Cases from the Community: Urologic Oncology Investigators Provide Perspectives on the Optimal Management of Prostate Cancer

Part 1 of a 2-Part CME Satellite Symposium Series in Conjunction with the AUA 2022 Annual Meeting

Friday, May 13, 2022

8:00 AM – 10:00 AM CT (9:00 AM – 11:00 AM ET)

Faculty

Raoul S Concepcion, MD
Fred Saad, MD
Matthew R Smith, MD, PhD

Moderator

Emmanuel S Antonarakis, MD

RTP RESEARCH TO PRACTICE

Faculty

Raoul S Concepcion, MD
Chief Science Officer
US Urology Partners
Nashville, Tennessee

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

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

Moderator

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

RTP
RESEARCH TO PRACTICE

Clinicians in the Meeting Room

Networked iPads are available.

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

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

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

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

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

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 premeeting survey before the meeting. Survey results will be presented and discussed throughout the meeting.

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

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

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

Cases from the Community: Urologic Oncology Investigators Provide Perspectives on the Optimal Management of Urothelial Bladder Cancer

Part 2 of a 2-Part CME Satellite Symposium Series in Conjunction with the AUA 2022 Annual Meeting

Friday, May 13, 2022

6:00 PM – 8:00 PM CT (7:00 PM – 9:00 PM ET)

Faculty

Matthew D Galsky, MD
Ashish M Kamat, MD, MBBS
Stephen B Williams, MD, MS

Moderator

Sumanta Kumar Pal, MD

RTP RESEARCH TO PRACTICE

Cases from the Community: Urologic Oncology Investigators Provide Perspectives on the Optimal Management of Prostate Cancer

Part 1 of a 2-Part CME Satellite Symposium Series in Conjunction with the AUA 2022 Annual Meeting

Friday, May 13, 2022

8:00 AM – 10:00 AM CT (9:00 AM – 11:00 AM ET)

Faculty

Raoul S Concepcion, MD
Fred Saad, MD
Matthew R Smith, MD, PhD

Moderator

Emmanuel S Antonarakis, MD

RTP RESEARCH TO PRACTICE

Commercial Support

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

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.

RTP
RESEARCH
TO PRACTICE

Dr Antonarakis — Disclosures

Advisory Committee	AIkido Pharma Inc, Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Blue Earth Diagnostics, Bristol-Myers Squibb Company, Constellation Pharmaceuticals, Curium Pharma, Exact Sciences, Foundation Medicine, Invitae, Ismar Healthcare NV, Merck, Orion Corporation, Tempus
Consulting Agreements	EcoR1 Capital LLC, KeyQuest Health
Contracted Research	AstraZeneca Pharmaceuticals LP, Celgene Corporation, Clovis Oncology
Other	QIAGEN: licenser of technology

Dr Concepcion — Disclosures

No relevant conflicts of interest to disclose

Dr Saad — Disclosures

Advisory Committee and Consulting Agreements	Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Janssen Biotech Inc, Myovant Sciences, Novartis, Pfizer Inc, Sanofi Genzyme
Contracted Research	Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Janssen Biotech Inc, Merck, Myovant Sciences, Novartis, Pfizer Inc, Sanofi Genzyme

Dr Smith — Disclosures

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

RTP RESEARCH TO PRACTICE

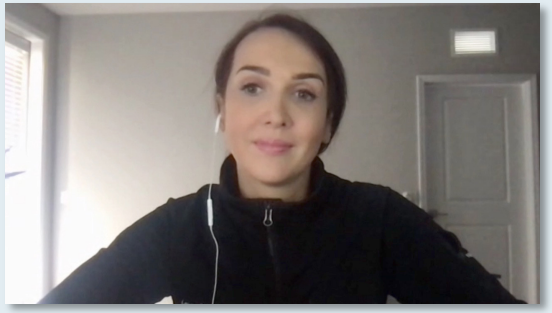
Agenda

MODULE 1: Management Approaches for Nonmetastatic Prostate Cancer — Dr Concepcion

MODULE 2: Role of Treatment Intensification in Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) — Dr Smith

MODULE 3: Selection and Sequencing of Therapy for Metastatic CRPC (mCRPC) — Dr Antonarakis

MODULE 4: Current and Future Integration of PARP Inhibitors in the Management of Prostate Cancer — Dr Saad



Laura Bukavina, MD, MPH
Fox Chase Cancer Center
Philadelphia, Pennsylvania

David S Morris, MD
Urology Associates
Nashville, Tennessee

Jason Hafron, MD
Oakland University William
Beaumont School of Medicine
West Bloomfield, Michigan

David A Taub, MD, MBA
Lynn Cancer Institute
Baptist Health South Florida
Boca Raton, Florida

Paul Markowski, MD
Atlantic Health System
Summit, New Jersey

RTP
RESEARCH
TO PRACTICE

MODULE 1: Management Approaches for Nonmetastatic Prostate Cancer

RTP
RESEARCH
TO PRACTICE

For your patients with high-risk biochemical (M0) recurrence after primary radiation therapy, in general, if you could access a PSMA PET scan, would you?

1. Yes
2. No

Case Presentation: A 70-year-old man with M0 HSPC

Dr Laura Bukavina (Philadelphia, Pennsylvania)

RTP
RESEARCH
TO PRACTICE

What form of ADT would you most likely recommend for a 53-year-old man with high-risk, node-positive prostate cancer at prostatectomy?

1. Relugolix
2. Leuprolide
3. Goserelin
4. Other

Case Presentation: A 53-year-old man with high-risk M0 HSPC and a slowly rising PSA

Dr David Morris (Nashville, Tennessee)

RTP RESEARCH TO PRACTICE

U.S. UROLOGY PARTNERS

Management Approaches for Nonmetastatic Prostate Cancer

Raoul S. Concepcion, MD, FACS

Chief Science Officer

Nashville TN

Clinical Challenges

- Detection of clinically significant disease
- Management of HG/HR disease, non-metastatic
- How will molecular imaging change the current landscape
- Optimizing therapeutic choices and SE profiles, nmCRPC

U.S. UROLOGY PARTNERS

Semantics

- Localized Prostate Cancer
  - Very Low Risk
  - Low Risk
  - Favorable Intermediate
  - High Risk
  - Very High Risk

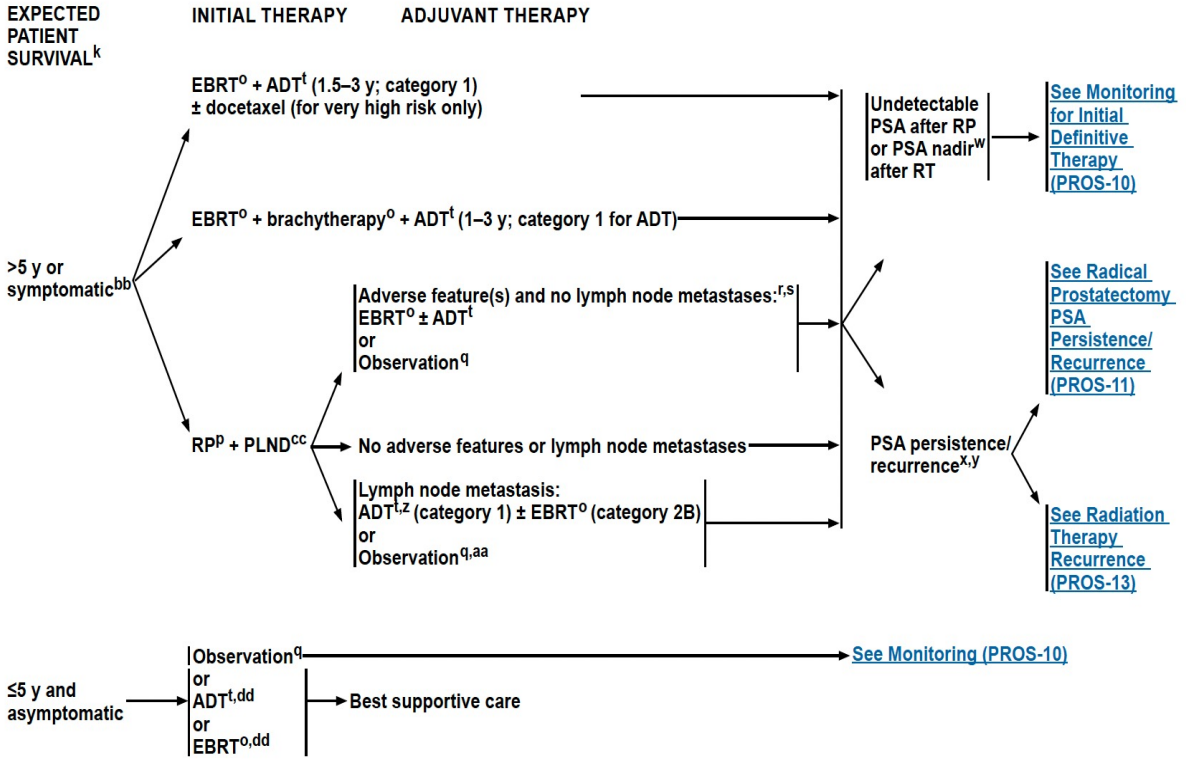
- Advanced Prostate Cancer
  - What defines?
- Metastatic Disease: Yes/No
- Continuous Hormonal Status: Yes/No
- CNPC/CSPC
- CRPC

U.S. UROLOGY PARTNERS

INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE[d]

Risk Group	Clinical/Pathologic Features (See Staging (ST-1))			Additional Evaluation[g,h]	Initial Therapy
Very low[e]	Has all of the following: • cT1c • Grade Group 1 • PSA <10 ng/mL • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core • PSA density <0.15 ng/mL/g			• Consider confirmatory prostate biopsy ± mpMRI if not performed prior to biopsy to establish candidacy for active surveillance	See PROS-3
Low[e]	Has all of the following but does not qualify for very low risk: • cT1–cT2a • Grade Group 1 • PSA <10 ng/mL			• Consider confirmatory prostate biopsy ± mpMRI if not performed prior to biopsy to establish candidacy for active surveillance	See PROS-4
Intermediate[e]	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRFs): ▸ cT2b–cT2c ▸ Grade Group 2 or 3 ▸ PSA 10–20 ng/mL	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive (eg, <6 of 12 cores)[f]	• Consider confirmatory prostate biopsy ± mpMRI if not performed prior to biopsy for those considering active surveillance	See PROS-5
		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥ 50% biopsy cores positive (eg, ≥ 6 of 12 cores)[f]	Bone and soft tissue imaging[i,j] • If regional or distant metastases are found, see PROS-8 or PROS-12	See PROS-6
High	Has no very-high-risk features and has exactly one high-risk feature: • cT3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL			Bone and soft tissue imaging[i,j] • If regional or distant metastases are found, see PROS-8 or PROS-12	See PROS-7
Very high	Has at least one of the following: • cT3b–cT4 • Primary Gleason pattern 5 • 2 or 3 high-risk features • >4 cores with Grade Group 4 or 5			Bone and soft tissue imaging[i,j] • If regional or distant metastases are found, see PROS-8 or PROS-12	See PROS-7

HIGH- OR VERY-HIGH-RISK GROUP



See Footnotes for Risk Groups (PROS-7A).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Ongoing Phase II & III Trials in High-Risk Prostate Cancer

Clinical trial ID	Description	Intervention	Size	Status	Primary outcome
		SECOND GENERATION ADT			
ARNEO trial (NCT03080116)	Interventional, single center, phase II, randomized, double-blind, placebo controlled	degarelix + apalutamide *vs* degarelix + placebo	84 (estimated)	Recruiting	Minimal residual disease after 12 weeks of neoadjuvant therapy
ATLAS trial (NCT02531516)	Interventional, multicenter, phase III, randomized, double-blind, placebo-controlled	Apalutamide + placebo + RT *vs* placebo + ADT + RT	1,503 (actual)	Not recruiting	Metastasis-free survival
ENZARAD trial (NCT02446444)	Interventional, phase III, randomized, open label	Enzalutamide + LHRHa + RT *vs* conventional NSAA + LHRHa + RT	802 (actual)	Not recruiting	Metastasis-free survival
PROTEUS trial (NCT03767244)	Interventional, phase III, randomized, double-blind, placebo controlled	Apalutamide + ADT + RP + pLND *vs* placebo + ADT + RP + pLND	1,500 (estimated)	Recruiting	Pathologic complete response (pCR) and metastasis-free survival
iPARP					
NADIR trial (NCT04037254)	Interventional, phase II, randomized, open label	ADT + IMRT *vs* niraparib + ADT + IMRT	180 (estimated)	Not recruiting	Maintenance of disease-free state
PARTICLE THERAPY					
NCT02672449	Prospective, multicenter, phase II, open label	Carbon ion boost followed by photon RT	65 (estimated)	Recruiting	G3 or G4 adverse events according to the RTOG / EORTC scale

ADT, androgen deprivation therapy; G, grade; IMRT, intensity-modulated RT; LHRHa, luteinizing hormone–releasing hormone analog; NSAA, non-steroidal anti-androgen; pCR, pathologic complete response; pLND, pelvic lymph node dissection; RP, radical prostatectomy; RT, radiotherapy.

Marvaso G et al. Front Oncol 2021;11:732766.

U.S. UROLOGY PARTNERS

BMJ Open

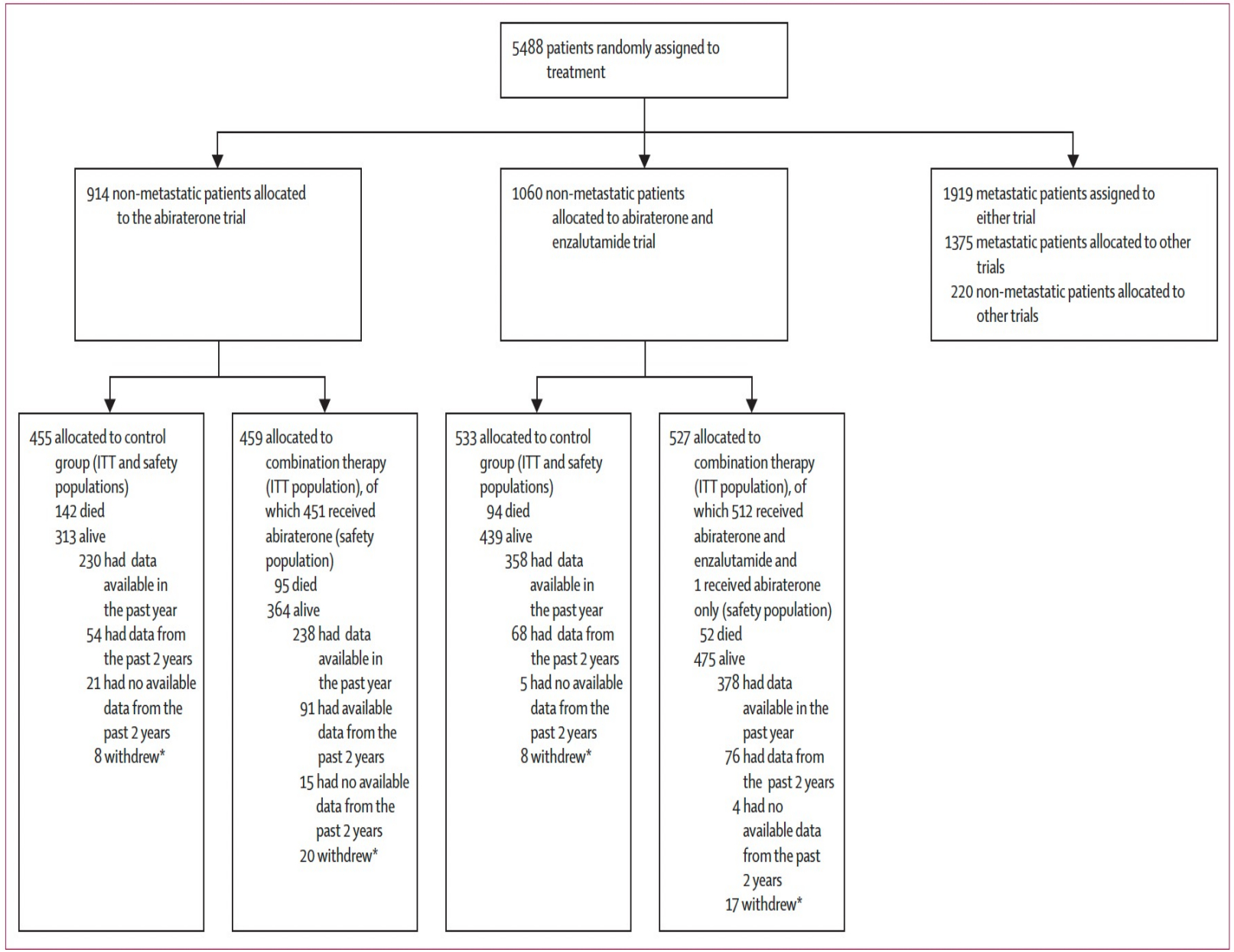
A phase 3 randomised study of enzalutamide plus leuprolide and enzalutamide monotherapy in high-risk non-metastatic hormone-sensitive prostate cancer with rising PSA after local therapy: EMBARK study design

Stephen J Freedland ,[1,2] Ugo De Giorgi,[3] Martin Gleave,[4] Brad Rosbrook,[5] Qi Shen,[6] Jennifer Sugg,[7] Gabriel P Haas,[8] Neal D Shore[9]

U.S. UROLOGY PARTNERS

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

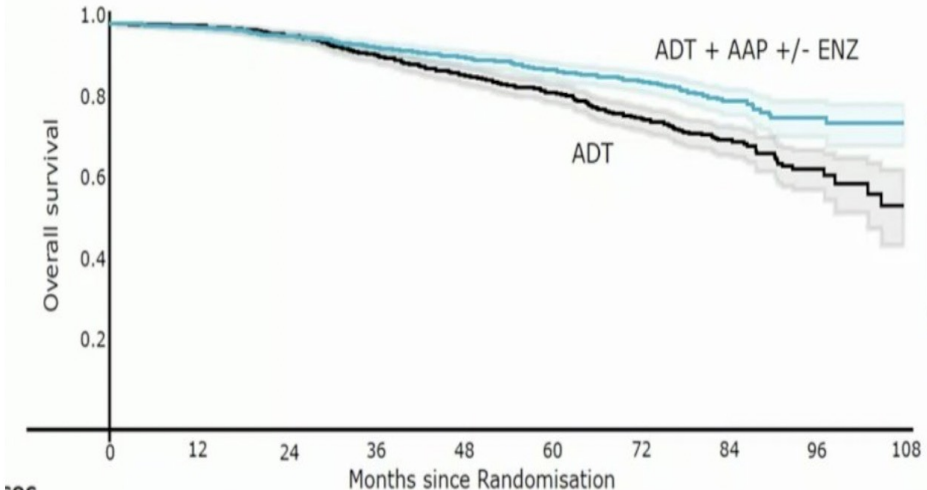
Gerhardt Attard, Laura Murphy, Noel W Clarke, William Cross, Robert J Jones, Christopher C Parker, Silke Gillessen, Adrian Cook, Chris Brawley, Claire L Amos, Nafisah Atako, Cheryl Pugh, Michelle Buckner, Simon Chowdhury, Zafar Malik, J Martin Russell, Clare Gilson, Hannah Rush, Jo Bowen, Anna Lydon, 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‡*



Attard G et al. Lancet 2022;399:447-60

U.S. UROLOGY PARTNERS

Overall survival



Events
147 ADT+AAP +/- ENZ
236 ADT

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

SOC										
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
SOC+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

6-year survival improved from 77% to 86%

Adverse events

Worst toxicity grade in 1st 2 years	ADT only (AAP comparison)		ADT only (AAP + ENZ comparison)		AAP		AAP + ENZ	
	N (454)	%	N (530)	%	N (456)	%	N (522)	%
3	118	26	160	30	151	33	**277**	**53**
4	12	3	12	2	17	4	**23**[¶]	**4**
5	0	0	0	0	**3***	**1**	**4^**	**1**

[¶]Toxicities with the largest difference between AAP vs AAP+ENZ = (Gr 3) erectile dysfunction, hypertension, fatigue, (Gr 3/4) transaminitis

*1 event each of rectal adenocarcinoma, pulmonary haemorrhage and a respiratory disorder

^2 events each of septic shock and sudden death

Attard G et al. Lancet 2022;399:447-60; Attard G et al. ESMO 2021;Abstract LBA4_PR.

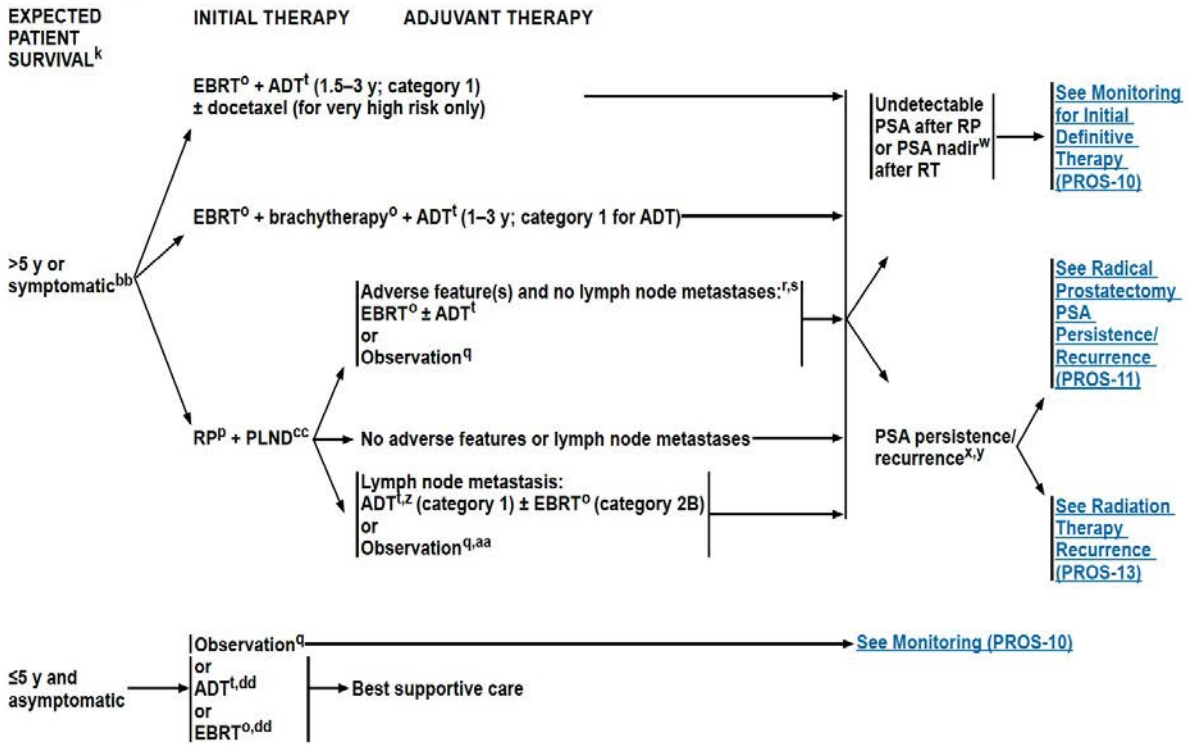
U.S. UROLOGY PARTNERS

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion

HIGH- OR VERY-HIGH-RISK GROUP



See Footnotes for Risk Groups (PROS-7A).

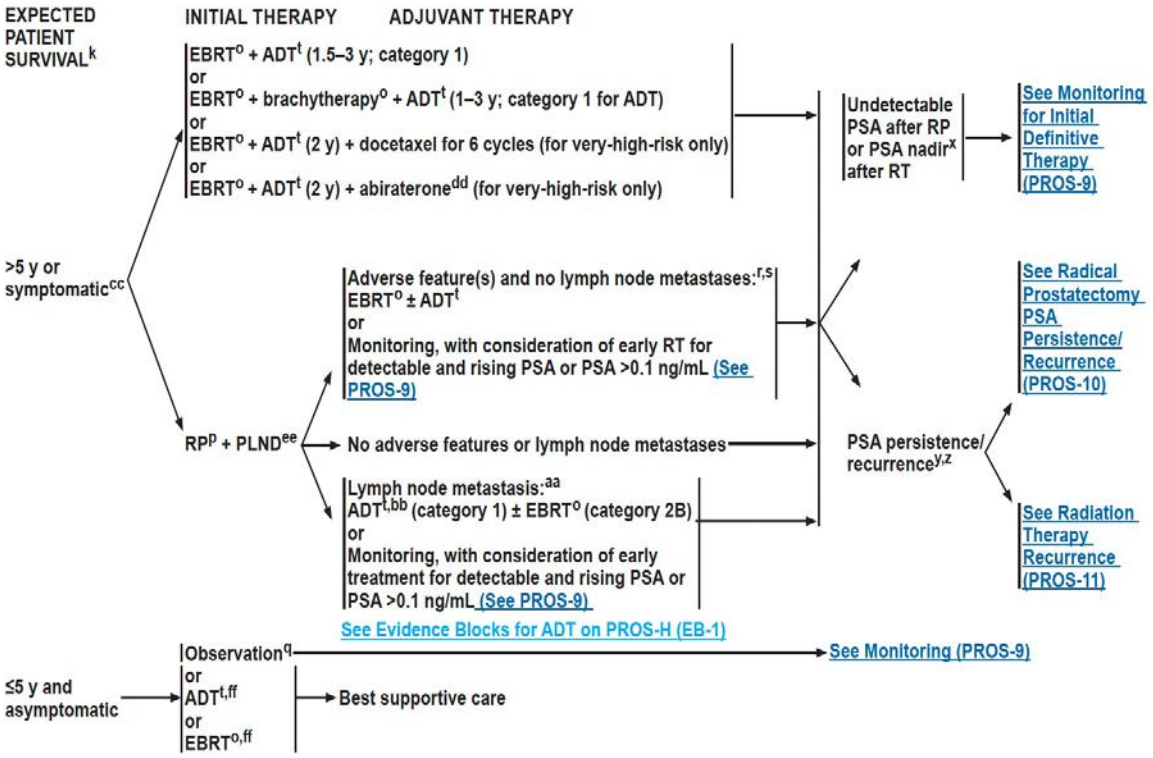
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Prostate Cancer
NCCN Evidence Blocks™

NCCN Guidelines Index
Table of Contents
Discussion

HIGH- OR VERY-HIGH-RISK GROUP



See Footnotes for Risk Groups (PROS-8A).

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Cardiovascular Morbidity in a Randomized Trial Comparing GnRH Agonist and GnRH Antagonist among Patients with Advanced Prostate Cancer and Preexisting Cardiovascular Disease

David Margel,*,† Avivit Peer, Yaara Ber, Liat Shavit-Grievink, Tzlil Tabachnik, Sivan Sela, Guy Witberg, Jack Baniel, Daniel Kedar, Wilhelmina C. M. Duivenvoorden, Eli Rosenbaum‡ and Jehonathan H. Pinthus,†,‡

From the Division of Urology (DM, YB, LS-G, TT, SS, JB, DK), Rabin Medical Center and Davidoff Cancer Centre (LS-G, ER) and Department of Cardiology (GW), Rabin Medical Center, Petach Tikva, Sackler Faculty of Medicine, Tel Aviv University (DM, JB, DK), Tel Aviv and Department of Oncology, Rambam Health Care Campus and Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa (AP), Israel, and Division of Urology, Department of Surgery, McMaster University (WCMD, JHP), Hamilton, Ontario, Canada

Table 3. *CVEs and MACCEs by study arm*

	GnRH Agonist	GnRH Antagonist	p Value (log-rank test)
No. CVEs and MACCEs:*			—
Pts	39	41	
Death	2	—	
Myocardial infarction	1	—	
Cerebrovascular accident	2	—	
Heart catheterization with stent	3	1	
Cardiac related emergency room visits	5	1	
Total No. (%):			
CVEs	13 (33.3)	2 (4.8)	0.001
MACCEs	8 (20.5)	1 (2.4)	0.013

* Cardiovascular related events included death, myocardial infarction, cerebrovascular accident, transient ischemic attack, heart catheterization with or without intervention and cardiac related hospitalization, and MACCEs included death, myocardial infarction, cerebrovascular accident and heart catheterization with stent.

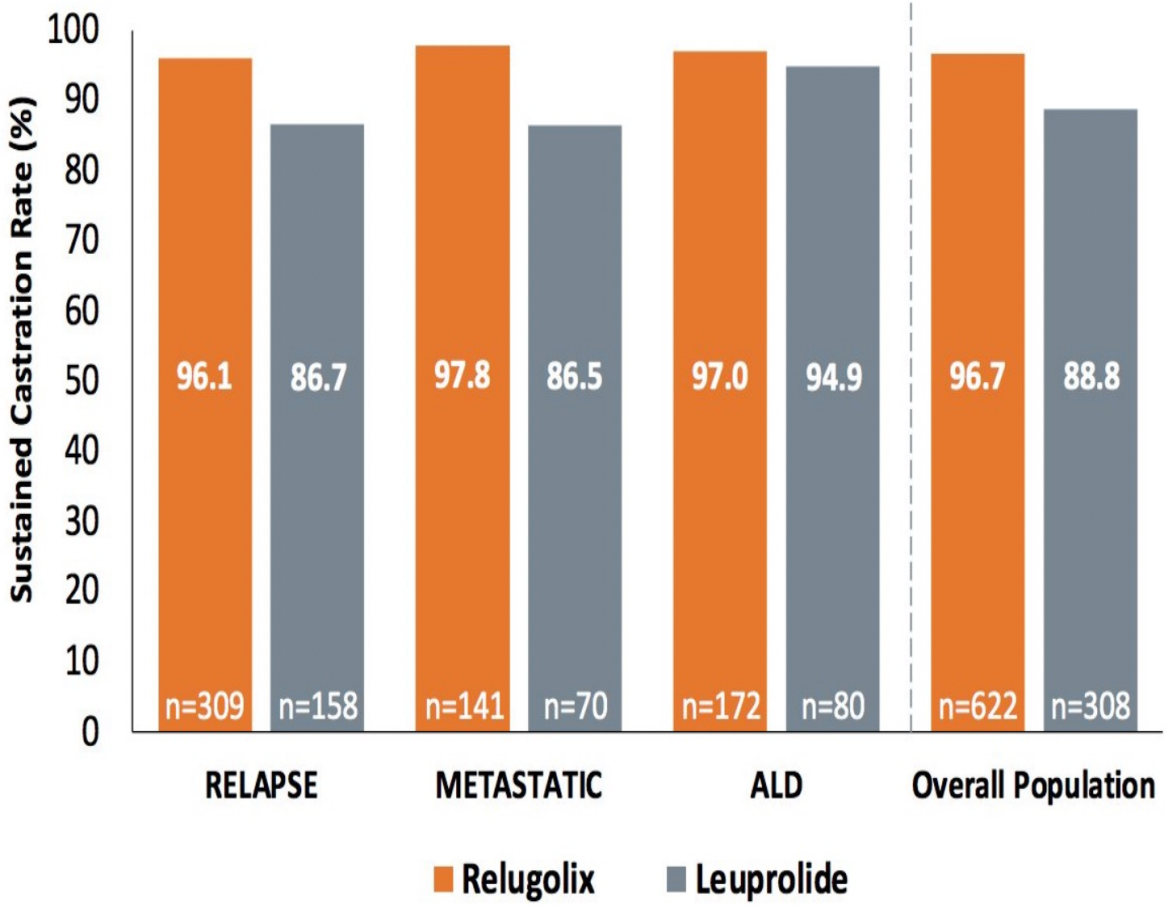
The NEW ENGLAND JOURNAL of MEDICINE

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

Oral Relugolix for Androgen-Deprivation Therapy in Advanced Prostate Cancer

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

HERO Study: Sustained Castration Rates by Clinical Subgroups



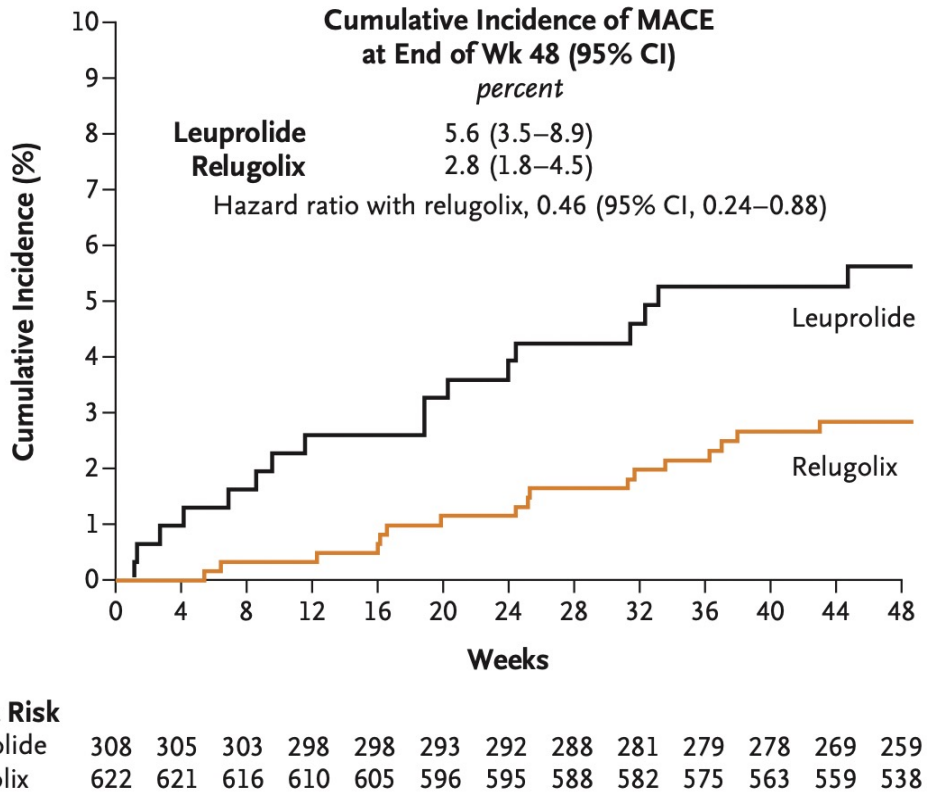


Figure 2. Cumulative Incidence of Major Adverse Cardiovascular Events (MACE).

Kaplan–Meier curves show the cumulative incidence of MACE in the relugolix group and the leuprolide group through 48 weeks of treatment. The hazard ratio was based on a Cox regression model.

Tombal B et al. ESMO 2021;Abstract 621P; Shore ND et al. N Engl J Med 2020;382(23):2187-2196.

U.S. UROLOGY PARTNERS

Efficacy Outcomes with Darolutamide, Apalutamide, Enzalutamide for nmCRPC

	ARAMIS (N=1509)[1]		SPARTAN (N=1207)[2,3]		PROSPER (N=1401)[4,5]	
	Daro + ADT (N=955)	PBO + ADT (N=554)	APA + ADT (N=806)	PBO + ADT (N=401)	ENZA + ADT (N=933)	PBO + ADT (N=468)
Primary endpoint						
MFS[b]						
Median, months	40.4 (34.33, NR)	18.7 (15.51, 22.34)	40.51 (NE, NE)	16.20 (14.59, 18.40)	36.6 (33.1, NR)	14.7 (14.2, 15.0)
HR (95% CI), *P*	0.41 (0.34, 0.50), *P*<0.001		0.28 (0.23, 0.35), *P*<0.0001		0.29 (0.24, 0.35), *P*<0.0001	
Secondary Endpoint						
OS						
Median, months	83%	77%	73.9	59.9	67	56.3
HR (95% CI), *P*	0.69 (0.53, 0.88), *P*=0.003		0.78 (0.64, 096), P < 0.0001		0.73 (0.61, 0.89), *P*=0.0011	
Follow up						
Median, months	29.0		52.0		48.0	48.0

1. Fizazi K et al. N Engl J Med 2020;383:1040-9. 2. Smith MR et al. N Engl J Med 2019;378:1408-18. 3. Smith MR et al. Eur Urol 2021;79(1):150-8.
4. Hussain M et al. N Engl J Med 2018;378:2465-74. 5. Sternberg CN et al. N Engl J Med 2020;382:2192-206.

Safety — Overview of TEAEs[a]

	ARAMIS (Daro vs PBO)[1]		SPARTAN (APA vs PBO)[2,3]		PROSPER (ENZA vs PBO)[4,5]	
	All (%)		All (%)		All (%)	
	Daro	PBO	APA	PBO	ENZA	PBO
Any AE	83.2	76.9	96.5	93.2	87	77
SAE	24.8	20.0	24.8	23.1	24	18
			25	23		
AE leading to discontinuation	8.9	8.7	11	Not reported	9.4	6.0
			10.6	7.0		
Death	3.9	3.2	1.2	0.3	3.4	0.6
			1	0.3		
AEs leading to dose modification	14.2	9.4	Not Reported	Not Reported	Not Reported	Not Reported
AEs leading to dose interruption or reduction	Not Reported	Not Reported	33%	Not Reported	Not Reported	Not Reported

1. Fizazi K et al. N Engl J Med 2019;380:1235-46. Smith MR et al. N Engl J Med 2019;378:1408-18. 3. Smith MR et al. Eur Urol 2021;79(1):150-8.
4. Hussain M et al. N Engl J Med 2018;378:2465-74. 5. Sternberg CN et al. N Engl J Med 2020;382:2192-206.

Safety — TEAEs of Interest (General)[a]

	ARAMIS (Daro vs PBO)[1] All Grades (%)		SPARTAN (APA vs PBO)[2] All Grades (%)		PROSPER (ENZA vs PBO)[3,4] All Grades[b] (%)	
	Daro	PBO	APA	PBO	ENZA	PBO
Hypertension	7.3	6.0	25	20	12	5.2
Rash	2.5	0.7	24	6	Not Reported	Not Reported
Pruritus	Not reported	Not Reported	6.2	2	Not Reported	Not Reported
Weight decreased	3.6	2.2	16	6	5.9	1.5
Diarrhea	6.9	5.6	20	15	10	10
Nausea	5.0	5.8	18	16	11	8.6
Decreased appetite	2.9	2.9	12	9	9.6	3.9
Hot flush	5.2	4.6	14	9	13.0	7.7
Arthralgia	8.1	9.2	16	8	8	7
Hypothyroidism	0.2	0	8.1	2	Not Reported	Not Reported
Cardiovascular events	Acute myocardial infarction		Ischemic heart disease		Major adverse cardiovascular event[c]	
	0.5	0.2	3.7	2		
	Cardiac failure		Heart failure		5	3
	1.9	0.9	2.2	1		

1. Fizazi K et al. N Engl J Med 2019;380:1235-46. 2. Smith MR et al. N Engl J Med 2019;378:1408-18.
3. Hussain M et al. N Engl J Med 2018;378:2465-74. 4. Sternberg CN et al. N Engl J Med 2020;382:2192-206.

U.S. UROLOGY PARTNERS

Safety — TEAEs of Interest (CNS)[a]

	ARAMIS (Daro vs PBO)[1]		SPARTAN (APA vs PBO)[2,3]		PROSPER (ENZA vs PBO)[4,5]	
	All Grades (%)		All Grades (%)		All Grades[b] (%)	
	Daro	PBO	APA	PBO	ENZA	PBO
Fatigue including Asthenia	15.8	11.4	39	28	40	20
Fatigue (alone)	12.1	8.7	30.4	21.1	33	14
Asthenia (alone)	Not Reported	Not Reported	Not Reported	Not Reported	9	6
Headache	3.9	2.5	Not Reported	Not Reported	9.1	4.5
Fracture	4.2	3.8	12	7	9.8	4.9
Fall	4.2	4.7	16	9	11	4.1
Seizure[c]	0.2	0.2	0.2	0	0.3	0
Dizziness[d]	3.7	2.5	9.3	6.3	12	5.2
Mental and cognitive changes						
Cognitive disorder	0.4	0.2	Not Reported	Not Reported	Not Reported	Not Reported
Memory impairment	0.5	1.3	Not Reported	Not Reported	Not Reported	Not Reported
Mental impairment disorder[e]	Not Reported	Not Reported	5.1	3.0	Not Reported	Not Reported
Cognitive and attention disorders[f]	Not Reported	Not Reported	Not Reported	Not Reported	4.6	1.5

1. Fizazi K et al. N Engl J Med 2019;380:1235-46. 2. Smith MR et al. N Engl J Med 2019;378:1408-18. 3. Smith MR et al. Eur Urol 2021;79(1):150-8.
4. Hussain M et al. N Engl J Med 2018;378:2465-74. 5. Sternberg CN et al. N Engl J Med 2020;382:2192-206.

MODULE 2: Role of Treatment Intensification in Metastatic Hormone-Sensitive Prostate Cancer

RTP
RESEARCH
TO PRACTICE

Regulatory and reimbursement issues aside, what systemic therapy would you typically employ for a 59-year-old man presenting with bulky, high-volume metastatic hormone-sensitive prostate cancer (mHSPC)?

1. ADT alone
2. ADT and abiraterone
3. ADT and apalutamide
4. ADT and enzalutamide
5. ADT and darolutamide
6. ADT and docetaxel
7. ADT with docetaxel and secondary hormonal therapy
8. Other

Dr Paul Markowski
Summit, New Jersey

A 59-year-old man with metastatic HSPC

Dr David Morris
Nashville, Tennessee

A 57-year-old man with metastatic HSPC – germline BRCA2 mutation

Regulatory and reimbursement issues aside, what systemic therapy would you typically employ for a 49-year-old man presenting with low-volume mHSPC?

