

A Conversation with the Investigators: Metastatic Castration-Resistant Prostate Cancer

**Tuesday, July 20, 2021
5:00 PM – 6:00 PM ET**

Faculty

**Emmanuel S Antonarakis, MD
Johann de Bono, MBChB, MSc, PhD
Julie N Graff, MD**

Moderator

Neil Love, MD

Faculty



Emmanuel S Antonarakis, MD
Professor of Oncology and Urology
Johns Hopkins University
The Sidney Kimmel Comprehensive Cancer Center
Baltimore, Maryland



Julie N Graff, MD
Associate Professor, Hematology and
Medical Oncology
OHSU Knight Cancer Institute
Portland, Oregon



Johann de Bono, MBChB, MSc, PhD
Regius Professor of Cancer Research
The Institute of Cancer Research
University of London
The Royal Marsden Hospital
London, United Kingdom



Moderator
Neil Love, MD
Research To Practice
Miami, Florida

Commercial Support

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

Dr Love — Disclosures

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

Dr Antonarakis — Disclosures

Consulting Agreements	Amgen Inc, Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Clovis Oncology, Dendreon Pharmaceuticals Inc, ESSA Pharma Inc, GlaxoSmithKline, Janssen Biotech Inc, Lilly, Medivation Inc, a Pfizer Company, Merck, Sanofi Genzyme
Contracted Research	AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Dendreon Pharmaceuticals Inc, Genentech, a member of the Roche Group, Janssen Biotech Inc, Johnson & Johnson Pharmaceuticals, Merck, Novartis, Sanofi Genzyme, Tokai Pharmaceuticals Inc
Ownership Interest (Licensor of Patent)	QIAGEN

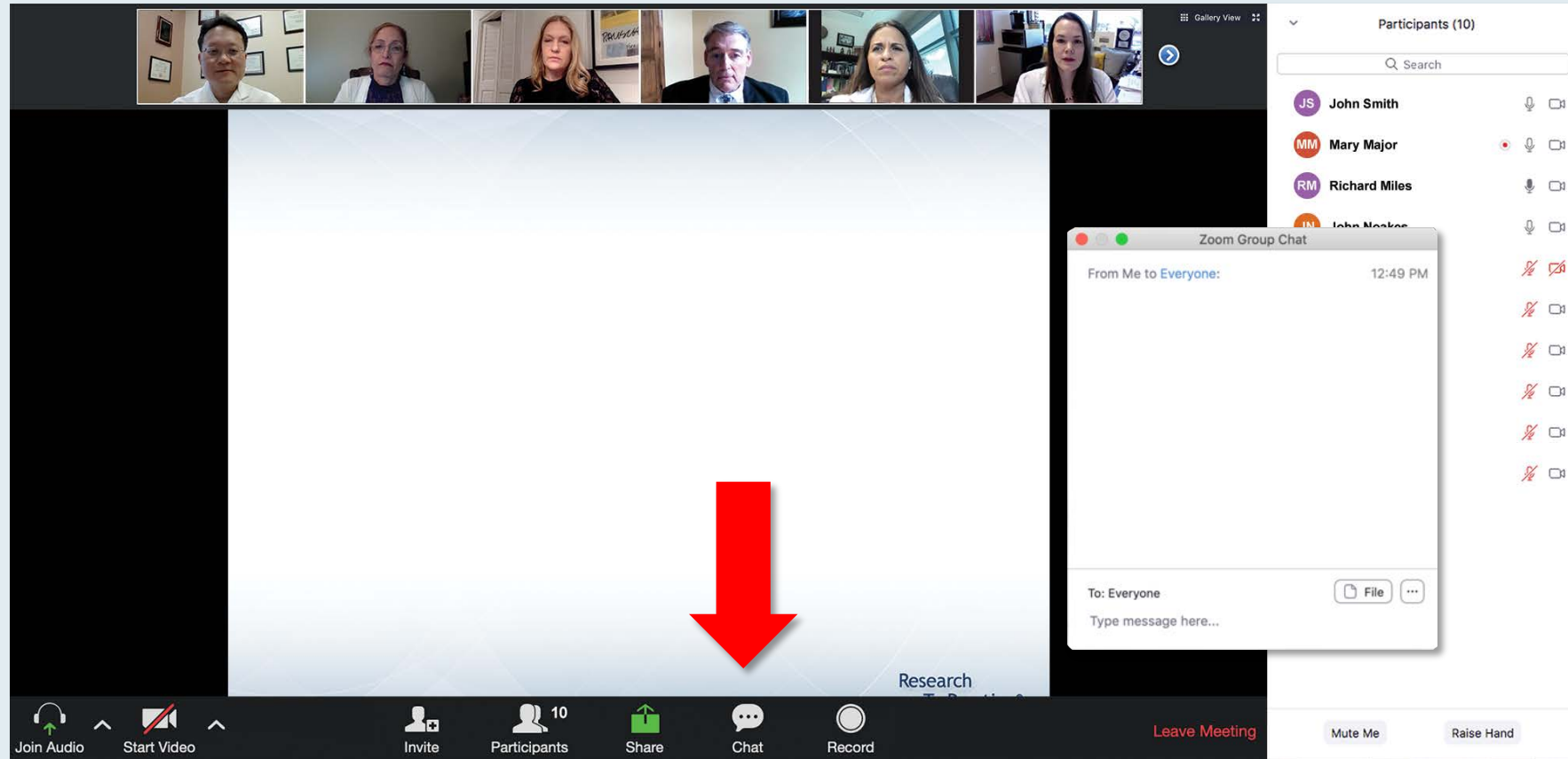
Professor de Bono — Disclosures

Advisory Committee, Consulting Agreements and Data and Safety Monitoring Board/Committee	Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, BioXcel Therapeutics Inc, Boehringer Ingelheim Pharmaceuticals Inc, CellCentric, Daiichi Sankyo Inc, Eisai Inc, Genentech, a member of the Roche Group, Genmab, GlaxoSmithKline, Janssen Biotech Inc, Merck Serono, Merck Sharp & Dohme Corp, Menarini Silicon Biosystems, Orion Corporation (Finland), Pfizer Inc, QIAGEN, Sanofi Genzyme, Sierra Oncology, Taiho Oncology Inc, Terumo Medical Corporation, Vertex Pharmaceuticals
Contracted Research (Institution – no personal income)	Astellas, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, CellCentric, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Genmab, GlaxoSmithKline, Janssen Biotech Inc, Merck Serono, Merck Sharp & Dohme Corp, Menarini Silicon Biosystems, Orion Corporation, Pfizer Inc, Sanofi Genzyme, Sierra Oncology, Taiho Oncology Inc, Vertex Pharmaceuticals
Ownership Interest	Inventor, with no financial interest, for patent 8,822,438.

Dr Graff — Disclosures

Research Funding to Institution	Astellas, Janssen Biotech Inc, Merck, Sanofi Genzyme.
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We Encourage Clinicians in Practice to Submit Questions



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

Familiarizing Yourself with the Zoom Interface

How to answer poll questions

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What is your usual treatment recommendation for a patient with MM who has been followed by ASCT for 1-5 years who then experiences an asymptomatic relapse?

