<0.0001	
rPFS by blinded independent central review		
HR (95% CI)	0.61 (0.49–0.74); *P*<0.0001	



Saad F et al. *NEJM Evidence*; 2022.

MAGNITUDE: Phase III Trial of Abi +/– Niraparib



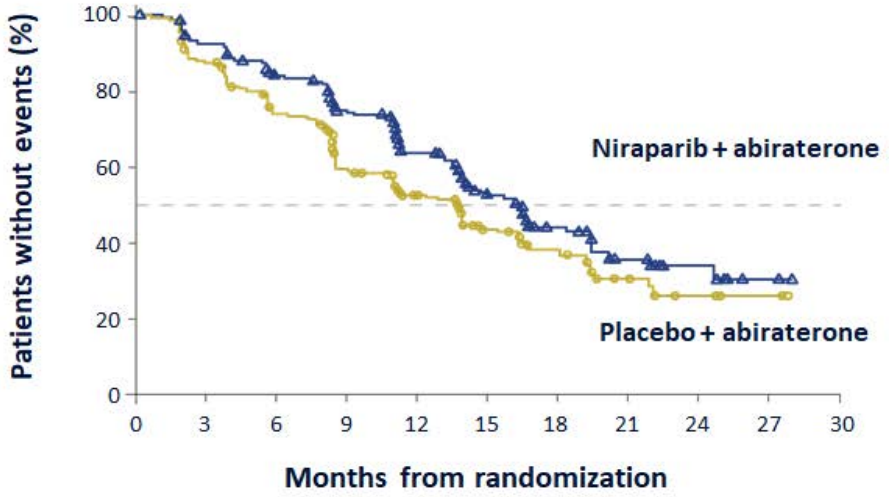
*HRR gene panel: ***ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2, PALB2***

†Plus prednisone 10 mg daily

Chi KN et al. *ASCO GU 2022*; abstr 12; NCT03748641.

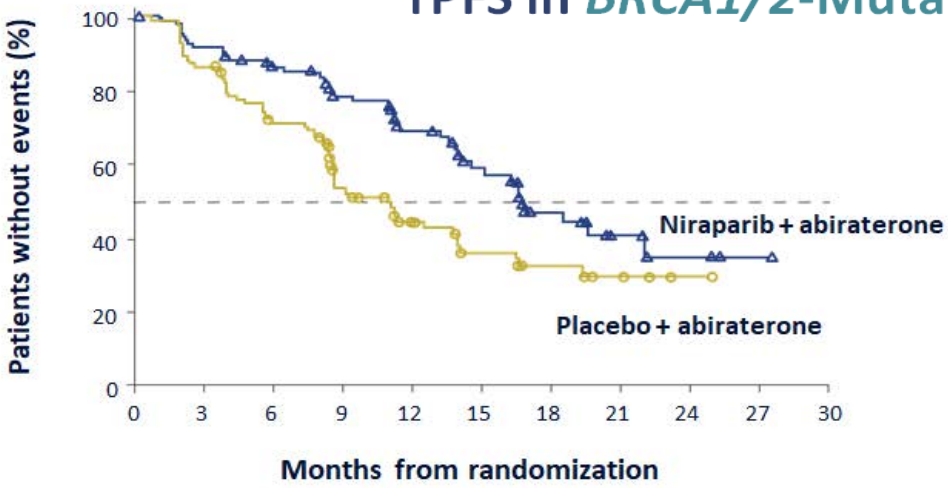
MAGNITUDE: Radiographic progression-free survival

rPFS in All HRR BM+ Cohort



	Niraparib + abiraterone (n=212)	Placebo + abiraterone (n=211)
rPFS by central review		
Median rPFS, months	16.5	13.7
HR (95% CI)	0.73 (0.56–0.96); *P*=0.0217	
rPFS assessed by investigator		
Median rPFS, months	19.0	13.9
HR (95% CI)	0.64 (0.49–0.86); *P*=0.0022	

rPFS in *BRCA1/2*-Mutated Group



	Niraparib + abiraterone (n=113)	Placebo + abiraterone (n=112)
rPFS by central review		
Median rPFS, months	16.6	10.9
HR (95% CI)	0.53 (0.36–0.79); *P*=0.0014	
rPFS assessed by investigator		
Median rPFS, months	19.3	12.4
HR (95% CI)	0.50 (0.33–0.75); *P*=0.0006	

Chi KN et al. *J Clin Oncol 2023*.

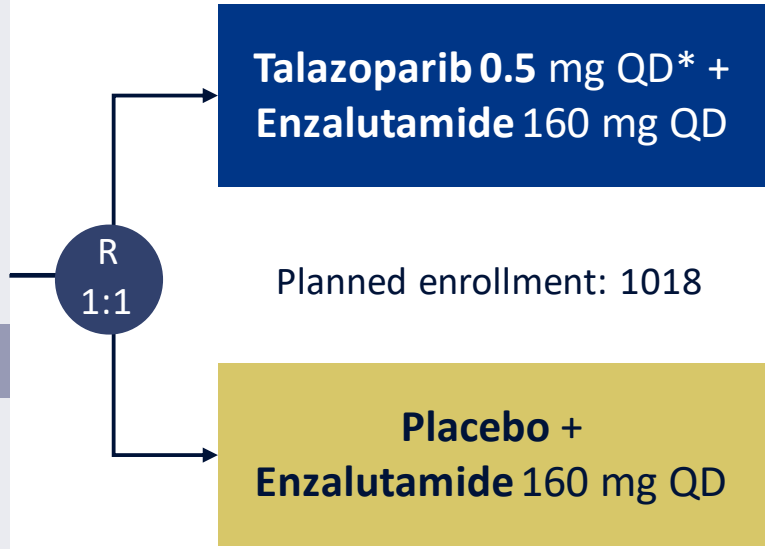
TALAPRO-2: Phase III Trial of Enza +/– Talazoparib

Patient population

- mCRPC with progression (PSA, bone, and/or soft tissue)
- Prior docetaxel and/or abiraterone in CSPC setting allowed
- Ongoing ADT or bilateral orchiectomy
- ECOG PS 0–1

Stratification factors

- Previous treatment with abiraterone or taxane-based chemotherapy for CSPC
- DDR# alteration status (deficient vs nondeficient/unknown)



Co-primary endpoints

- rPFS by BICR per RECIST 1.1 and PCWG3 in **All-comers (Cohort 1), n=804**
- rPFS by BICR in patients with **DDR# alterations (Cohort 2), n=214**

Key secondary endpoints (analyzed for both cohorts separately)