1. ADT alone
2. ADT and abiraterone
3. ADT and apalutamide
4. ADT and enzalutamide
5. ADT and darolutamide
6. ADT and docetaxel
7. ADT with docetaxel and secondary hormonal therapy
8. Other

Case Presentation: A 49-year-old man with regionally advanced HSPC

Dr David Taub (Boca Raton, Florida)

RTP
RESEARCH
TO PRACTICE

Role of Treatment Intensification for Patients with Metastatic Hormone-Sensitive Prostate Cancer (mHSPC)

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

HARVARD MEDICAL SCHOOL

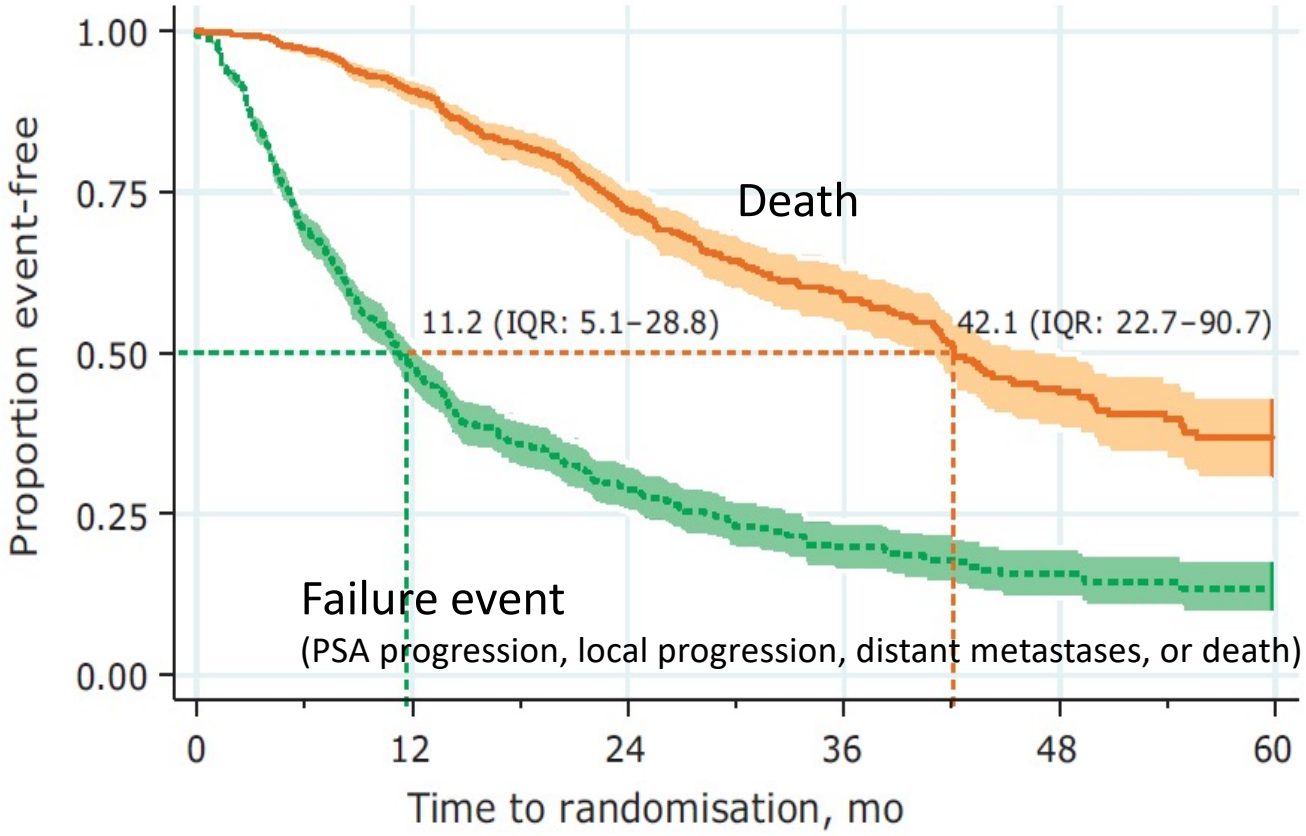
Matthew R. Smith, M.D.,Ph.D.
Professor of Medicine, Harvard Medical School
Director, MGH Genitourinary Malignancies Program

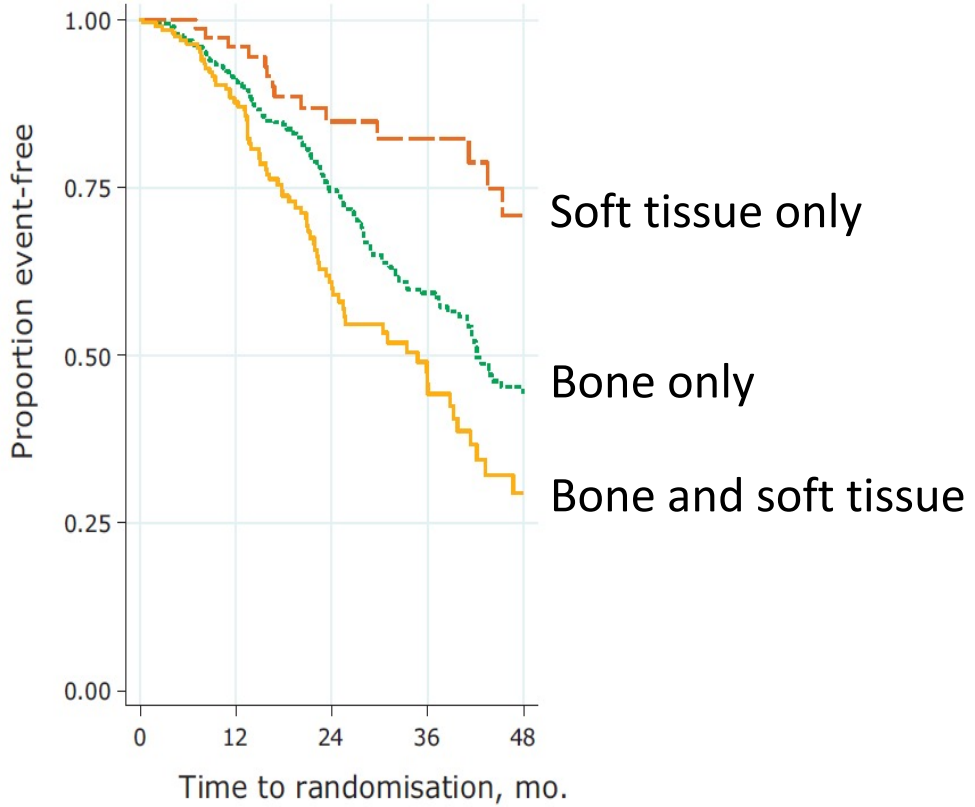
Context

- Men receiving androgen deprivation therapy (ADT) alone for metastatic prostate cancer have poor clinical outcomes
- Survival is related to location and extent of disease
- Treatment intensification by early addition of either docetaxel or an androgen receptor pathway inhibitor (ARPI) to ADT significantly improves overall survival
- The addition of darolutamide or abiraterone to ADT and docetaxel improves overall survival

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

Clinical Outcomes in Metastatic Prostate Cancer: STAMPEDE Experience with ADT



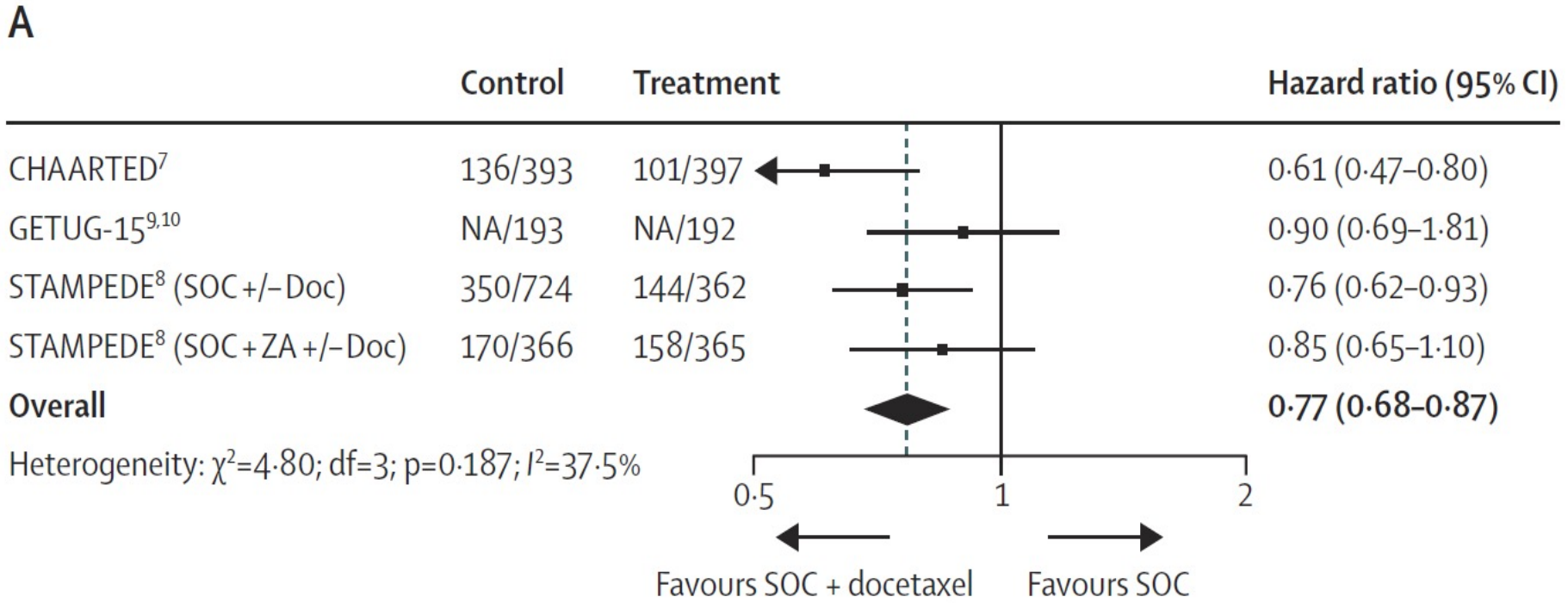


STAMPEDE Control Arm
- metastatic disease
- accrued 10/2005-1/2014
- N=917

James ND *et al* (2015) Eur Urol 67: 1028-1038

Meta-Analysis of RCTs of Docetaxel in mHSPC

Overall Survival

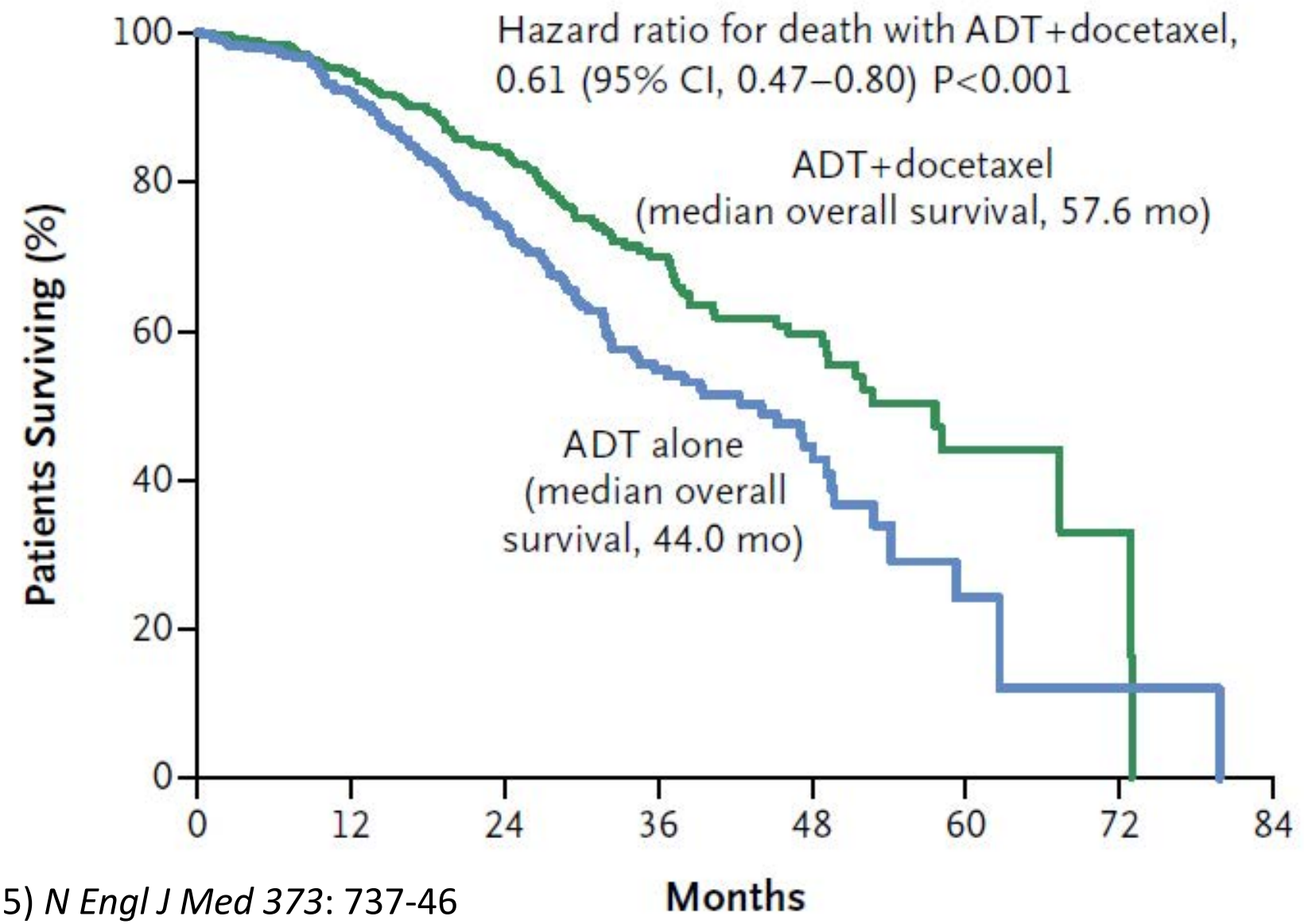


- Results based on 2992 men/2204 events
- 9% absolute improvement in survival at 4 years

Vale et al. Lancet Oncol 2016; 17(2):243-56

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

CHAARTED: Docetaxel for mHSPC

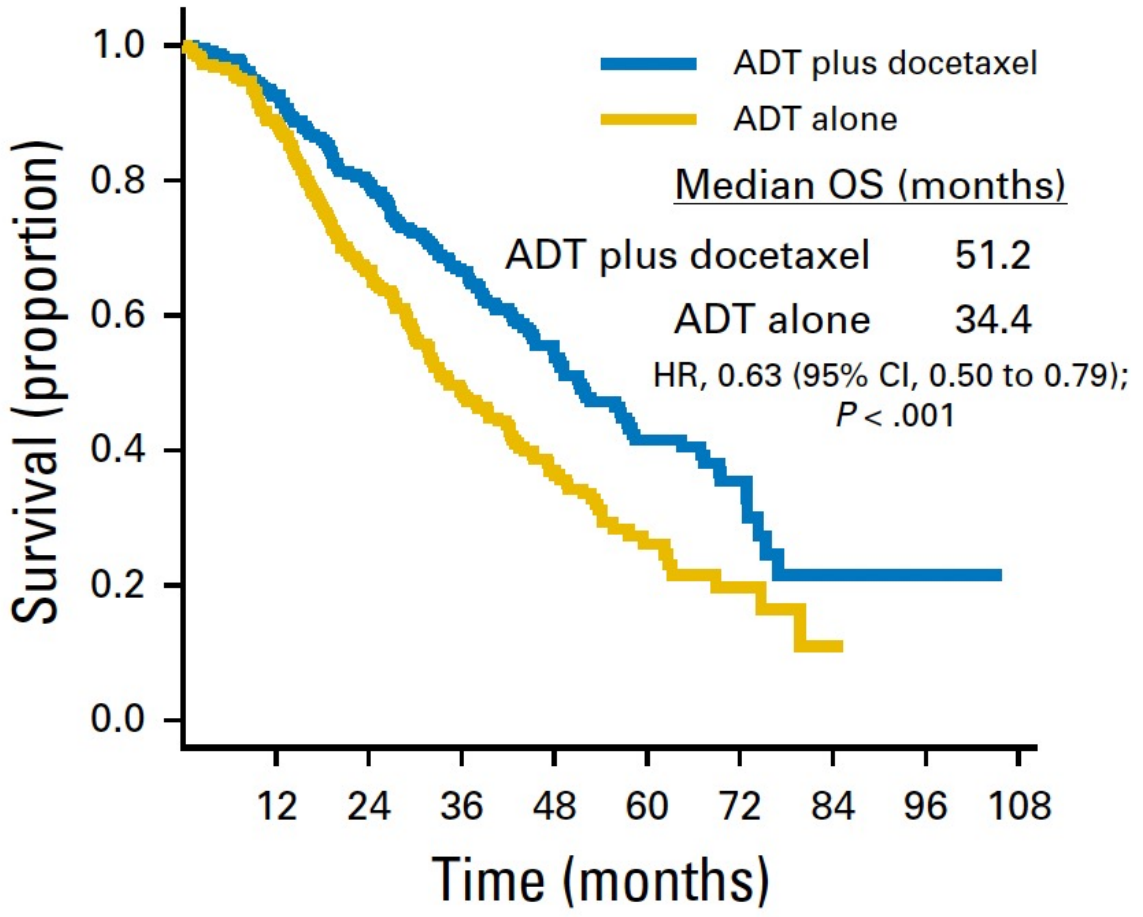


Sweeney et al (2015) *N Engl J Med 373*: 737-46

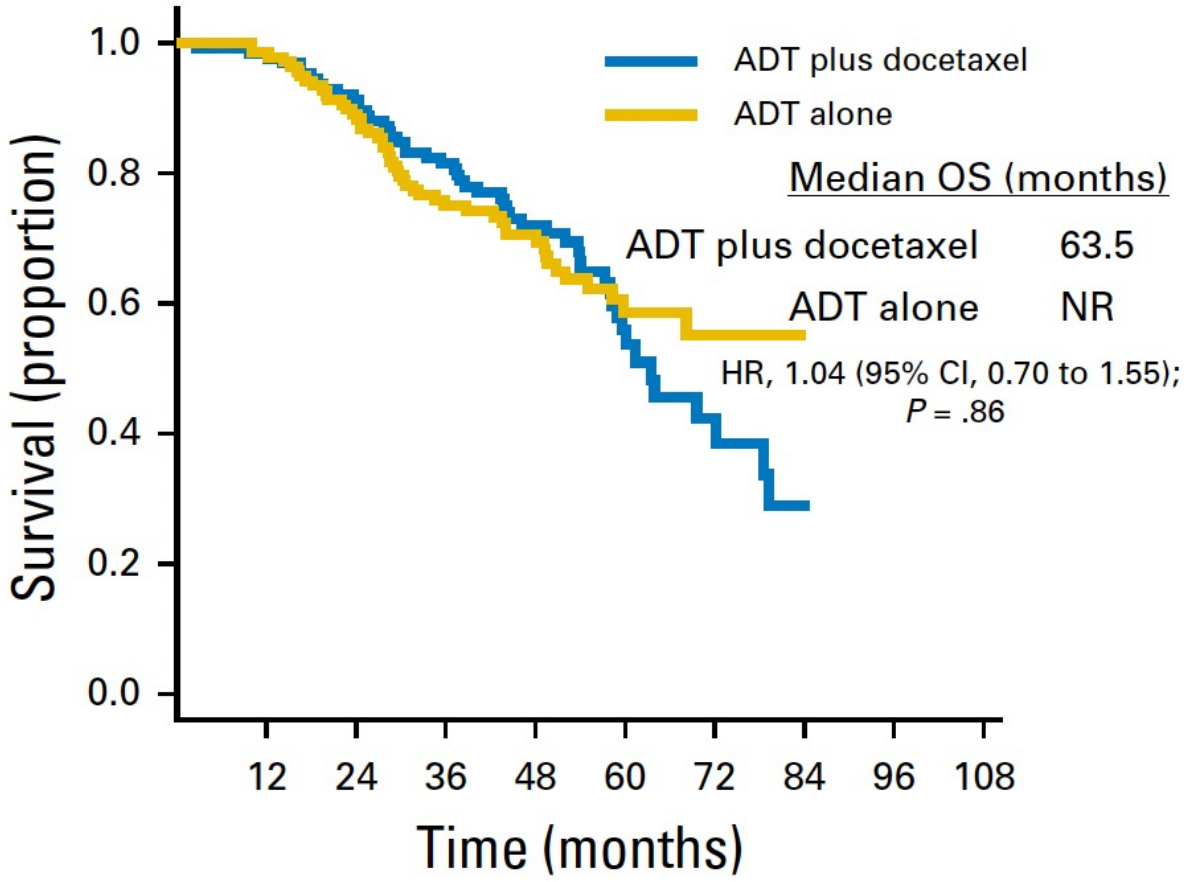
MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

CHAARTED: OS for High vs Low Volume Disease

High Volume



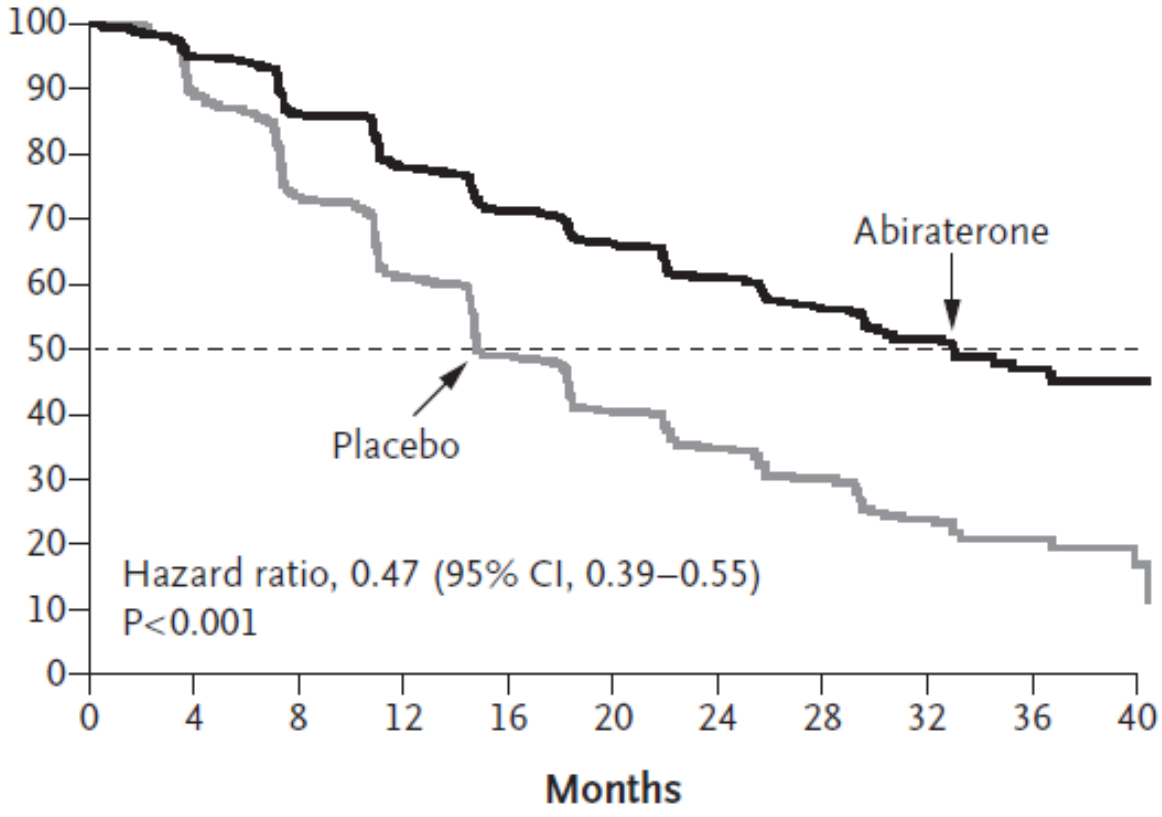
Low Volume



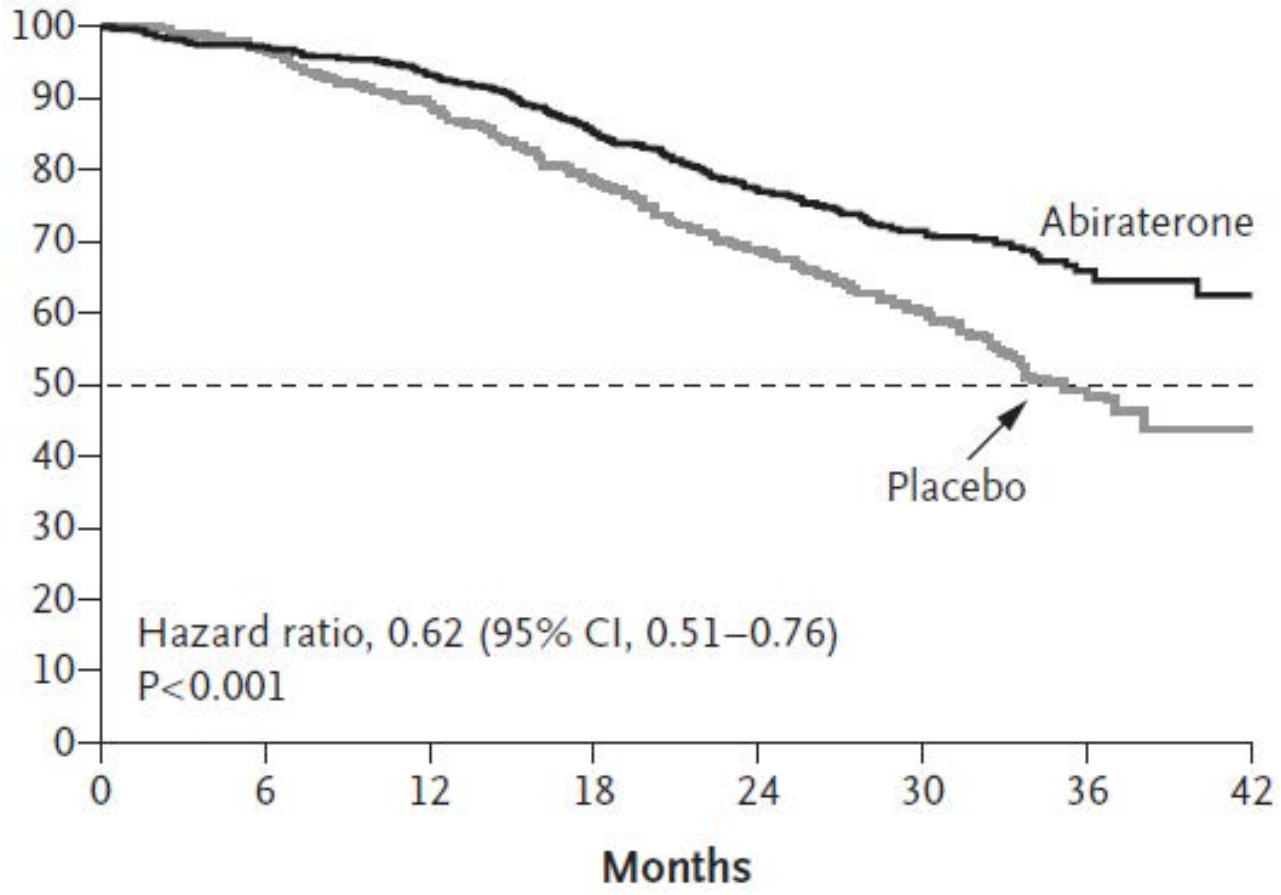
Kyriakopoulos et al (2018) *J Clin Oncol 36*: 1080-0187

LATITUDE: Abiraterone Acetate for mHSPC

Radiographic Progression-Free Survival



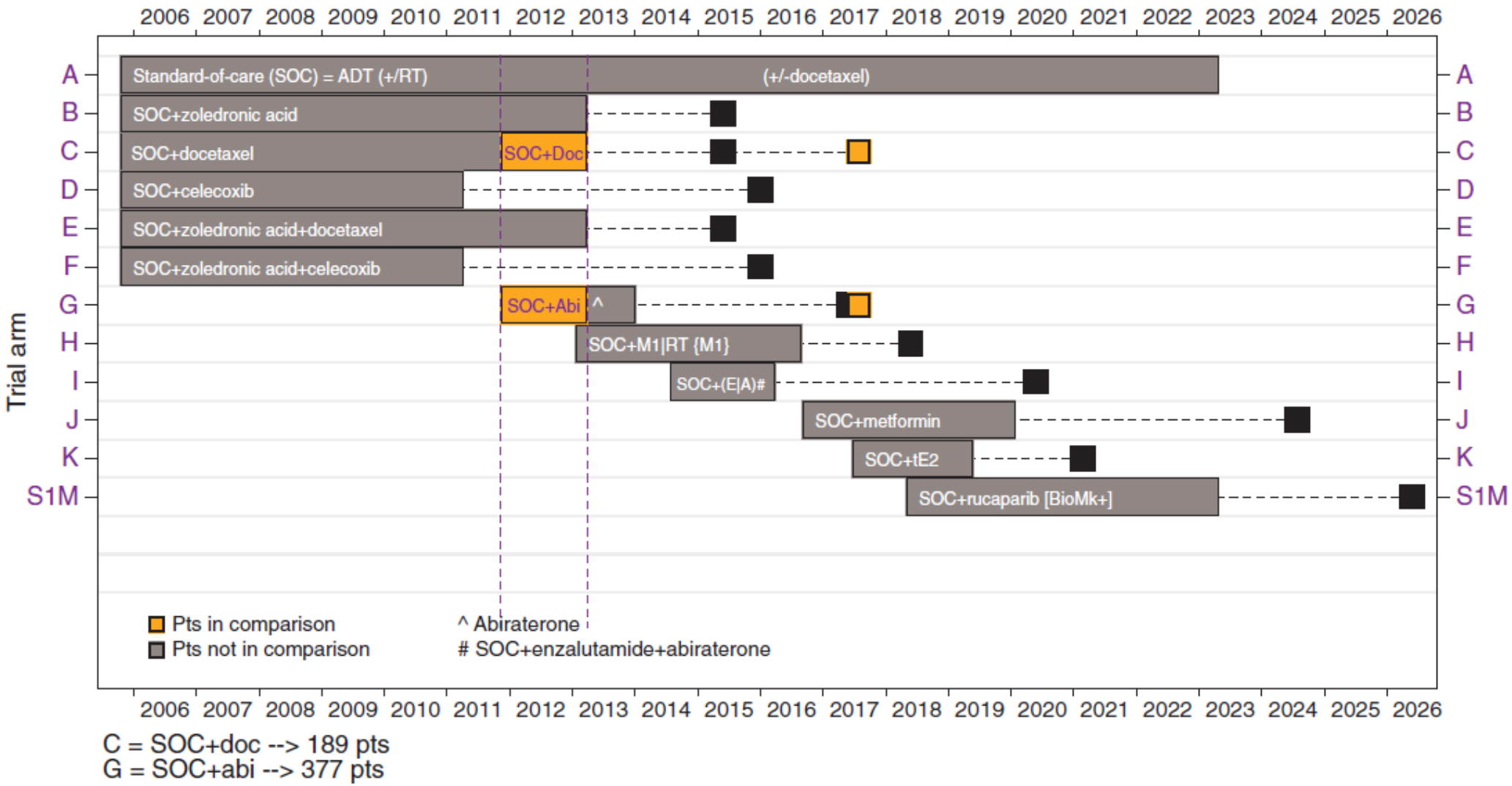
Overall Survival



Fizazi et al (2017) *N Engl J Med 377*: 352-60

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

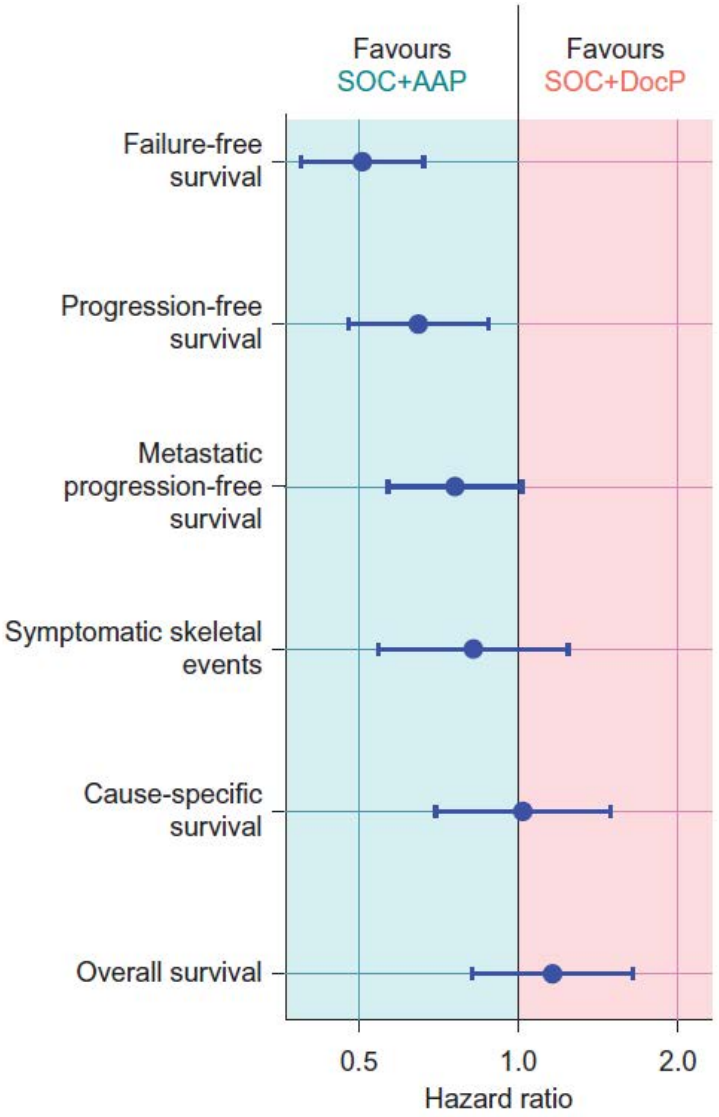
STAMPEDE: Docetaxel vs Abiraterone Comparison



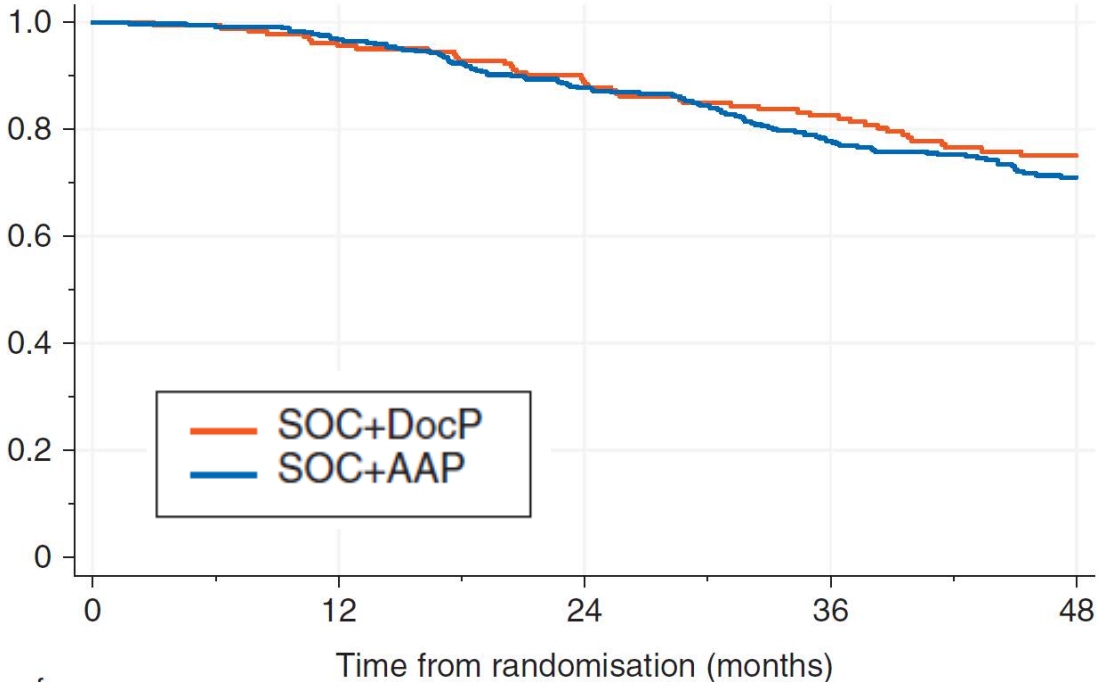
Sydes et al (2018) *Annals of Oncology* 29:1235-1248

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

STAMPEDE: Docetaxel vs Abiraterone Comparison



Overall Survival

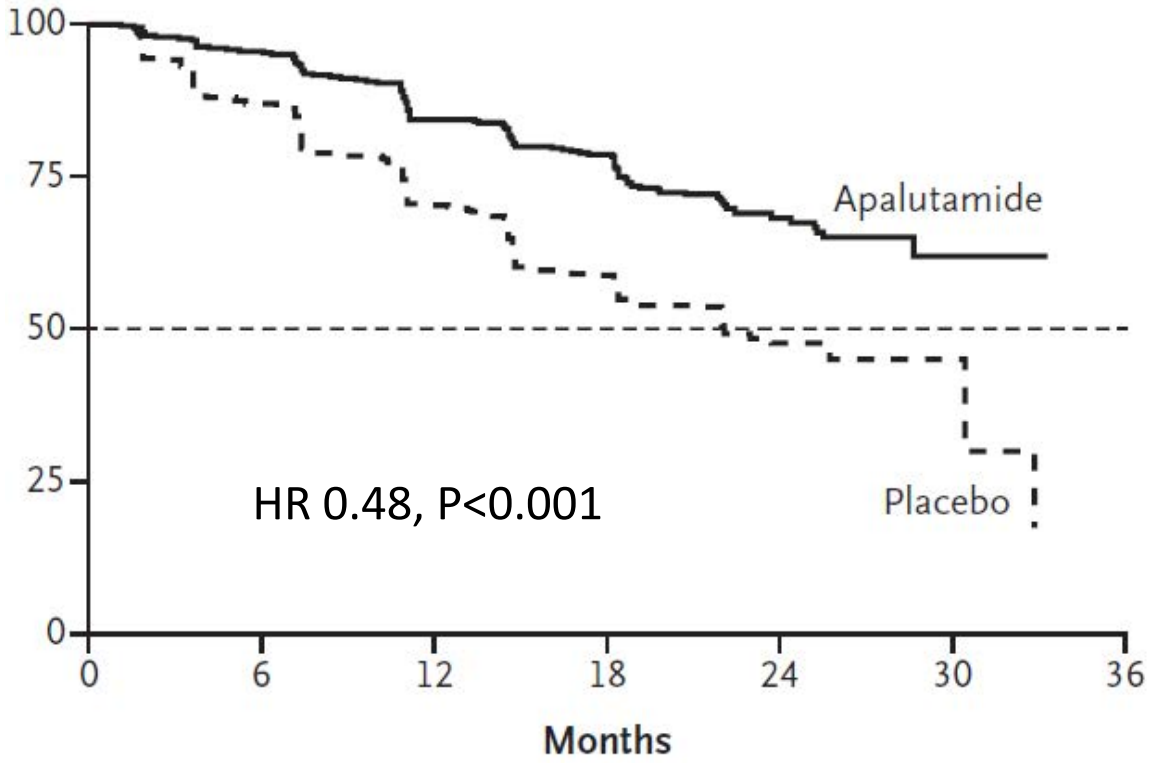


Sydes et al (2018) *Annals of Oncology* 29:1235-1248

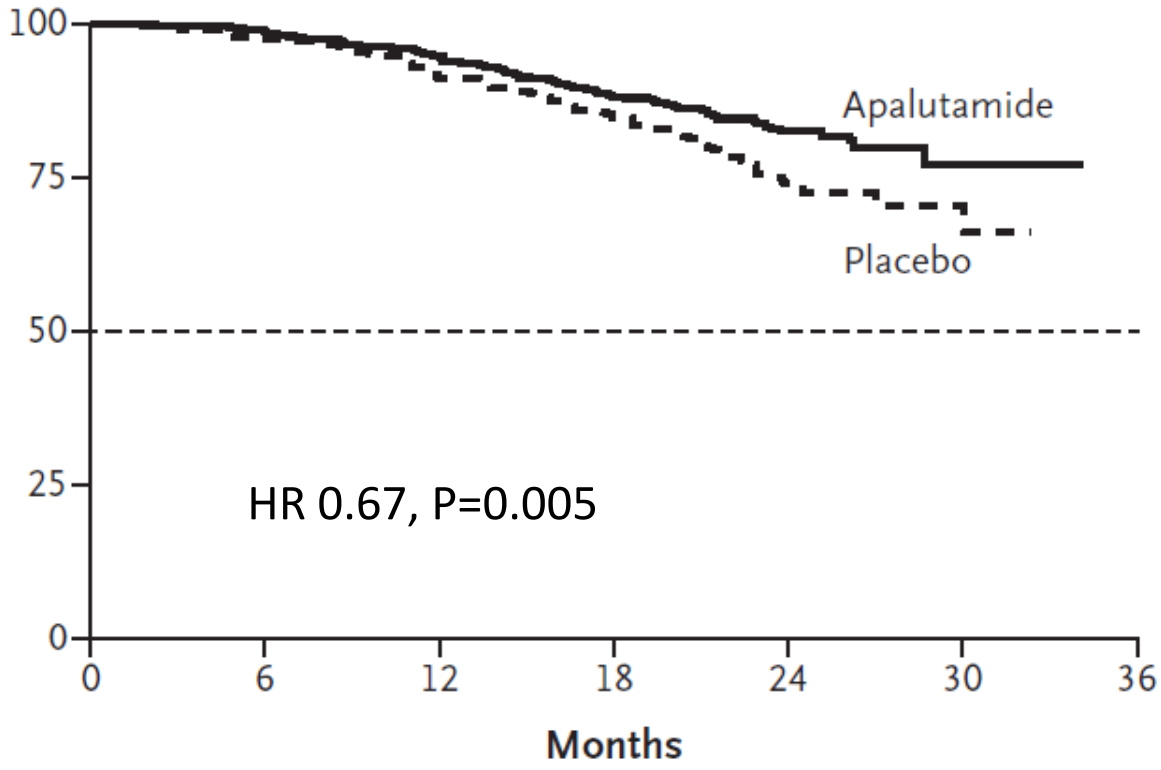
MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

TITAN: Apalutamide for mHSPC

Radiographic Progression-Free Survival



Overall Survival



Chi et al (2019) *N Engl J Med 381*: 13-24

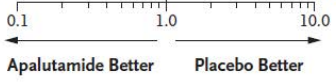
MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