Quick Poll

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- ☐ Ixazomib + Rd
- ☐ Other

Submit

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Join Audio Start Video Invite Participants Share Chat Record Leave Meeting

Participants (10)

Search

- JS John Smith
- MM Mary Major
- RM Richard Miles
- JN John Noakes
- AS Alice Suarez
- JP Jane Perez
- RS Robert Stiles
- JF Juan Fernandez
- AK Ashok Kumar
- JS Jeremy Smith

Mute Me Raise Hand

When a poll question pops up, click your answer choice from the available options.
Results will be shown after everyone has answered.

Familiarizing Yourself with the Zoom Interface

Expand chat submission box

The screenshot shows a Zoom meeting interface. At the top, there's a header bar with participant names: RTP Coordinat..., Kirsten Miller, RTP Mike Rivera, and Lisa Suarez. Below this is a slide titled "Meet The Professor Program Steering Committee" featuring six members with their photos and titles:

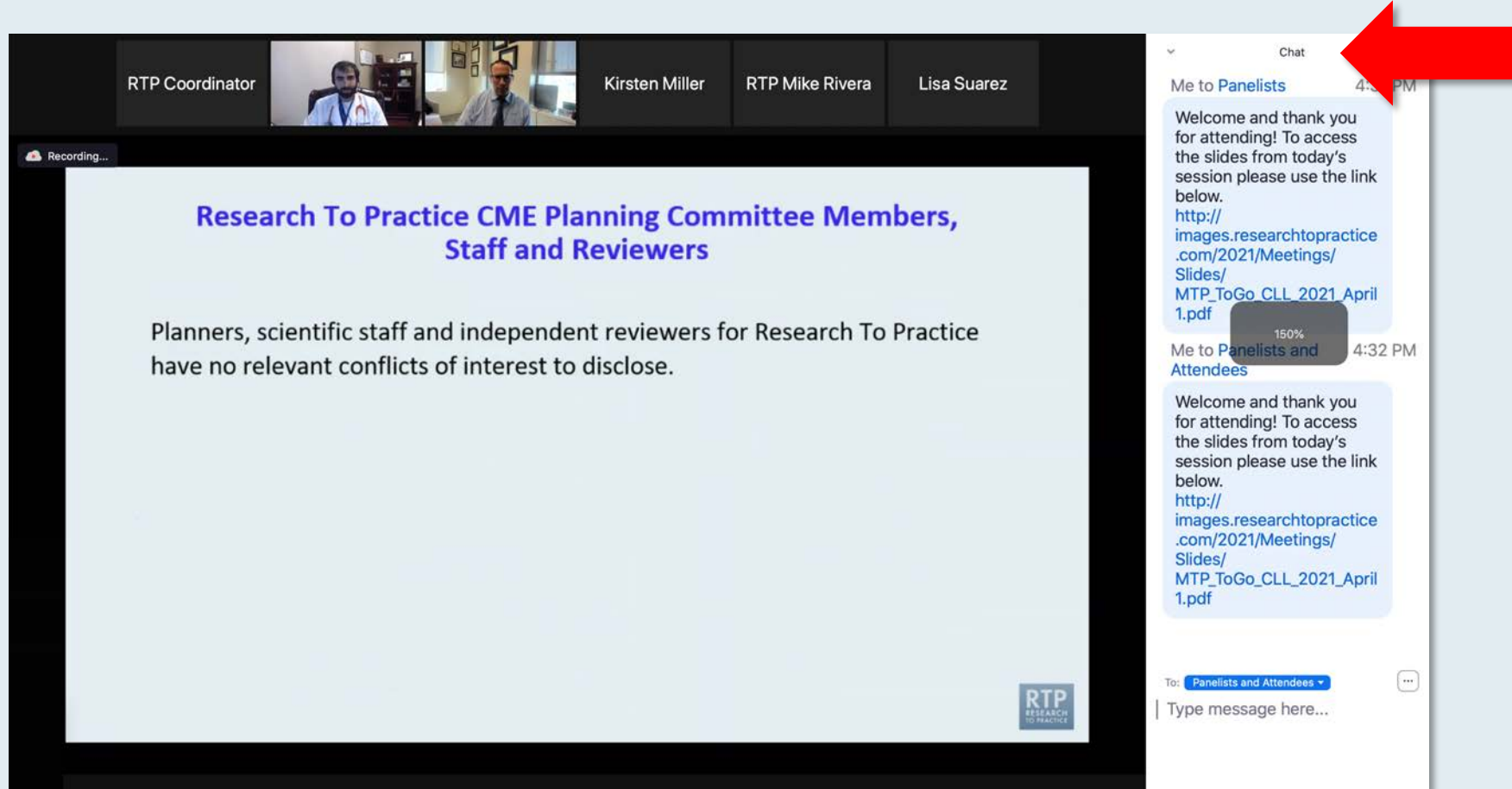
- John N Allan, MD**
Assistant Professor of Medicine
Weill Cornell Medicine
New York, New York
- Ian W Flinn, MD, PhD**
Director of Lymphoma Research Program
Sarah Cannon Research Institute
Tennessee Oncology
Nashville, Tennessee
- Steven Coutre, MD**
Professor of Medicine (Hematology)
Stanford University School of Medicine
Stanford, California
- Prof John G Gribben, MD, DSc, FMedSci**
Chair of Medical Oncology
Barts Cancer Institute
Queen Mary University of London
Charterhouse Square
London, United Kingdom
- Matthew S Davids, MD, MMSc**
Associate Professor of Medicine
Harvard Medical School
Division of Lymphoma
Dana-Farber Cancer Institute
Boston, Massachusetts
- Brian T Hill, MD, PhD**
Director, Lymphoid Malignancy Program
Cleveland Clinic Taussig Cancer Institute
Cleveland, Ohio

On the right side, the chat window is expanded. It shows two messages from "Me to Panelists" and "Me to Panelists and Attendees" at 4:31 PM and 4:32 PM respectively. The messages contain a welcome message and a link to a PDF file: http://images.researchtopractice.com/2021/Meetings/Slides/MTP_ToGo_CLL_2021_April1.pdf. At the bottom of the chat window, there's a "To:" dropdown menu set to "Panelists and Attendees" and a text input field labeled "Type message here...". A large red arrow points to the white line above the submission box, indicating where to drag to expand the chat area.