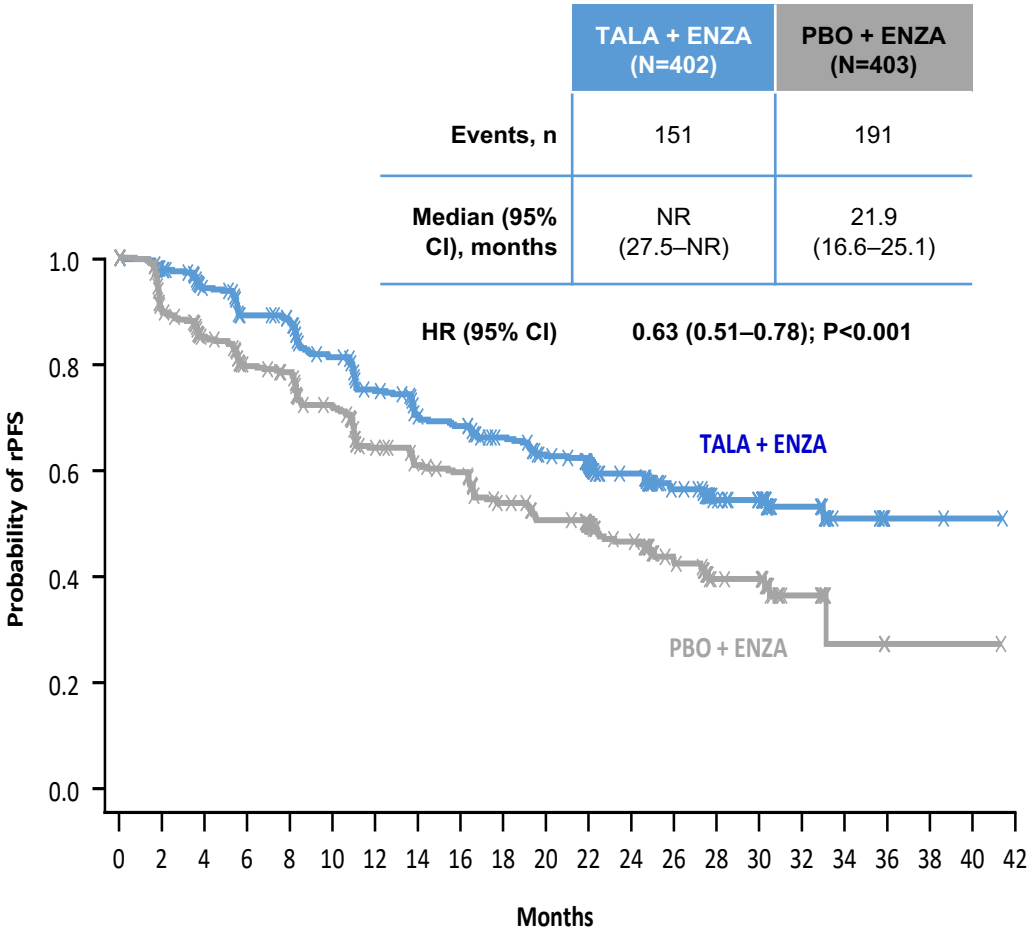
- OS
- OR per RESIST 1.1 (measurable disease)
- PSA response ≥50%
- Time to PSA progression
- Time to initiation of cytotoxic CT or antineoplastic therapy
- Time to first symptomatic skeletal event
- PFS2
- Safety
- Patient-reported outcomes

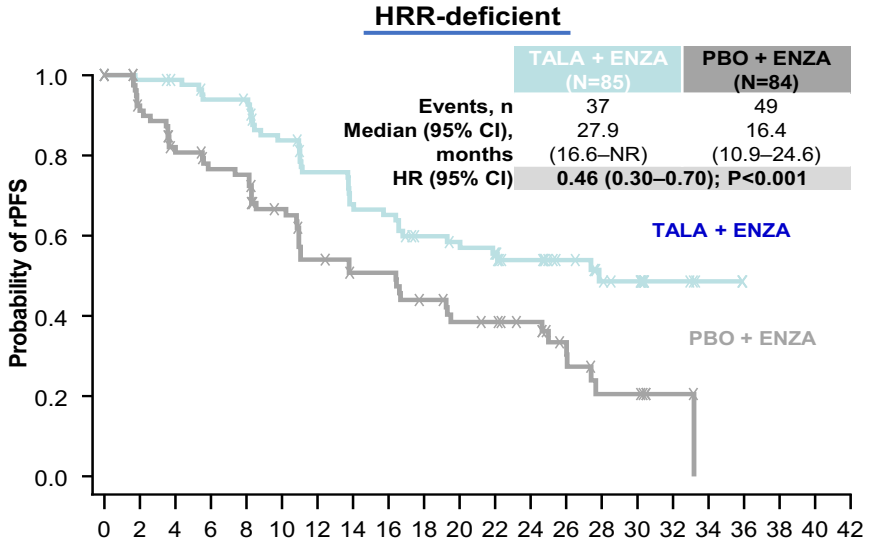
*0.35 mg QD if moderate renal impairment

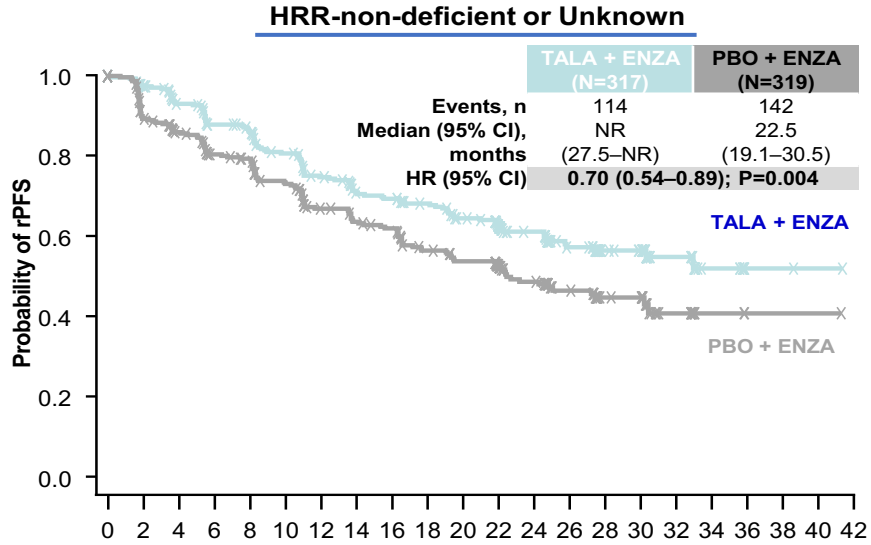
DDR alterations (*BRCA1/2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, CDK12*).

Agarwal N et al. *Future Oncol.* 2022;18:425-436; NCT03395197.

TALAPRO-2: Phase III Trial of Enza +/– Talazoparib







Agarwal N et al. *ASCO GU 2023*; abstr LBA17.

ODAC Meeting (on PROpel) – 4/28/2023

FDA Panel Votes Proposed Olaparib/Abiraterone Indication Should Be Restricted to BRCA-Mutant mCRPC

Apr 28, 2023
Kyle Doherty

In an 11-to-1 vote, the FDA's Oncologic Drugs Advisory Committee voted that the proposed indication of olaparib in combination with abiraterone acetate and prednisone or prednisolone for the initial treatment of patients with metastatic castration-resistant prostate cancer should be restricted to those whose tumors harbor a BRCA mutation.

In an 11-to-1 vote, the FDA's Oncologic Drugs Advisory Committee (ODAC) voted the indication of the PARP inhibitor olaparib in combination with abiraterone acetate and prednisone or prednisolone for the initial treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) should be restricted to patients whose tumors harbor a BRCA mutation.[1]

FDA Decision (on PROpel) – 5/31/2023

FDA approves olaparib with abiraterone and prednisone (or prednisolone) for BRCA-mutated metastatic castration-resistant prostate cancer

On May 31, 2023, the Food and Drug Administration approved olaparib with abiraterone and prednisone for adult patients with deleterious or suspected deleterious BRCA-mutated (*BRCAm*) metastatic castration-resistant prostate cancer (mCRPC), as determined by an FDA-approved companion diagnostic test.