TITAN Subgroup Analyses

Overall Survival

B Subgroup Analysis

Subgroup	Apalutamide no. of events/no. of patients	Placebo no. of events/no. of patients	Apalutamide median overall survival (mo)	Placebo median overall survival (mo)	Hazard Ratio for Death (95% CI)
All patients	83/525	117/527	NE	NE	0.68 (0.51–0.90)
Baseline ECOG performance status					
0	41/328	60/348	NE	NE	0.71 (0.47–1.05)
1	42/197	57/178	NE	NE	0.59 (0.40–0.89)
Geographic region					
North America and European Union	21/173	29/173	NE	NE	0.71 (0.40–1.25)
Other	62/352	88/354	NE	NE	0.66 (0.48–0.91)
Bone metastasis only at baseline					
Yes	28/289	53/269	NE	NE	0.47 (0.30–0.75)
No	55/236	64/258	NE	NE	0.88 (0.61–1.26)
Visceral disease and bone metastasis at baseline					
Yes	20/56	25/72	NE	26.6	0.99 (0.55–1.77)
No	63/469	92/455	NE	NE	0.63 (0.46–0.87)
Gleason score at diagnosis					
≤7	21/174	34/169	NE	NE	0.56 (0.33–0.97)
>7	62/351	83/358	NE	NE	0.73 (0.52–1.01)
Previous docetaxel use					
Yes	11/58	9/55	NE	NE	1.27 (0.52–3.09)
No	72/467	108/472	NE	NE	0.63 (0.47–0.85)
Age					
<65 yr	21/149	43/182	NE	NE	0.56 (0.33–0.94)
65–74 yr	42/243	51/232	NE	NE	0.73 (0.48–1.10)
≥75 yr	20/133	23/113	NE	NE	0.74 (0.41–1.35)
Baseline PSA above median					
Yes	58/285	66/241	NE	NE	0.68 (0.48–0.97)
No	25/240	51/286	NE	NE	0.56 (0.35–0.91)
Baseline LDH above ULN					
Yes	18/60	25/60	NE	NE	0.68 (0.37–1.24)
No	62/443	86/442	NE	NE	0.69 (0.49–0.95)
Baseline ALP above ULN					
Yes	40/177	61/180	NE	NE	0.63 (0.42–0.93)
No	43/346	56/345	NE	NE	0.73 (0.49–1.09)
Disease volume					
High	69/325	97/335	NE	NE	0.68 (0.50–0.92)
Low	14/200	20/192	NE	NE	0.67 (0.34–1.32)
Metastasis stage at initial diagnosis					
M0	7/85	11/59	NE	NE	0.40 (0.15–1.03)
M1	71/411	101/441	NE	NE	0.72 (0.53–0.98)

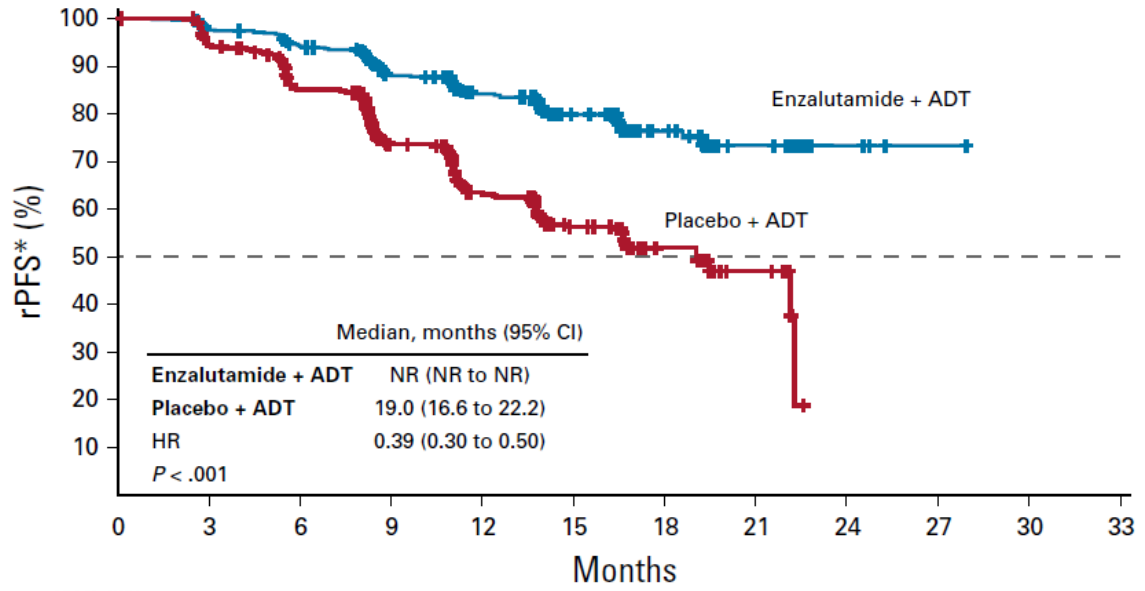


Chi et al (2019) *N Engl J Med 381*: 13-24

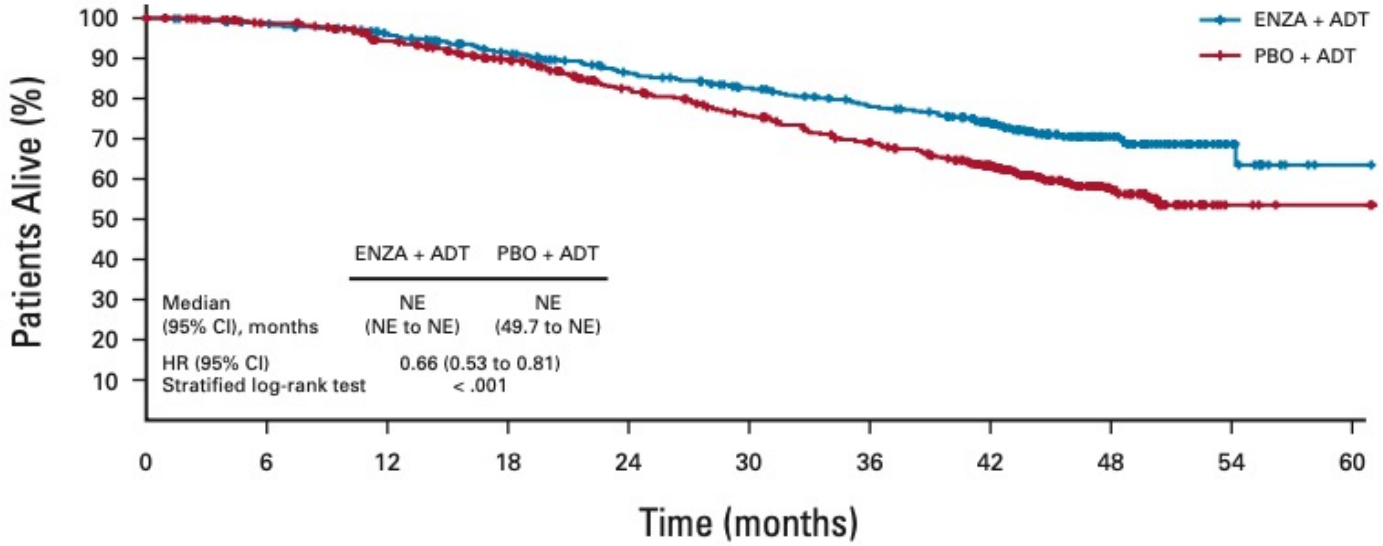
MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

ARCHES: Enzalutamide for mHSPC

rPFS



OS

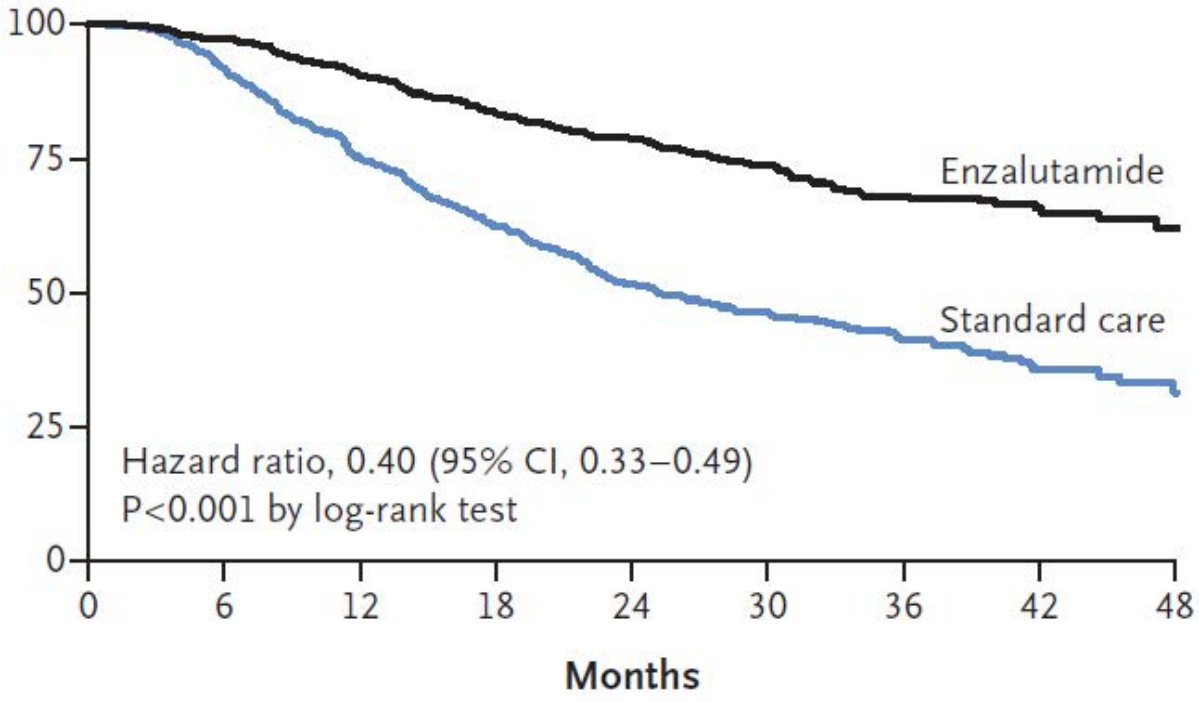


Armstrong et al (2019) *J Clin Oncol 37:* 2974-2986; Armstrong et al (2022) *J Clin Oncol* DOI: 10.1200/JCO.22.00193

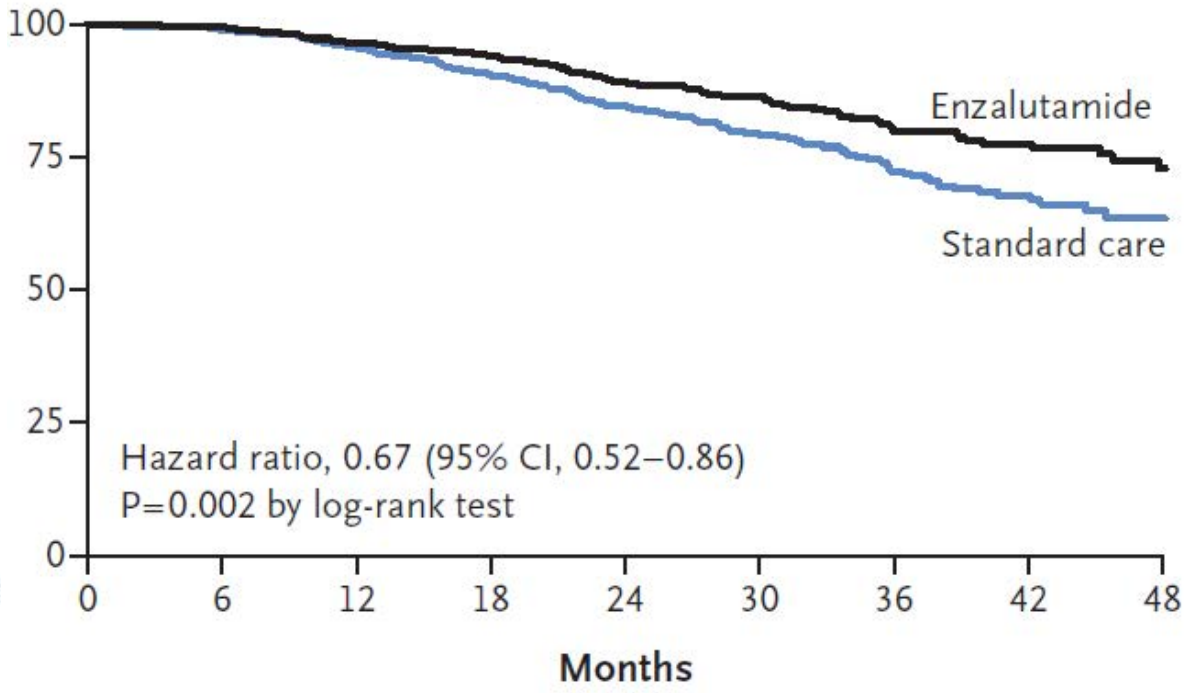
MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

ENZAMET: Enzalutamide for mHSPC

Clinical Progression-Free Survival



Overall Survival



Davis et al (2019) *N Engl J Med 381*: 121-131

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

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

Docetaxel × 6

→ **Darolutamide 600 mg twice daily + ADT**

→ **Placebo twice daily + ADT**

Docetaxel × 6

FPFV: Nov 2016
LPFV: June 2018

Data cut-off
Oct 25, 2021

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

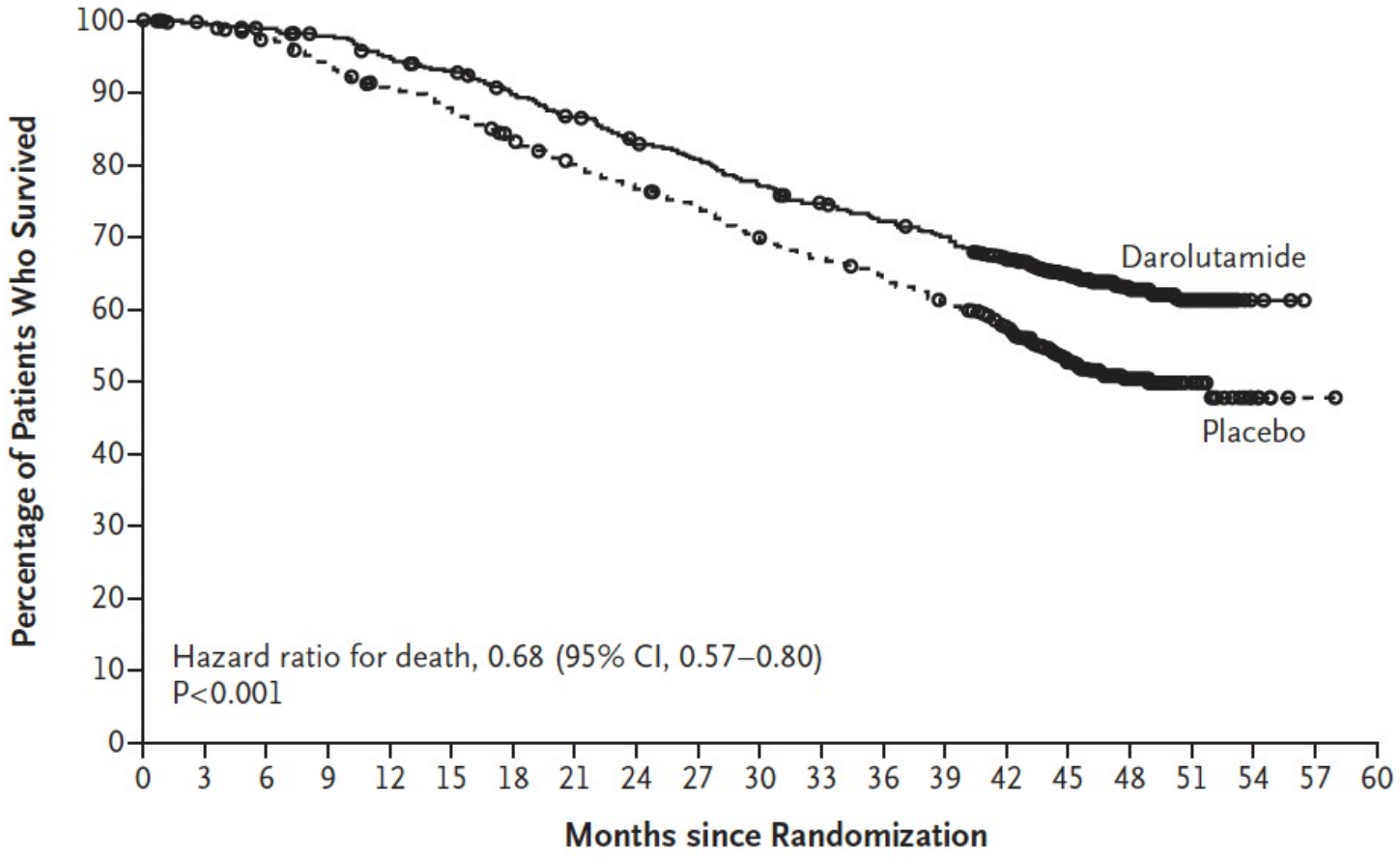
- The primary analysis was planned to occur after ~509 deaths
- Secondary efficacy endpoints were tested hierarchically

***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.**

Smith *et al* (2022) N Engl J Med DOI: 10.1056/NEJMoa2119115

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

ARASENS Primary Endpoint: Overall Survival



	Median Survival (95% CI) *mo*
Darolutamide	NE
Placebo	48.9 (44.4–NE)

No. at Risk

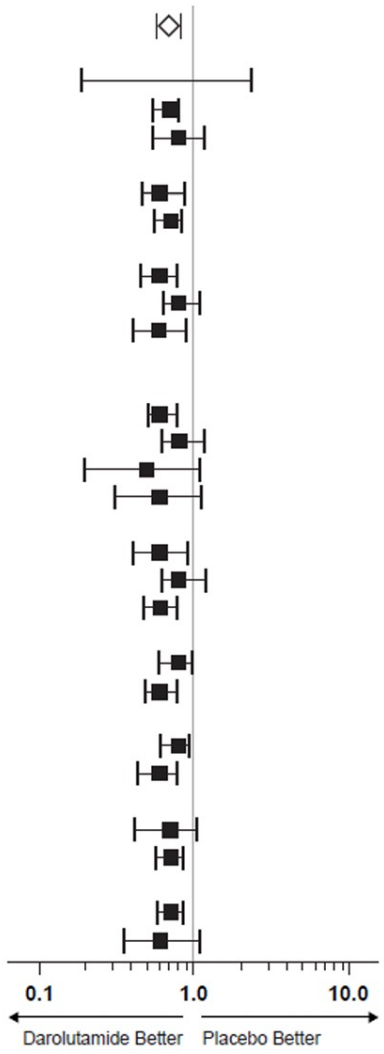
Darolutamide	651	645	637	627	608	593	570	548	525	509	486	468	452	436	402	267	139	56	9	0	0
Placebo	654	646	630	607	580	565	535	510	488	470	441	424	402	383	340	218	107	37	6	1	0

Smith *et al* (2022) N Engl J Med DOI: 10.1056/NEJMoa2119115

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

ARASENS: Subgroup Analyses for Overall Survival

	Darolutamide+ Docetaxel No. of Events/No. of Patients	Placebo+ Docetaxel No. of Events/No. of Patients	Hazard Ratio (95% CI)
Overall	229/651	304/654	0.689 (0.580–0.818)
Extent of disease (eCRF)			
Non-regional lymph node metastasis	5/23	5/16	0.651 (0.188–2.249)
Bone metastasis	171/517	237/520	0.668 (0.548–0.813)
Visceral metastasis	53/111	62/118	0.792 (0.549–1.143)
ALP stratification factor (eCRF)			
Below upper limit of normal	62/290	93/291	0.636 (0.461–0.877)
At or above upper limit of normal	167/361	211/363	0.692 (0.564–0.847)
Age (years)			
<65 yr	80/243	117/234	0.592 (0.446–0.787)
65–74 yr	107/303	124/306	0.821 (0.634–1.064)
75–84 yr	40/102	60/110	0.606 (0.406–0.904)
≥85 yr	2/3	3/4	
Race			
White	131/345	173/333	0.633 (0.504–0.794)
Asian	74/230	93/245	0.838 (0.617–1.137)
Black or African American	8/26	16/28	0.460 (0.196–1.077)
Other or not reported	16/50	22/48	0.579 (0.303–1.107)
Geographical region			
North America	42/125	56/119	0.611 (0.409–0.913)
Asia Pacific	74/229	92/244	0.849 (0.625–1.153)
Rest of the world	113/297	156/291	0.612 (0.480–0.780)
PSA at baseline			
Below median	110/315	142/337	0.765 (0.596–0.981)
At or above median	119/336	162/316	0.618 (0.488–0.783)
ECOG at baseline			
0	150/466	188/462	0.753 (0.608–0.934)
1	79/185	115/190	0.575 (0.432–0.766)
Gleason score			
<8	33/122	44/118	0.653 (0.416–1.025)
≥8	187/505	248/516	0.708 (0.586–0.856)
Metastatic stage at initial diagnosis			
M1	206/558	271/566	0.707 (0.590–0.848)
M0	22/86	30/82	0.605 (0.348–1.052)

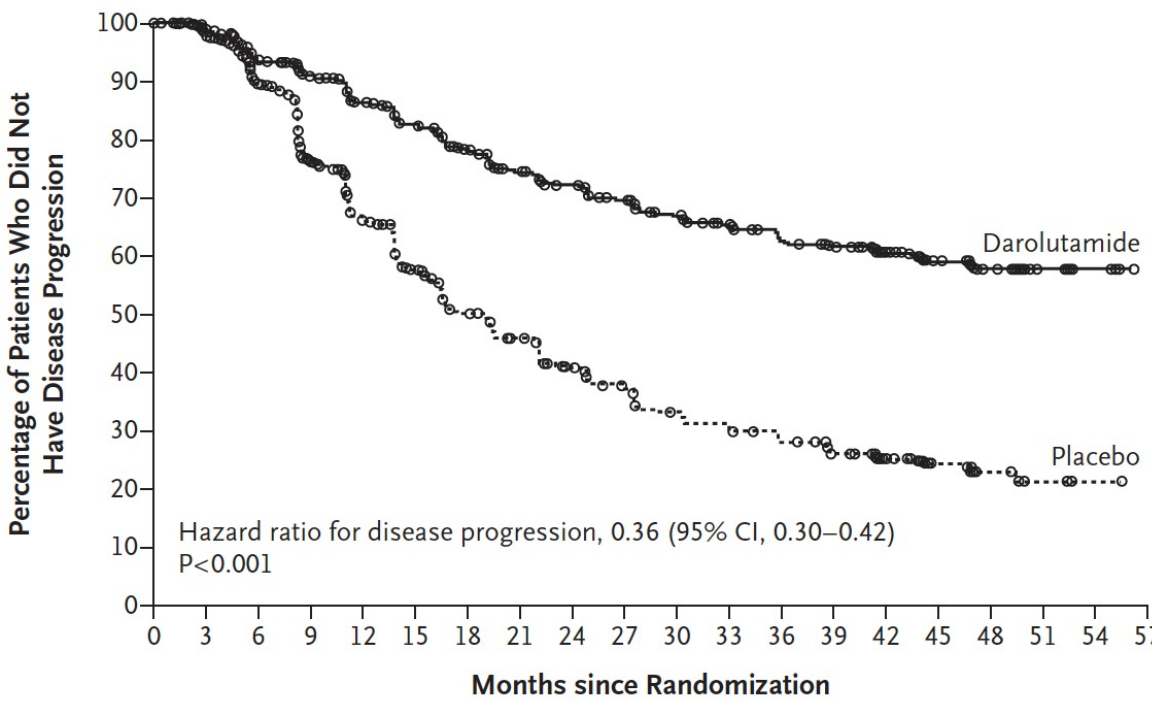


Smith *et al* (2022) N Engl J Med DOI: 10.1056/NEJMoa2119115

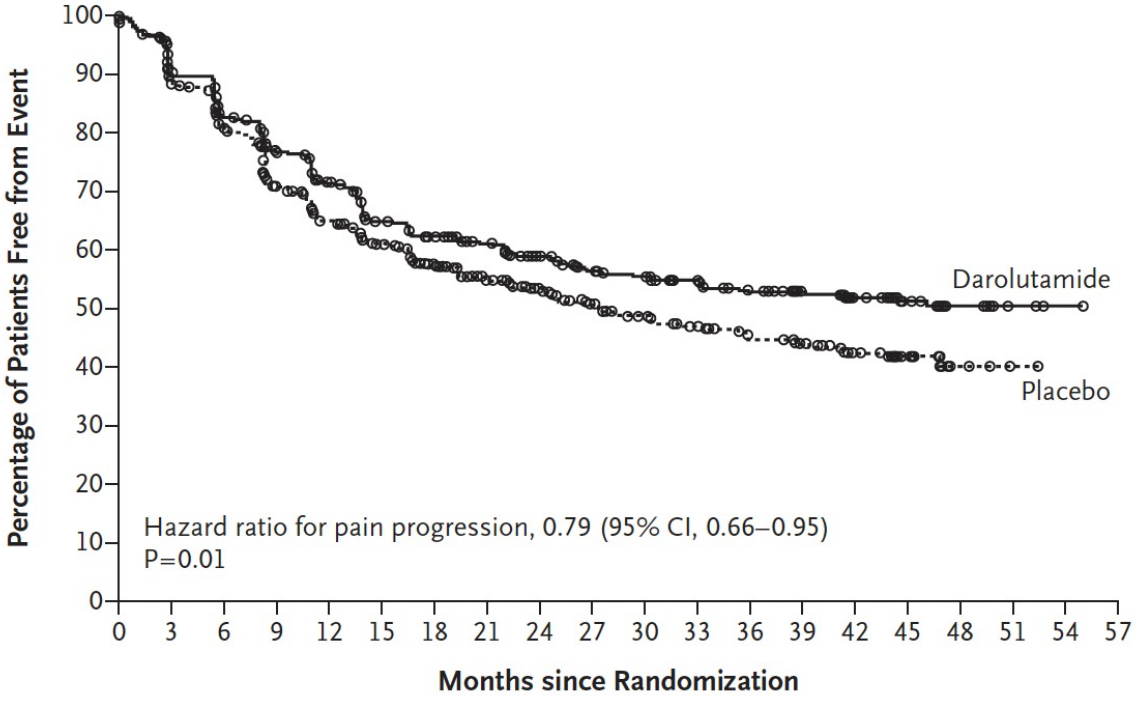
MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

ARASENS: Key Secondary Endpoints

Time to Castration-Resistant Prostate Cancer



Time to Pain Progression



Smith *et al* (2022) N Engl J Med DOI: 10.1056/NEJMoa2119115

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

ARASENS: Safety

Event	Darolutamide–ADT–Docetaxel (N = 652)†	Placebo–ADT–Docetaxel (N = 650)†
	number of patients (percent)	
Any adverse event	649 (99.5)	643 (98.9)
Worst grade		
Grade 1	28 (4.3)	35 (5.4)
Grade 2	162 (24.8)	169 (26.0)
Grade 3	248 (38.0)	232 (35.7)
Grade 4	183 (28.1)	181 (27.8)
Grade 5	27 (4.1)	26 (4.0)
Serious adverse event	292 (44.8)	275 (42.3)
Adverse event leading to permanent discontinuation of trial agent		
Darolutamide or placebo	88 (13.5)	69 (10.6)
Docetaxel	52 (8.0)	67 (10.3)
Selected grade 3 or 4 adverse events‡		
Neutropenia§	220 (33.7)	222 (34.2)
Febrile neutropenia	51 (7.8)	48 (7.4)
Hypertension	42 (6.4)	21 (3.2)
Anemia	31 (4.8)	33 (5.1)
Pneumonia	21 (3.2)	20 (3.1)
Hyperglycemia	18 (2.8)	24 (3.7)
Increased ALT level	18 (2.8)	11 (1.7)
Increased AST level	17 (2.6)	7 (1.1)
Increased weight	14 (2.1)	8 (1.2)
Urinary tract infection	13 (2.0)	12 (1.8)

Smith *et al* (2022) N Engl J Med DOI: 10.1056/NEJMoa2119115

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

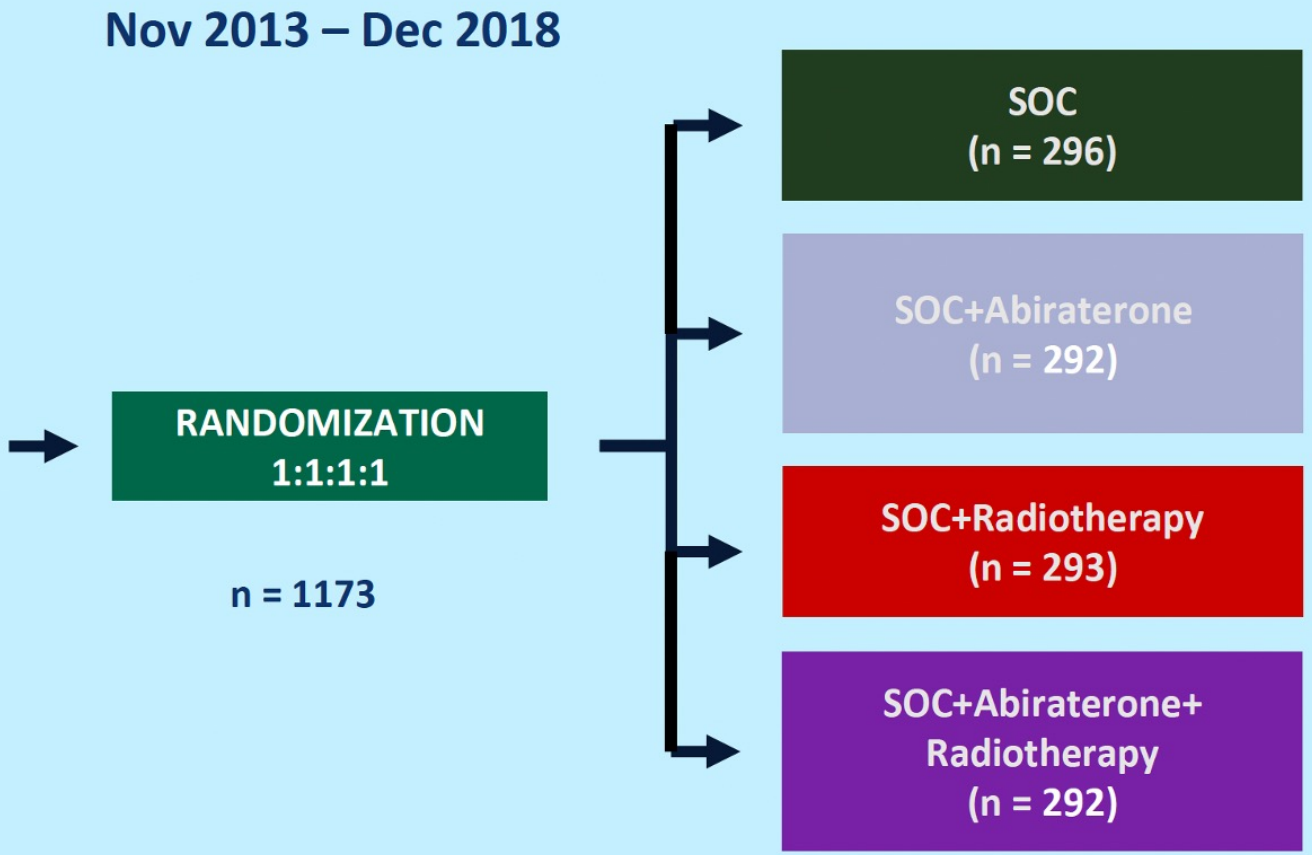
PEACE-1 Study Design

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

On-Study Requirement
Continuous ADT

Permitted
ADT ≤ 3 months

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

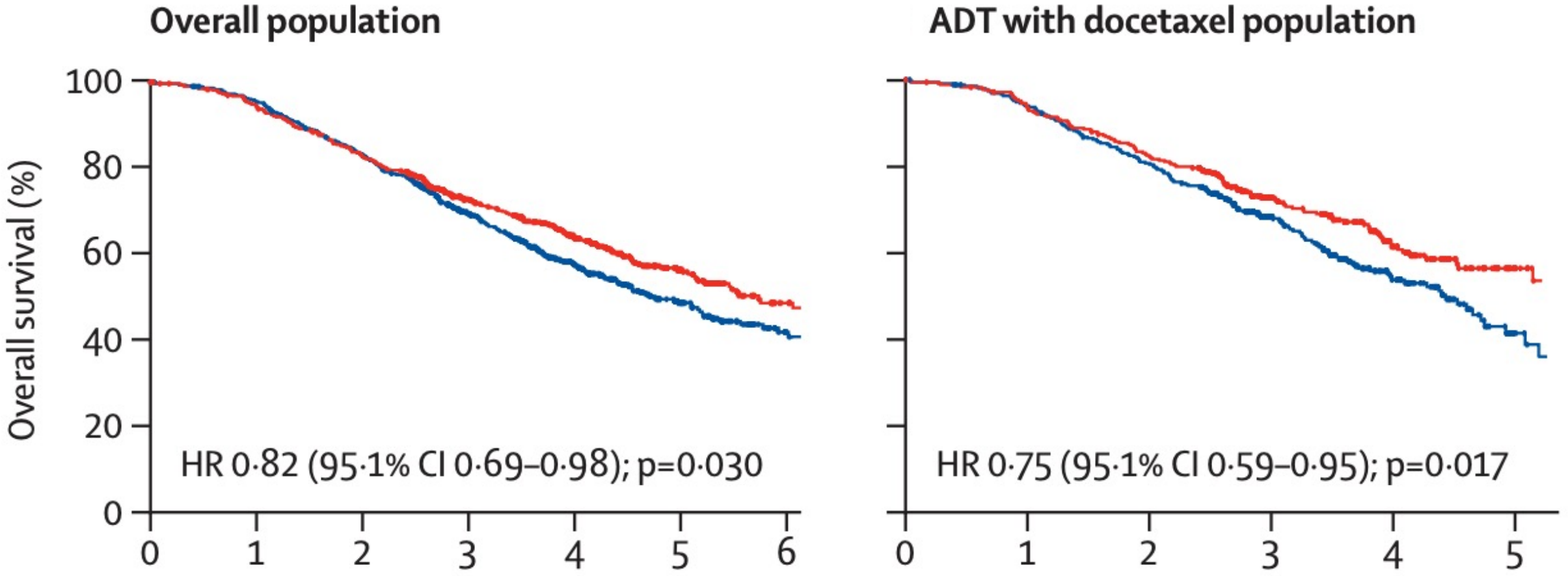


ECOG PS, Eastern Cooperative Oncology Group performance status

2021 ESMO congress

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

PEACE-1: Overall Survival



Fizazi et al (2022) *Lancet* https://doi.org/10.1016/ S0140-6736(22)00367-1

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

PEACE-1: Safety in Docetaxel Subgroup

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

Fizazi et al (2022) *Lancet* https://doi.org/10.1016/ S0140-6736(22)00367-1

Conclusions

- ADT alone is no longer a standard of care for most patients with mHSPC
- Treatment intensification improves overall survival in mHSPC
  - ADT + docetaxel > ADT alone
  - ADT + ARPI >ADT alone
  - ADT + docetaxel + darolutamide > ADT + docetaxel
  - ADT + docetaxel + abiraterone > ADT + docetaxel
- Most/all patients with mHSPC should receive an ARPI:
  - ADT +ARPI
  - ADT + docetaxel + ARPI (darolutamide or abiraterone)

MODULE 3: Selection and Sequencing of Therapy for Metastatic CRPC

RTP
RESEARCH
TO PRACTICE

An 83-year-old man with metastatic castration-resistant prostate cancer (mCRPC) to the bone who previously received ADT + enzalutamide prefers not to receive chemotherapy at this time. Regulatory and reimbursements issues aside, what systemic treatment would you most likely recommend?

1. Abiraterone
2. Sipuleucel-T
3. Radium-223
4. ^{177}Lu-PSMA-617
5. Abiraterone + olaparib
6. Other

RTP
RESEARCH
TO PRACTICE

Dr Jason Hafron
West Bloomfield, Michigan

An 83-year-old man with metastatic CRPC – CHEK2, AR and APC gene mutations

Dr Jason Hafron
West Bloomfield, Michigan

A 67-year-old man with metastatic CRPC who received ^{177}Lu-PSMA-617

RTP
RESEARCH
TO PRACTICE

In general, do you offer sipuleucel-T to patients with asymptomatic mCRPC?

1. Yes
2. Yes, in select patients
3. No

Dr Paul Markowski
Summit, New Jersey

An 81-year-old man with metastatic CRPC and disease progression on multiple therapies

Dr Paul Markowski
Summit, New Jersey

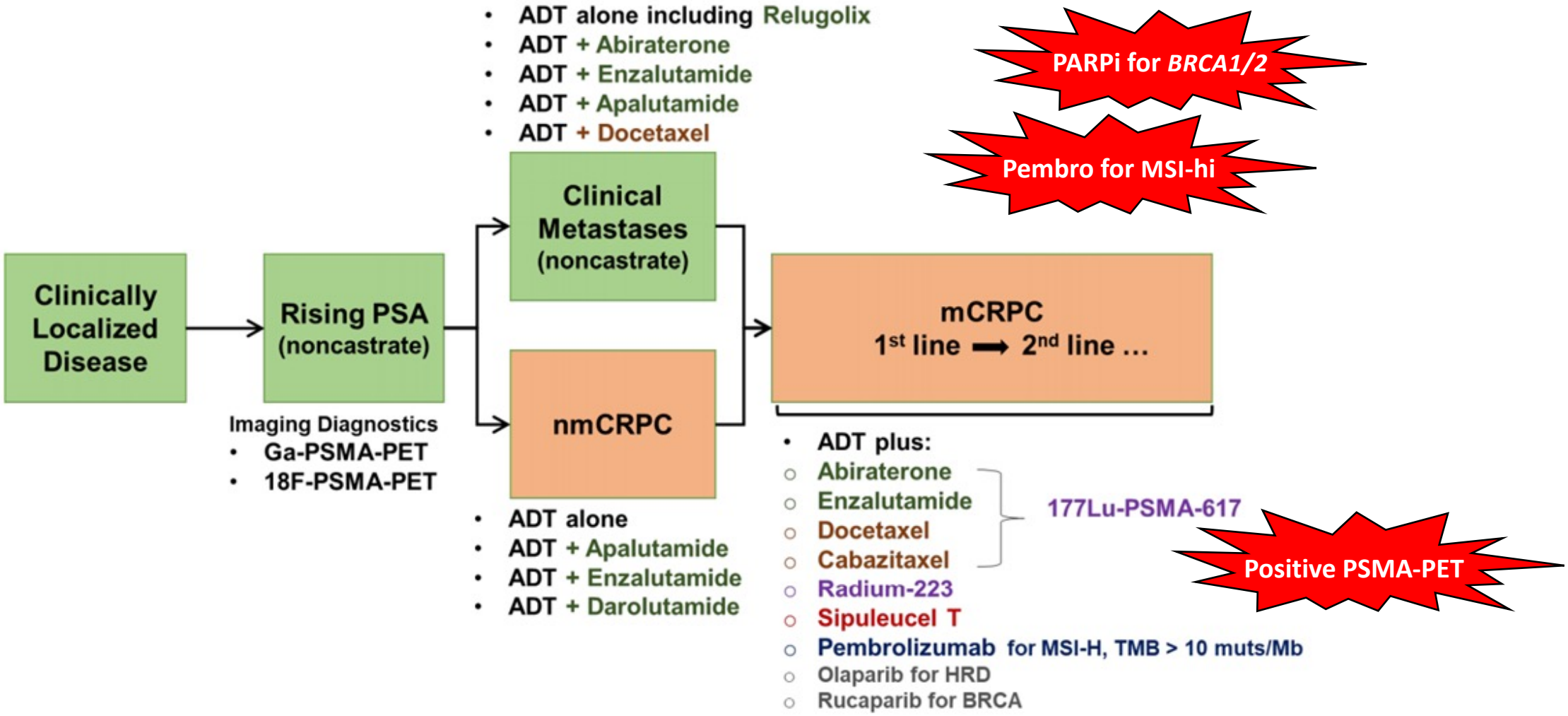
A 62-year-old man with metastatic CRPC and asymptomatic bone metastases

RTP
RESEARCH
TO PRACTICE

Sequencing of Therapy for Metastatic CRPC (mCRPC)

Emmanuel S. Antonarakis, M.D.
Clark Endowed Professor of Medicine
Division of Hematology/Oncology and Transplantation
University of Minnesota, Masonic Cancer Center
Minneapolis, MN

Treatment Landscape for mCRPC



Selection and Sequencing of Therapy

AR-V7

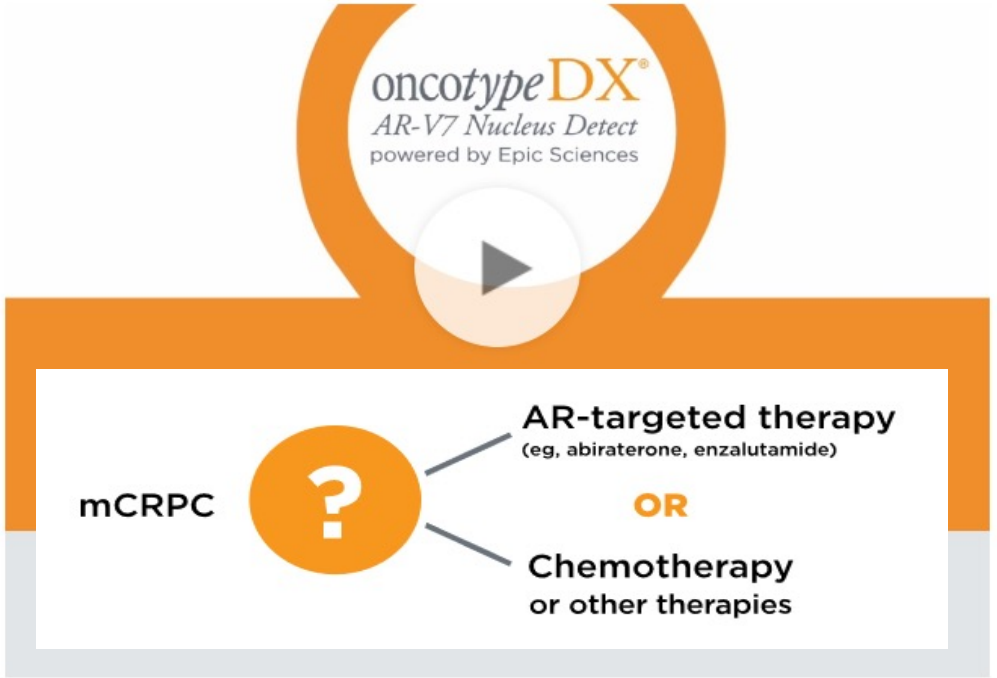
Genomic Health LIFE. CHANGING. | oncotype DX AR-V7 Nucleus Detect | POWERED BY Epic Sciences

ONCOTYPE DX AR-V7 NUCLEUS DETECT

About the Oncotype DX AR-V7 Nucleus Detect test

Share

Why Order the Oncotype DX AR-V7 Nucleus Detect Test?



Therapy Sequencing in mCRPC …. Complicated!