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

Familiarizing Yourself with the Zoom Interface

Increase chat font size



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

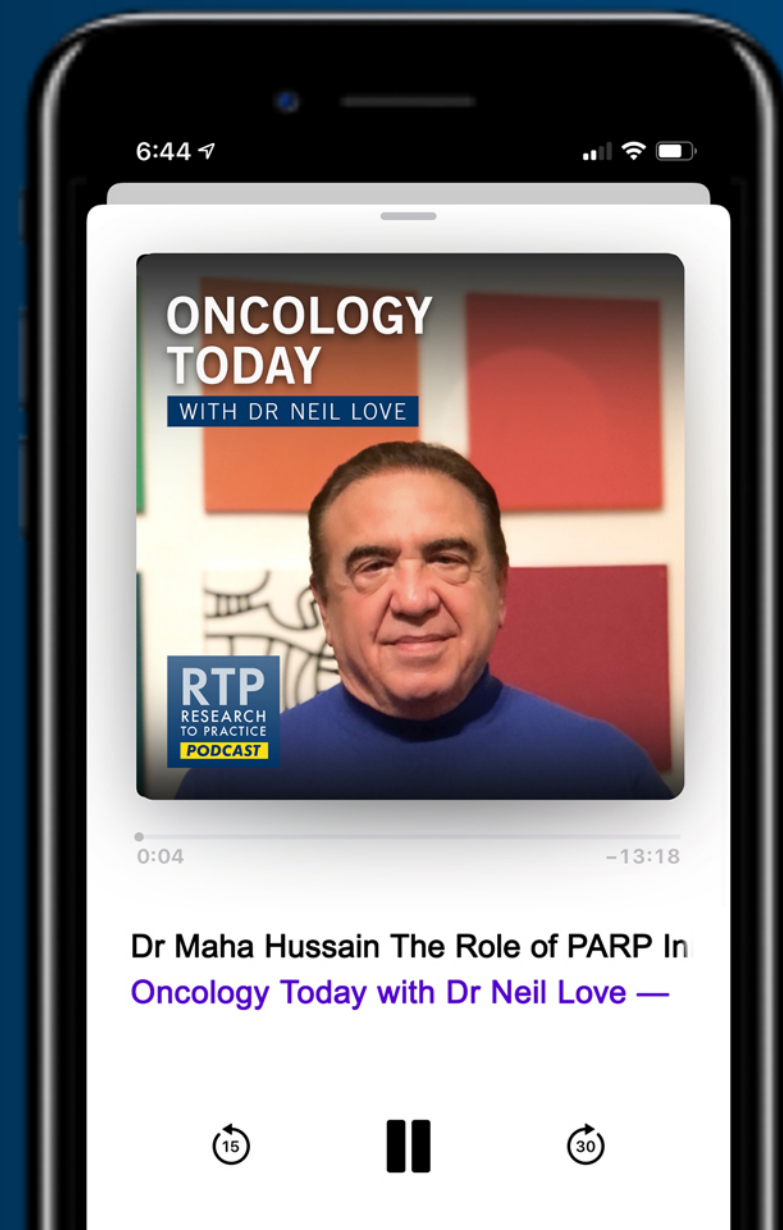
ONCOLOGY TODAY

WITH DR NEIL LOVE

The Role of PARP Inhibition in the Management of Prostate Cancer



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Daniel P Petrylak, MD
Arlene Siefker-Radtke, MD**

Moderator

Neil Love, MD

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Optimizing the Selection and Sequencing of Therapy for Patients with Renal Cell Carcinoma

Thursday, July 22, 2021

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David F McDermott, MD

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Neil Love, MD

A Conversation with the Investigators: Endometrial and Cervical Cancers

**Monday, July 26, 2021
5:00 PM – 6:00 PM ET**

Faculty

**Mansoor Raza Mirza, MD
David M O'Malley, MD
Angeles Alvarez Secord, MD, MHSc**

Moderator

Neil Love, MD

What General Medical Oncologists Want to Know About Targeted Therapy for Non-Small Cell Lung Cancer

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Zofia Piotrowska, MD, MHS
Gregory J Riely, MD, PhD

Moderator

Neil Love, MD

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David R Spigel, MD
Heather Wakelee, MD**

Moderator

Neil Love, MD

Consensus or Controversy?

Clinical Investigator Perspectives on the Current and Future Management of Mantle Cell, Diffuse Large B-Cell and Hodgkin Lymphoma

**Monday, August 2, 2021
5:00 PM – 6:00 PM ET**

Faculty

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Craig Moskowitz, MD
Laurie H Sehn, MD, MPH**

Moderator

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Dustin Deming, MD
Eric Van Cutsem, MD, PhD
Zev Wainberg, MD, MSc**

Moderator

Neil Love, MD

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 2 to 3 business days.

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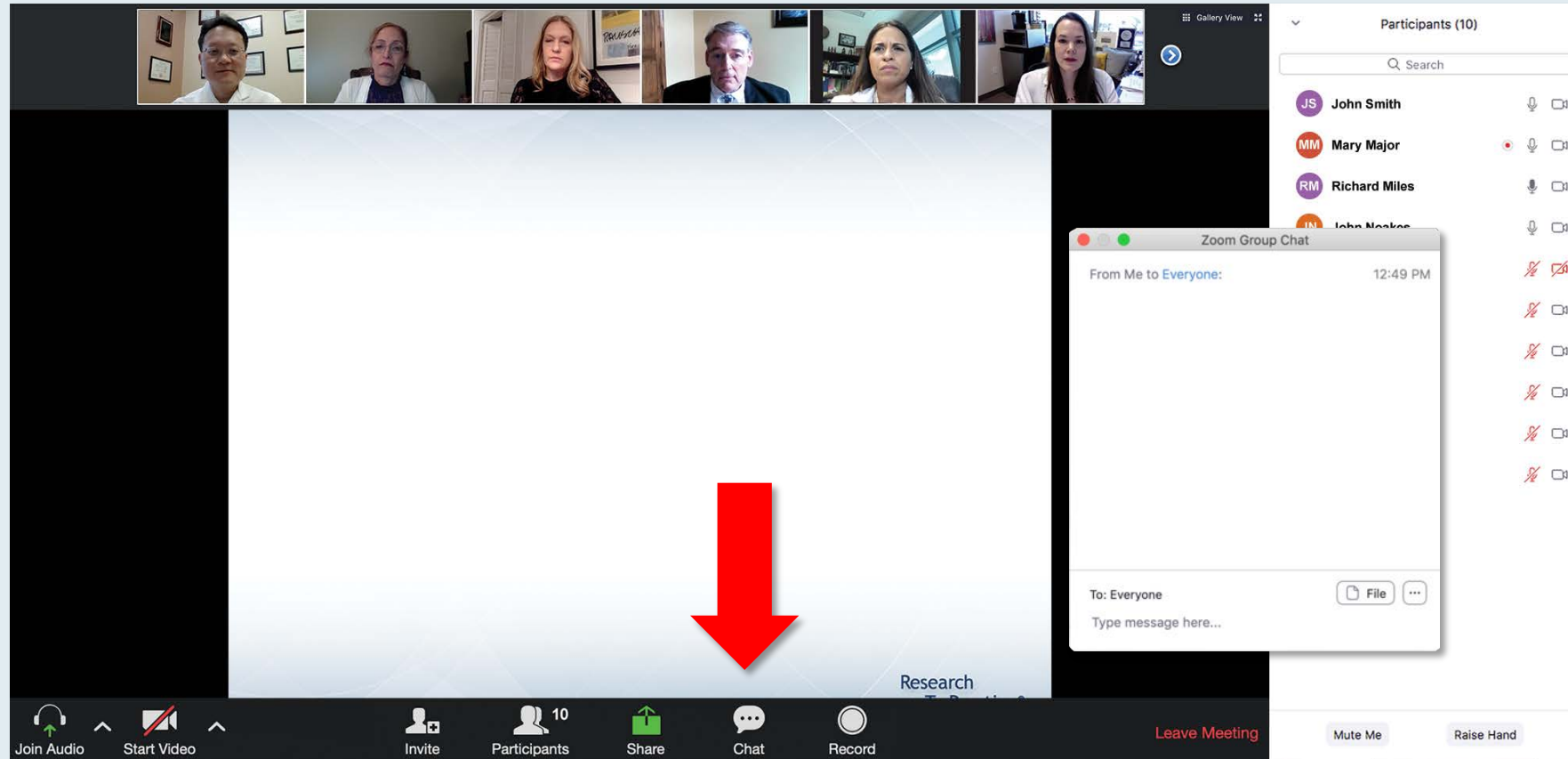