Conclusions

- Germline and somatic HRR mutations are common in mCRPC
- Olaparib is approved for HRR-mutated metastatic CRPC, and Rucaparib is approved for *BRCA1/2*-mutated mCRPC
- PROpel (Abi + Olap) improved rPFS in unselected mCRPC; MAGNITIDE (Abi + Nira) improved rPFS only in HRRm mCRPC
- TALAPRO-2 (Enza + Tala) improved rPFS in unselected mCRPC patients, and in HRRm as well as HRRwt subgroups
- Abi + Olap became FDA-approved for *BRCA1/2*-altered mCRPC

Agenda

Module 1 – Current Management of Nonmetastatic Prostate Cancer — Dr Morgans

Module 2 – New Considerations in Treatment Intensification for Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) — Prof Fizazi

Module 3 – Available and Emerging Strategies for Newly Diagnosed Metastatic Castration-Resistant Prostate Cancer (mCRPC) — Dr McKay

Module 4 – Identification and Management of mCRPC with a Homologous Recombination Repair (HRR) Gene Abnormality — Dr Antonarakis

Module 5 – Management of Progressive mCRPC — Dr Sartor

RTP
RESEARCH
TO PRACTICE

Case Presentation: 77-year-old man with multiregimen-refractory mCRPC and a gBRCA2 mutation receives olaparib with a sustained response for several years

Dr Sandy Srinivas (Stanford, California)

RTP RESEARCH TO PRACTICE

Case Presentation: 65-year-old man with multiregimen-refractory PSMA-positive metastatic CRPC currently on a clinical trial due to scarcity of lutetium Lu 177 vipivotide tetraxetan

Dr Neeraj Agarwal (Salt Lake City, Utah)

RTP RESEARCH TO PRACTICE

Management of Progressive mCRPC With Emphasis on Radium-223, Cabazitaxel, and PSMA-617 Lu-177

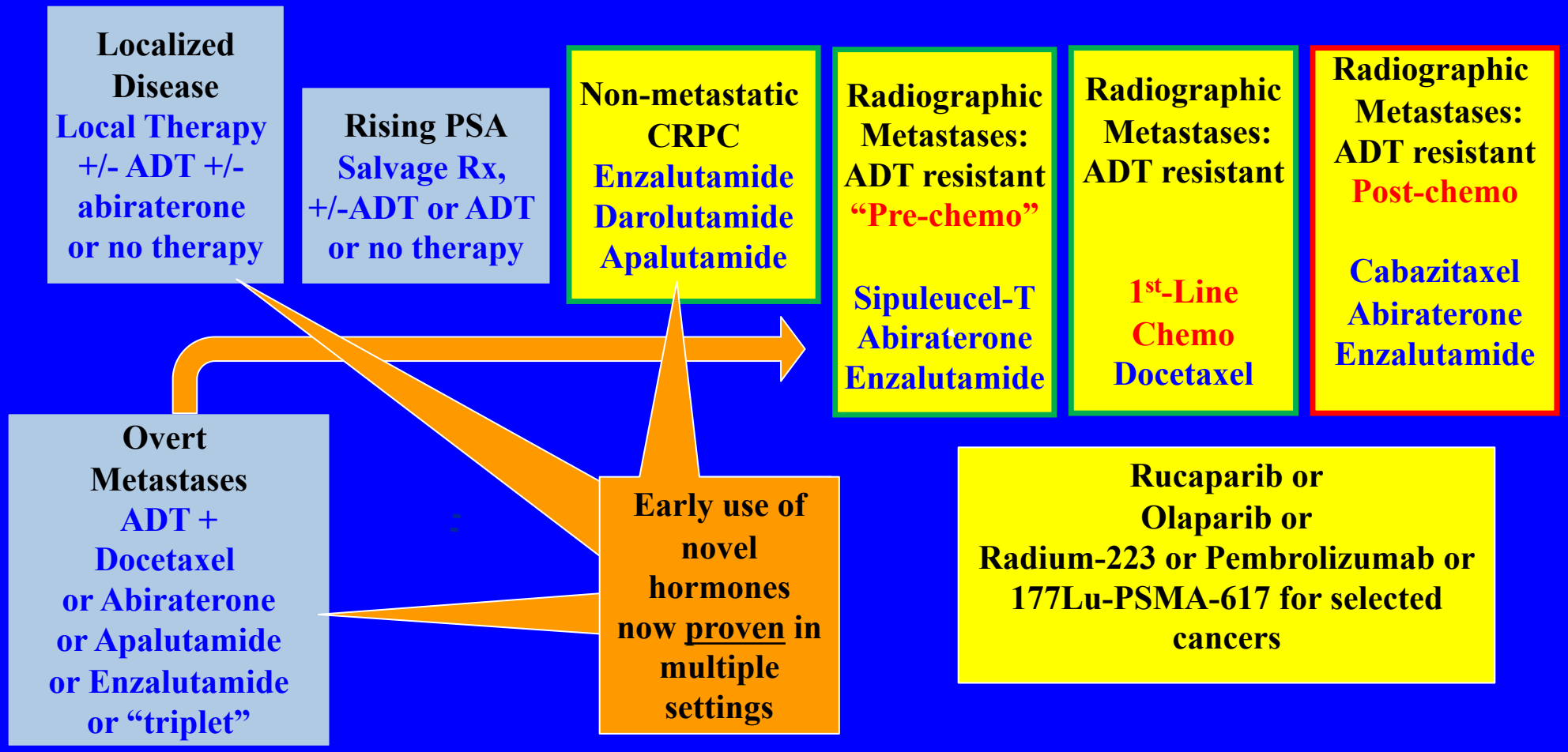
Oliver Sartor, MD

Director of Radiopharmaceutical Clinical Trials

Mayo Clinic

Rochester, MN

Standard Therapies Today: New hormonal agents are moving earlier and earlier leaving a changed CRPC



Mechanisms of Action

- Radium-223
  - Alpha emitter that binds to bone stroma (hydroxyapatite) targeting areas of active bone turnover (blastic lesions)
- Cabazitaxel
  - Binds to tubulin and inhibits microtubular function
- PSMA-617 Lu-177
  - Beta emitter that binds to PSMA on the cell surface