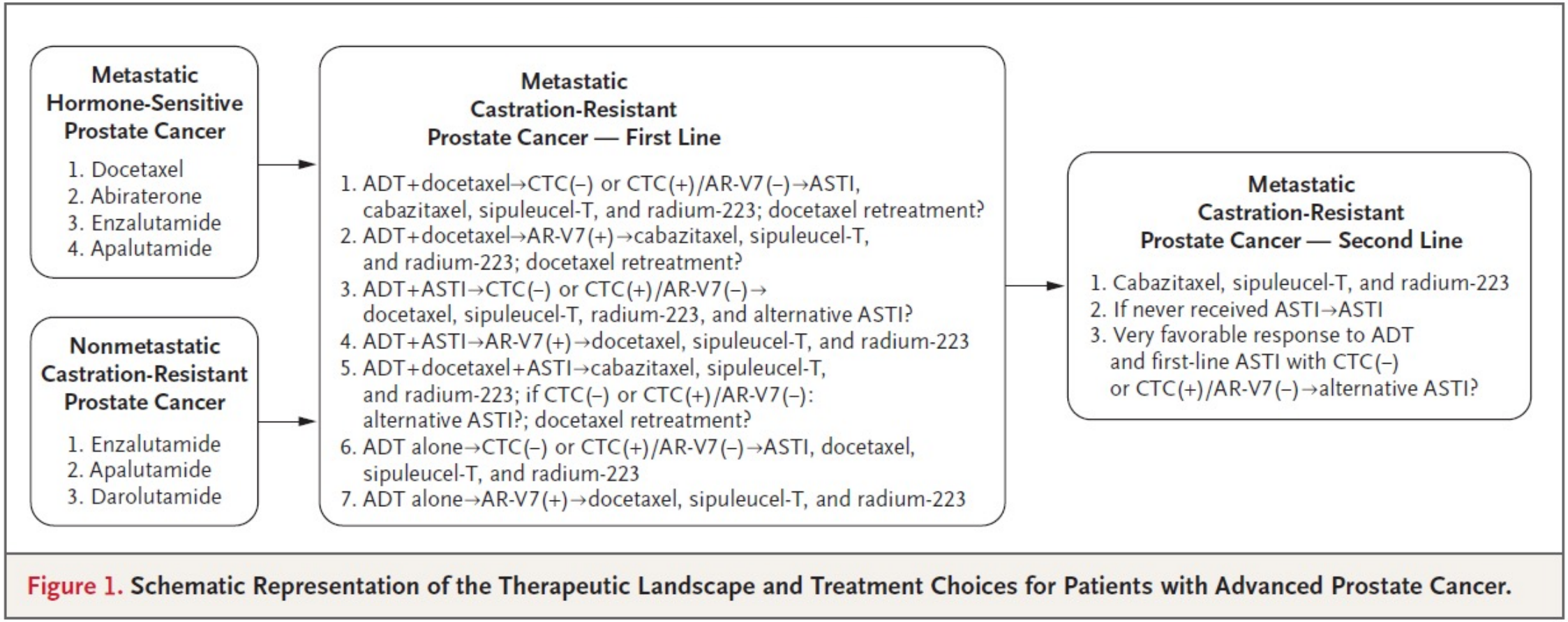
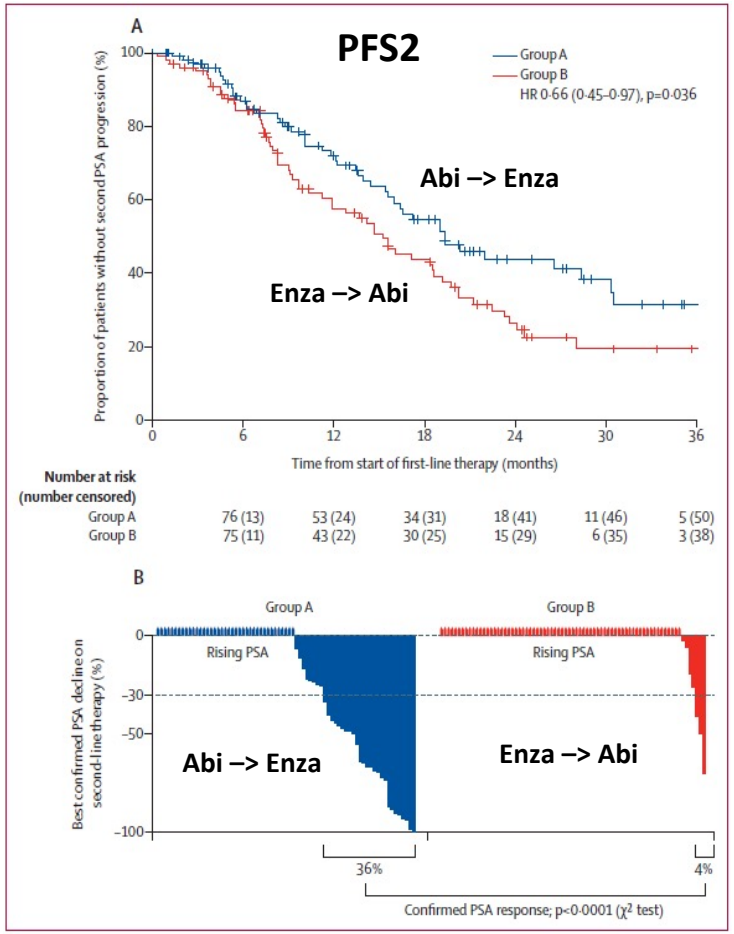


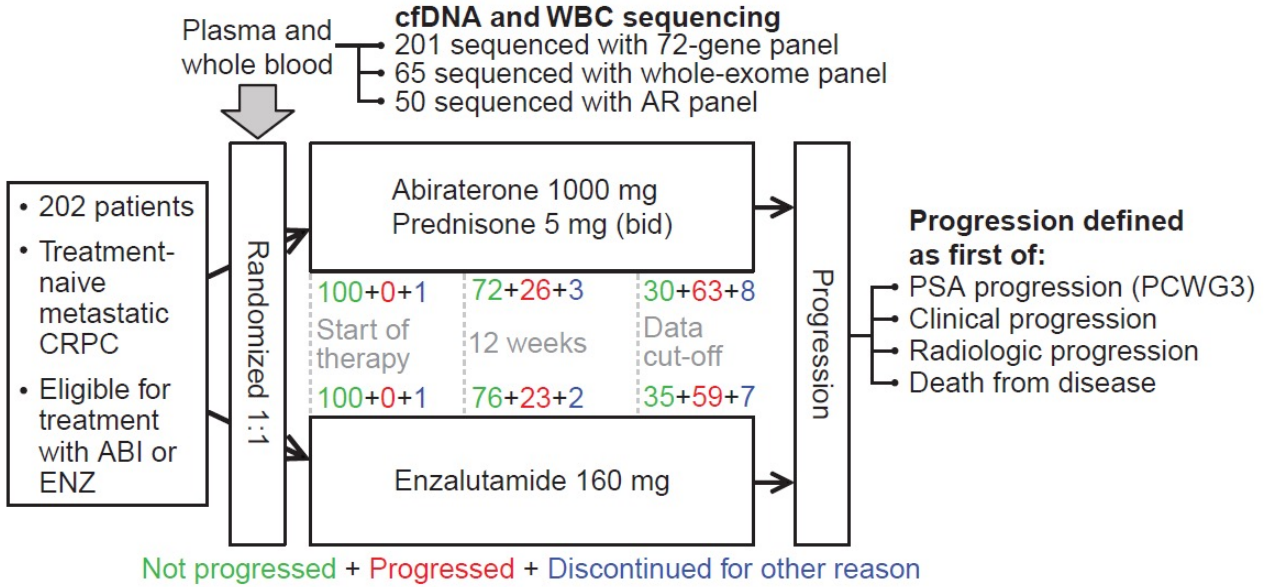
Figure 1. Schematic Representation of the Therapeutic Landscape and Treatment Choices for Patients with Advanced Prostate Cancer.

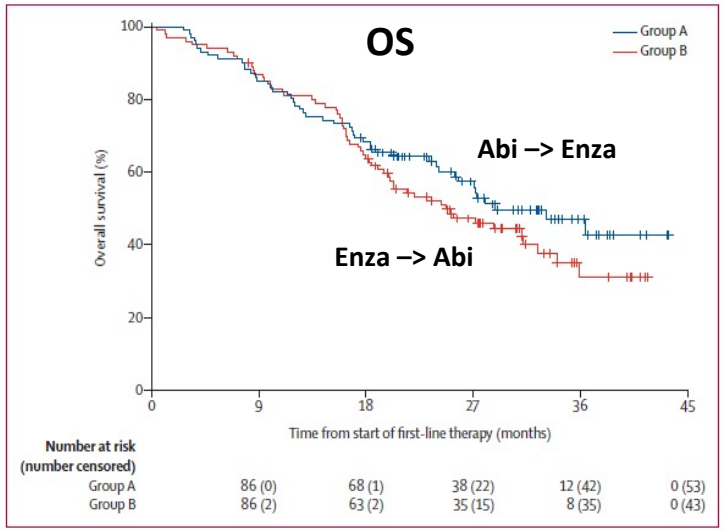
Eisenberger MA, Antonarakis ES. *NEJM* 2019; 381: 2564-2566.

Abi → Enza vs Enza → Abi

GUTG-001 Study



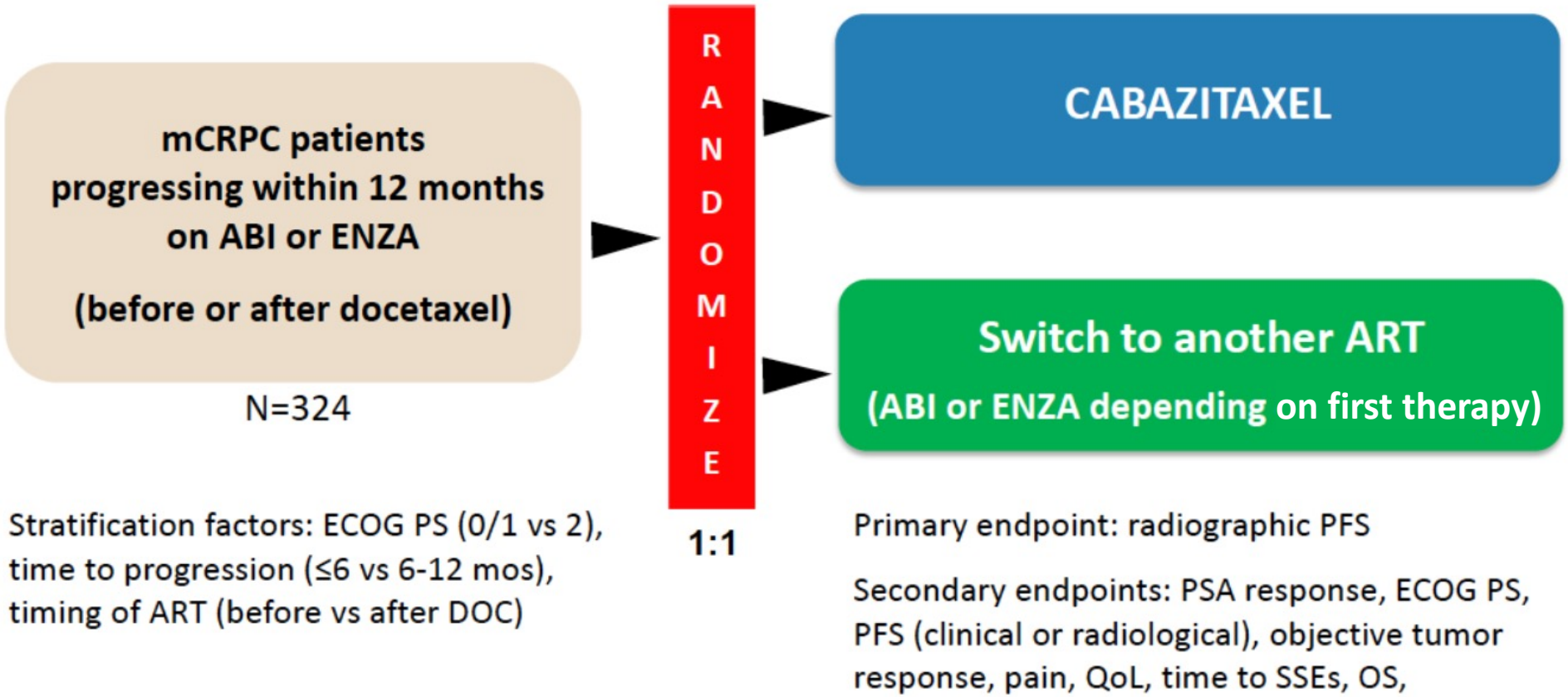




Khalaf DJ, et al. *Lancet Oncol 2019*; 20: 1730-39.

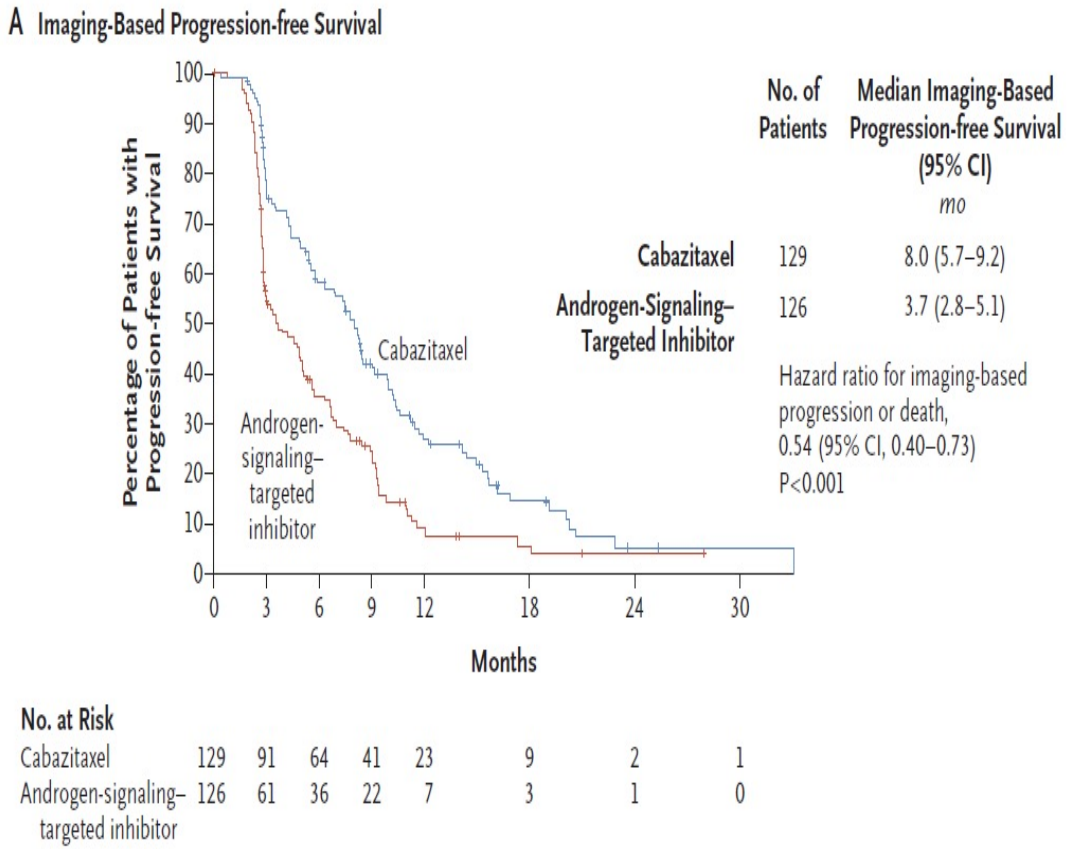
The CARD trial

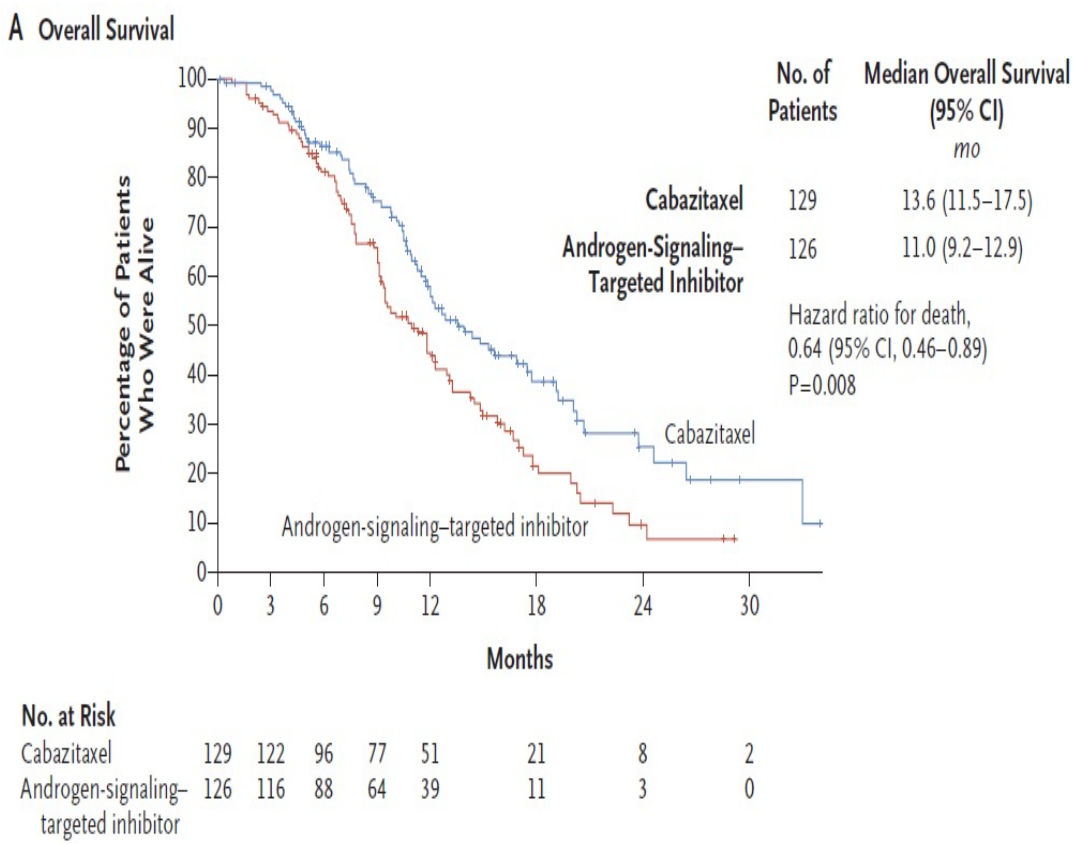
CARD Study



de Wit R, et al. *NEJM* 2019; 381: 2506-2518.

The CARD trial





de Wit R, et al. *NEJM* 2019; 381: 2506-2518.

Table 2. Adverse Events (Safety Population).

Event	Cabazitaxel (N=126)		Androgen-Signaling–Targeted Inhibitor (N=124)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any adverse event — no. (%)	124 (98.4)	—	117 (94.4)	—
Any grade ≥3 adverse event — no. (%)	—	71 (56.3)	—	65 (52.4)
Any serious adverse event — no. (%)	49 (38.9)	—	48 (38.7)	—
Any adverse event leading to permanent discontinuation of treatment — no. (%)	25 (19.8)	—	11 (8.9)	—
Any adverse event leading to death — no. (%)*	7 (5.6)	—	14 (11.3)	—
Common adverse events — no. (%)†				
Asthenia or fatigue	67 (53.2)	5 (4.0)	45 (36.3)	3 (2.4)
Diarrhea	50 (39.7)	4 (3.2)	8 (6.5)	0
Infection	40 (31.7)	10 (7.9)	25 (20.2)	9 (7.3)
Musculoskeletal pain or discomfort‡	34 (27.0)	2 (1.6)	49 (39.5)	7 (5.6)
Nausea or vomiting	33 (26.2)	0	29 (23.4)	2 (1.6)
Peripheral neuropathy	25 (19.8)	4 (3.2)	4 (3.2)	0
Constipation	19 (15.1)	0	13 (10.5)	0
Hematuria	19 (15.1)	1 (0.8)	7 (5.6)	2 (1.6)
Laboratory abnormalities — no./total no. (%)††				
Anemia	124/125 (99.2)	10/125 (8.0)	118/124 (95.2)	6/124 (4.8)
Leukopenia	93/125 (74.4)	40/125 (32.0)	39/124 (31.5)	2/124 (1.6)
Neutropenia	81/123 (65.9)	55/123 (44.7)	8/124 (6.5)	4/124 (3.2)
Thrombocytopenia	51/125 (40.8)	4/125 (3.2)	20/124 (16.1)	2/124 (1.6)
Aspartate aminotransferase increased	27/124 (21.8)	4/124 (3.2)	35/124 (28.2)	0/124
Alanine aminotransferase increased	24/124 (19.4)	1/124 (0.8)	11/124 (8.9)	0/124
Hypokalemia	15/125 (12.0)	1/125 (0.8)	19/124 (15.3)	1/124 (0.8)

de Wit R, et al. *NEJM* 2019; 381: 2506-2518.

The Canadian (OZM-054) trial

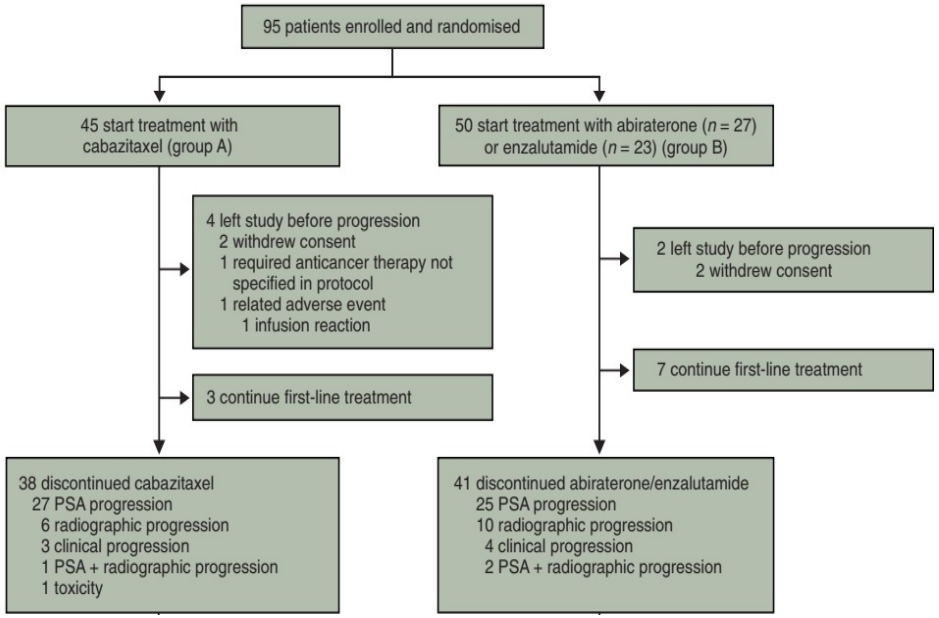
The OZM-054 trial

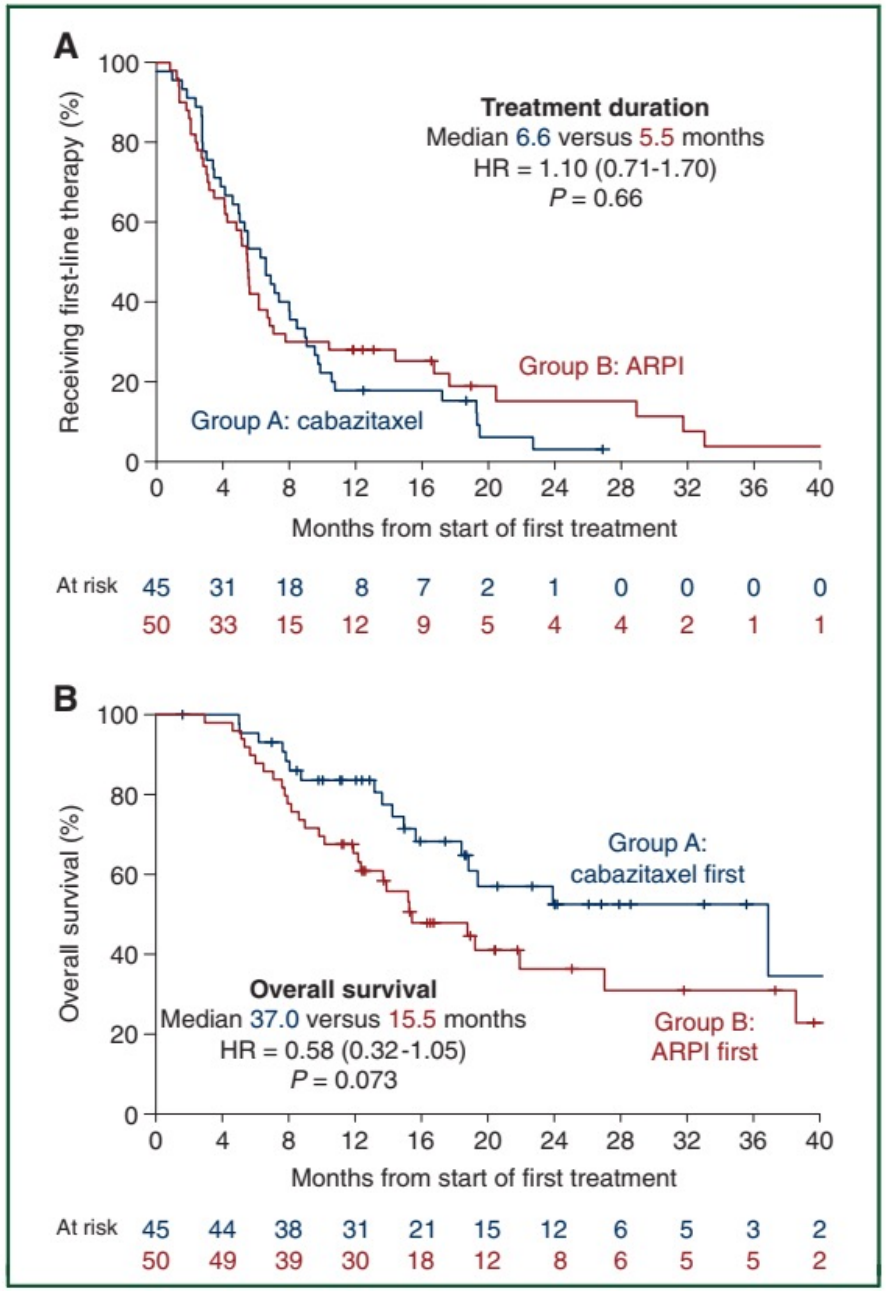
Poor prognosis:

liver mets,

CRPC <12 months,

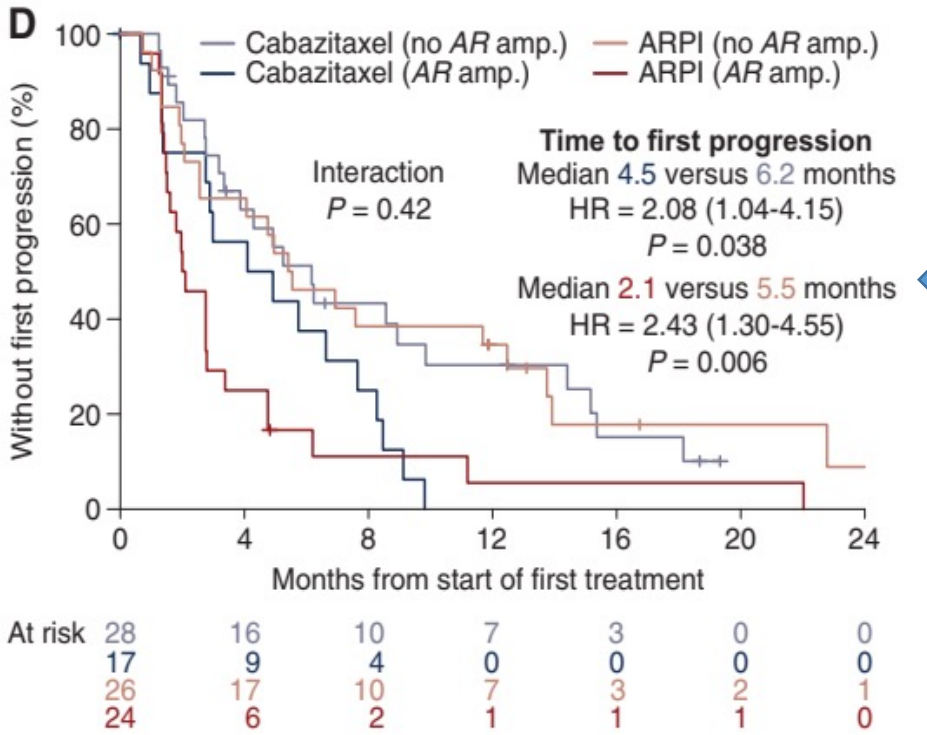
or >3 of 6 (LDH, ECOG, visceral, albumin, ALP, <36 mo from Dx)

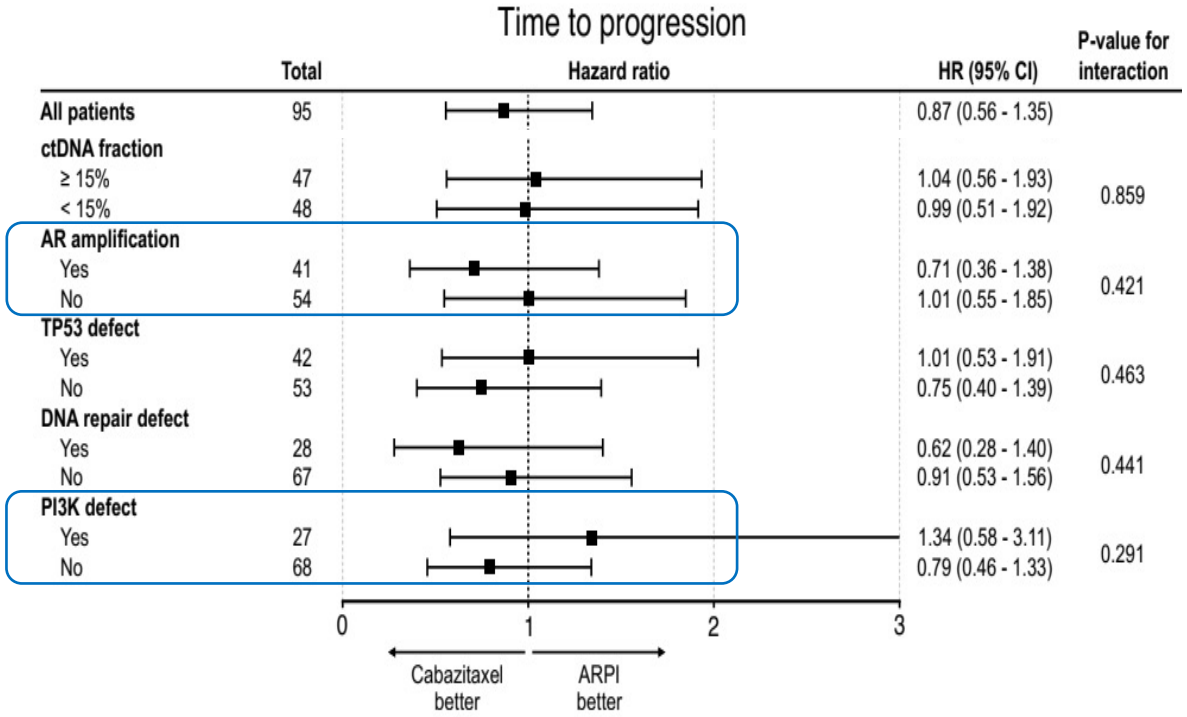




Annala M, et al. *Ann Oncol* 2021; 32: 896-905.

Biomarkers of differential response?

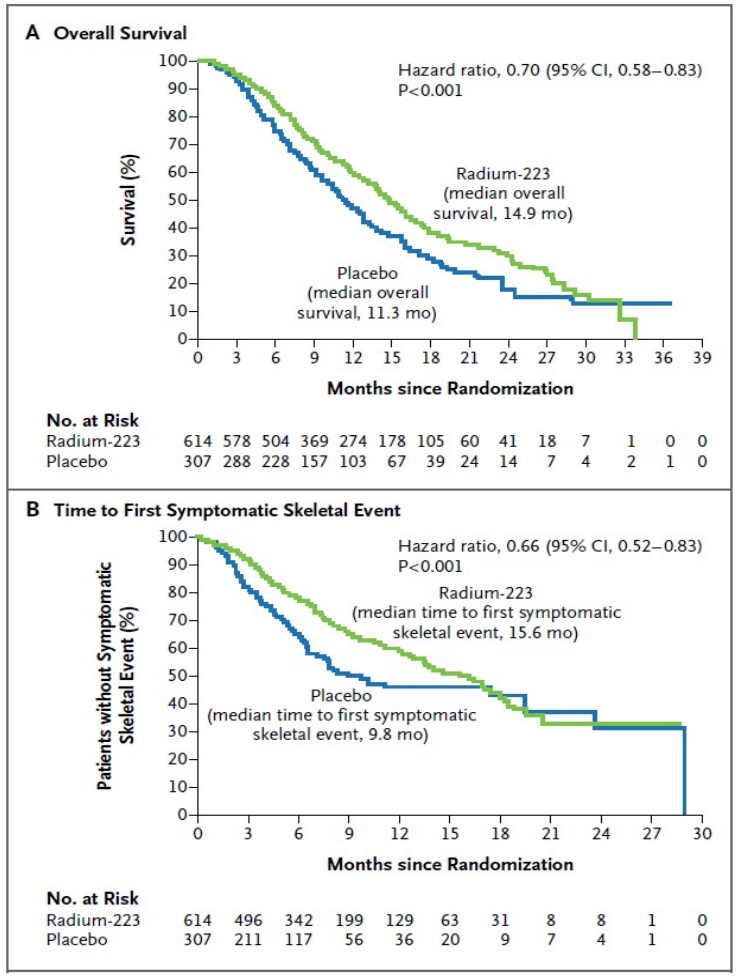




Annala M, et al. *Ann Oncol* 2021; 32: 896-905.

Optimal integration of radium-223

Radium-223: the ALSYMPCA trial



Subgroup	Radium-223	Placebo	Radium-223	Placebo	Hazard Ratio (95% CI)
	no. of patients		*median overall survival (mo)*		
All patients	614	307	14.9	11.3	0.70 (0.58–0.83)
Total ALP level at baseline					
<220 U/liter	348	169	17.0	15.8	0.82 (0.64–1.07)
≥220 U/liter	266	138	11.4	8.1	0.62 (0.49–0.79)
Current bisphosphonate use					
Yes	250	124	15.3	11.5	0.70 (0.52–0.93)
No	364	183	14.5	11.0	0.74 (0.59–0.92)
Previous docetaxel use					
Yes	352	174	14.4	11.3	0.71 (0.56–0.89)
No	262	133	16.1	11.5	0.74 (0.56–0.99)
Baseline ECOG performance-status score					
0 or 1	536	265	15.4	11.9	0.68 (0.56–0.82)
≥2	77	41	10.0	8.4	0.82 (0.50–1.35)
Extent of disease					
<6 metastases	100	38	27.0	NE	0.95 (0.46–1.95)
6–20 metastases	262	147	13.7	11.6	0.71 (0.54–0.92)
>20 metastases	195	91	12.5	9.1	0.64 (0.47–0.88)
Superscan	54	30	11.3	7.1	0.71 (0.40–1.27)
Opioid use					
Yes	345	168	13.9	10.4	0.68 (0.54–0.86)
No	269	139	16.4	12.8	0.70 (0.52–0.93)

Parker C, et al. *N Engl J Med* 2013; 369: 213-223.

Ideal patient for Radium-223 treatment

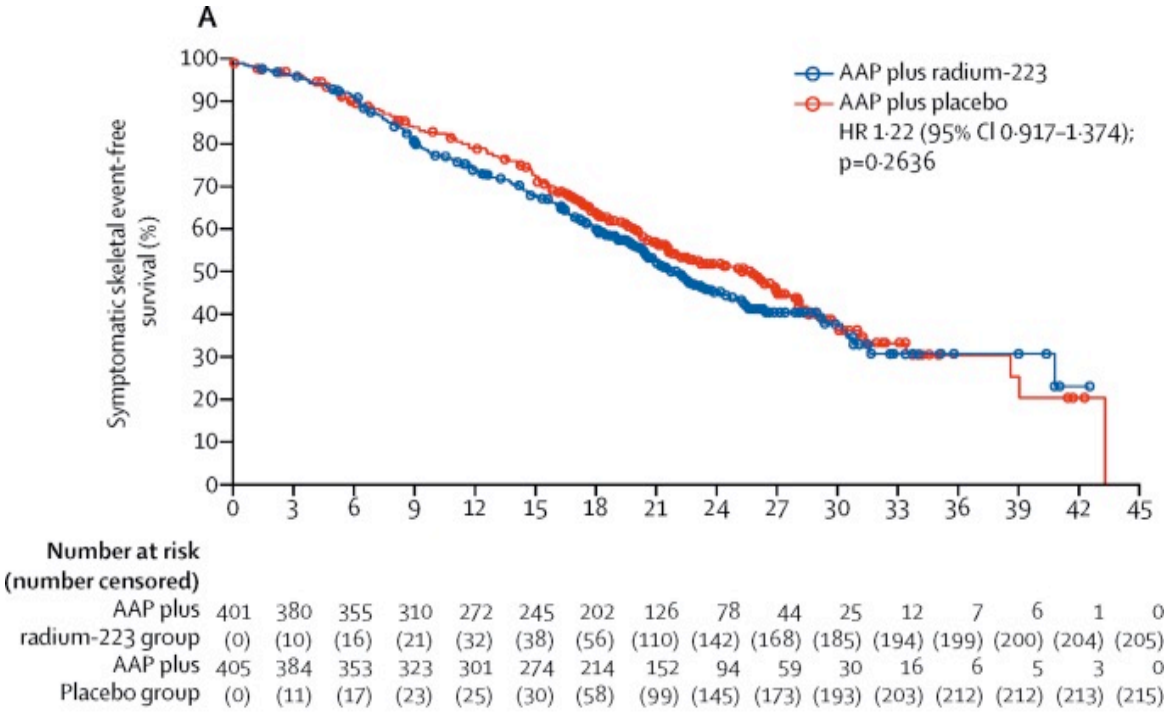
- mCRPC with symptomatic bone metastases
- Mild bone pain (1-4/10), but not severe bone pain (≥5/10)
- Few bone metastases (5-10), but not too many (≥20)
- No impending pathologic fracture or cord compression
- Adequate bone marrow function (Hgb ≥9, ANC ≥1000, Plt ≥100K)
- No visceral mets (≥10 mm) or bulky nodal mets (≥30 mm)
- No concurrent Abi; use Denosumab with concurrent Enza
- ECOG 0-1; avoid if ECOG 2-4

The PEACE-3 (EORTC-1333) trial

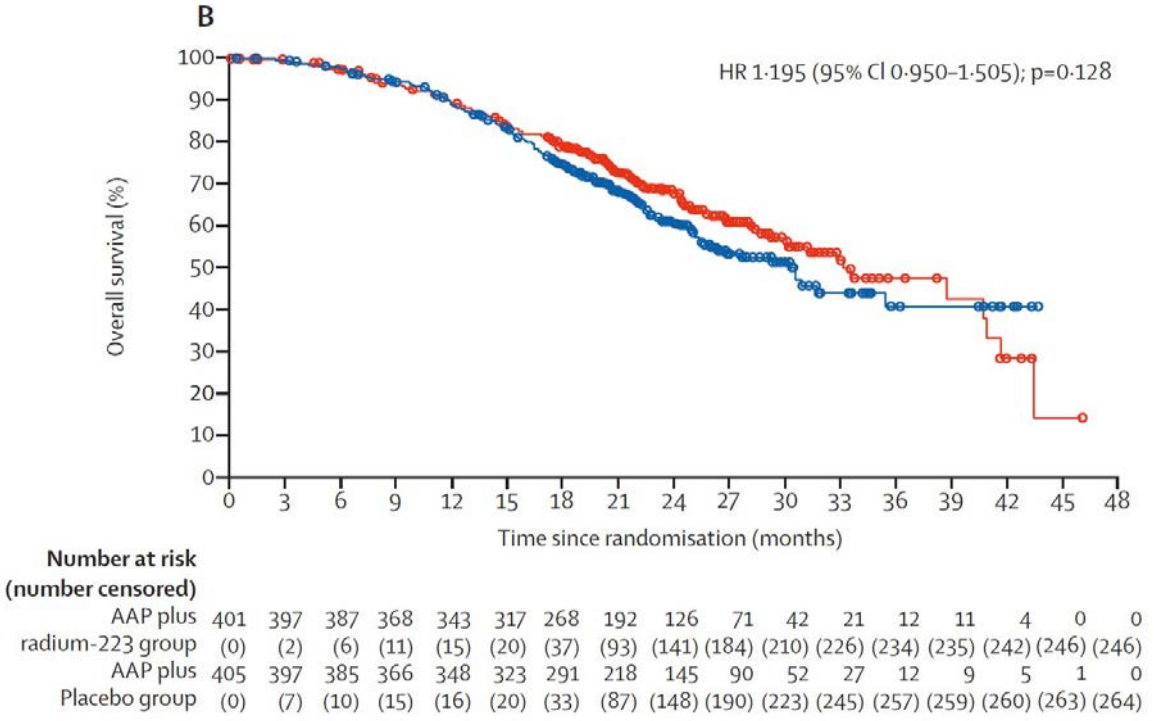
ERA-223 study: A cautionary note

60% of patients did *not* receive a bone-protecting agent

SSE-free

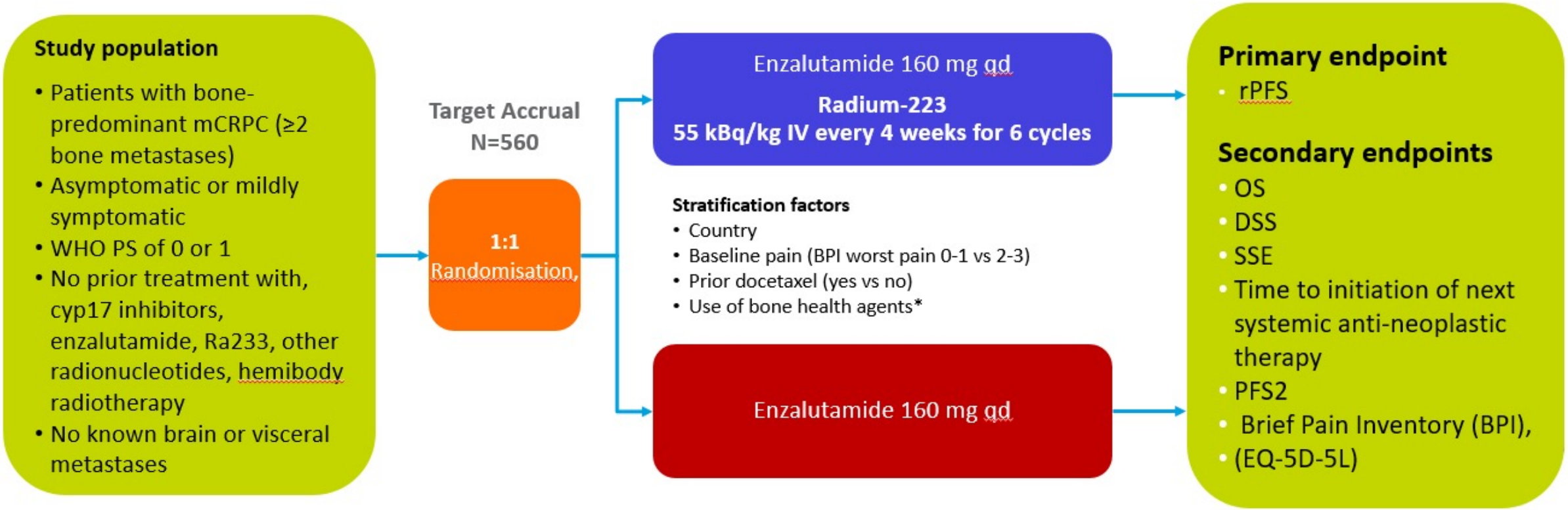


OS



Smith MR, et al. *Lancet Oncol* 2019; 20: 408-419.