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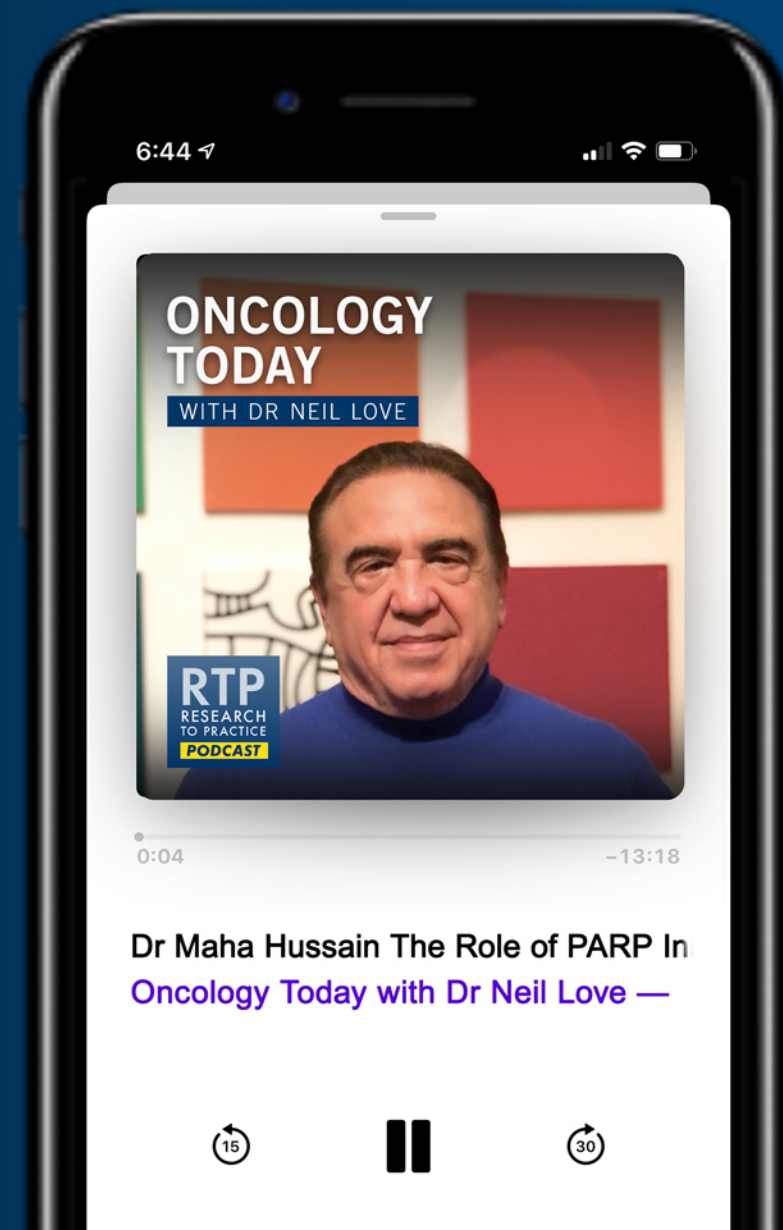
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ASCO 2021 Metastatic Castration-Resistant Prostate Cancer Presentation Library



Selection and Sequencing of Therapy for Patients with mCRPC

Emmanuel S Antonarakis, MD

[Download Slides](#)



Integration of PARP Inhibitors into the Management of mCRPC

Johann de Bono, MBChB, MSc, PhD

[Download Slides](#)



Novel and Investigational Strategies for Patients with mCRPC

Julie N Graff, MD

[Download Slides](#)

Agenda

Module 1: Integration of PARP Inhibitors into the Management of Metastatic Castration-Resistant Prostate Cancer (mCRPC)

- Genomic biology of prostate cancer
- Faculty cases
- PROfound: Olaparib versus AR-targeted therapy in men with HRR mutation-selected mCRPC
- TRITON2: Rucaparib monotherapy for mCRPC previously treated with AR-targeted therapy and a taxane
- TALAPRO-1: Talazoparib in men with DNA damage repair mutations and mCRPC

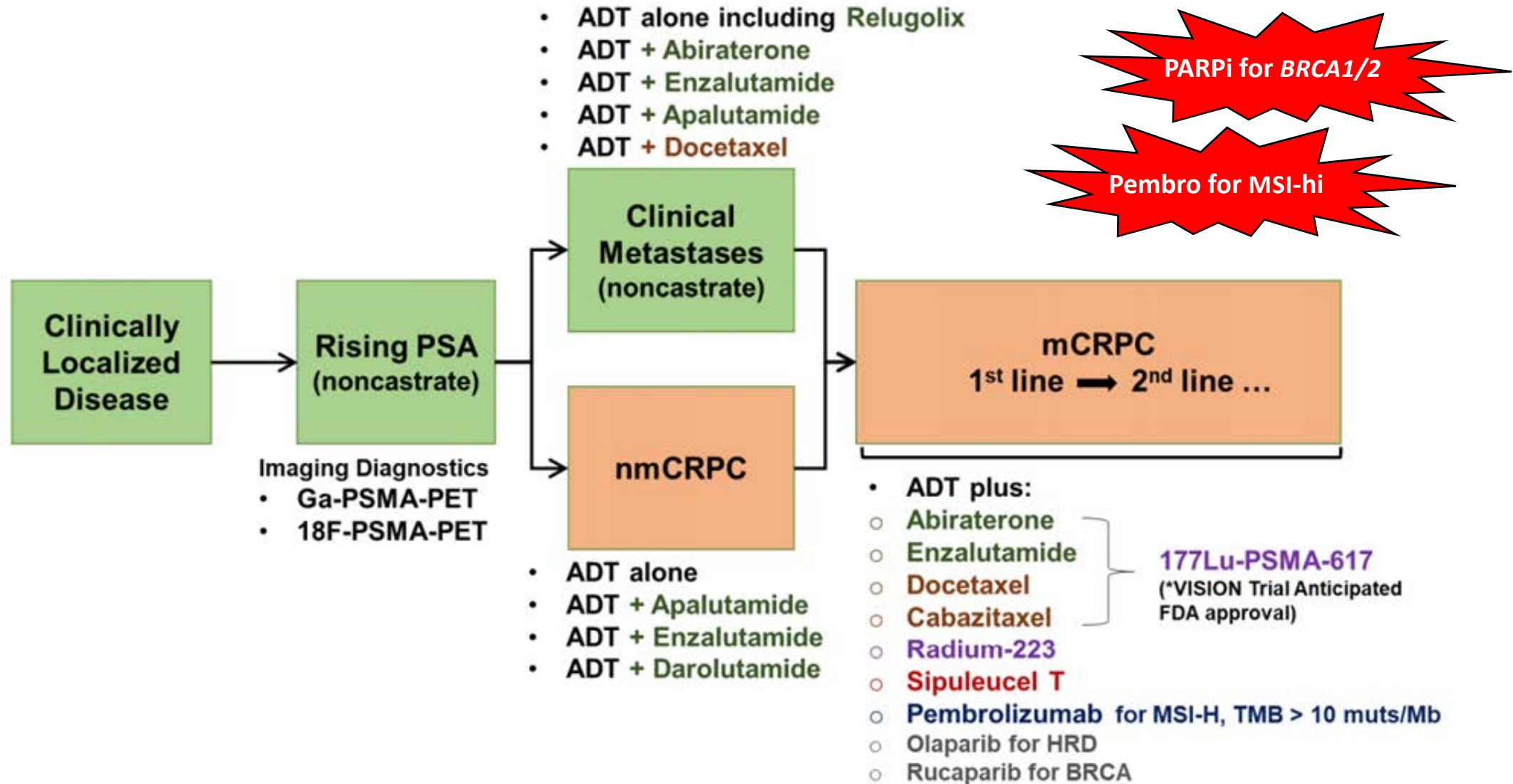
Module 2: Selection and Sequencing of Therapy in mCRPC