The NEW ENGLAND JOURNAL of MEDICINE

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

Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

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

2013

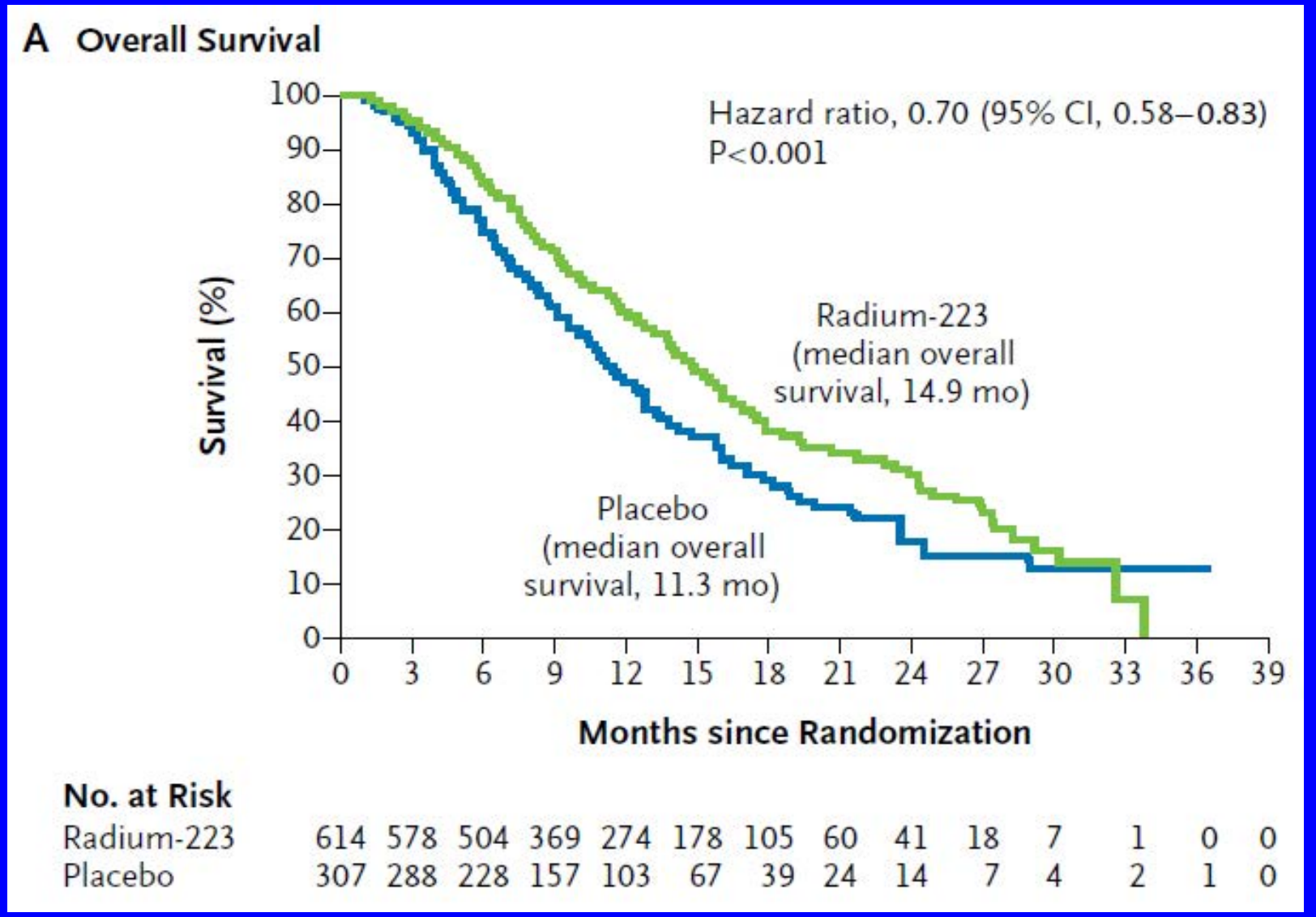
Pretreatments ADT or ADT + Docetaxel

Population: Bone scan positive and symptomatic (excludes viscera)

Control Arm "Standard of Care" excluding Chemotherapy

Overall Survival ALSYMPCA

Parker et al. NEJM 369: 213-23, 2013



Radium-223 only goes to bone stroma!

Radium-223 moved the field forward but lack of positive trials since 2013 is problematic given the dramatically changing landscape

Radium-223 needs new trials to remain relevant for today's patient

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer

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

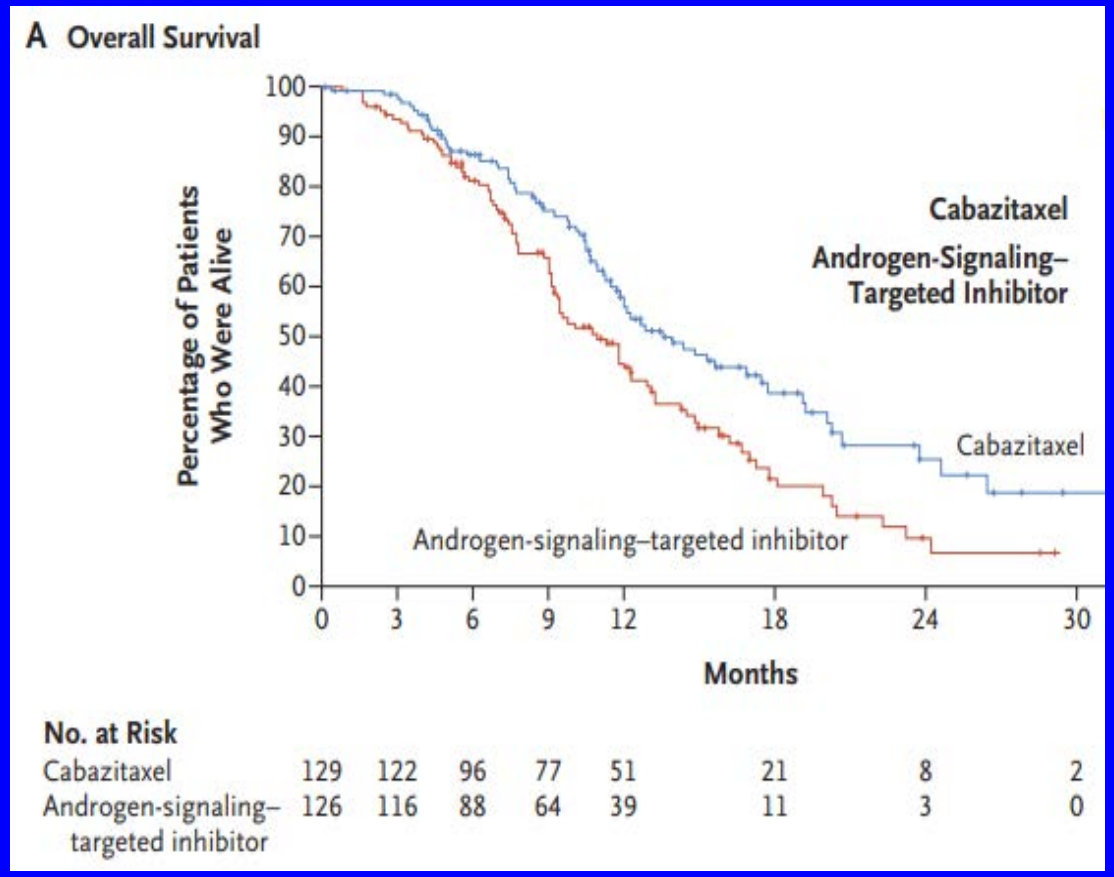
2019

Pretreatments ADT + docetaxel + abiraterone or enzalutamide
Population: mCRPC without selection
Control of “alternate” abiraterone or enzalutamide