EORTC 1333 (PEACE III) original design



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

Tombal B, et al. *ASCO* 2019; Abstract 5007.

PEACE-3: Timelines, impact of ERA 223 and role of IDMC

Apr 2018: IDMC review incorporating results of ERA 223: **BPA (at the SRE preventing dose)** should be used in both arms

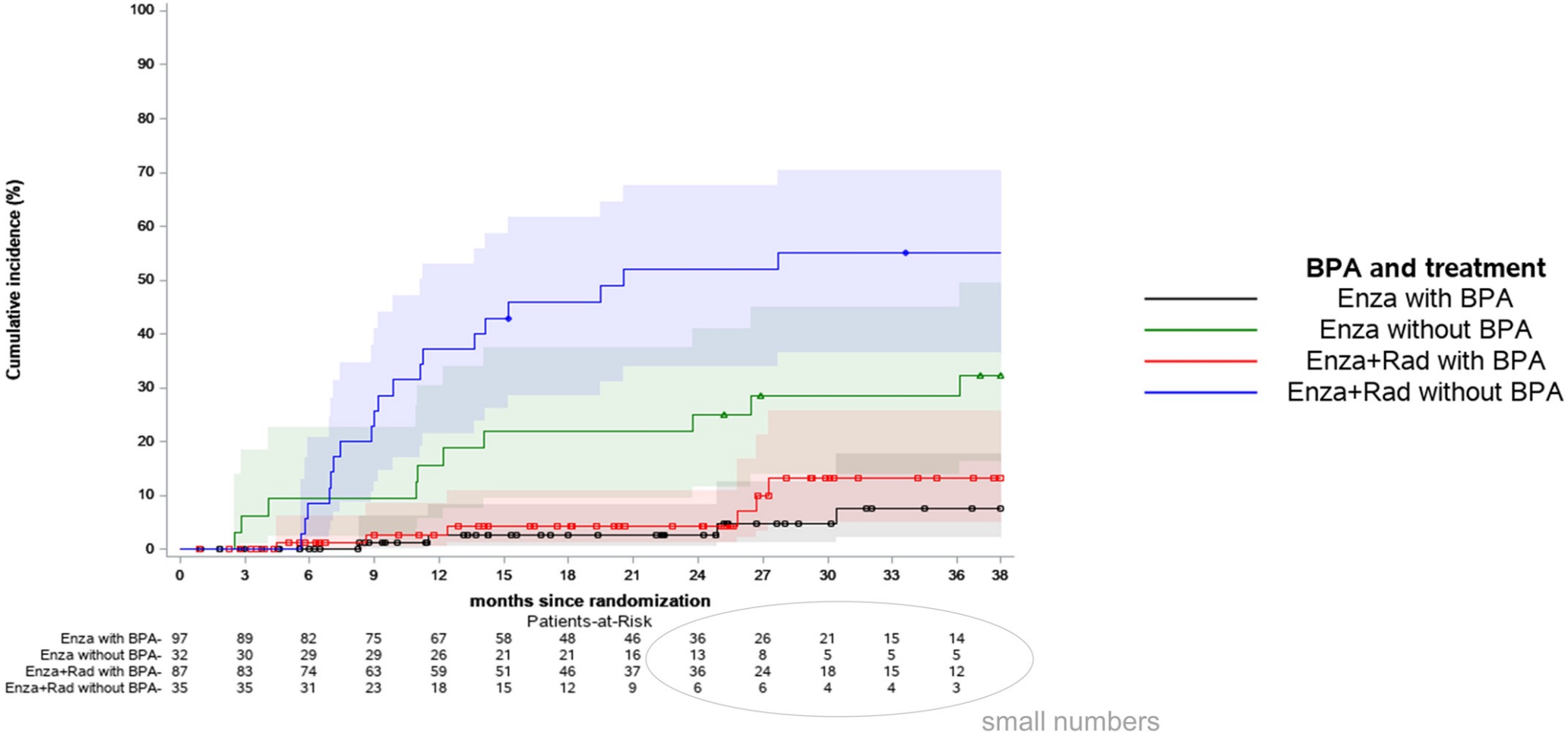
Mar 2018: **Urgent Safety Letter: Mandatory use of bone protecting agent** at least 6 weeks before first injection of Ra223

Jun 2019: **ASCO Abstract #260193:** Decreased fracture rate by mandating bone-protecting agents in the EORTC 1333/PEACE-3 trial: **An early safety analysis**

Dec 2020: IDMC **recommends a presentation of the updated figures** regarding bone fractures to the scientific community:
→ **ASCO 2021 abstract submission**

Gillessen S, et al. *ASCO* 2021; Abstract 5002.

Cumulative incidence of fractures by treatment arm and use of bone protecting agents



Gillessen S, et al. *ASCO* 2021; Abstract 5002.

Bone fractures and cumulative incidence - safety population

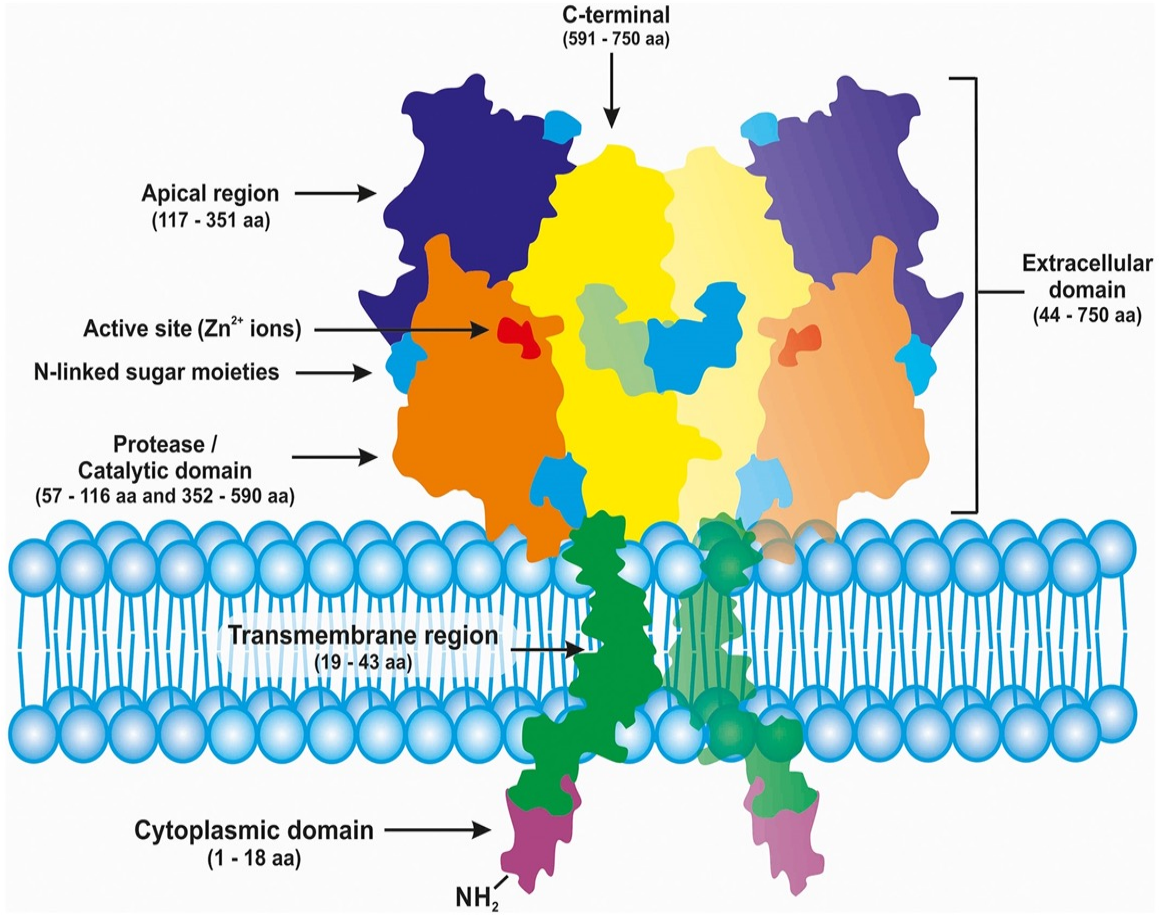
Time point	Without BPA		With BPA	
	Enza+Rad (N=35)	Enza (N=32)	Enza+Rad (N=87)	Enza (N=97)
	Cum Incidence (95% CI)	Cum Incidence (95% CI)	Cum Incidence (95% CI)	Cum Incidence (95% CI)
9 months	25.7 (12.6-41.0)	9.4 (2.3-22.5)	2.7 (0.5-8.5)	1.3 (0.1-6.1)
12 months	**37.1 (21.3-53.0)**	**15.6 (5.6-30.3)**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

Gillessen S, et al. *ASCO* 2021; Abstract 5002.

^{177}Lutetium–PSMA–617

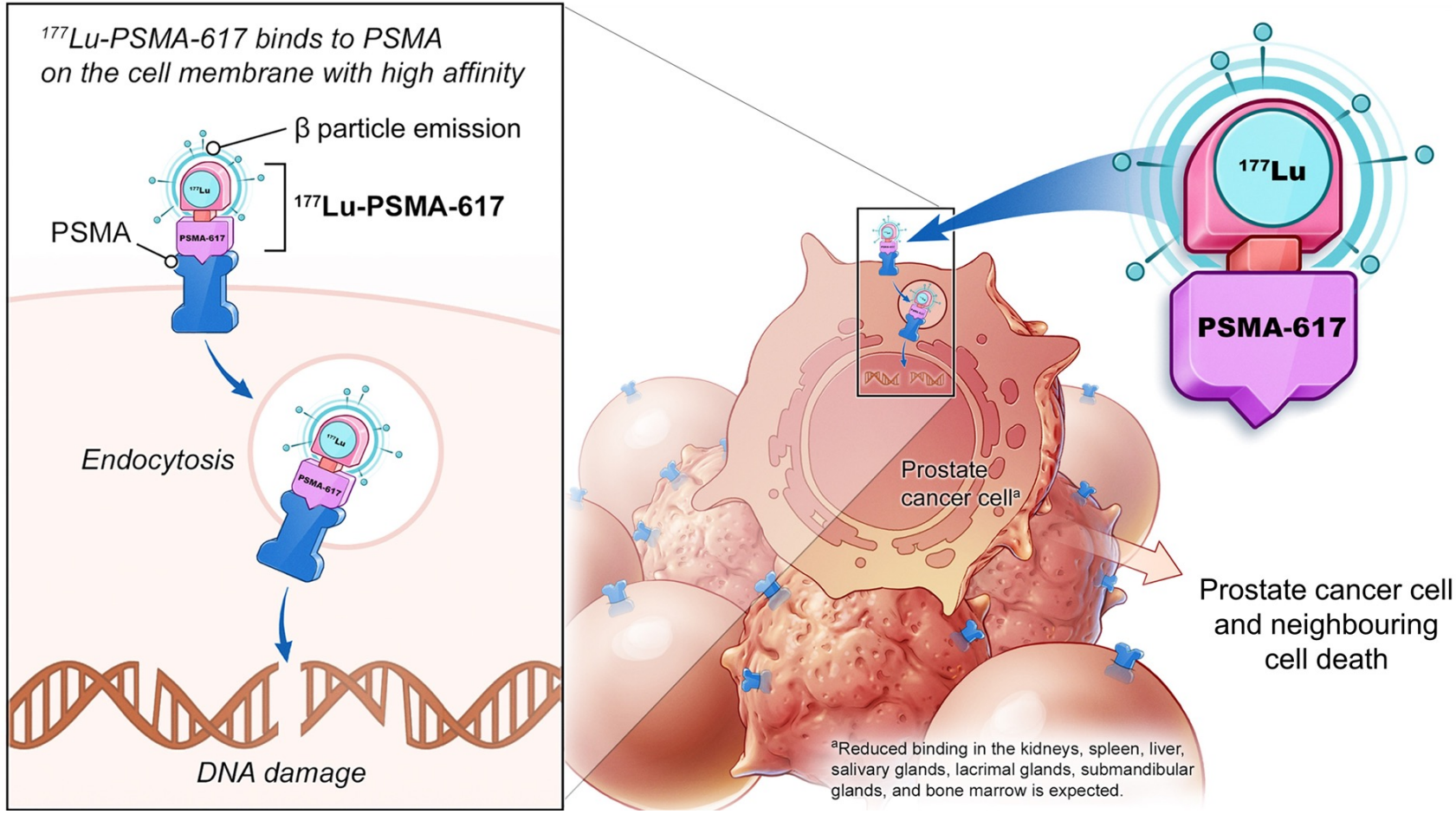
PSMA: Target for imaging and therapy

- Transmembrane carboxypeptidase
- Highly expressed in prostate cancer including metastatic lesions
- Relatively restricted normal expression
  - E.g. salivary and lacrimal glands
- Excellent target for PET imaging



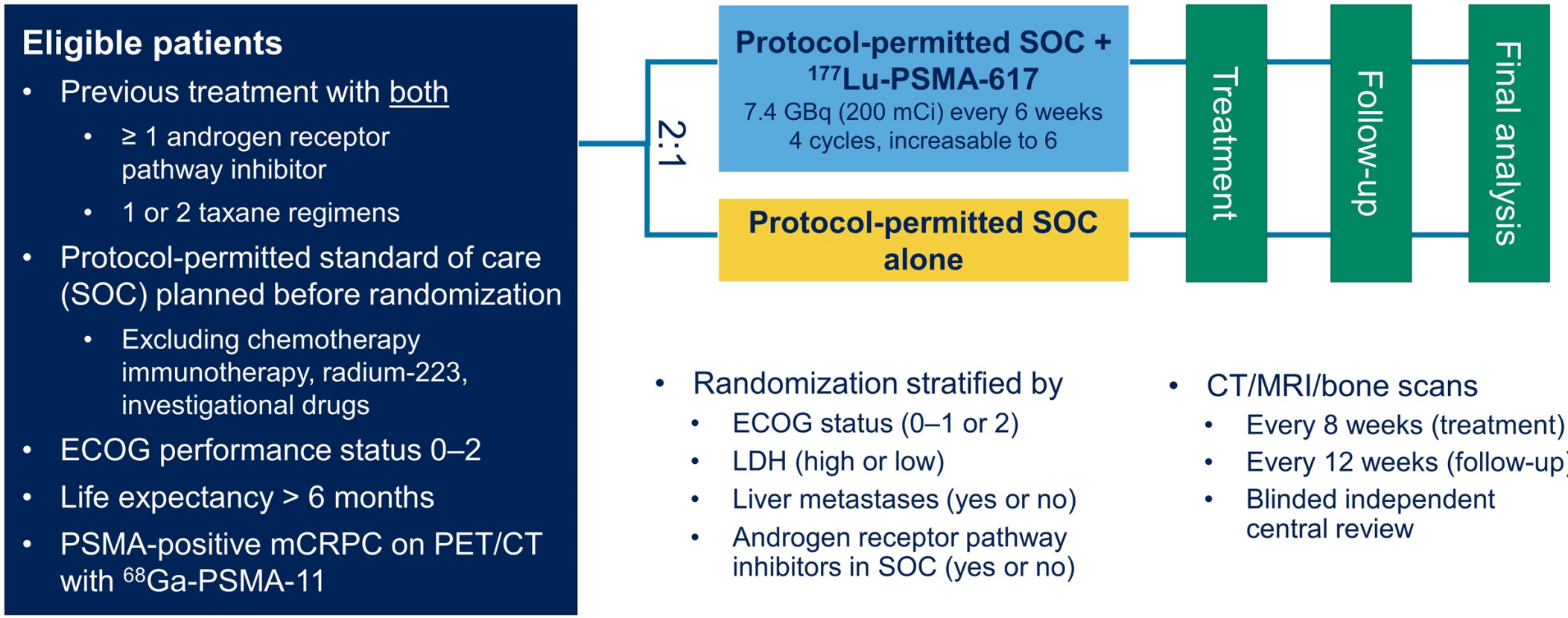
Evans JC, *et al. Br J Pharmacol* 2016; 173: 3041-79.

^{177}Lu-PSMA-617 Radioligand therapy



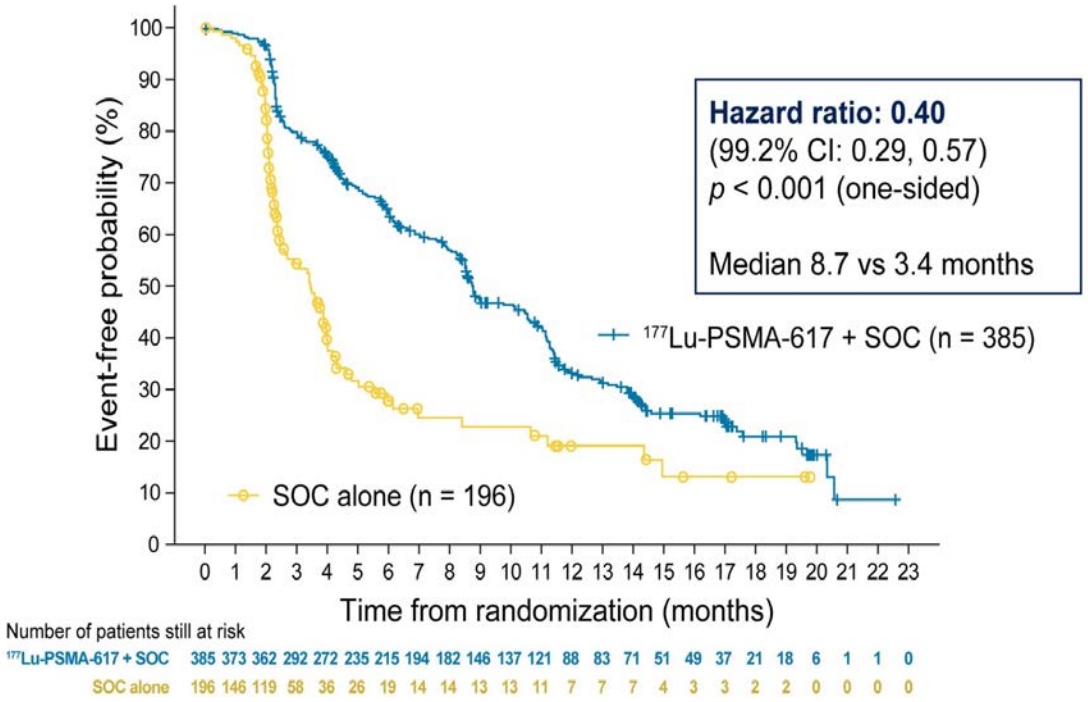
Morris MJ, *et al.* J Clin Oncol 39; 2021 (ASCO abstract LBA4).

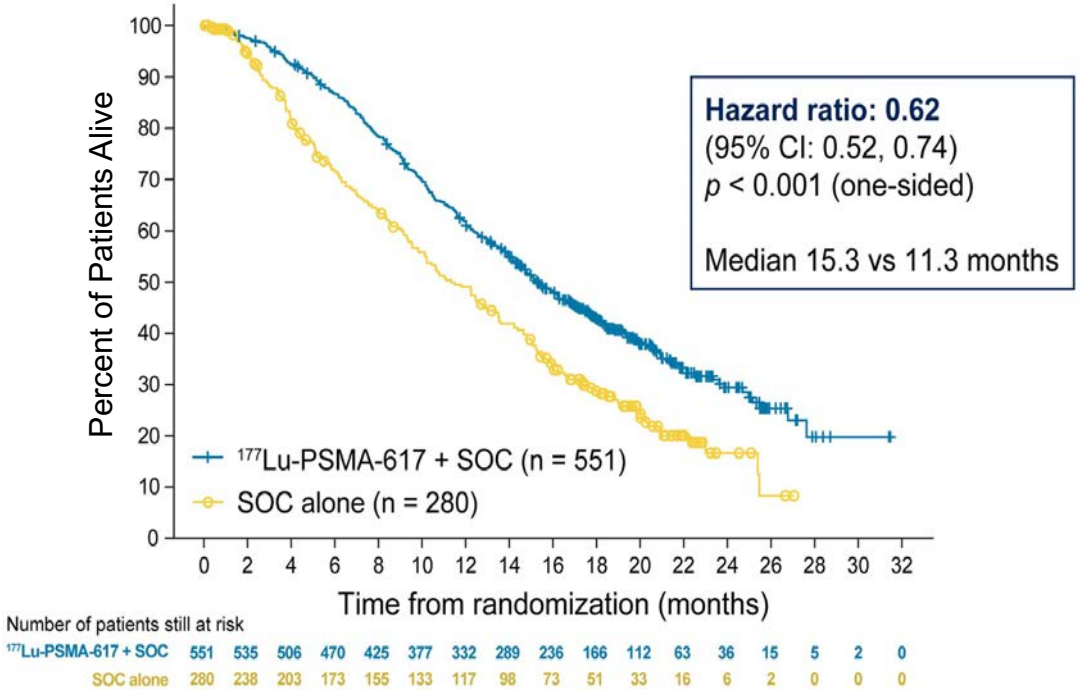
VISION trial for patients with PSMA+ mCRPC



Morris MJ, *et al.* J Clin Oncol 39; 2021 (ASCO abstract LBA4). Sartor O, et al. *NEJM* 2021.

VISION trial: rPFS and OS



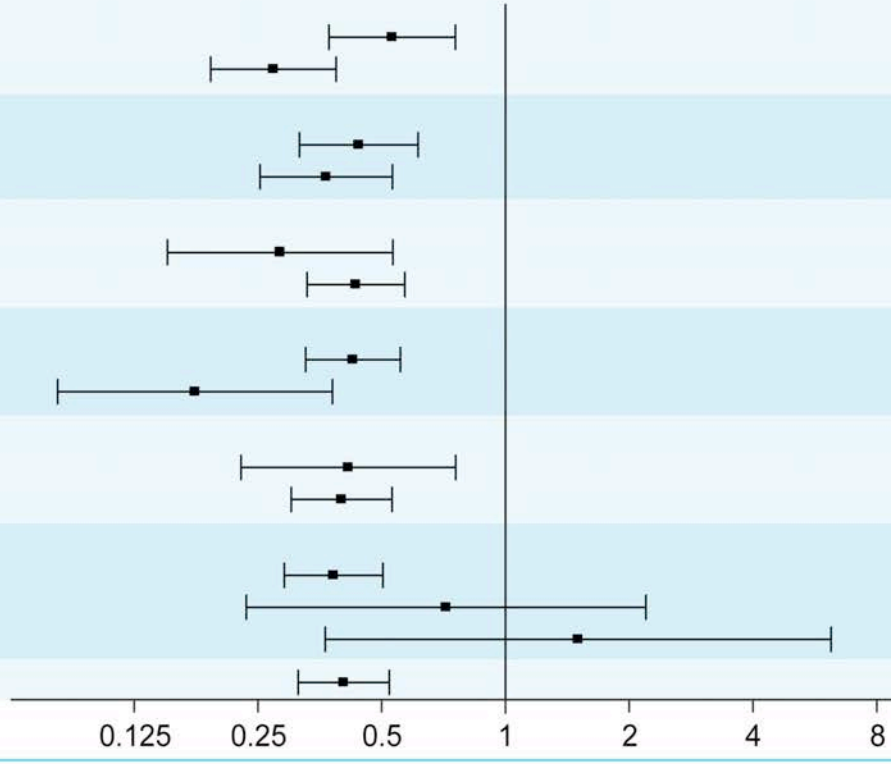


Morris MJ, *et al.* J Clin Oncol 39; 2021 (ASCO abstract LBA4) .

Sartor O, et al. *NEJM* 2021.

VISION trial: rPFS forest plot

Subgroup	^{177}Lu-PSMA-617 + SOC (n = 385)	SOC alone (n = 196)	Hazard ratio (95% CI)
Androgen receptor pathway inhibitors as part of planned SOC			
Yes	170	107	0.53 (0.37, 0.76)
No	215	89	0.27 (0.19, 0.39)
LDH			
≤ 260 IU/L	244	120	0.44 (0.32, 0.61)
> 260 IU/L	140	75	0.37 (0.25, 0.53)
Liver metastases			
Yes	37	22	0.28 (0.15, 0.53)
No	348	174	0.43 (0.33, 0.57)
ECOG score			
0 or 1	352	179	0.43 (0.33, 0.56)
2	33	17	0.18 (0.08, 0.38)
Age			
< 65 years	96	39	0.42 (0.23, 0.76)
≥ 65 years	289	157	0.40 (0.30, 0.53)
Race			
White	336	166	0.38 (0.29, 0.50)
African American or Black	29	14	0.72 (0.23, 2.20)
Asian	6	9	1.50 (0.36, 6.19)
All patients	385	196	0.40 (0.31, 0.52)



Morris MJ, *et al.* J Clin Oncol 39; 2021 (ASCO abstract LBA4) . Sartor O, et al. *NEJM* 2021.

VISION trial: Adverse Events

Table 2. Adverse Events.*

Event	^{177}Lu-PSMA-617 plus Standard Care (N=529)		Standard Care Alone (N=205)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Any adverse event	519 (98.1)	279 (52.7)	170 (82.9)	78 (38.0)
Adverse event that occurred in >12% of patients				
Fatigue	228 (43.1)	31 (5.9)	47 (22.9)	3 (1.5)
Dry mouth	205 (38.8)	0	1 (0.5)	0
Nausea	187 (35.3)	7 (1.3)	34 (16.6)	1 (0.5)
Anemia	168 (31.8)	68 (12.9)	27 (13.2)	10 (4.9)
Back pain	124 (23.4)	17 (3.2)	30 (14.6)	7 (3.4)
Arthralgia	118 (22.3)	6 (1.1)	26 (12.7)	1 (0.5)
Decreased appetite	112 (21.2)	10 (1.9)	30 (14.6)	1 (0.5)
Constipation	107 (20.2)	6 (1.1)	23 (11.2)	1 (0.5)
Diarrhea	100 (18.9)	4 (0.8)	6 (2.9)	1 (0.5)
Vomiting	100 (18.9)	5 (0.9)	13 (6.3)	1 (0.5)
Thrombocytopenia	91 (17.2)	42 (7.9)	9 (4.4)	2 (1.0)
Lymphopenia	75 (14.2)	41 (7.8)	8 (3.9)	1 (0.5)
Leukopenia	66 (12.5)	13 (2.5)	4 (2.0)	1 (0.5)

Morris MJ, *et al.* J Clin Oncol 39; 2021 (ASCO abstract LBA4) . Sartor O, et al. *NEJM* 2021.

^{177}Lutetium–PSMA–617: FDA Approval!

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

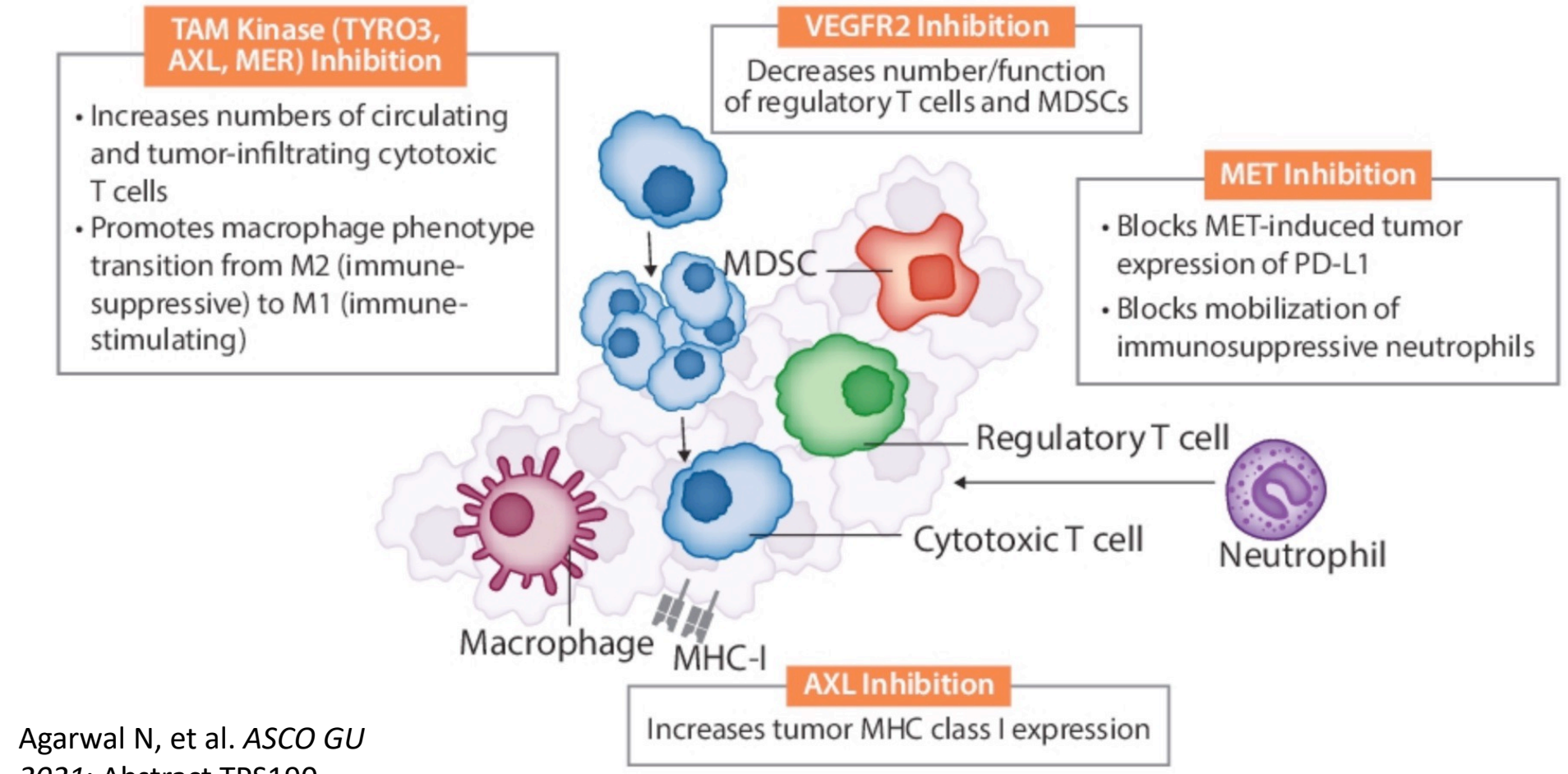
Press Release — March 23, 2022

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

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

Novel strategies for mCRPC

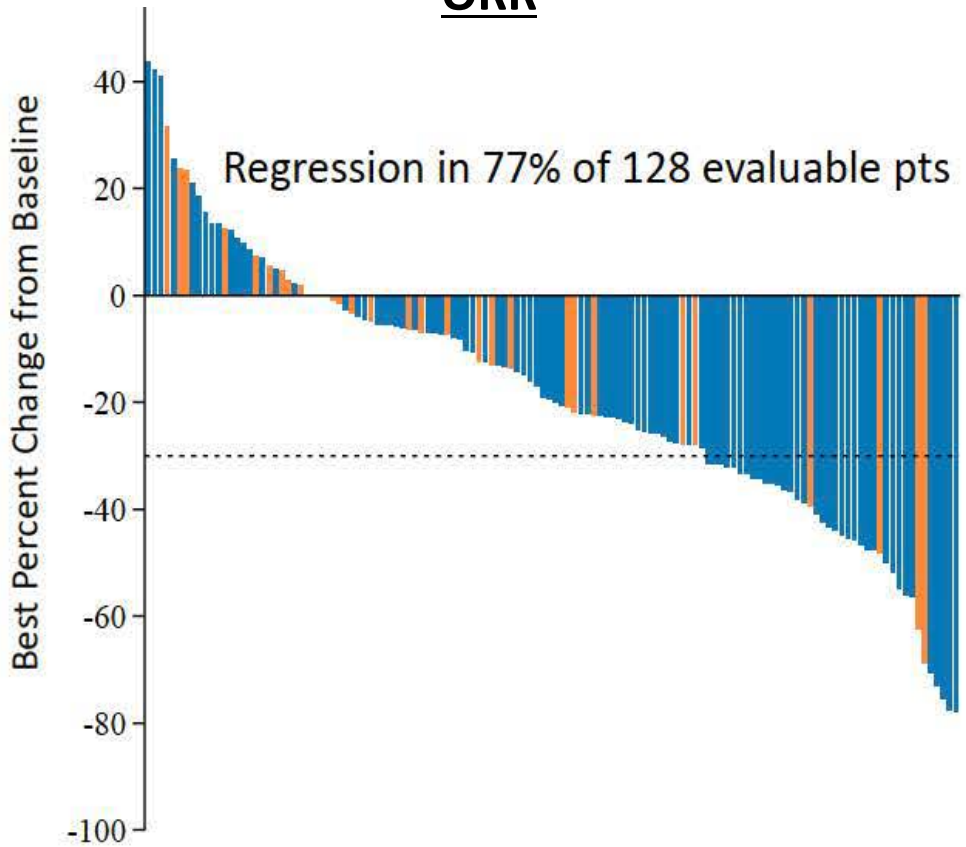
Cabozantinib + Atezo: Rationale



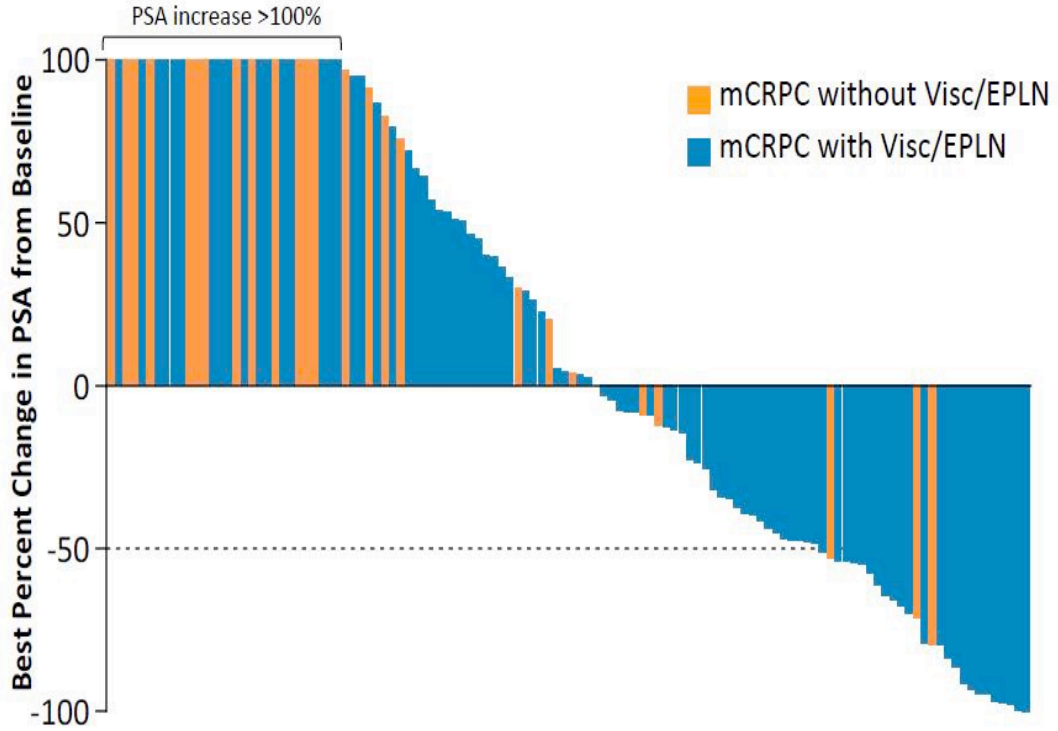
Agarwal N, et al. *ASCO GU 2021*; Abstract TPS190.

COSMIC-021: ORR and PSA response

ORR

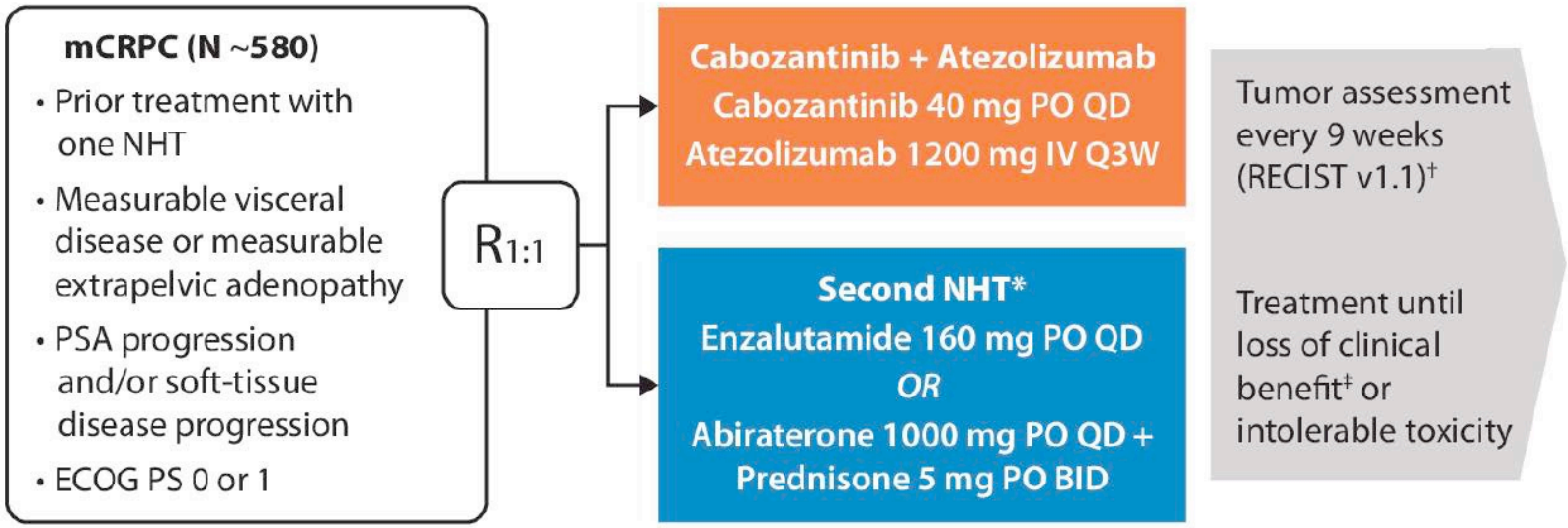


PSA_{50} Response



Agarwal N, et al. *ESMO 2021*; Abstract LBA24.

CONTACT-02: Phase III Trial Schema



Stratification

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

Primary Endpoints:

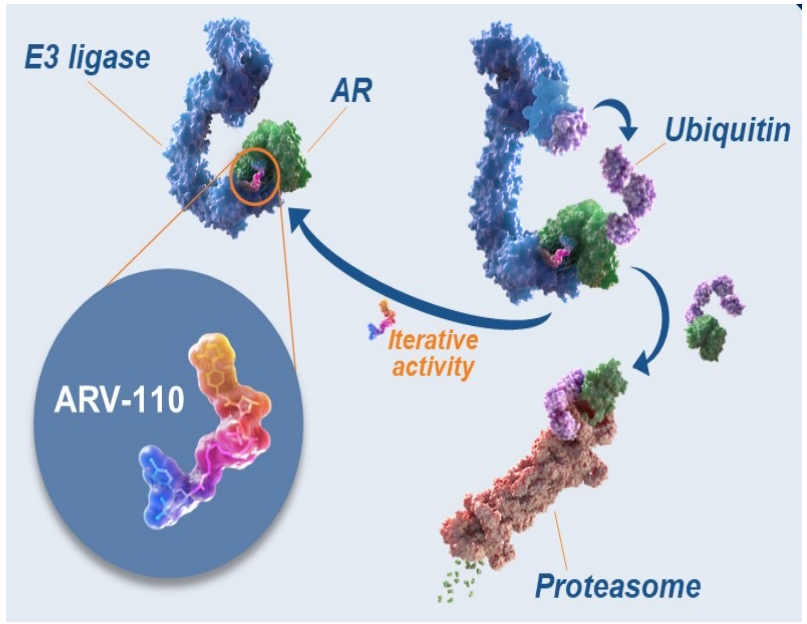
- PFS per RECIST v1.1 by BIRC
- OS

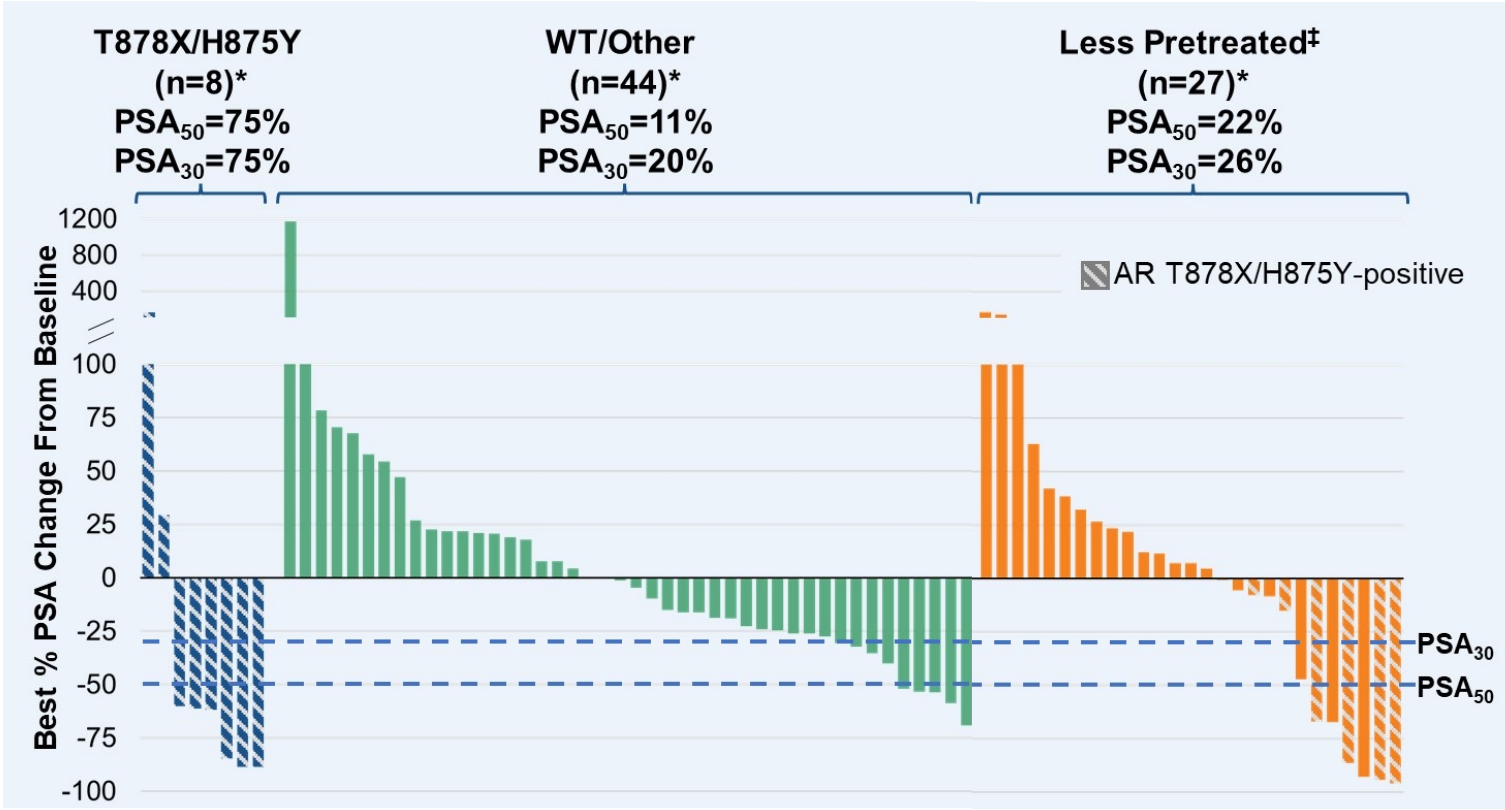
Secondary Endpoint:

- ORR per RECIST v1.1 by BIRC

Agarwal N, et al. *ASCO GU Symposium 2021*; Abstract TPS190.