- CARD: Cabazitaxel versus an AR-targeted agent for mCRPC
- OSTRICH: Cabazitaxel versus an AR-targeted agent for patients with poor-prognosis mCRPC
- PEACE III: Addition of bone-protecting agents during treatment with radium-223/enzalutamide
- Faculty cases

Module 3: Novel and Investigational Strategies for Patients with mCRPC

- VISION: ¹⁷⁷Lu-PSMA-617 for patients with progressive PSMA-positive mCRPC
- COSMIC-021: Cabozantinib with atezolizumab for mCRPC
- Faculty cases

Treatment Landscape for mCRPC



Agenda

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BRCA2 →

1145

Ligase IV

BRCA1/2 → p53

BRCA

genotype

guardian

of the genome

factor

ATM

sensor of DNA
damage

PALB2 — BRCA3

haploinsufficiency

“P53 is the guardian of the genome”

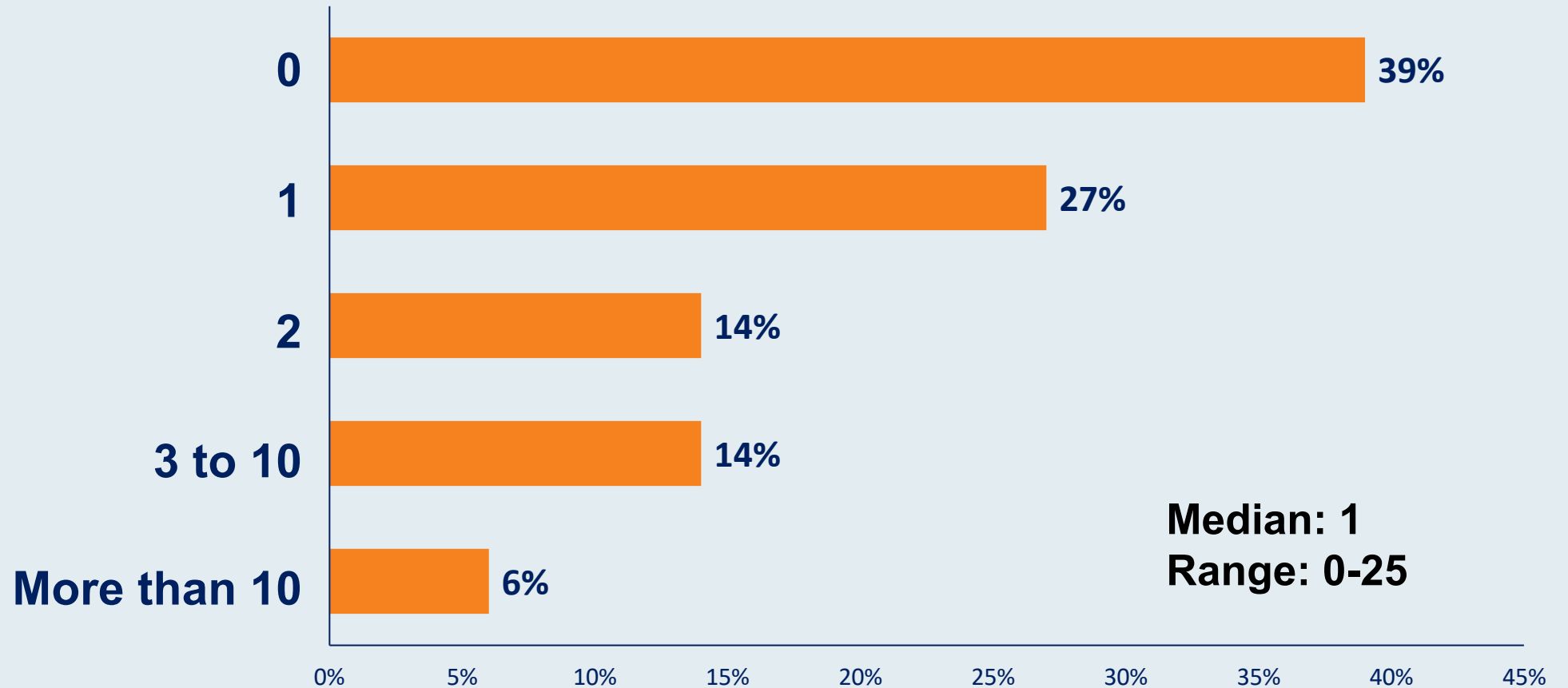
“ATM is the sensor of DNA damage”