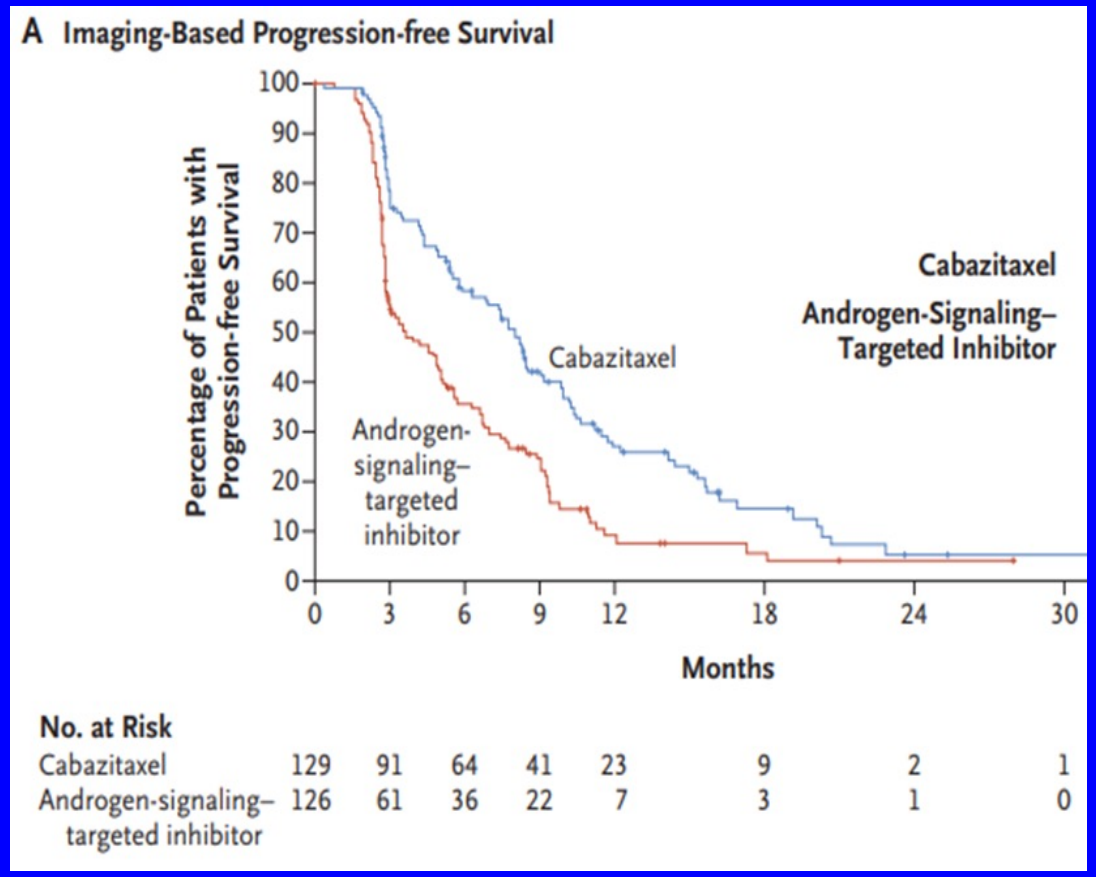
CARD: Cabazitaxel phase III trial

CARD met both primary endpoint PFS and secondary OS endpoint

OS: HR 0.64 (95% CI 0.46-0.89)

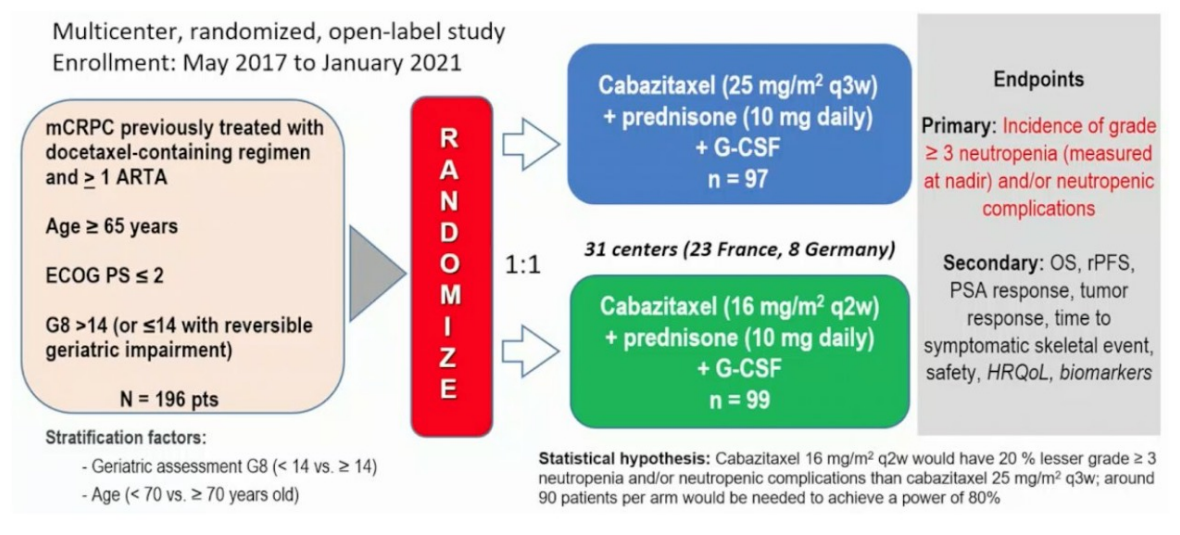


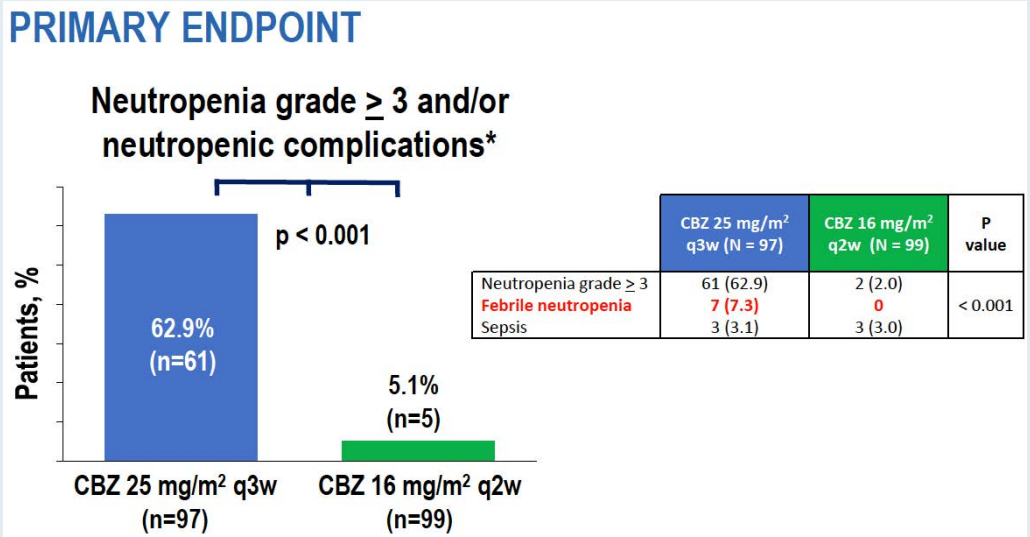
rPFS: HR 0.54 (95% CI 0.40-0.73)