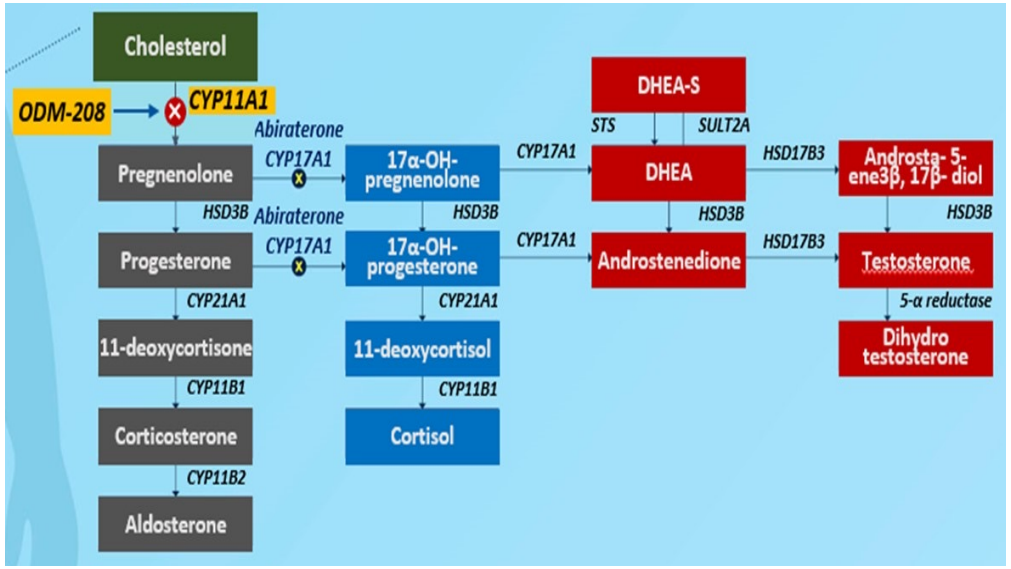
ARV-110: AR-directed PROTAC

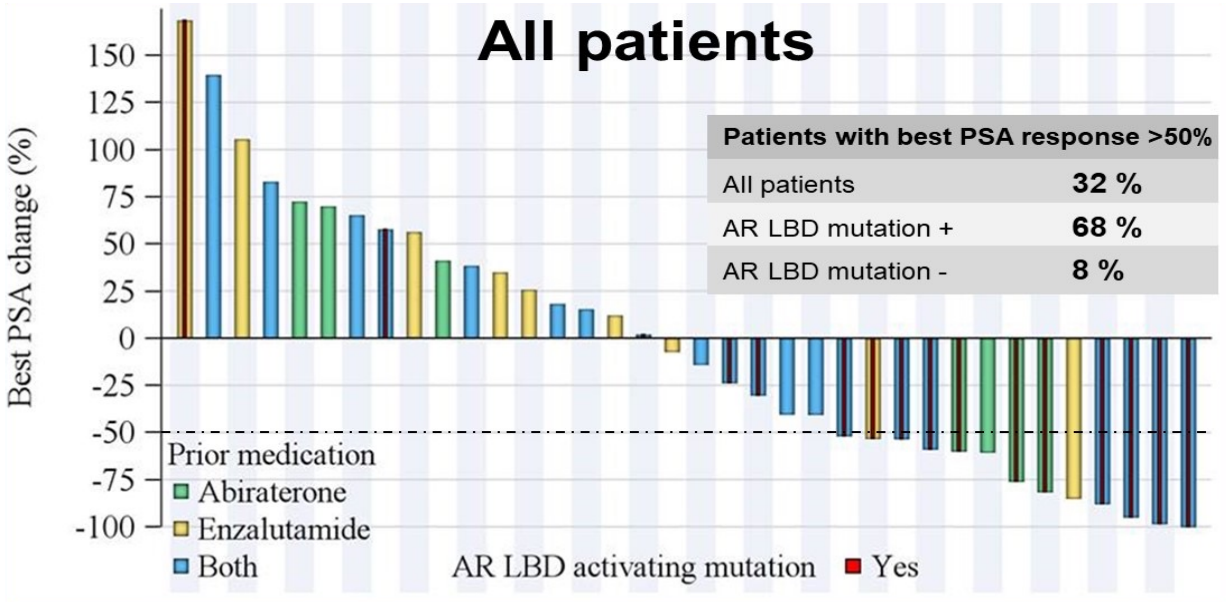


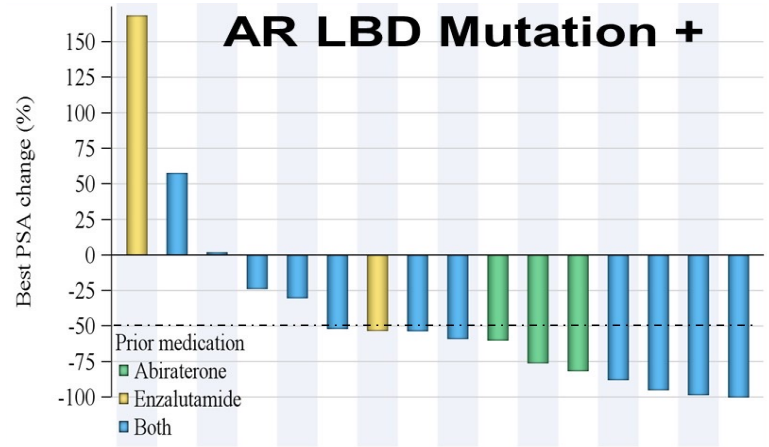


Gao X, et al. *ASCO GU 2022*; Abstract 17.

ODM-208: CYP11A1 inhibitor







Fizazi K, et al. *ASCO GU 2022*; Abstract 18.

MODULE 4: Current and Future Integration of PARP Inhibitors in the Management of Prostate Cancer

RTP
RESEARCH
TO PRACTICE

Regulatory and reimbursement issues aside, which of the following patients with prostate cancer and no relevant family history should undergo germline genetic testing?

1. Patients with locally advanced disease who are going to receive radiation therapy and hormonal therapy
2. Patients with previously untreated metastatic disease
3. Patients with metastatic disease after progression on first-line therapy
4. All of the above
5. a and b only
6. a and c only
7. b and c only

Germline mutation testing; selection of PARP inhibitor therapy

Dr Jason Hafron (West Bloomfield, Michigan)

RTP
RESEARCH
TO PRACTICE

Regulatory and reimbursement issues aside, for which patients with mCRPC who are about to begin secondary hormonal therapy would you generally add a PARP inhibitor as well?

1. Patients with a germline BRCA mutation
2. Patients with a somatic BRCA mutation
3. Patient without HRR gene mutations
4. All of the above
5. a and b only
6. a and c only
7. b and c only

Case Presentation: A 73-year-old man with metastatic CRPC – germline BRCA2 mutation

Dr David Morris (Nashville, Tennessee)

RTP
RESEARCH
TO PRACTICE

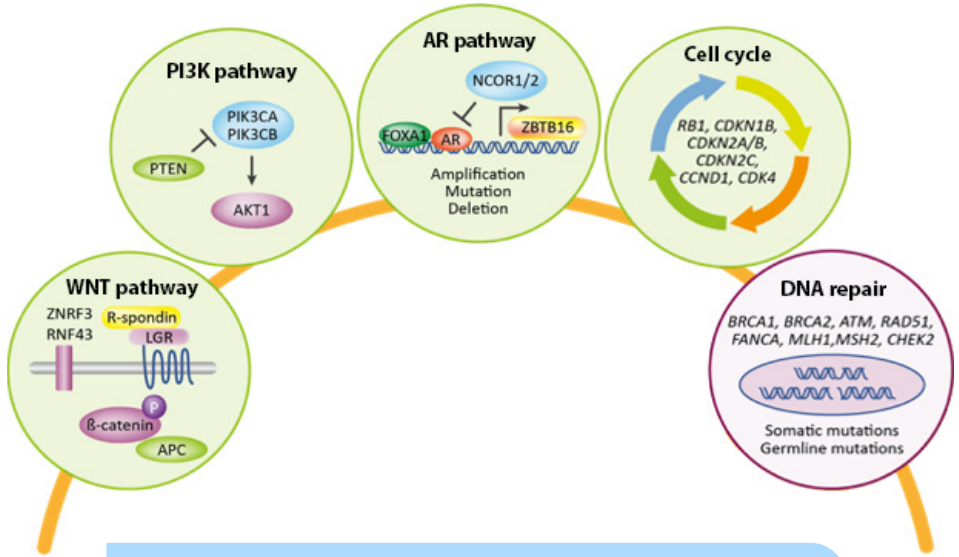
Current and Future Integration of PARP Inhibitors in the Management of Prostate Cancer

Fred Saad MD FRCS
Professor and Chairman of Urology
Director of GU Oncology
Raymond Garneau Chair in Prostate Cancer
University of Montreal Hospital Center
Montreal, QC, Canada

CHUM

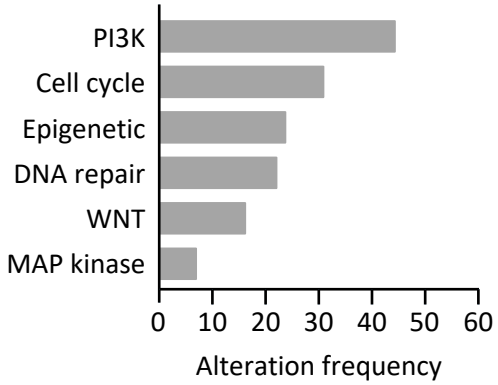
Metastatic prostate cancer is biologically heterogeneous

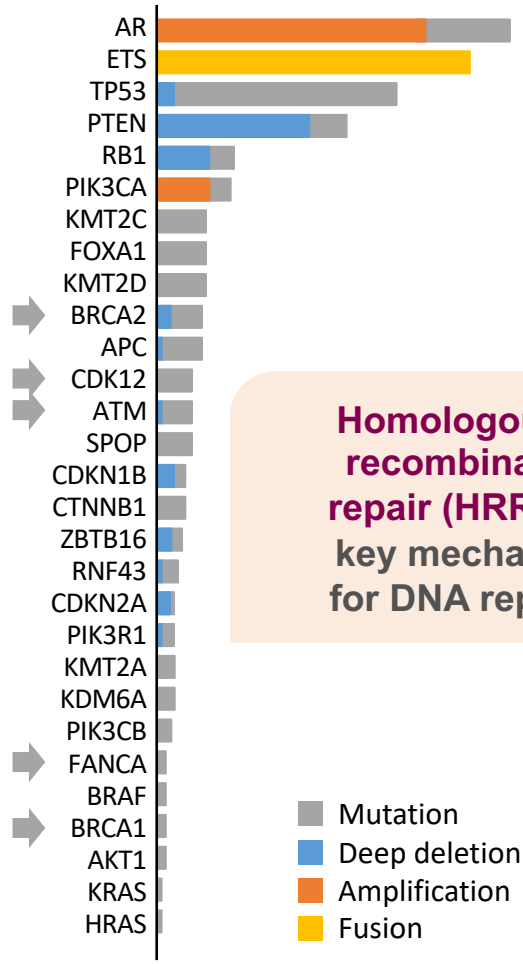
Multiple pathways have been identified with genomic alterations in association with advanced prostate cancer[1]



~23% of mutations were identified in DNA repair pathways[1]

Approximately 25% of patients with mCRPC have alterations associated with DNA repair pathways*[2]





Homologous recombination repair (HRR) is a key mechanism for DNA repair[3,4]

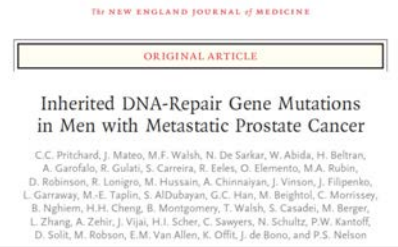
*A multi-institutional study profiling N=444 tumours from 429 mCRPC patients

AR=androgen receptor; DDR=DNA damage repair; mCRPC=metastatic castration-resistant prostate cancer; PI3K=phosphoinositide 3-kinase; WNT=wingless integration

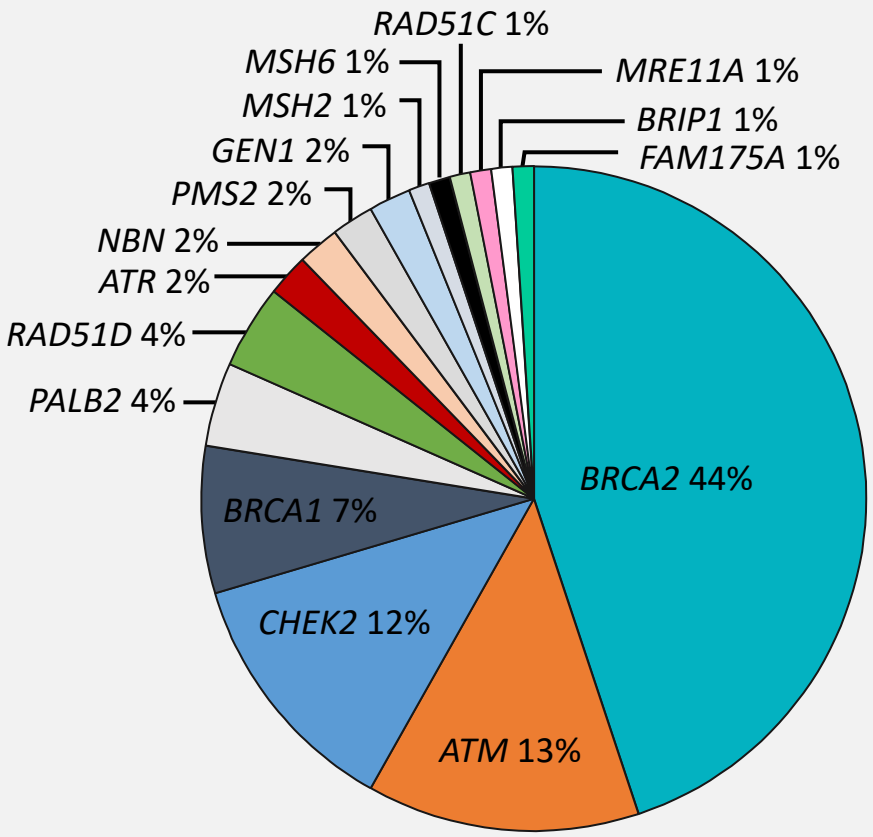
1. Robinson D, et al. *Cell.* 2015;161:1215–1228; 2. Abida W, et al. *PNAS* 2019;116:11428-436 ; 3. Lord CJ and Ashworth A. *Nature*. 2012;481:287–293; 4. O'Connor MJ. *Mol Cell*. 2015;60:547–560.

CHUM

> 1 in 10 Men with mCRPC have Germline Mutations



Distribution of presumed pathogenic germline mutations



- Inherited germline DDR mutations
  - mCRPC: 11.8% (82/692)
  - Localized disease: 4.6% (23/499)

Presumed pathogenic germline mutations in metastatic cases (N = 692)

Gene	No. of Mutations	% of Men
BRCA2	37	5.35
ATM	11	1.59
*CHEK2**	10	1.87
BRCA1	6	0.87

*n = 534; data censored for metastatic cases with inadequate sequencing

Using germline testing alone
~50% of patients with a BRCA1/2, or ATM mutation will be missed

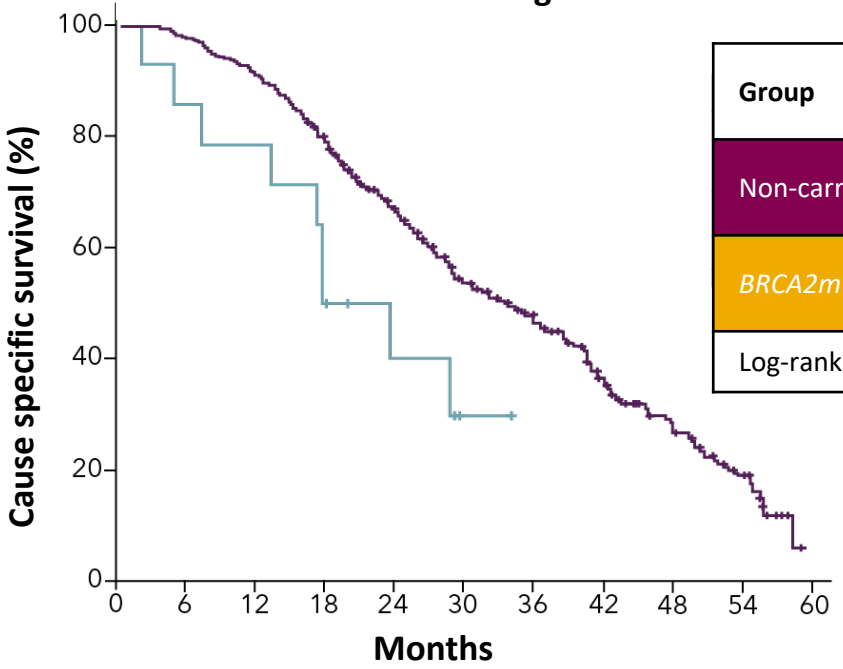
CHUM

Patients with HRRm including *BRCA2*m are more likely to have poor outcomes on standard of care therapies[1-3]

Patients with **germline HRRm** including *BRCA2*m are more likely to have **poor outcomes** on standard of care therapies[1,2]

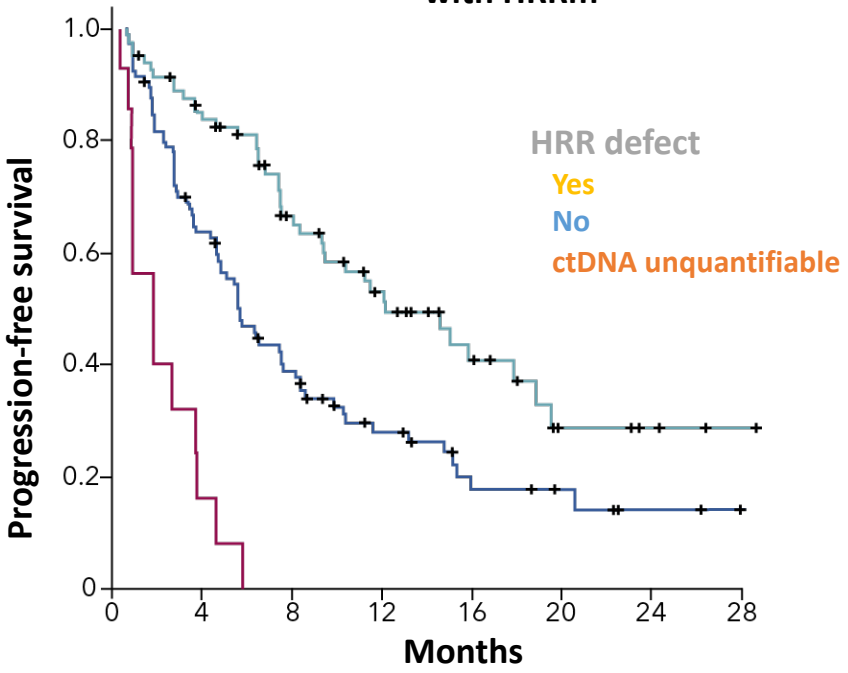
Poor responses to standard therapy also seen for **tumour HRRm**[3]

Cancer specific survival in mCRPC patients with g*BRCA2*m[1]



Group	Median CSS (95% CI)
Non-carriers	33.2 months (29.0–37.4)
BRCA2m	17.4 months (10.7–24.2)
Log-rank test p=0.0266	

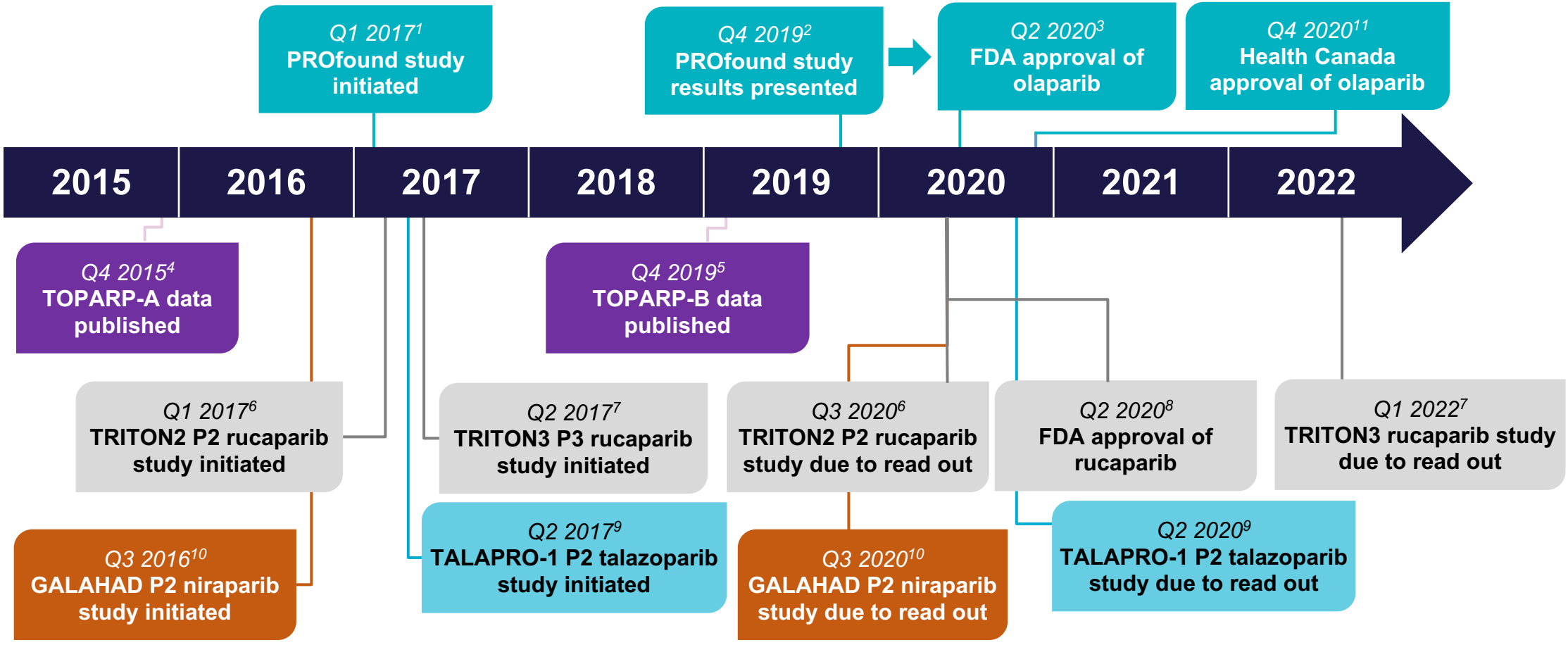
Time to progression in mCRPC patients with HRRm[3]



1. Castro E, et al. *J Clin Oncol.* 2019;6:490–503; 2. Annala M, et al. *Eur Urol.* 2017;72:34–42; 3. Annala M, et al. *Cancer Discovery.* 2018;doi:10.1158/2159-8290.CD-17-0937

CHUM

PARP Inhibitor Trials and approvals in mCRPC

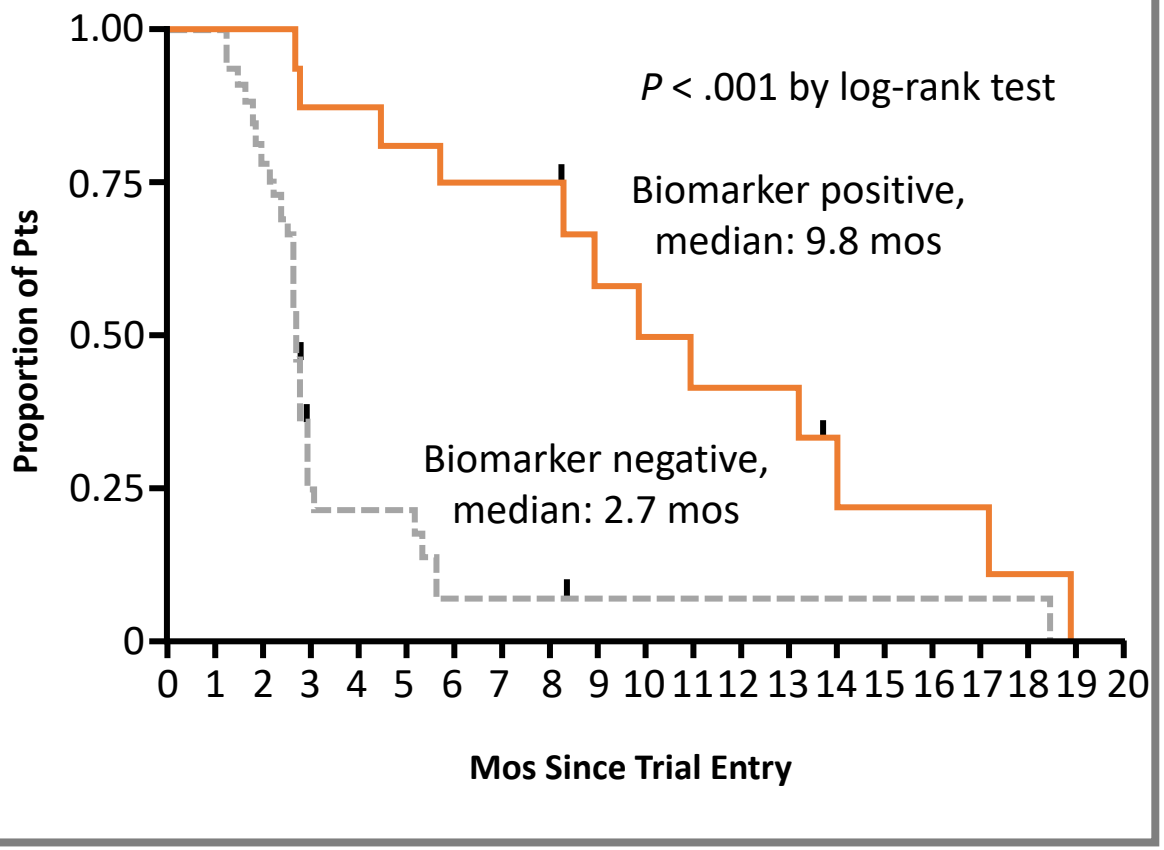


HLR, high level results; HRRm, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; PARP, poly(ADP-ribose) polymerase; P, phase

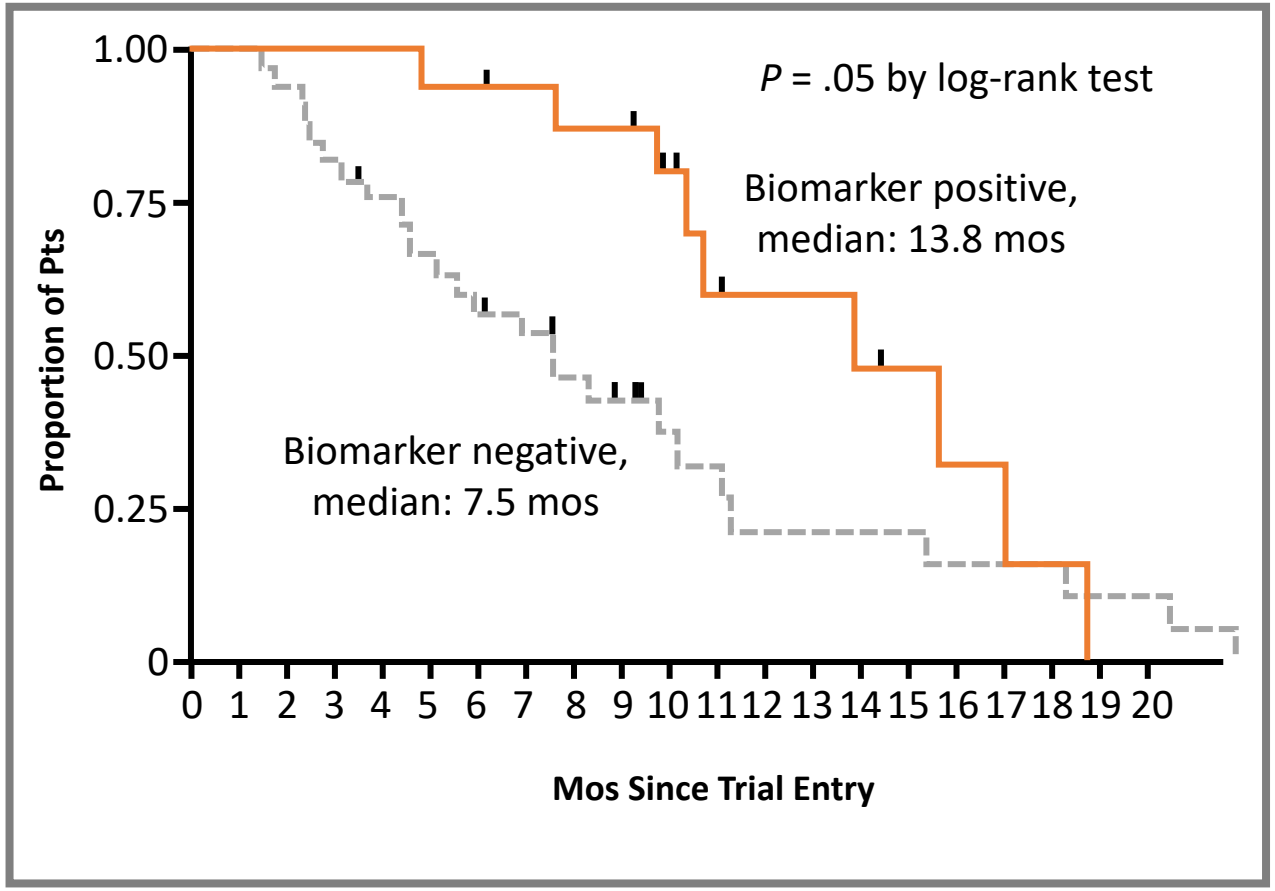
1. de Bono J et al. *NEJM* 2020;382:2091-102; 2. AstraZeneca press release, 7 August 2019; 3. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-olaparib-hrr-gene-mutated-metastatic-castration-resistant-prostate-cancer; 4. Mateo J et al. *NEJM* 2015; 373:1697-708; 5. Mateo J et al. *J Clin Oncol* 2019;37:Abstr 5005; 6. https://clinicaltrials.gov/ct2/show/NCT02952534;
7. https://clinicaltrials.gov/ct2/show/NCT02975934; 8. https://www.fda.gov/drugs/fda-grants-accelerated-approval-rucaparib-brca-mutated-metastatic-castration-resistant-prostate;
9. https://clinicaltrials.gov/ct2/show/NCT03148795; 10. https://clinicaltrials.gov/ct2/show/NCT02854436; 11. Lynparza (olaparib) Canadian Product Monograph.

TOPARP-A: PFS and OS by Presence of DDR Defects

Radiographic PFS



OS



DDR, DNA damage response; OS, overall survival; PFS, progression-free survival

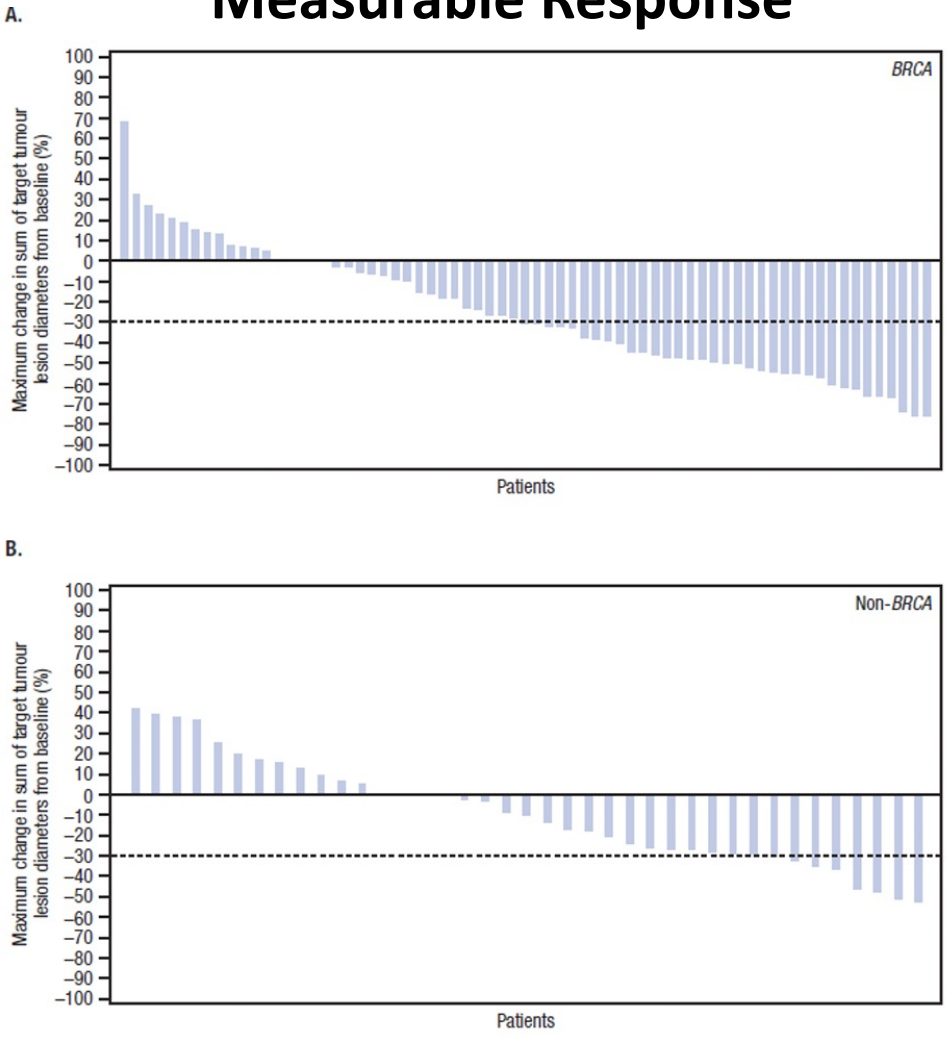
Mateo J et al. *NEJM* 2015;373:1697-708.