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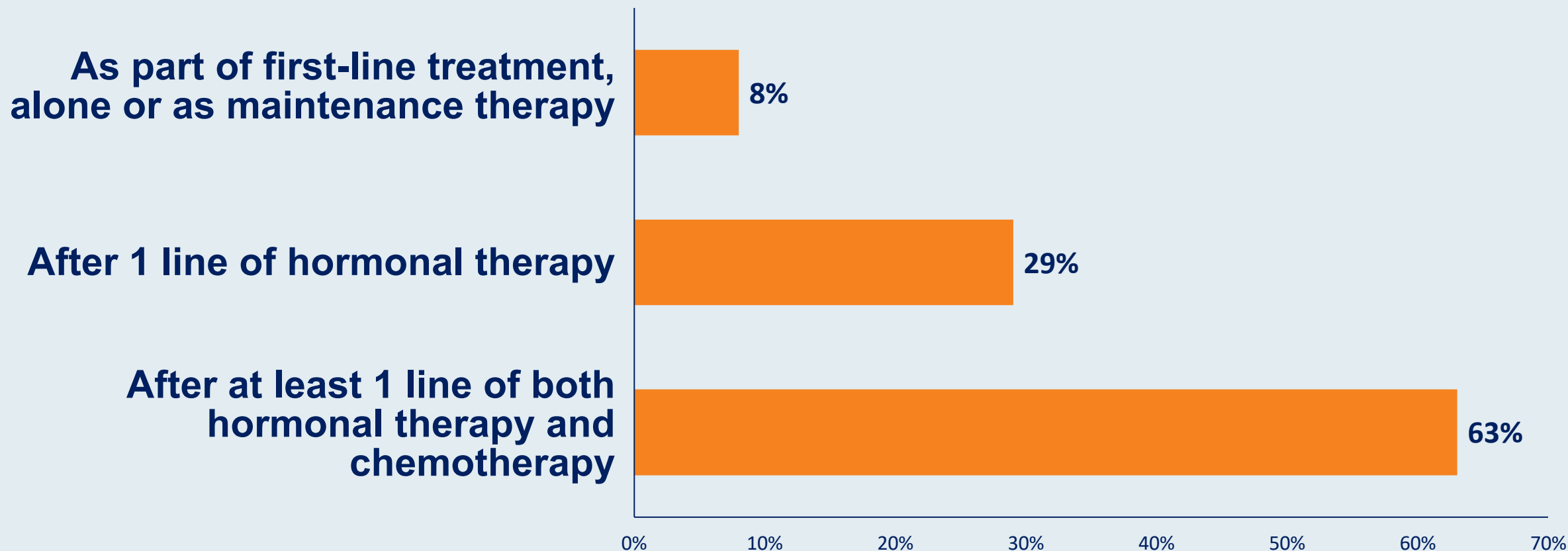


Interview with Prof Johann de Bono, July 8, 2021

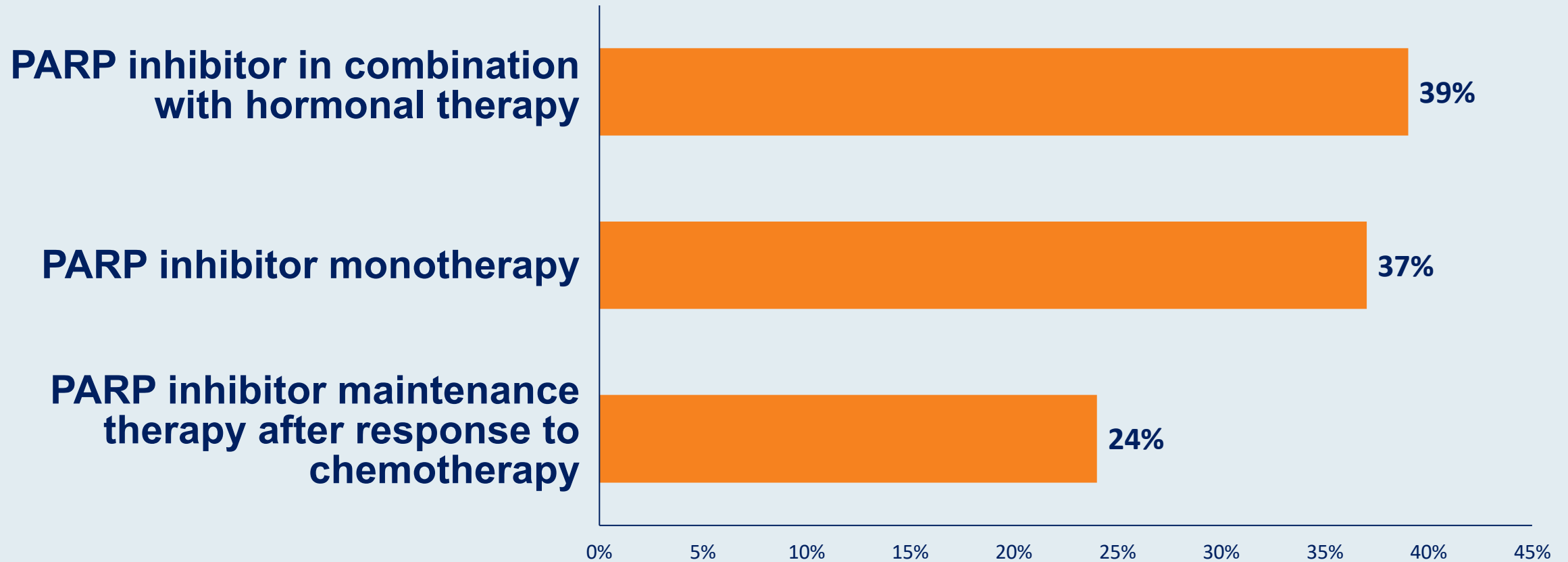
Approximately how many times have you prescribed a PARP inhibitor to a patient with prostate cancer?



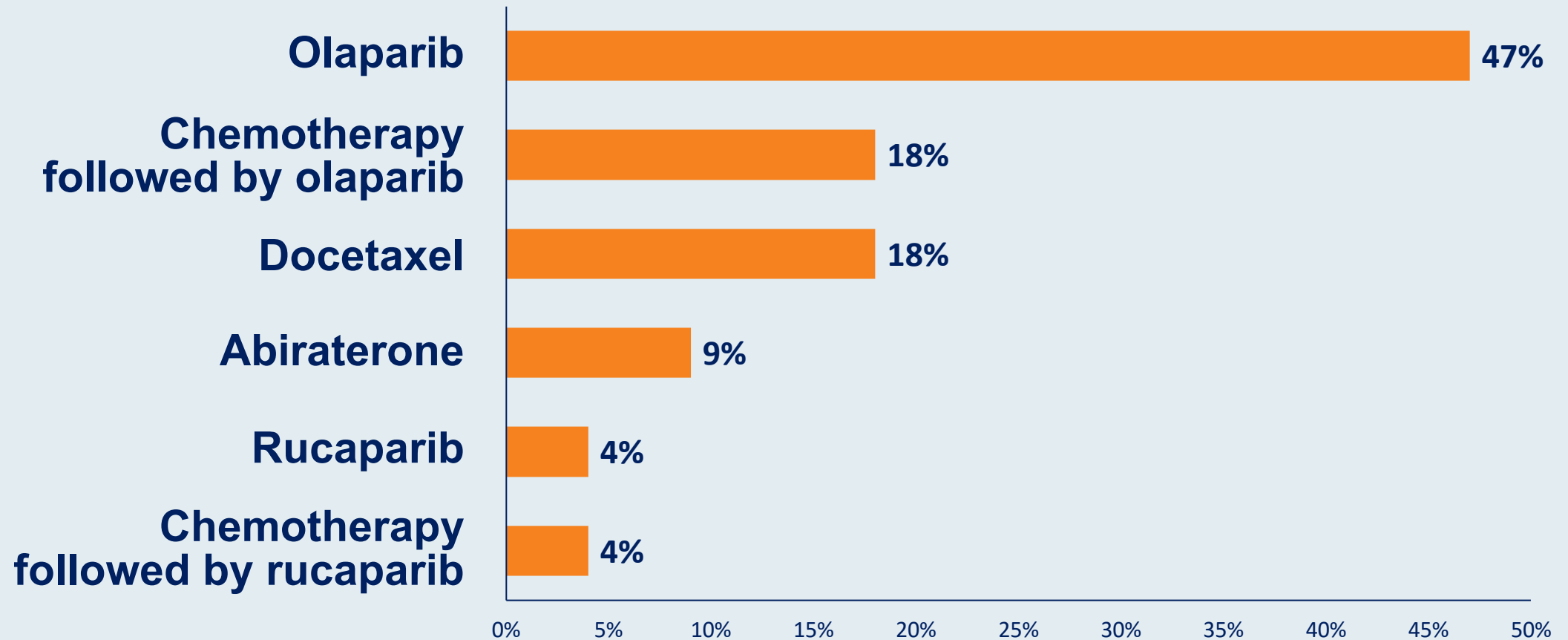
At what point, if any, do you generally recommend a PARP inhibitor to a patient with mPC and a germline BRCA mutation?