Other Recently Reported Trials Investigating Cabazitaxel for mCRPC

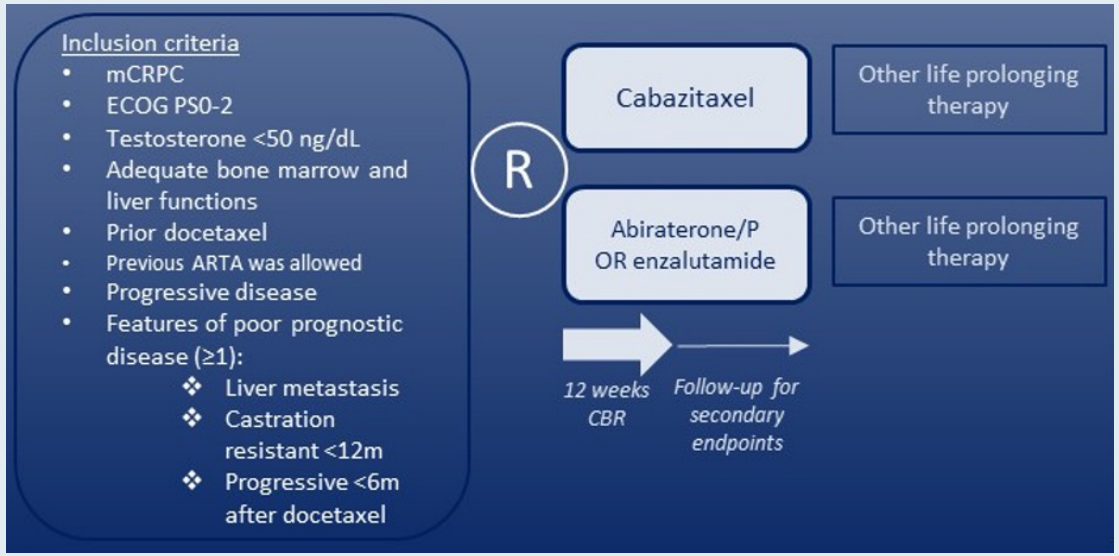
CABASTY[1]





	CBZ 25 mg/m² q3w (N = 97)	CBZ 16 mg/m² q2w (N = 99)	P value
Neutropenia grade ≥ 3	61 (62.9)	2 (2.0)	
Febrile neutropenia	7 (7.3)	0	< 0.001
Sepsis	3 (3.1)	3 (3.0)	

OSTRICh[2]



Conclusion

- No significant difference in CBR between CBZ and ARTA treated patients at 12 weeks
- Visceral metastases were more frequent in CBZ patients
- Radiological response and stable disease at 12 weeks was significantly higher in patients treated with CBZ than with ARTA
- Time to clinical progression was significantly prolonged in patients treated with ARTA
- Overall survival and rPFS was similar in both groups

[1] Oudard S et al. ESMO 2022;Abstract 1363MO; [2] van der Zande K et al. ASCO 2021;Abstract 5059.

RTP RESEARCH TO PRACTICE

Cabazitaxel is an important step forward in the post-docetaxel space since 2010 when TROPIC trial improved OS vs mitoxantrone

Limitation is that only about 50% of mCRPC patients in the USA are treated with chemotherapy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

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

2021

Pretreatments ADT + abiraterone/enzalutamide/both + docetaxel/cabazitaxel/both

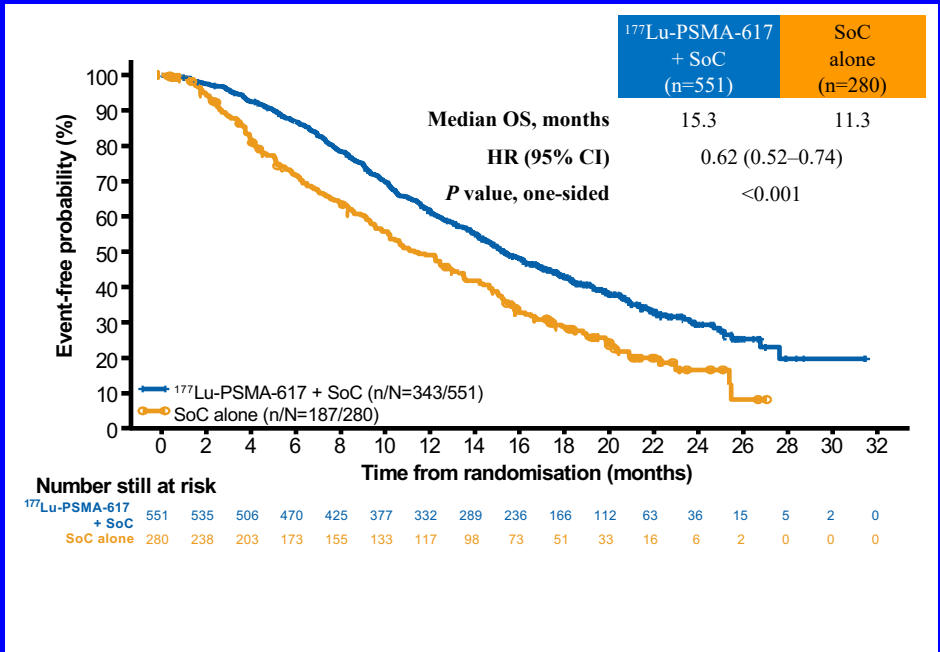
Population: PSMA PET positive (87% of screened)

Control Arm “Standard of Care” excluding Chemotherapy

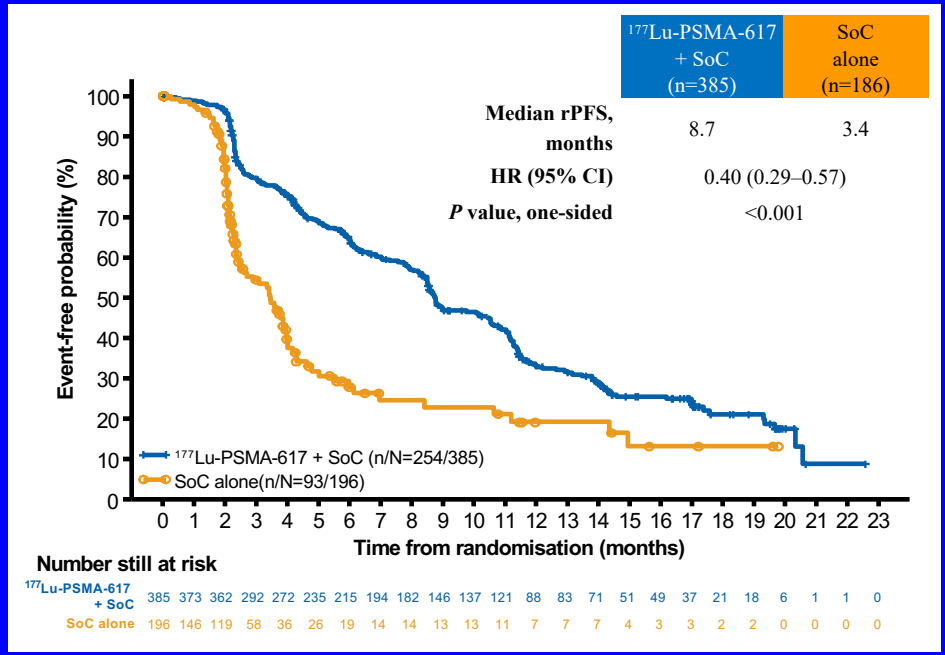
VISION: ^{177}Lu-PSMA-617 Phase III trial

VISION met both primary endpoints of OS and rPFS

OS: HR 0.62 (95% CI 0.52-0.74)