CHUM

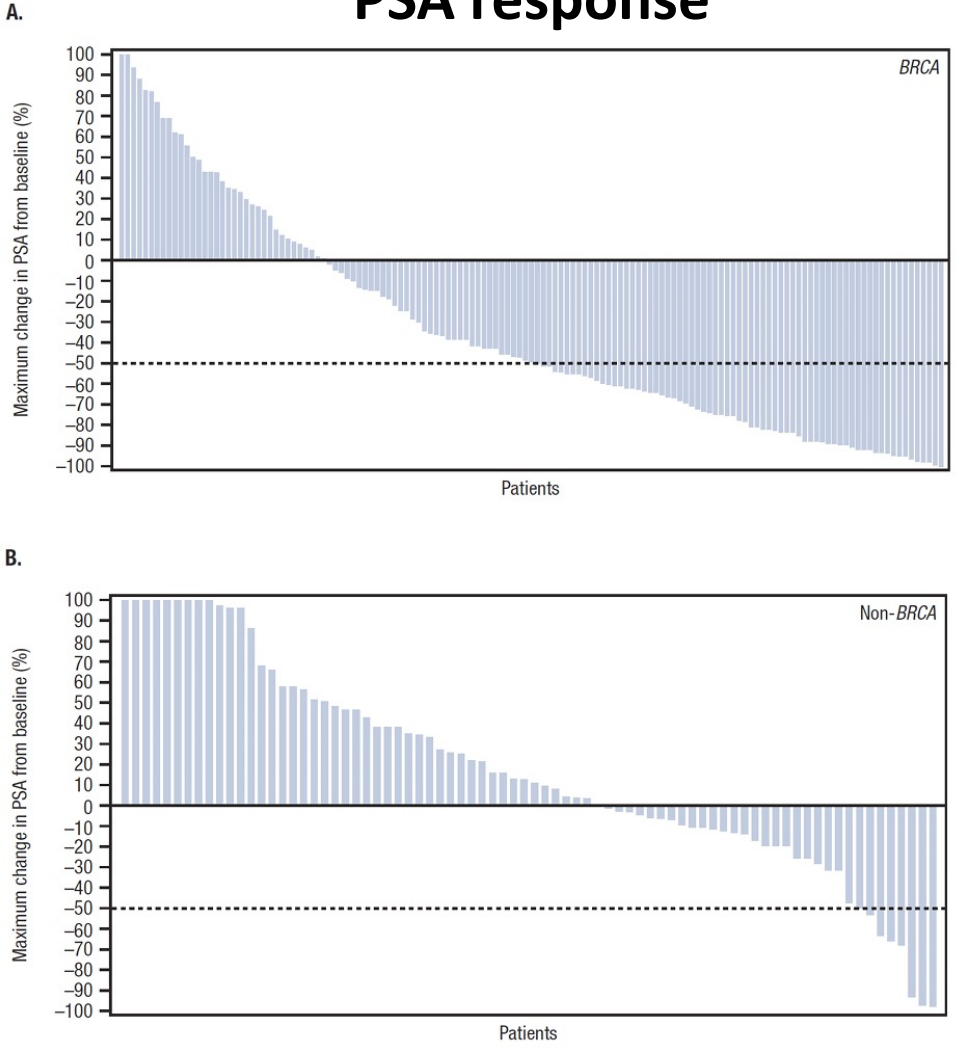
GALAHAD: Niraparib Monotherapy

Results for BRCA vs Non-BRCA

Measurable Response

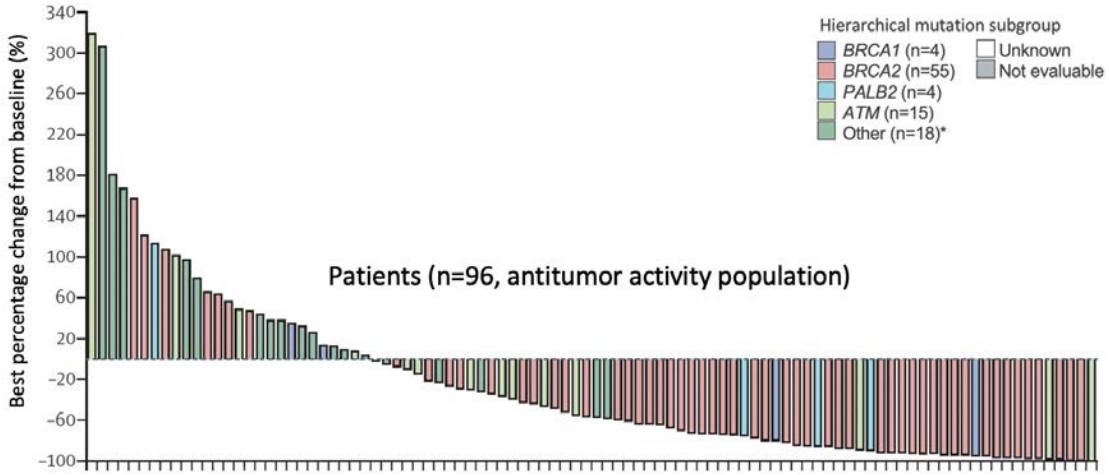


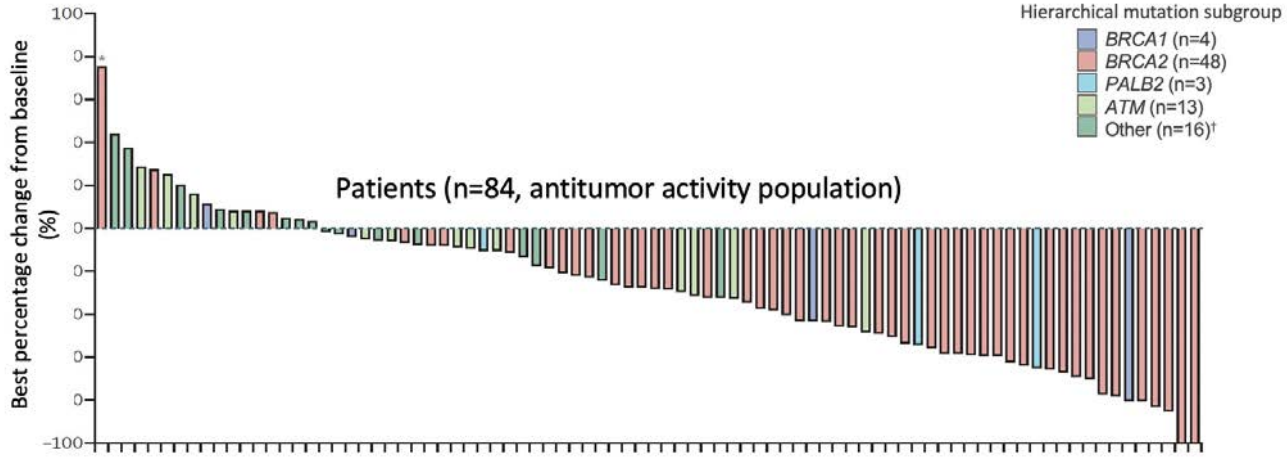
PSA response

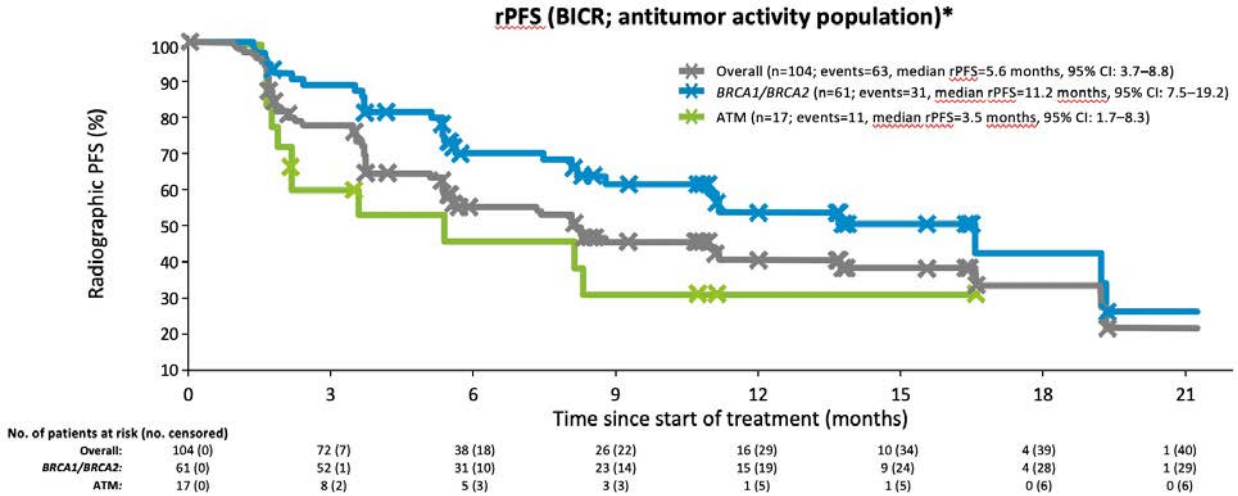


CHUM

TALAPRO-1: Efficacy of Talazoparib Monotherapy

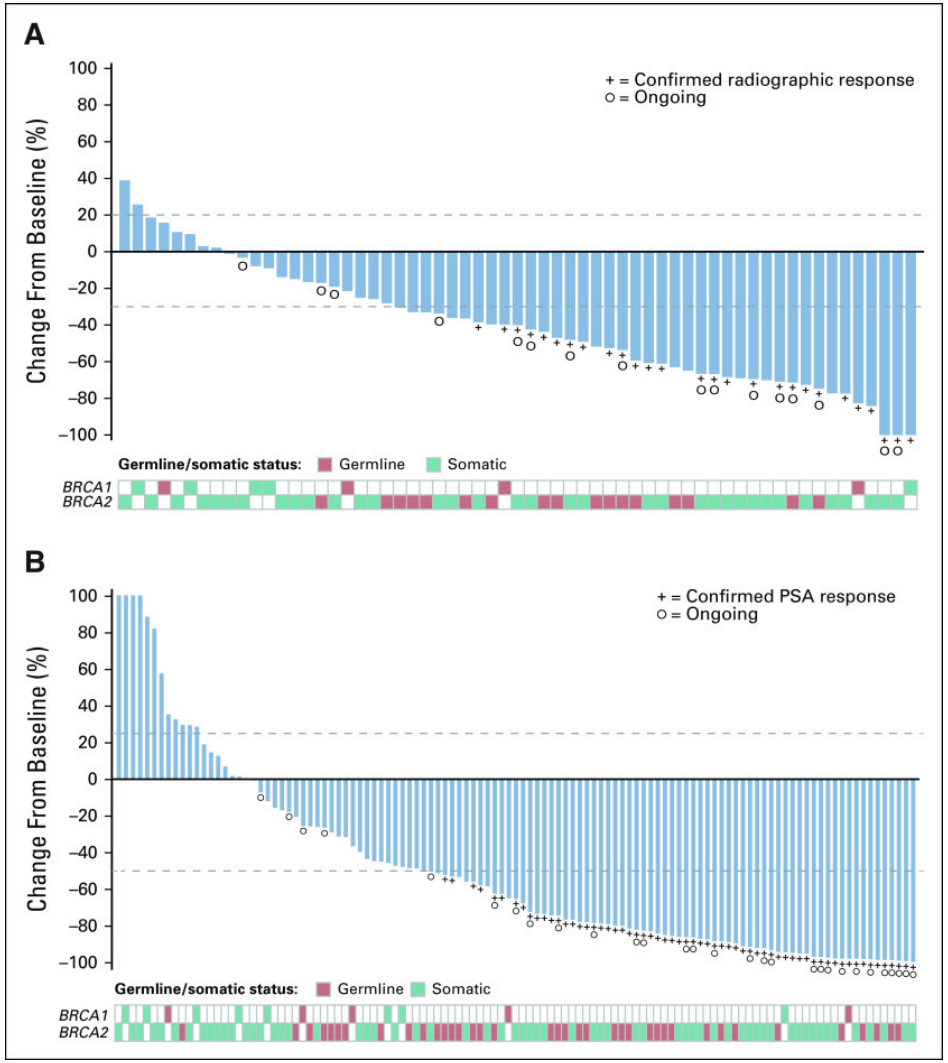


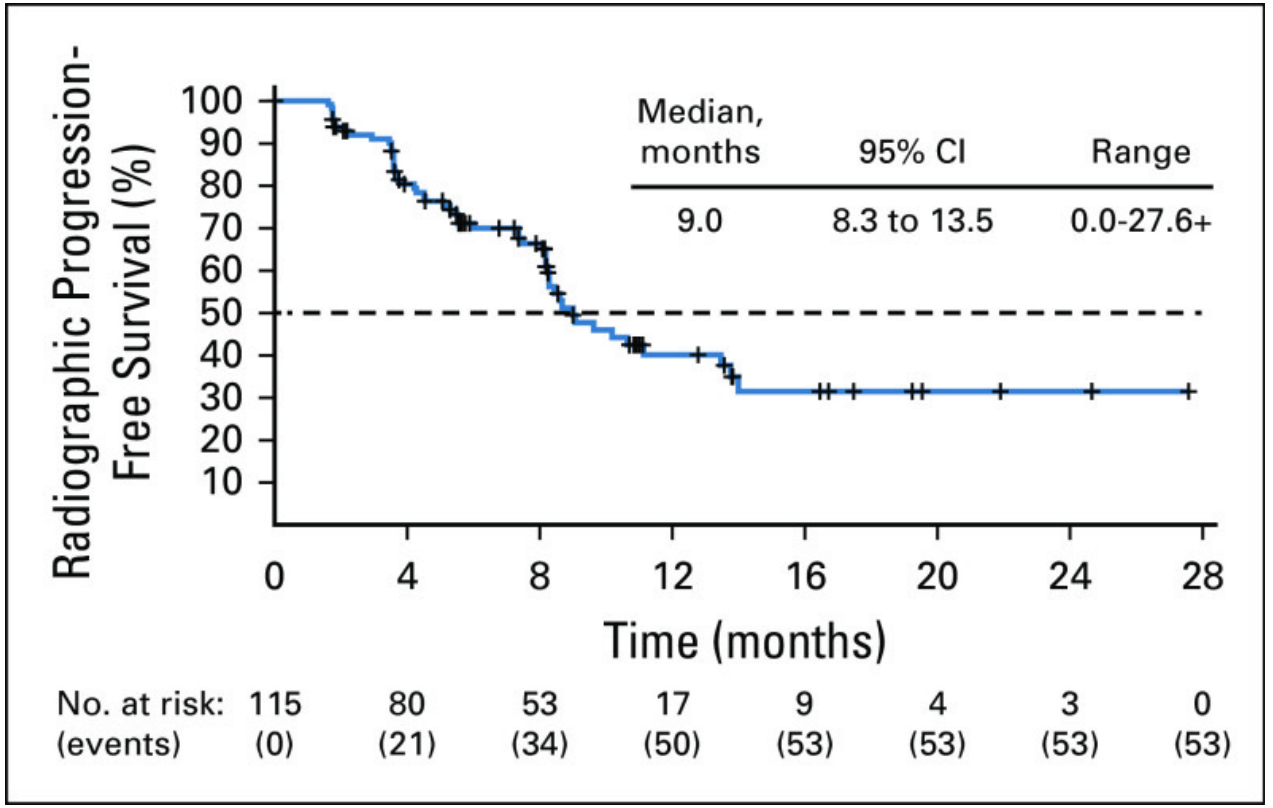




CHUM

TRITON 2: Efficacy of Rucaparib Monotherapy in mCRPC with *BRCA1* or *BRCA2*





Abida W. et al. J Clin Oncol . 2020 Nov 10;38(32):3763-3772

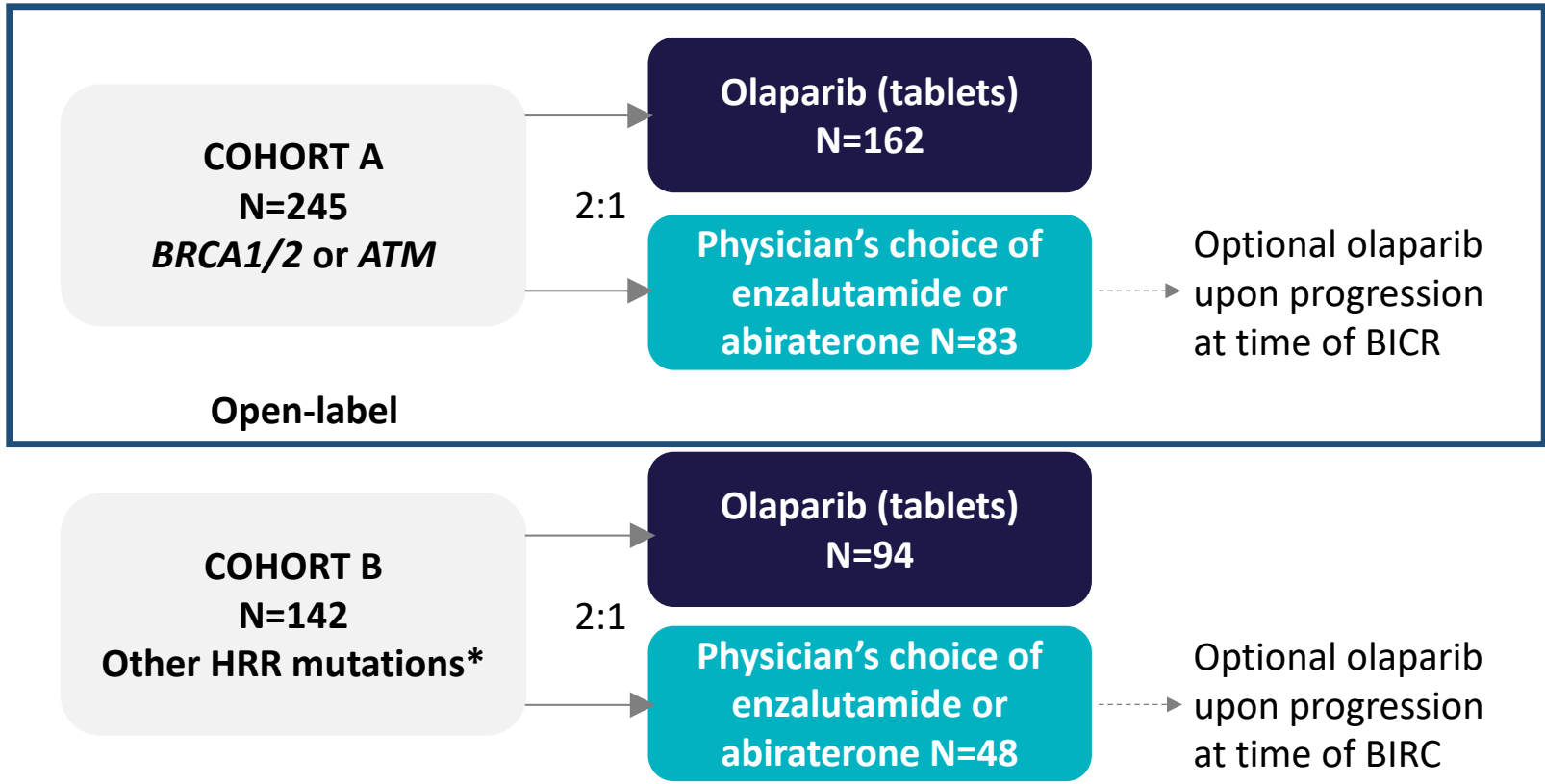
CHUM

PROfound: First Phase 3 RCT of a PARP Inhibitor in mCRPC (Olaparib vs Enzalutamide or Abiraterone)

Randomised, open-label phase 3 study

Key eligibility criteria

- mCRPC with disease progression on prior NHA eg abiraterone or enzalutamide
- Alterations in ≥1 of any qualifying gene with a direct or indirect role in HRR



Primary endpoint: Radiographic PFS by BICR using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria (cohort A)

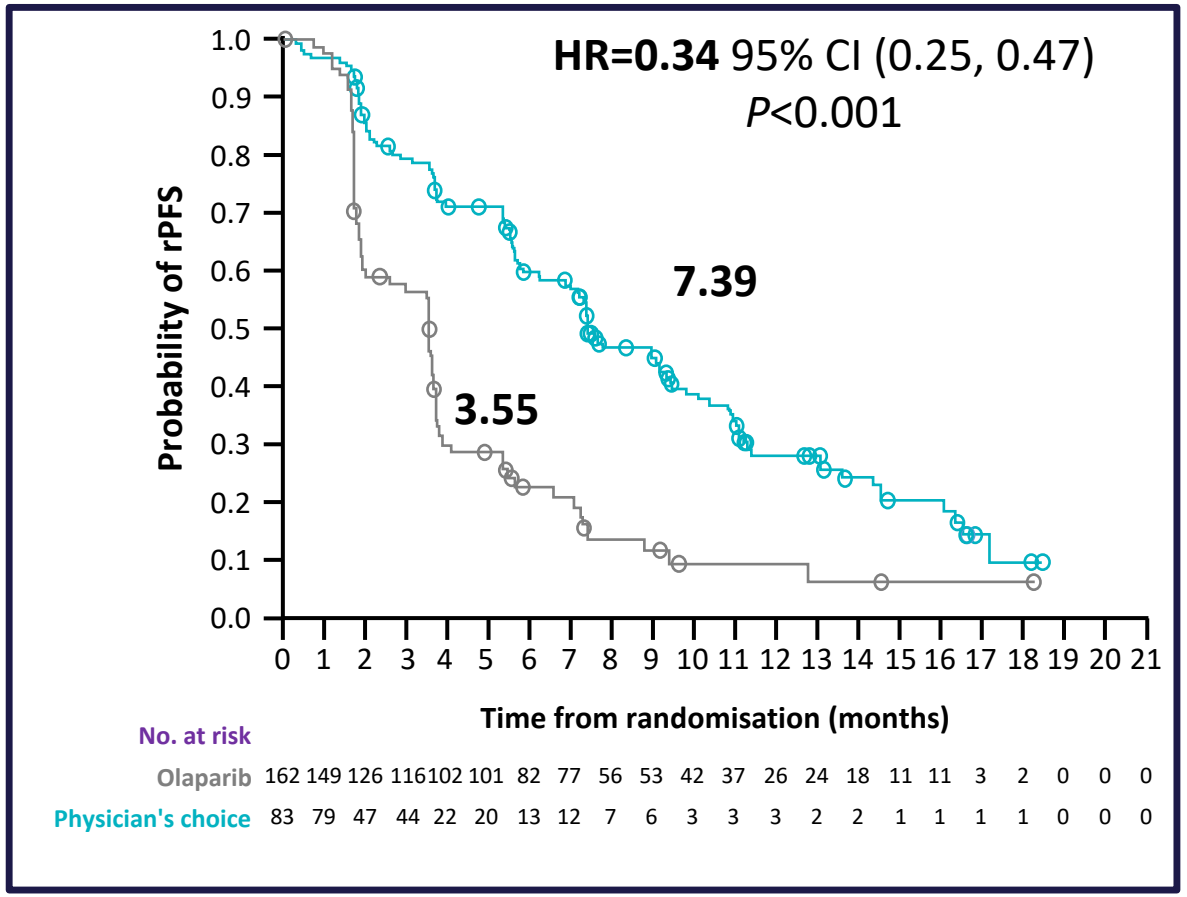
Key secondary endpoints:
- Cohort A: Confirmed ORR, time to pain progression, overall survival
- Cohort A + B: radiographic PFS

*Cohort B included patients with *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L* mutations. ARAT, ARAT, androgen receptor-axis-targeted therapies; BICR, blinded independent central review; EGOC, Eastern Cooperative Oncology Group; HRR, homologous recombination repair; mCRPC, metastatic castrate resistant prostate cancer; mPC, metastatic prostate cancer; ORR, objective response rate; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival. de Bono JS et al. *NEJM* 2020;382:2091-102.

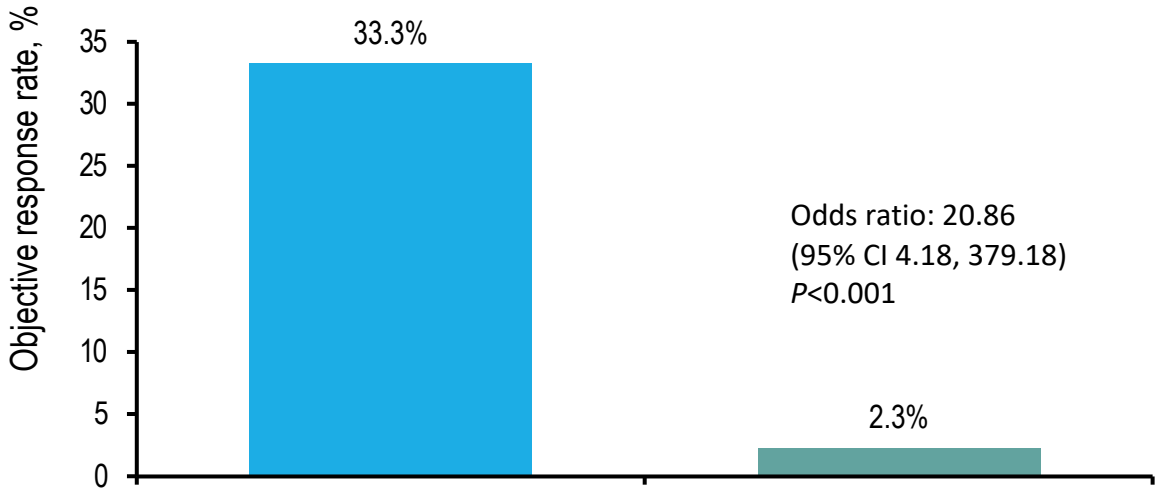
CHUM

PROfound Primary Endpoint: Significant Improvement in rPFS in mCRPC with *BRCA1/2* or *ATM* Mutations (Cohort A)

66% reduction in risk of progression or death with olaparib vs. physician's choice



Confirmed ORR in Cohort A



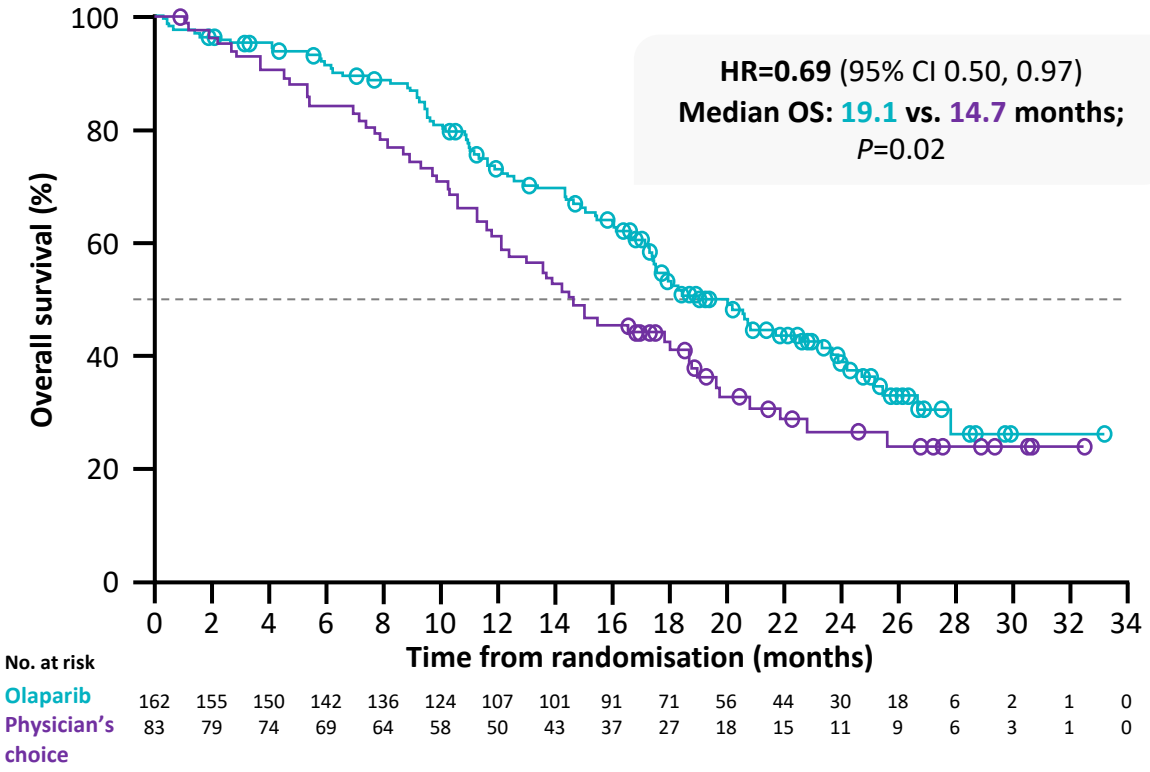
de Bono JS et al. *NEJM* 2020;382:2091-102.

CHUM

PROfound Secondary Endpoint: Significant Improvement in OS in mCRPC with BRCA1/2 or ATM Mutations (Cohort A)

31% Reduction in Risk Of Death with Olaparib vs. Physician's Choice

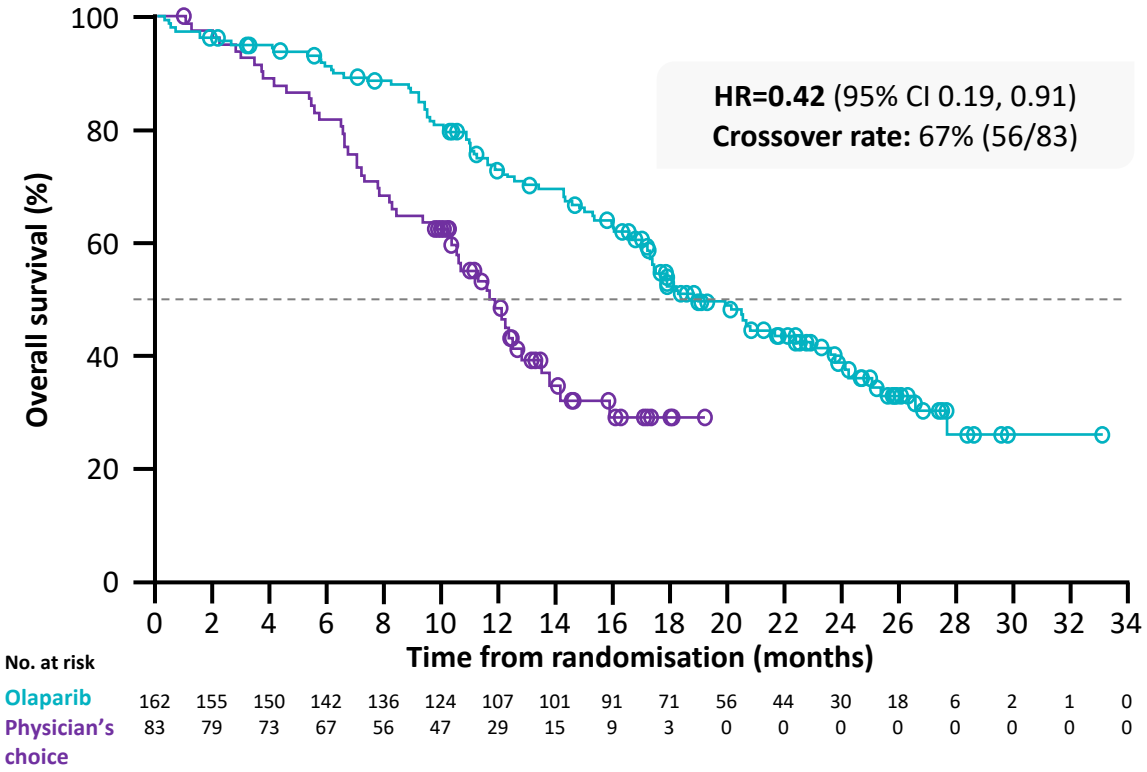
Cohort A



No. at risk

Olaparib	162	155	150	142	136	124	107	101	91	71	56	44	30	18	6	2	1	0
Physician's choice	83	79	74	69	64	58	50	43	37	27	18	15	11	9	6	3	1	0

Cohort A with adjustment for crossover*



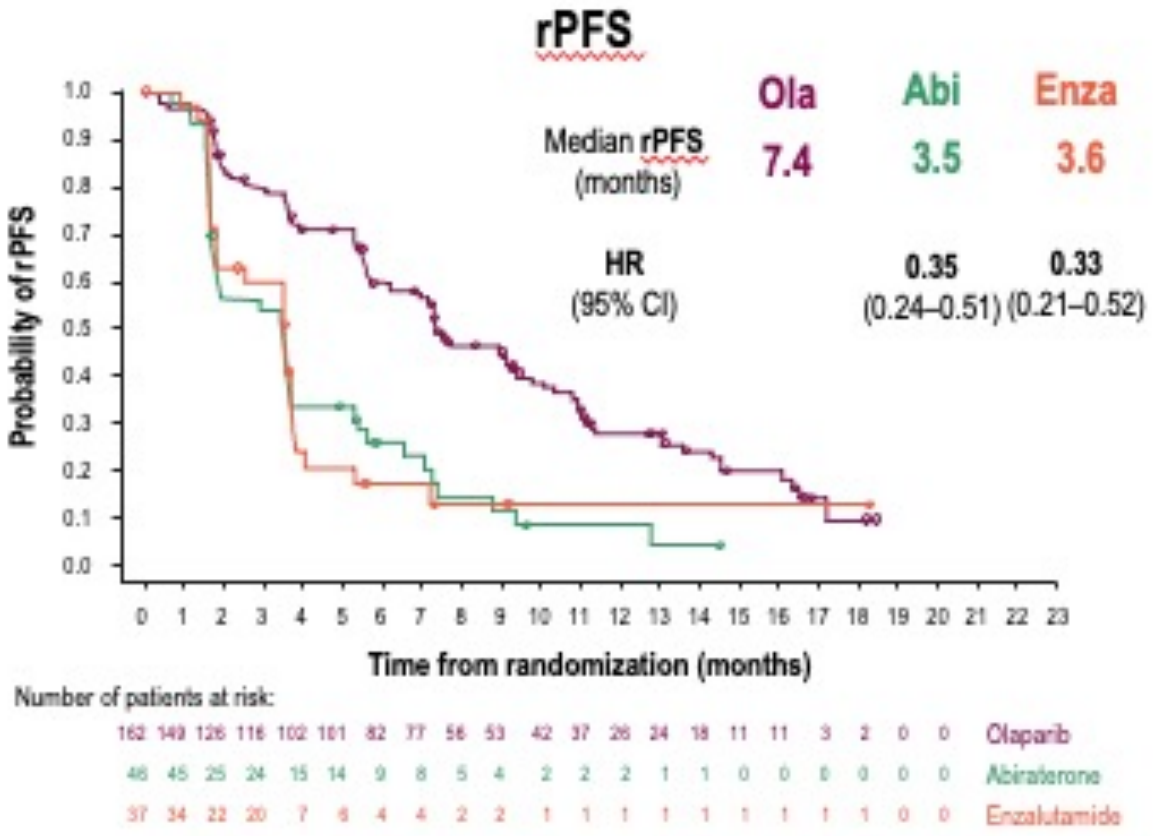
No. at risk

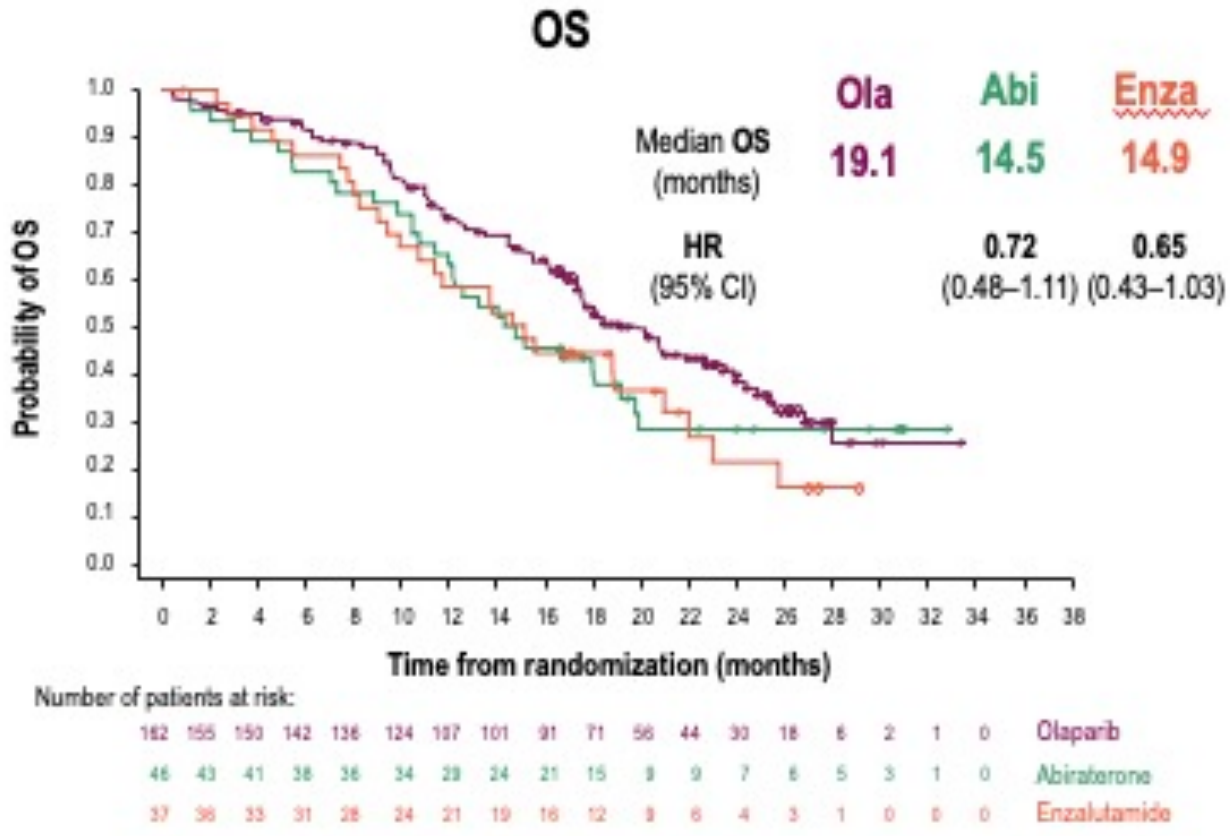
Olaparib	162	155	150	142	136	124	107	101	91	71	56	44	30	18	6	2	1	0
Physician's choice	83	79	73	67	56	47	29	15	9	3	0	0	0	0	0	0	0	0

Median follow-up duration for censored patients : olaparib, 21.9 months; control, 21.0 months. *Re-censored; conducted using rank-preserving structural failure time model (RPSFTM) to demonstrate the impact on OS of crossover of patients from the control arm to receive olaparib as a first subsequent anticancer therapy. CI, confidence interval; HR, hazard ratio; OS, overall survival. 1. Hussain M, et al. *NEJM* 2020;Online: doi10.1056/NEJMoa2022485

CHUM

rPFS and OS benefit for olaparib was shown against both enzalutamide and abiraterone (Cohort A)



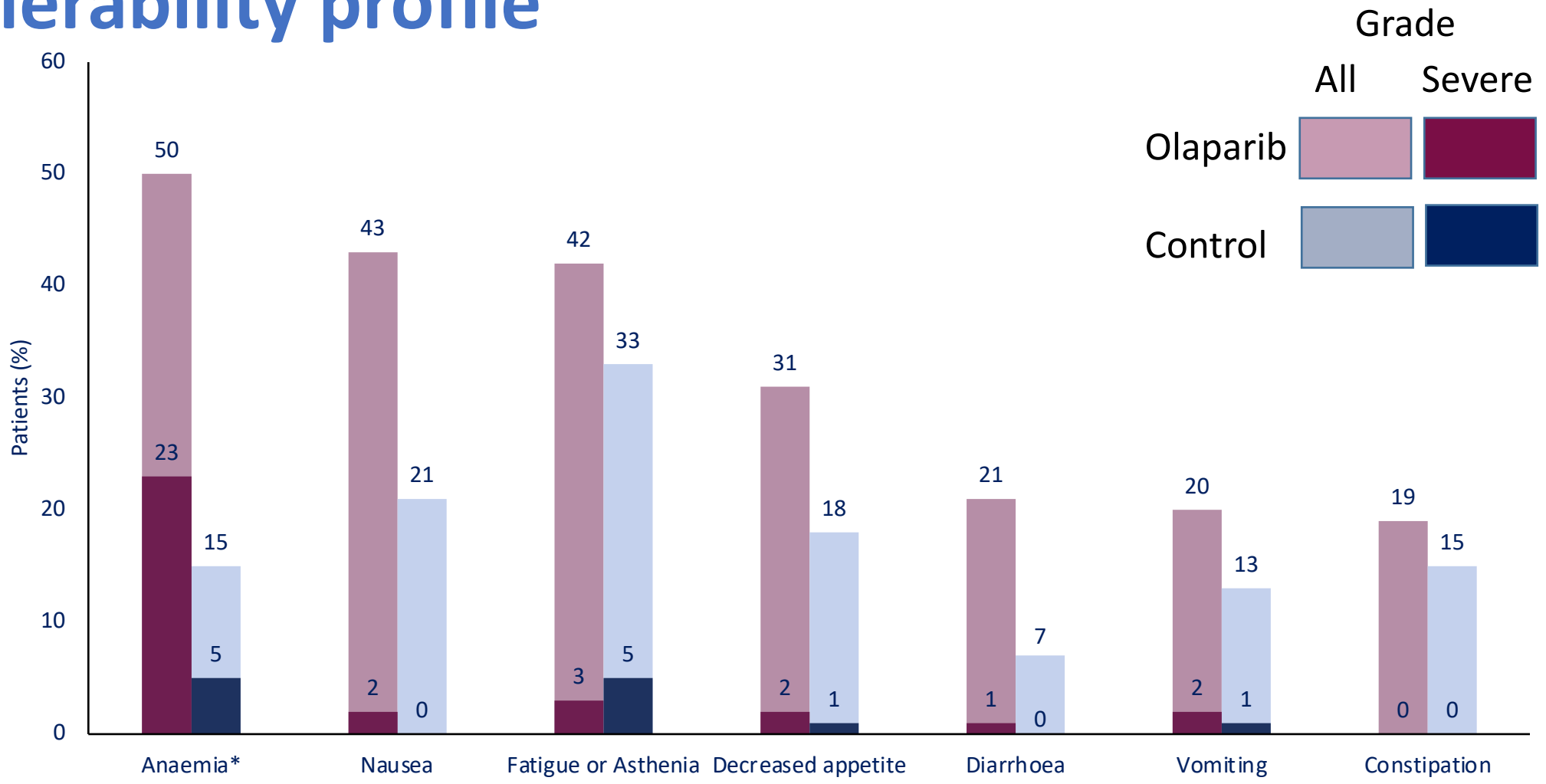


Findings suggest that sequential use of an NHA may be of limited benefit

Saad F., et al. AUA 2021

CHUM

Tolerability profile

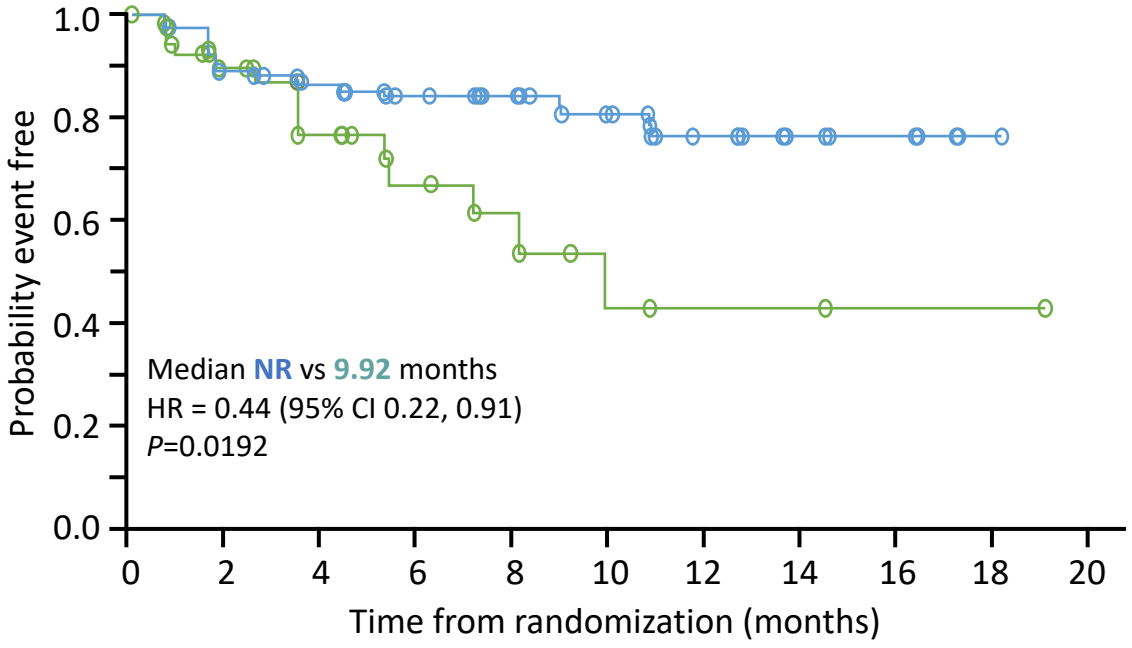


median duration of treatment was
7.6 mo. in the olaparib arm and 3.9 mo. in the control arm

CHUM

PROfound Secondary Endpoints: Improvements in Multiple Clinical and Patient-reported Endpoints in mCRPC With BRCA1/2 or ATM Mutations (Cohort A)

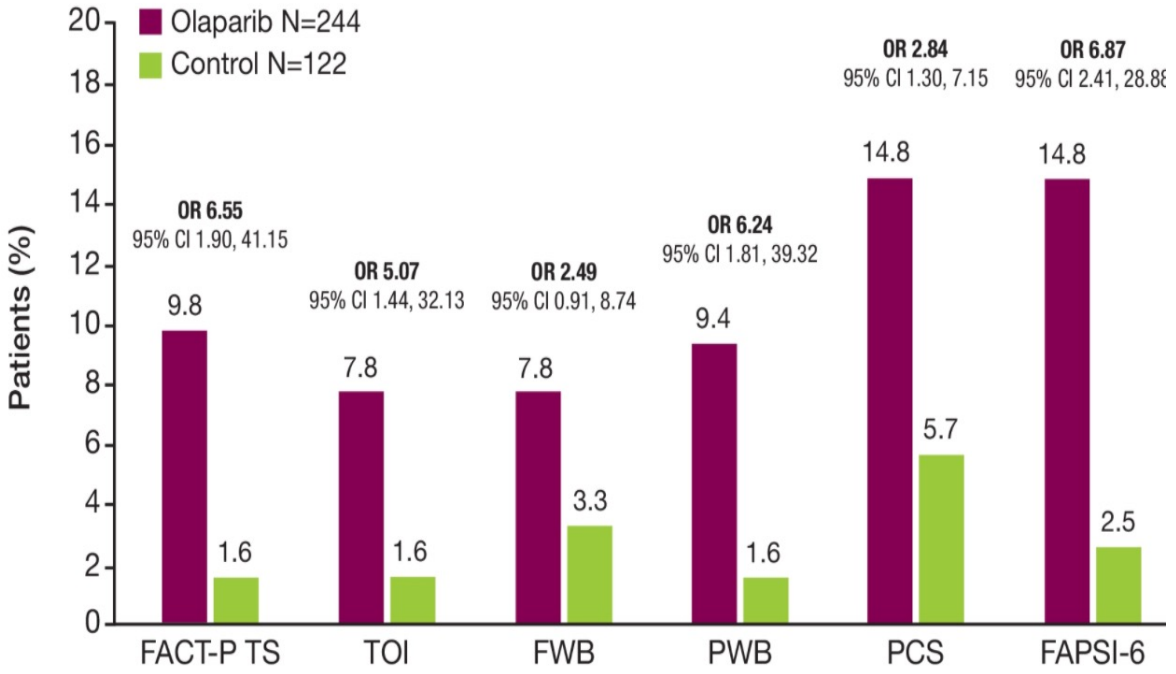
Time to pain progression in Cohort A



Improvement in patient reported HR-QoL

Olaparib

Physician's choice



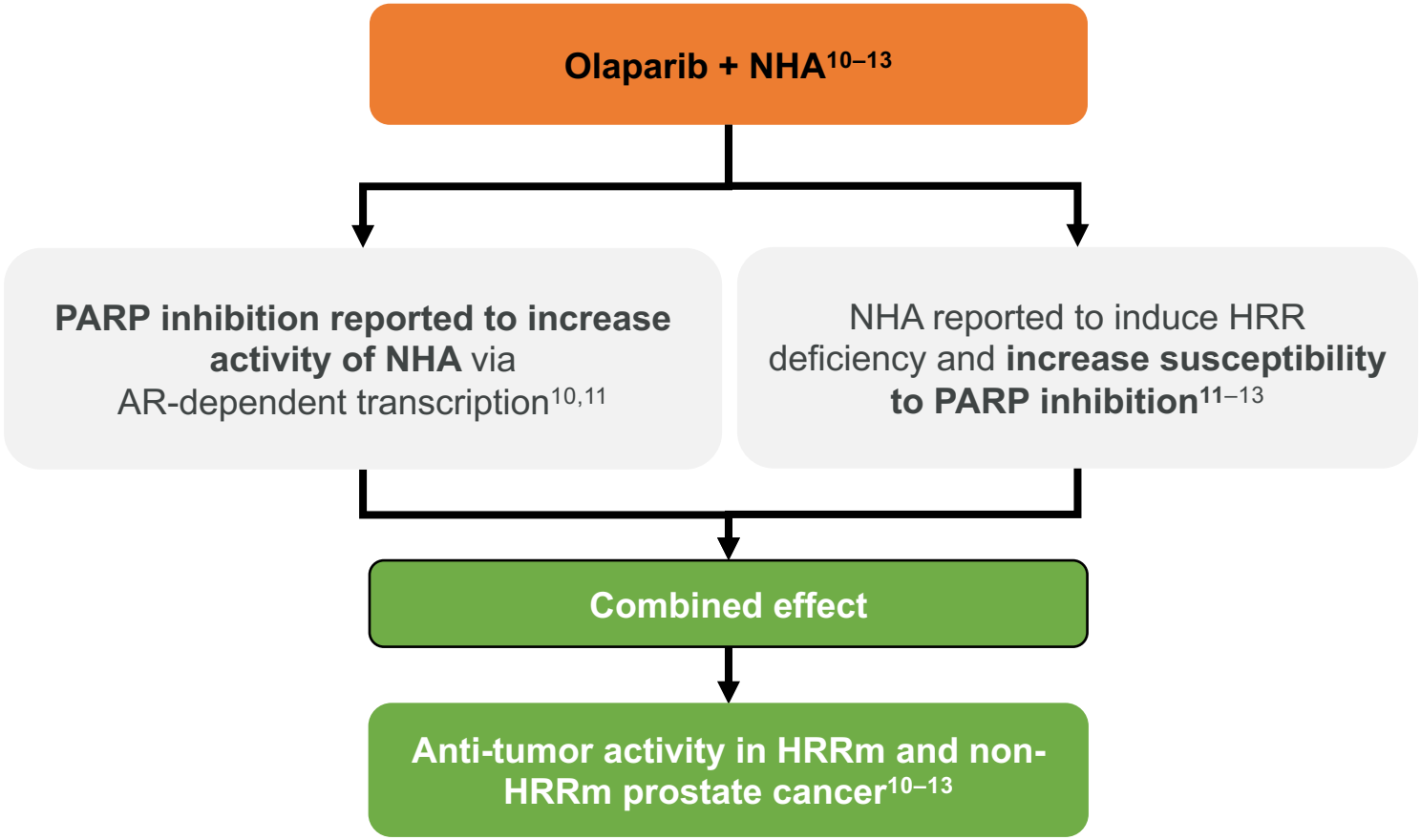
de Bono JS et al. *NEJM* 2020;382:2091-102.