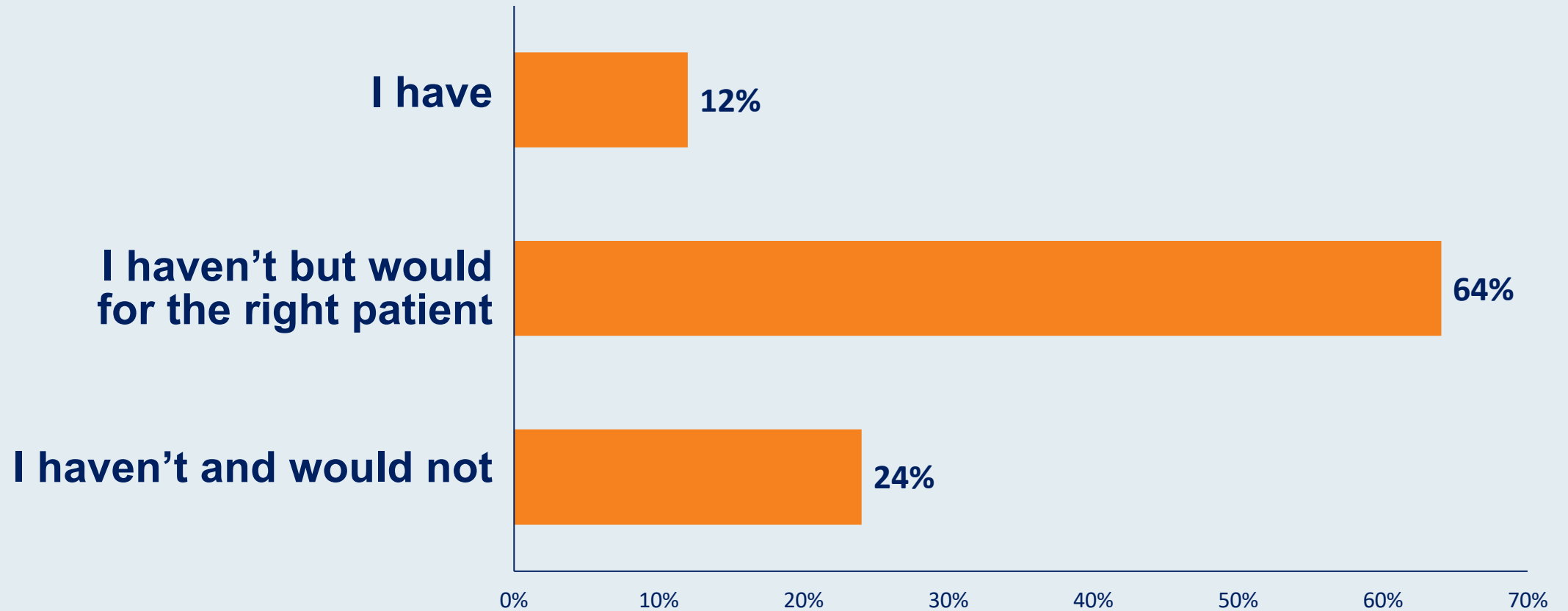
For a patient with mPC and a germline BRCA mutation to whom you would administer a PARP inhibitor at some point, what treatment strategy would you likely use?



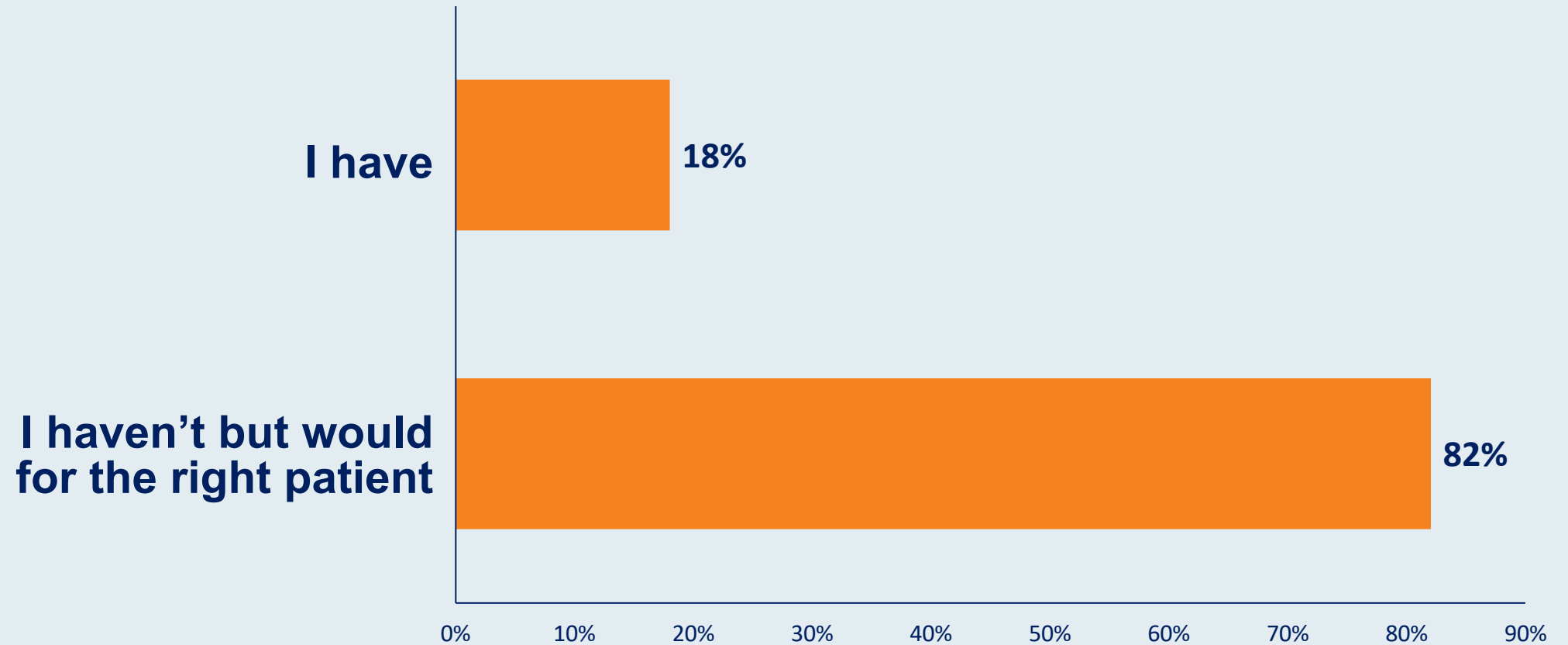
A 65-year-old man with a germline BRCA mutation presents with minimally symptomatic PC metastatic to the bone and receives enzalutamide and ADT with response followed by disease progression. What would you recommend?