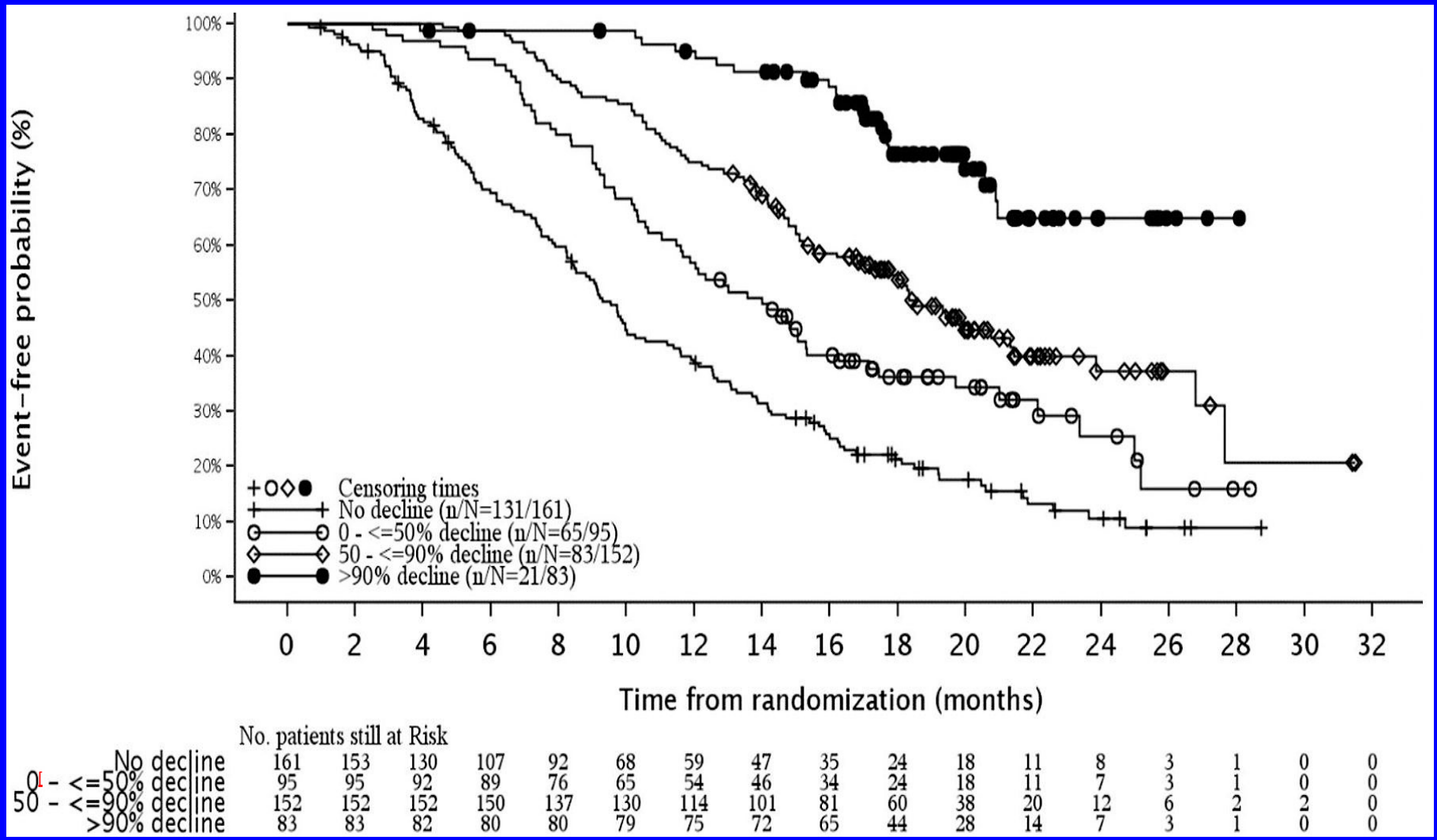


rPFS: HR 0.40 (95% CI 0.29-57)



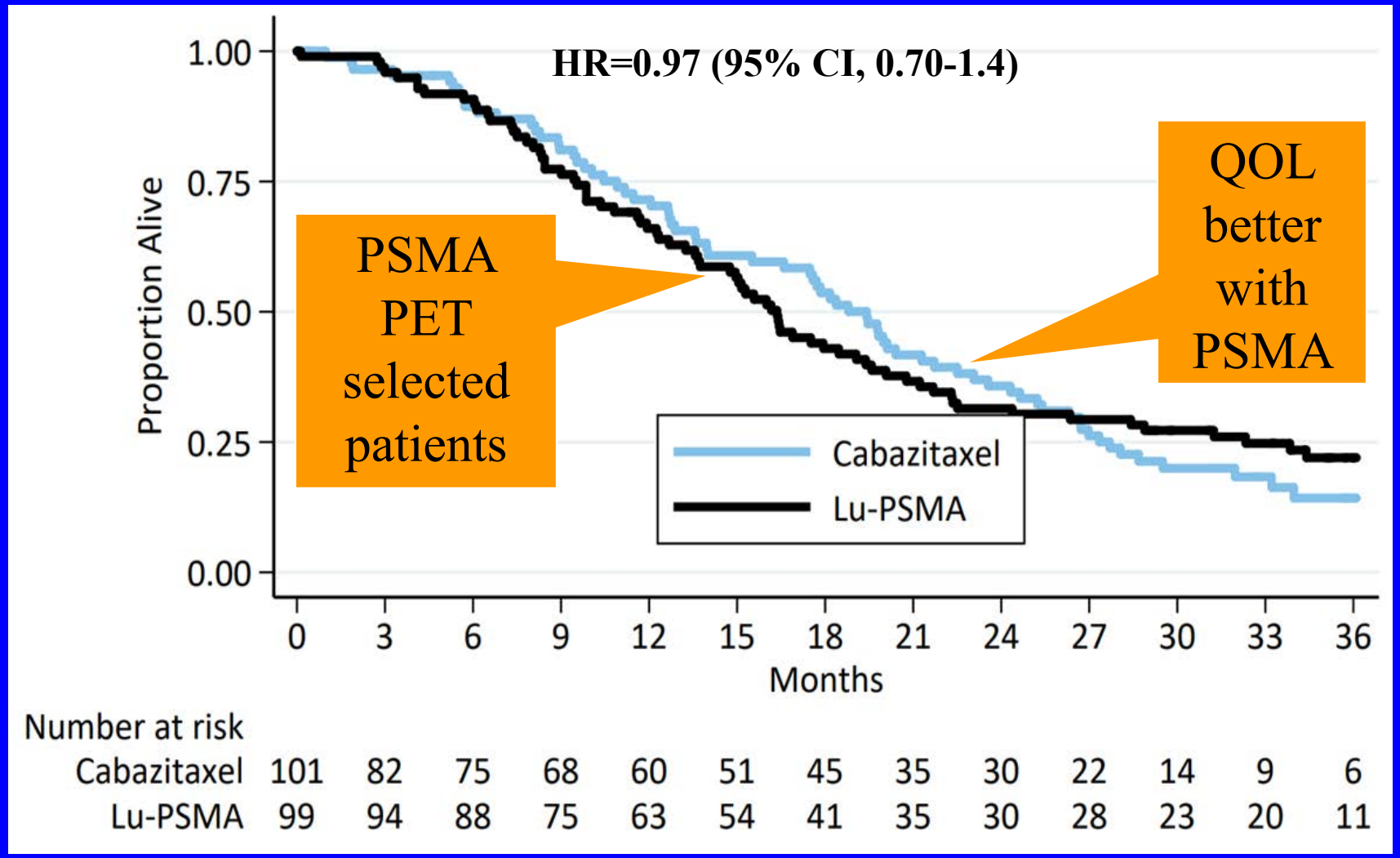
PSA Decline at <12 weeks and Overall Survival

Armstrong et al. Annals of Oncology (2022) 33 (suppl_7): S616-S652.