CHUM

The Future

Earlier introduction?
Combination trials?
In all-comers?

Rationale for combining PARP inhibitors and NHAs



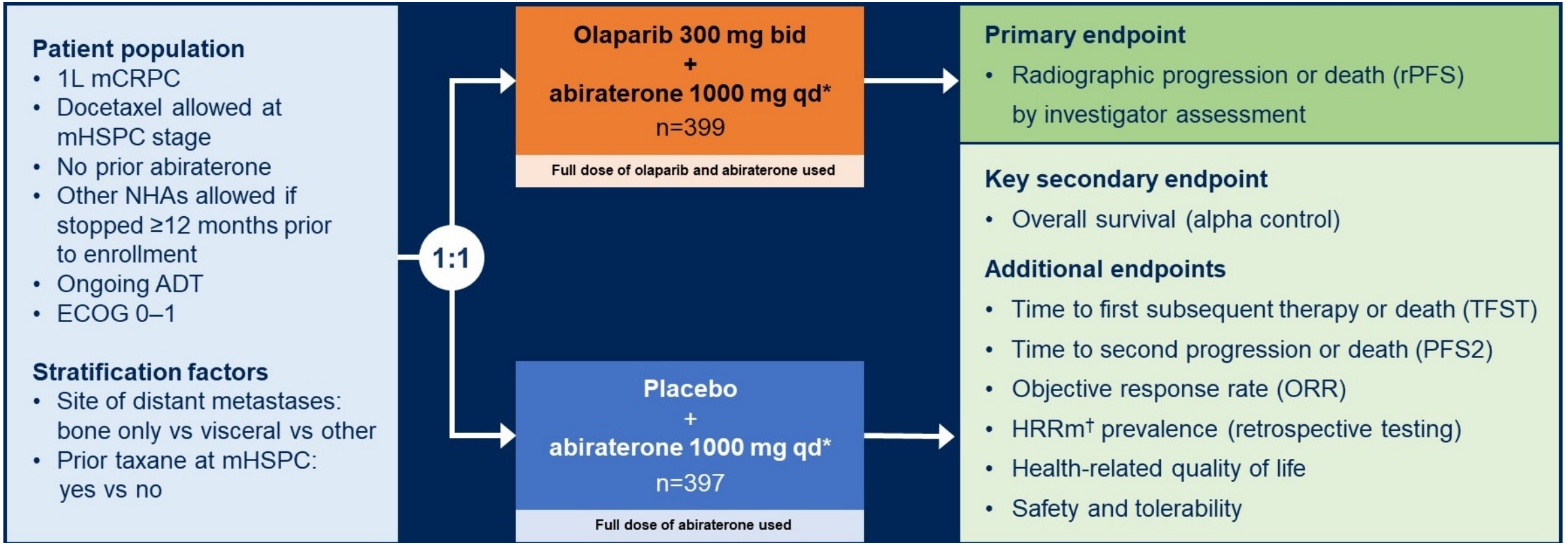
phase 2 olaparib + NHA combination study showed benefit in all patients

1. Mateo J, et al. *N Engl J Med* 2015;373:1697–1708; 2. Schiewer MJ, et al *Cancer Discov* 2012;2:1134–1149; 3. Polkinghorn WR, et al. *Cancer Discov* 2013;3:1245–1153; 4. Asim M, et al. *Nat Commun* 2017;8:374

CHUM

PROpel

Randomized, double-blind, placebo-controlled Phase III trial



Baseline demographics:
HRRm status

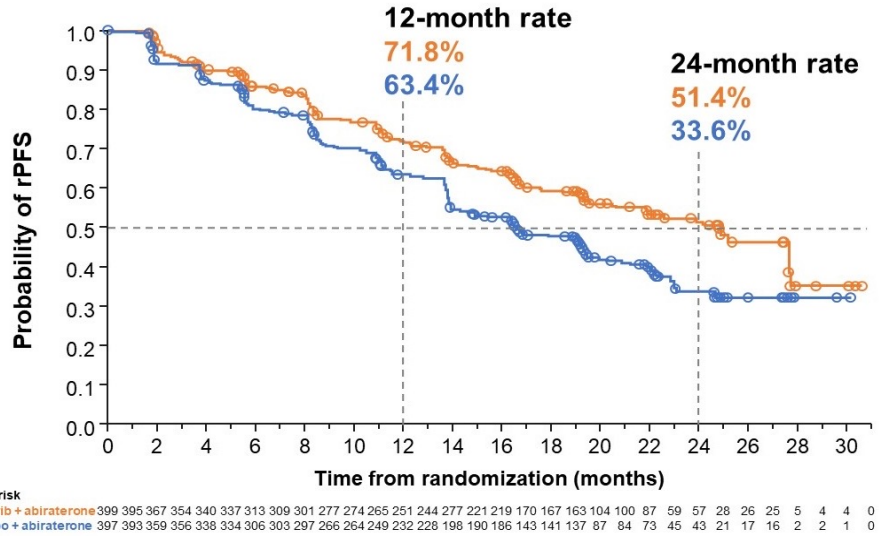
HRRm status†		
HRRm	111 (27.8)	115 (29.0)
Non-HRRm	279 (69.9)	273 (68.8)
HRRm unknown	9 (2.3)	9 (2.3)

CHUM

PROpel

Primary endpoint

rPFS by investigator assessment

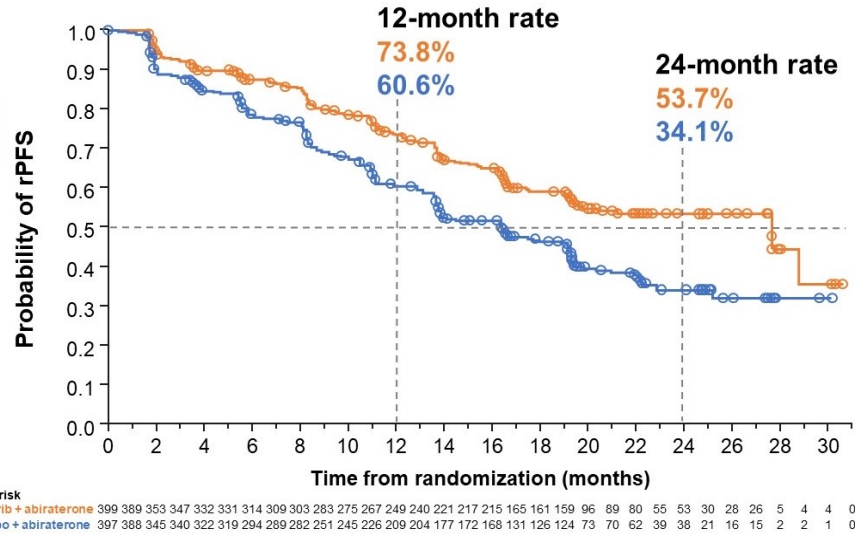


	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Events, n (%)	168 (42.1)	226 (56.9)
Median rPFS (months)	24.8	16.6
HR (95% CI)	0.66 (0.54–0.81); *P*<0.0001	

Pre-specified 2-sided alpha: 0.0324

Median rPFS improvement of 8.2 months favors olaparib + abiraterone*

rPFS by blinded independent central review



	Olaparib + abiraterone (n=399)	Placebo + abiraterone (n=397)
Events, n (%)	157 (39.3)	218 (54.9)
Median rPFS (months)	27.6	16.4
HR (95% CI)	0.61 (0.49–0.74) *P*<0.0001†	

Median rPFS improvement of 11.2 months favors olaparib + abiraterone‡

- **34% risk reduction for progression or death with olaparib + abiraterone (HR 0.66; 95% CI 0.54–0.81; *P*<0.0001)**

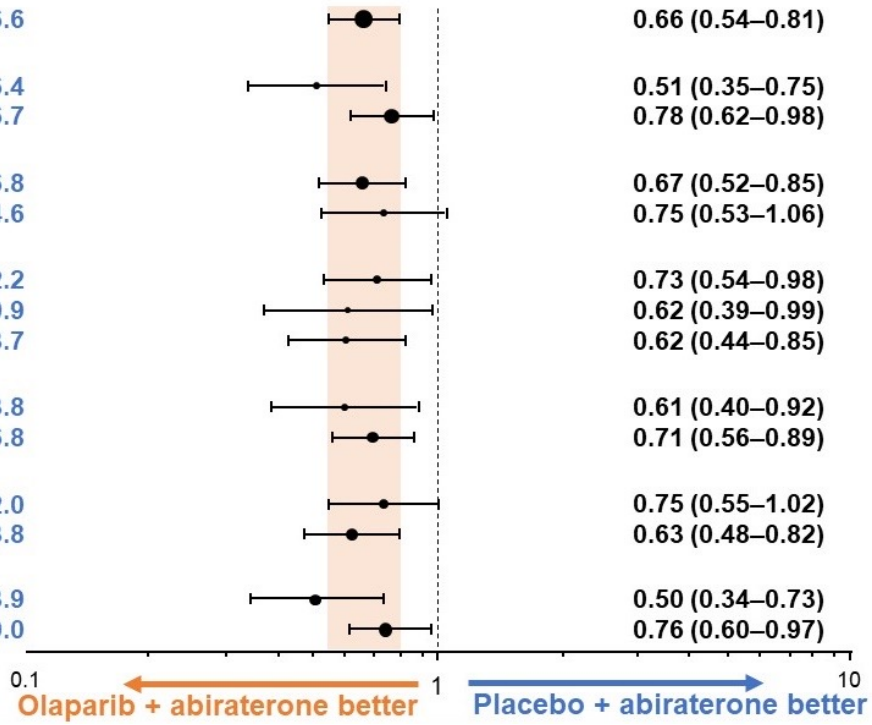
Saad F, et al. Oral presentation at the 2022 ASCO GU Symposium; Feb 17, 2022; Abstract #11

CHUM

PROpel

rPFS subgroup analysis

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



- **rPFS benefit observed across all pre-specified subgroups**

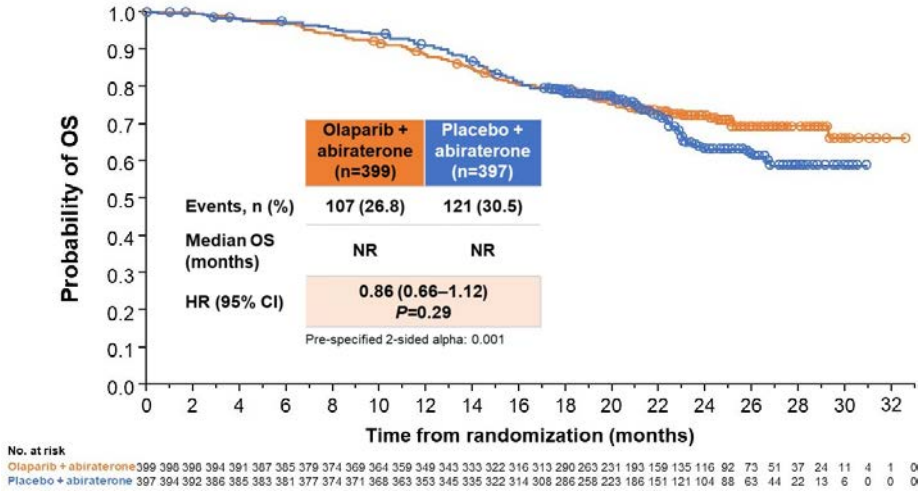
Saad F, et al. Oral presentation at the 2022 ASCO GU Symposium; Feb 17, 2022; Abstract #11

CHUM

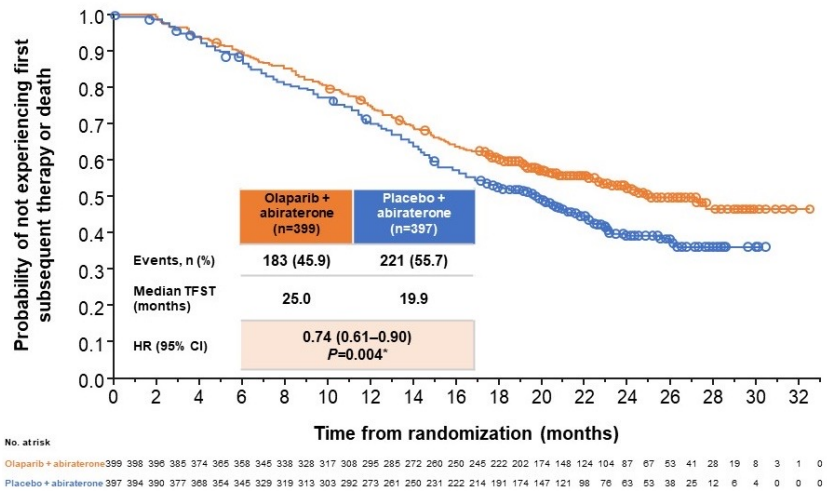
PROpel

Key secondary endpoints

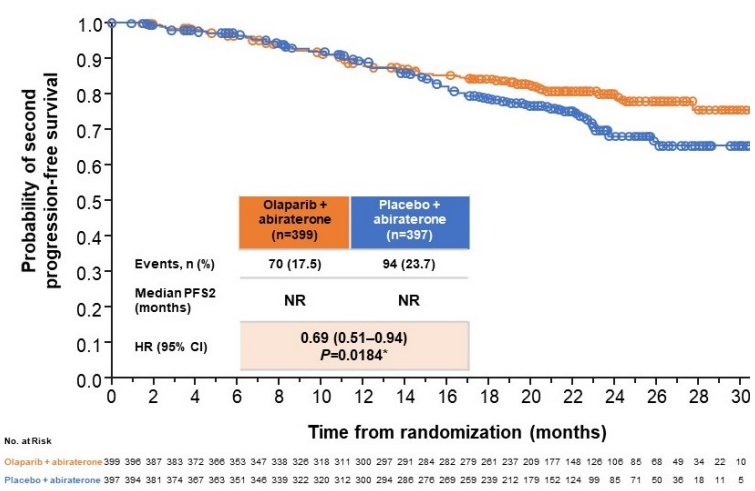
Overall survival



Time to first subsequent therapy or death (TFST)



Time to second progression or death (PFS2)



- OS data immature, but trend towards improved OS with olaparib + abiraterone
- TFST (HR 0.74; 95% CI 0.61–0.90) and PFS2 (HR 0.69; 95% CI 0.51–0.94) supportive of long-term benefits

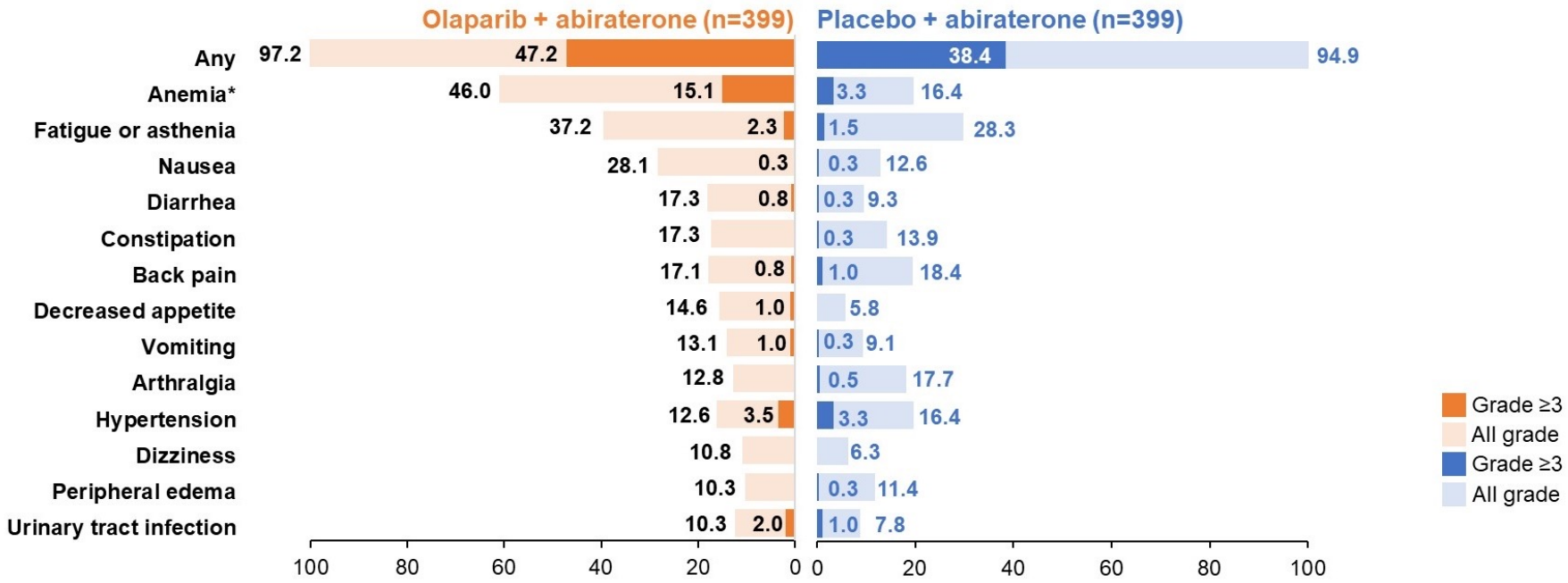
Saad F, et al. Oral presentation at the 2022 ASCO GU Symposium; Feb 17, 2022; Abstract #11

CHUM

PROpel

Safety data

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



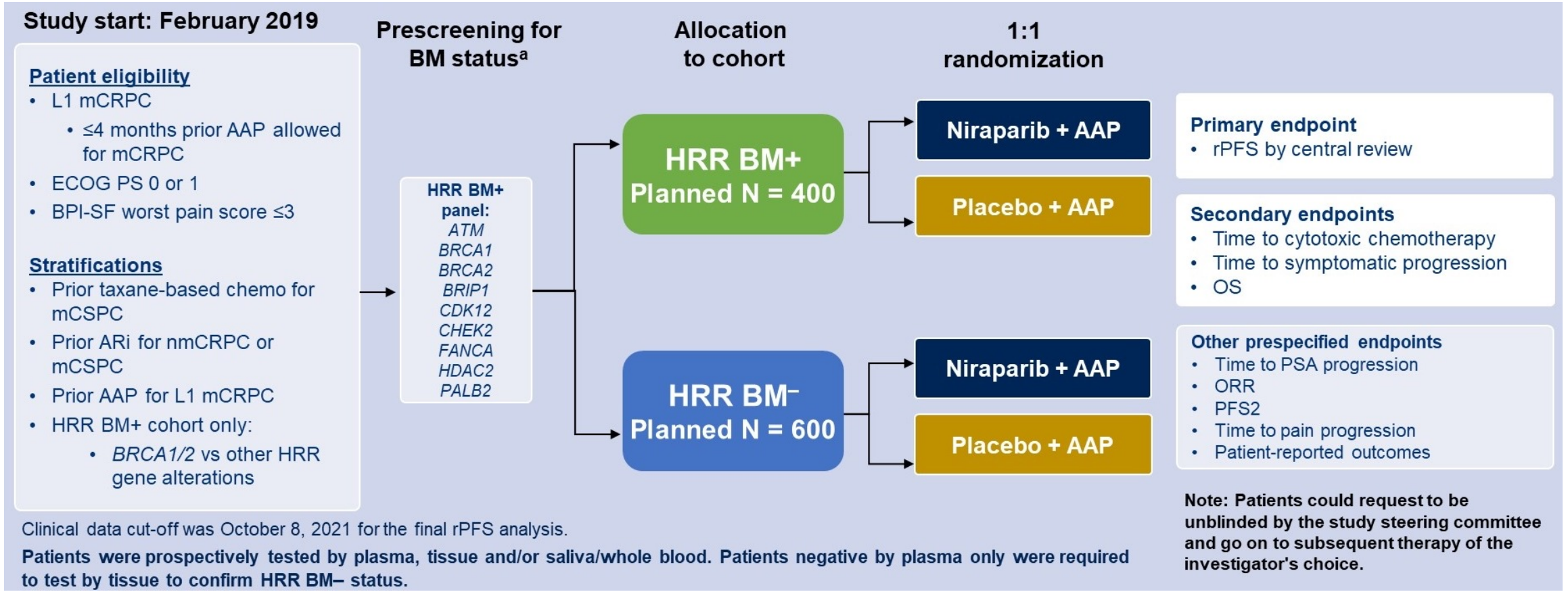
- Safety and tolerability profile consistent with the known safety profiles of individual drugs
- The most common grade ≥3 AE was anemia (15.1% vs 3.3%)

*Anemia category includes anemia, decreased hemoglobin level, decreased red-cell count, decreased hematocrit level, erythropenia, macrocytic anemia, normochromic anemia, normochromic normocytic anemia, and normocytic anemia.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events v4.03.
Saad F, et al. Oral presentation at the 2022 ASCO GU Symposium; Feb 17, 2022; Abstract #11

CHUM

MAGNITUDE

Randomized, double-blind, placebo-controlled Phase III trial



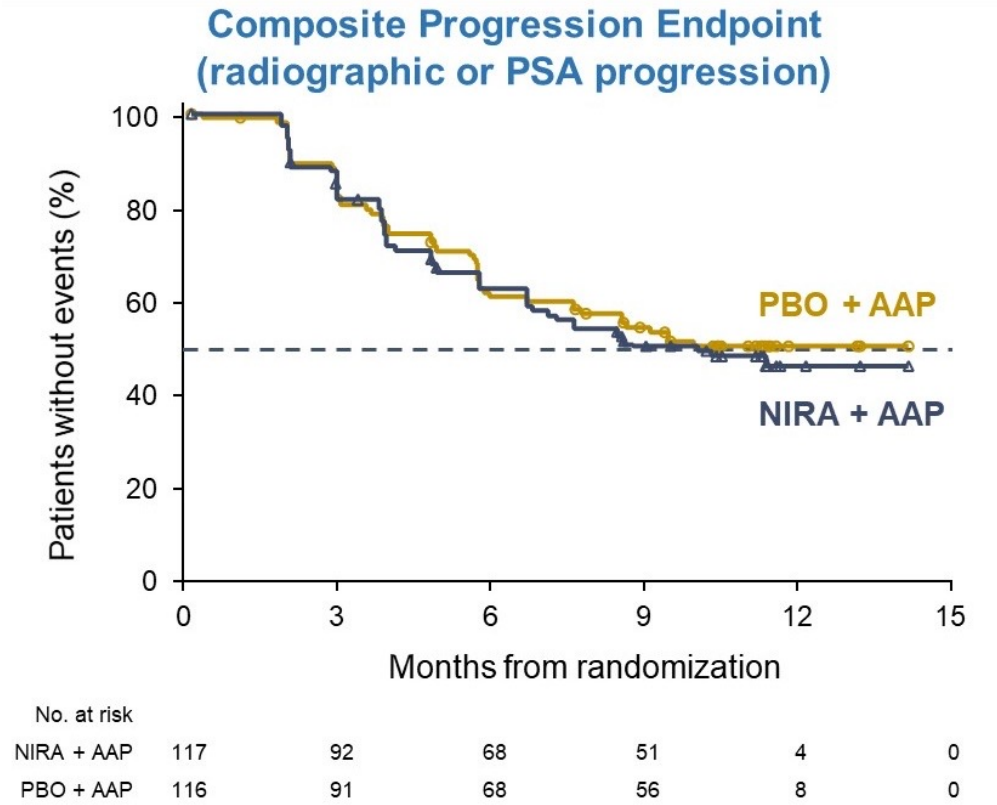
Clinical data cut-off was October 8, 2021 for the final rPFS analysis.

Patients were prospectively tested by plasma, tissue and/or saliva/whole blood. Patients negative by plasma only were required to test by tissue to confirm HRR BM– status.

CHUM

MAGNITUDE

Pre-specified futility analysis: HRR BM–



- Composite endpoint[a] (N = 233)
  HR = 1.09 (95% CI 0.75-1.59)
  [futility was defined as ≥1]
- Additional grade 3/4 toxicity was observed using NIRA + AAP vs PBO + AAP
- With added toxicity and no added efficacy in patients with HRR BM⁻ mCRPC, the IDMC recommend stopping enrollment in this cohort

Breakdown of composite endpoint events
83 PSA events (HR = 1.03, 95% CI 0.67-1.59)
65 rPFS events (HR = 1.03, 95% CI 0.63-1.67)

- **No benefit of adding NIRA to AAP in the pre-specified composite endpoint (HR, 1.09; 95% CI 0.75–1.59)**

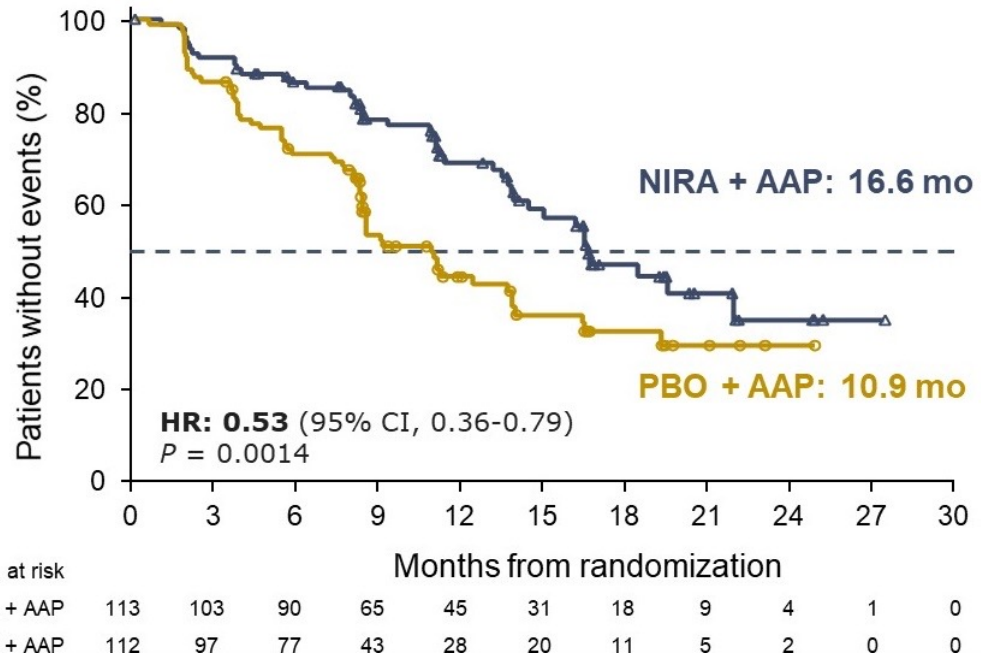
Chi KN, et al. Oral presentation at the 2022 ASCO GU Symposium; Feb 17, 2022; Abstract #12

CHUM

MAGNITUDE

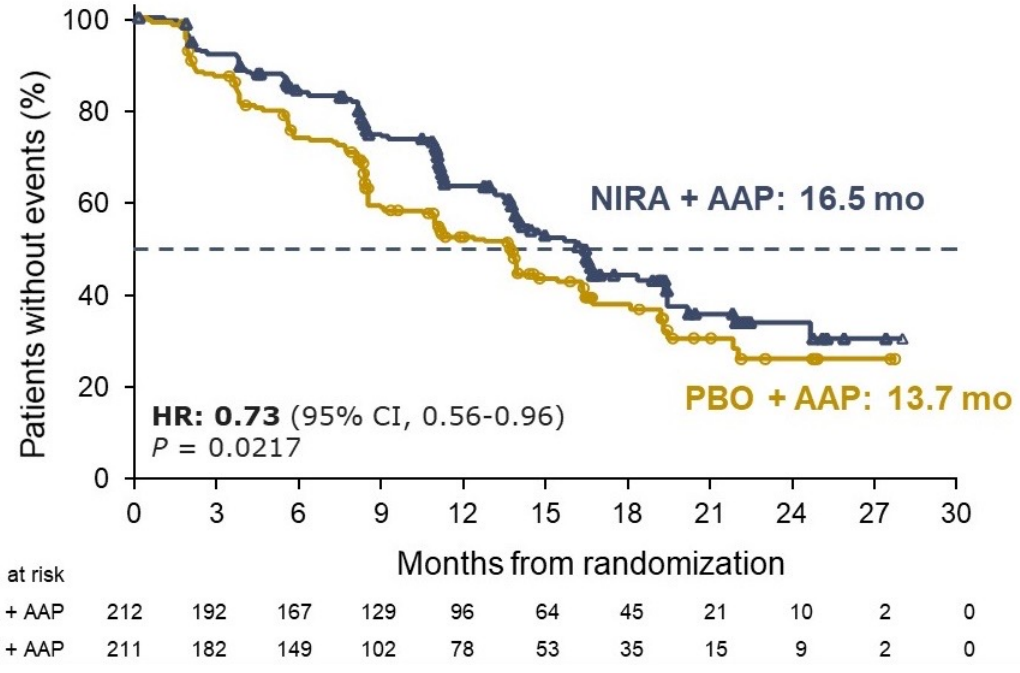
Primary endpoint: rPFS by central review

BRCA1/2-mutated



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

All HRR BM+



No. at risk											
NIRA + AAP	212	192	167	129	96	64	45	21	10	2	0
PBO + AAP	211	182	149	102	78	53	35	15	9	2	0

- 47% improvement in rPFS in patients with *BRCA1/2* alterations (HR 0.53; 95% CI 0.36–0.79; *P*=0.0014)
- 27% improvement in rPFS across all HRR BM+ patients (HR 0.73; 95% CI 0.56–0.96; *P*=0.0217)

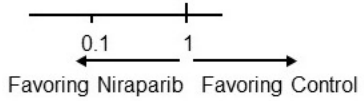
Chi KN, et al. Oral presentation at the 2022 ASCO GU Symposium; Feb 17, 2022; Abstract #12

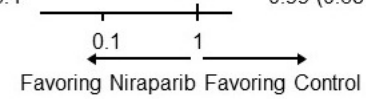
CHUM

MAGNITUDE

rPFS subgroup analysis: All HRR BM+

Variable	Subgroup	Median (months) niraparib	Median (months) control	HR (95% CI)	Events/N niraparib	Events/N control
All HRR+ patients	All	16.5	13.7	0.74 (0.57–0.97)	100/212	117/211
Age group	<65	13.9	13.9	1.01 (0.61–1.66)	32/61	30/62
	≥65-74	19.4	13.6	0.58 (0.38–0.89)	34/88	57/100
	≥75	16.4	10.9	0.76 (0.46–1.24)	34/63	30/49
Race group	Asian	22.0	10.9	0.48 (0.22–1.05)	9/29	22/41
	White	14.4	13.8	0.83 (0.61–1.13)	82/160	83/153
	Other	18.4	9.0	0.47 (0.20–1.14)	9/23	12/17
Baseline ECOG performance status	0	19.5	13.9	0.65 (0.46–0.92)	53/130	76/146
	1	13.1	10.5	0.84 (0.55–1.28)	47/82	41/65
Baseline BPI-SF#3 Score	0	16.7	16.8	0.75 (0.51–1.12)	47/108	53/103
	1 to 3	13.9	10.5	0.78 (0.52–1.17)	46/88	50/86
	>3	13.7	13.7	0.68 (0.26–1.79)	6/14	14/22
Region	Asia Pacific	19.5	13.8	0.64 (0.35–1.17)	17/43	27/52
	Europe	14.4	13.7	0.82 (0.58–1.14)	68/128	71/120
	North and South America	16.6	16.4	0.60 (0.30–1.18)	15/41	19/39
Past taxane–based chemotherapy	Yes	13.4	10.9	0.89 (0.48–1.66)	20/40	21/41
	No	16.6	13.8	0.71 (0.53–0.96)	80/172	96/170
Past androgen receptor-targeted therapy[a]	Yes	NE	4.3	0.19 (0.03–1.23)	2/8	3/4
	No	16.5	13.8	0.76 (0.58-1.00)	98/204	114/207
Prior AAP use[b]	Yes	13.9	14.6	0.95 (0.54–1.67)	23/47	26/45
	No	16.7	12.7	0.71 (0.52–0.96)	77/165	91/166
Presence of visceral metastases	Yes	11.0	8.1	1.03 (0.60–1.77)	34/51	22/39
	No	19.4	13.8	0.64 (0.47–0.87)	66/161	95/172
Bone only metastasis at entry	Yes	19.4	15.4	0.72 (0.45–1.14)	32/78	41/85
	No	14.8	10.9	0.73 (0.53–1.02)	68/134	76/126
Number of bone lesions at baseline	≤10	19.4	15.4	0.76 (0.53–1.10)	54/127	65/128
	>10	13.8	8.4	0.69 (0.47–1.04)	46/85	52/83
Baseline PSA above median	Yes	15.7	8.3	0.58 (0.40–0.82)	56/110	66/101
	No	16.7	18.2	0.93 (0.62–1.40)	44/102	51/110
Gene mutation type	BRCA	16.6	10.9	0.55 (0.38–0.81)	45/113	64/112
	Other HRR	14.8	16.4	0.99 (0.68–1.45)	55/99	53/99





CHUM

MAGNITUDE

Safety data: HRR BM+

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)

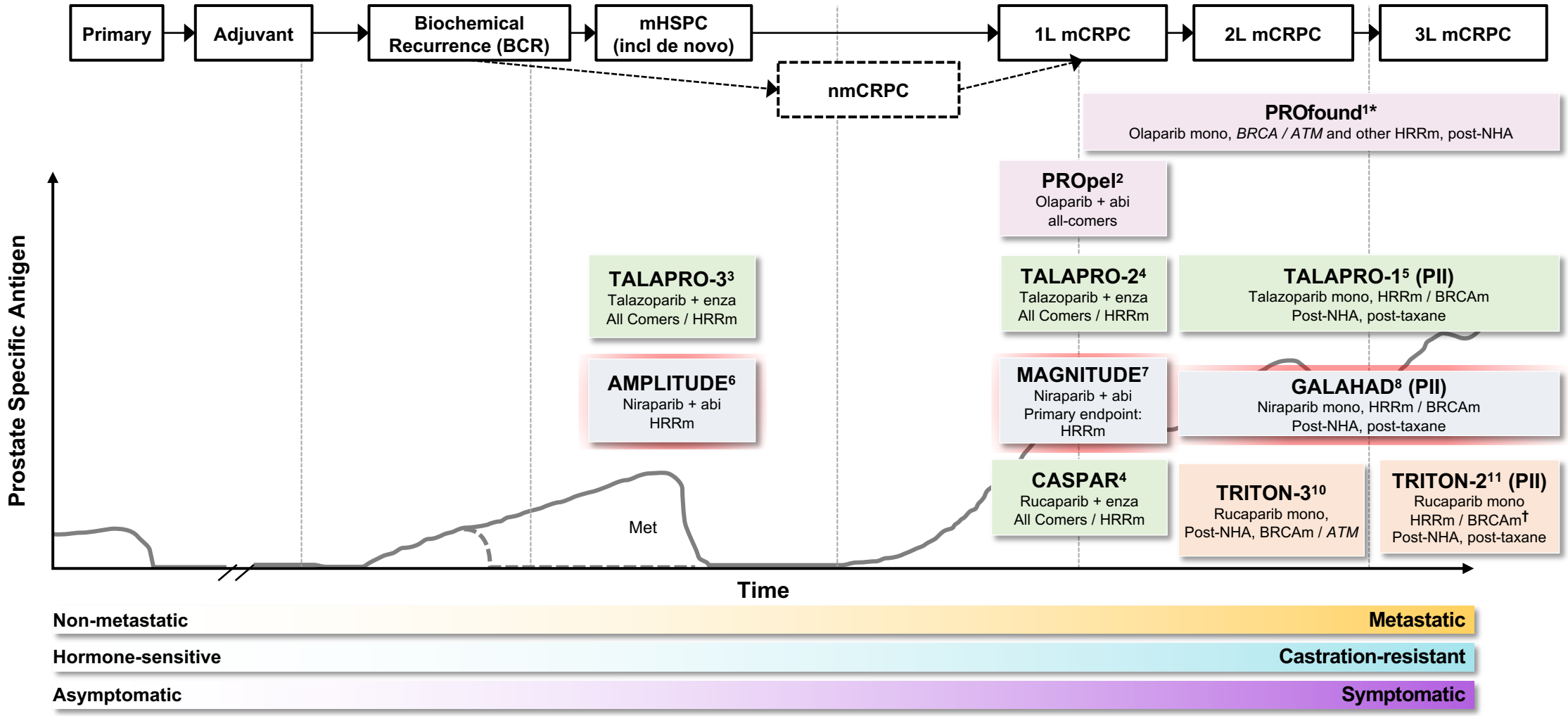
Treatment-emergent adverse events occurring at >20% in the NIRA arm or otherwise of clinical interest, n (%)		NIRA + AAP, n = 212		PBO + AAP, n = 211	
		All grades	Grade ≥3	All grades	Grade ≥3
Hematologic	Anemia	98 (46.2)	63 (29.7)	43 (20.4)	16 (7.6)
	Thrombocytopenia	45 (21.2)	14 (6.6)	18 (8.5)	5 (2.4)
	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]

- Most common AEs leading to dose reduction with NIRA + AAP: anemia (13.2%), thrombocytopenia (2.8%)
- Median relative dose intensity in the NIRA + AAP group: 99%

- **TEAEs consistent with known safety profile for each individual therapy**

CHUM

Ongoing trials investigating PARPi in advanced PC



Please see slide notes for references

*As a result of the data from PROfound, olaparib monotherapy was approved for treatment of mCRPC in patients with HRRm (FDA approval) or for patients with mutations in only *BRCA1/2* (EMA approval) after progression on a NHA[12,13]

†As a result of the data from TRITON2, rucaparib monotherapy was approved by the FDA only for the treatment of mCRPC in patients with a *BRCA1/2*m who have disease progression after treatment with prior AR-directed therapy and prior taxane[14]

Abi=abiraterone; BCR=biochemical recurrence; enza=enzalutamide; FDA=US Food and Drug Administration; HRRm=homologous recombination repair mutation; mCRPC=metastatic castration-resistant prostate cancer; met=metastasis; mono=monotherapy; mHSPC=metastatic hormone-sensitive prostate cancer; NHA=new hormonal agent; nmCRPC=non-metastatic castration-resistant prostate cancer; P2=Phase II; P3=Phase III.

CHUM

Conclusion

- Patients in the mCRPC state live less than 3 years even with the best available treatments
- A significant proportion of men destined to die of prostate cancer harbor HRR mutations
  - Treatment improves progression free survival and overall survival
  - Strategies to identify patients are challenging but critically important
- Future will likely include earlier introduction of PARPi and possibly treatment beyond patients with HRR/DDR mutations

CHUM

Cases from the Community: Urologic Oncology Investigators Provide Perspectives on the Optimal Management of Urothelial Bladder Cancer

Part 2 of a 2-Part CME Satellite Symposium Series in Conjunction with the AUA 2022 Annual Meeting

Friday, May 13, 2022

6:00 PM – 8:00 PM CT (7:00 PM – 9:00 PM ET)

Faculty

Matthew D Galsky, MD
Ashish M Kamat, MD, MBBS
Stephen B Williams, MD, MS

Moderator

Sumanta Kumar Pal, MD

RTP RESEARCH TO PRACTICE

Thank you for attending!

CME Credit Information

For those participating in person today, please remit your CME credit form as you exit the meeting room.

For all others, a CME credit link will be provided in the chat room at the conclusion of the program.

RTP
RESEARCH
TO PRACTICE