PSMA-617 Lu-177 vs cabazitaxel in mCRPC (TheraP) randomized phase 2 trial

Hofman et al. ASCO 2022



New important prechemotherapy theranostic trials in mCRPC

- PSMAfore — Announced positive
  - PSMAfore: A Phase III, Open-label, Multi-Center, Randomized Study Comparing 177Lu-PSMA-617 vs. a Change of Androgen Receptor-directed Therapy in the Treatment of Taxane Naïve Men With Progressive mCRPC
- SPLASH — Completed accrual
  - A Phase 3, Open-Label, Randomized Study Evaluating Metastatic Castrate Resistant Prostate Cancer Treatment Using PSMA [Lu-177]-PNT2002 Therapy After Second-line Hormonal Treatment (SPLASH)
- ECLIPSE
  - A Multi-Center, Open-Label, Randomized Phase 3 Trial Comparing the Safety and Efficacy of 177Lu-PSMA-I&T Versus Hormone Therapy in Patients With mCRPC

PSMA-617 Lu-177 is an important step forward but the supply chain has been hugely problematic

Therapy has been well tolerated as a whole and this therapy will move earlier in the treatment paradigm

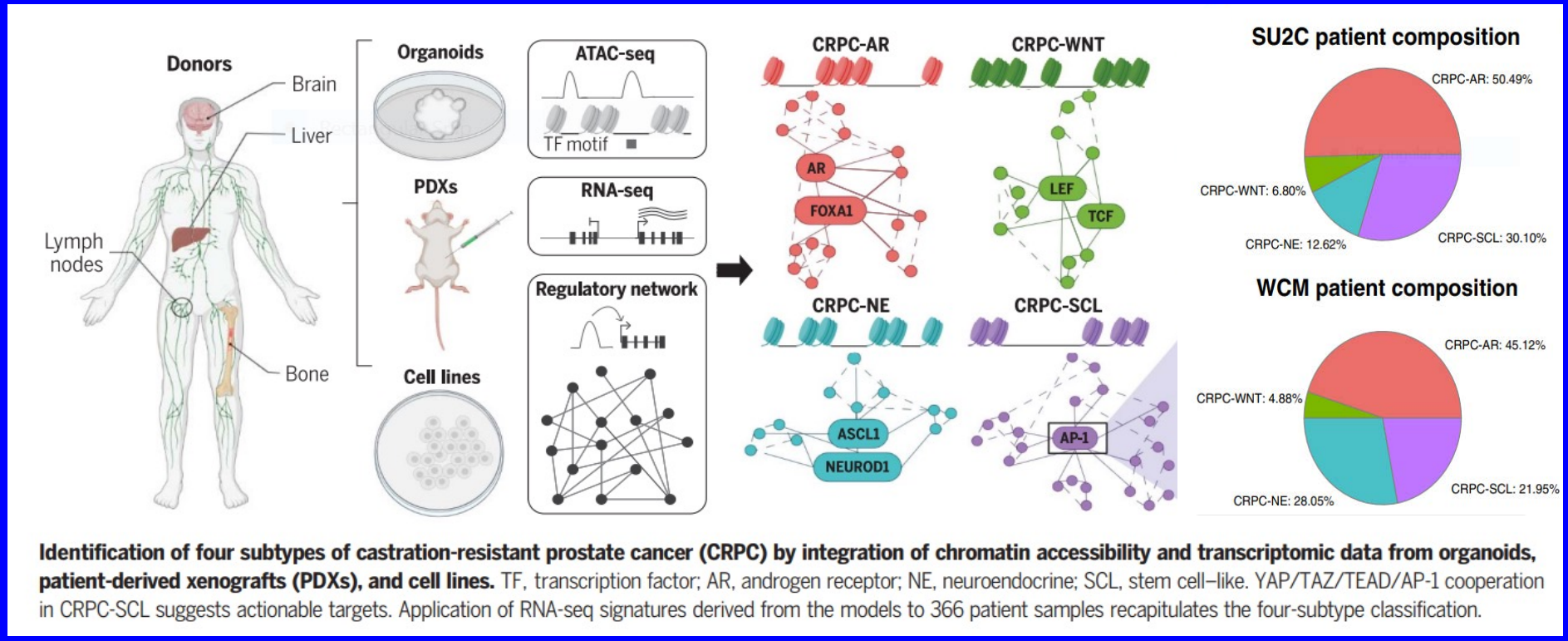
CANCER GENOMICS

Chromatin profiles classify castration-resistant prostate cancers suggesting therapeutic targets

Fanying T… y,
Cindy J. L… ic Minwei Liu,
Ann Palla… leneses,
Elisa de S… ra,
Himisha Beltran, Cora N. Sternberg, Ping Chi, Howard I. Scher, Andrea Sboner, Yu Chen*, Ekta Khurana*

What are we missing? AR-driven only 45-50% of the story and much more than neuroendocrine!

Science May 2022



Identification of four subtypes of castration-resistant prostate cancer (CRPC) by integration of chromatin accessibility and transcriptomic data from organoids, patient-derived xenografts (PDXs), and cell lines. TF, transcription factor; AR, androgen receptor; NE, neuroendocrine; SCL, stem cell–like. YAP/TAZ/TEAD/AP-1 cooperation in CRPC-SCL suggests actionable targets. Application of RNA-seq signatures derived from the models to 366 patient samples recapitulates the four-subtype classification.

Second Opinion: Investigators Discuss How They and Their Colleagues Apply Available Clinical Research in the Care of Patients with Prostate Cancer

A CME Symposium Held in Conjunction with the 2023 ASCO® Annual Meeting

Saturday, June 3, 2023

7:00 PM – 9:00 PM CT

Faculty

Emmanuel S Antonarakis, MD

Prof Karim Fizazi, MD, PhD

Rana R McKay, MD

Alicia K Morgans, MD, MPH

A Oliver Sartor, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

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

David S Morris, MD
President and Co-Director of Advanced Therapeutics Center
Urology Associates
Nashville, Tennessee

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

POSTMEETING SURVEY – Available Now

Clinicians in Attendance: The postmeeting survey is now available on the iPads for attendees in the room and on Zoom for those attending virtually. We appreciate your completing this survey before the end of the program.

Thank you for your input.

RTP
RESEARCH
TO PRACTICE

Breakfast with the Investigators: Ovarian Cancer

A CME Symposium Held in Conjunction with the 2023 ASCO® Annual Meeting

Sunday, June 4, 2023

6:45 AM – 7:45 AM CT

Faculty

Philipp Harter, MD, PhD

David M O'Malley, MD

Shannon N Westin, MD, MPH

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us!
Your feedback is very important to us.

Please complete the survey currently up on the iPads for attendees in the room and on Zoom for those attending virtually. The survey will remain open up to 5 minutes after the meeting ends.

How to Obtain CME Credit

In-person attendees: Please refer to the program syllabus for the CME credit link or QR code. You may also use the iPads available in the meeting room to complete the course evaluation.

Online/Zoom attendees: The CME credit link is posted in the chat room.

RTP
RESEARCH
TO PRACTICE