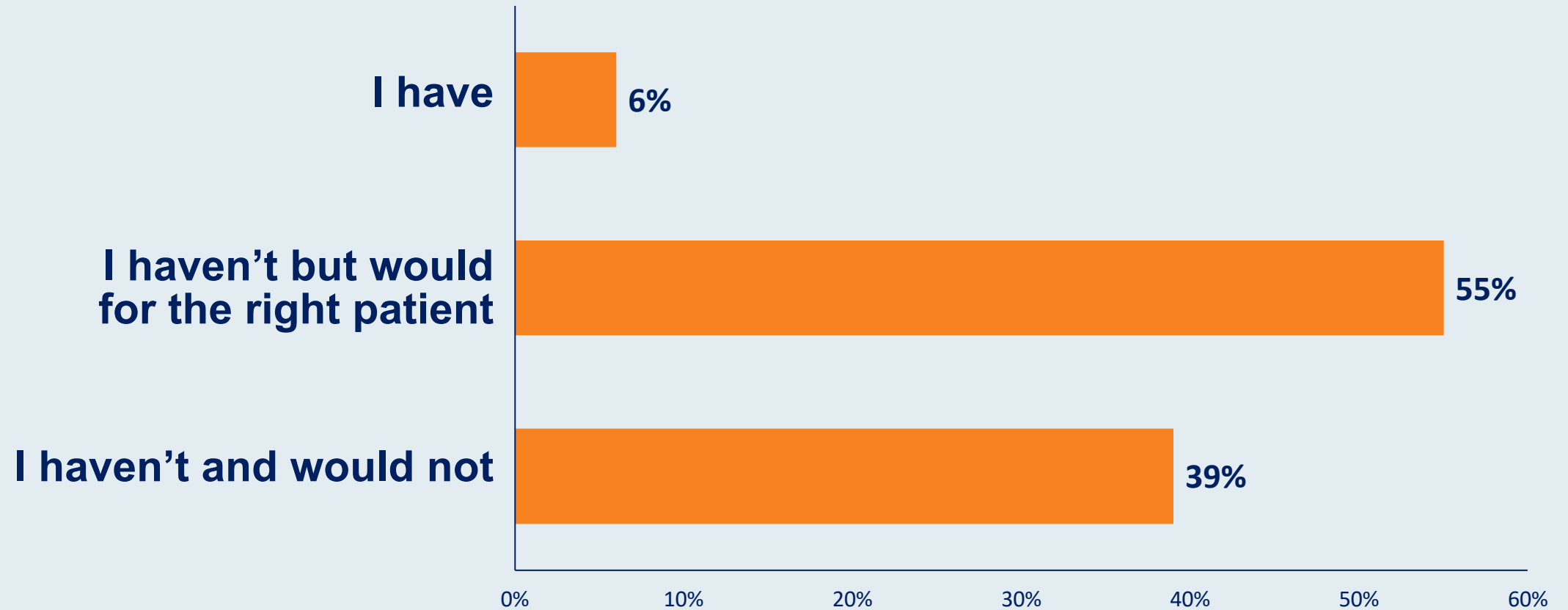
Have you or would you prescribe a PARP inhibitor to a patient with mPC and a germline ATM mutation?



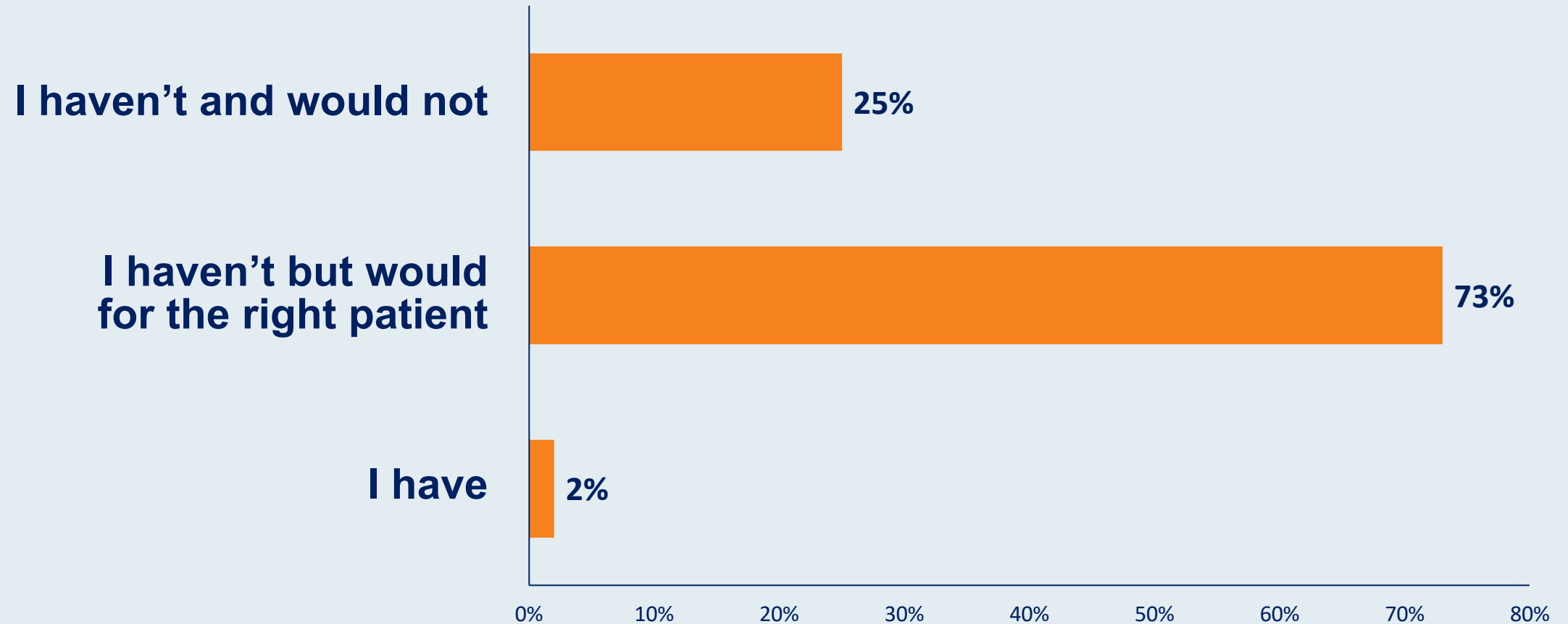
Have you or would you prescribe a PARP inhibitor to a patient with mPC and a somatic BRCA mutation?



Have you or would you prescribe a PARP inhibitor to a patient with mPC and a high LOH score?



Have you or would you prescribe a PARP inhibitor to a patient with mPC and a germline PALB2 mutation?



DNA repair defects in mCRPC

- Many mCRPCs have DNA repair defects
 - TP53 alterations
 - BRCA2 alterations and alterations in other homologous recombination genes including PALB2, RAD51, FANCA
 - ATM alterations
 - CDK12 and mismatch repair gene alterations

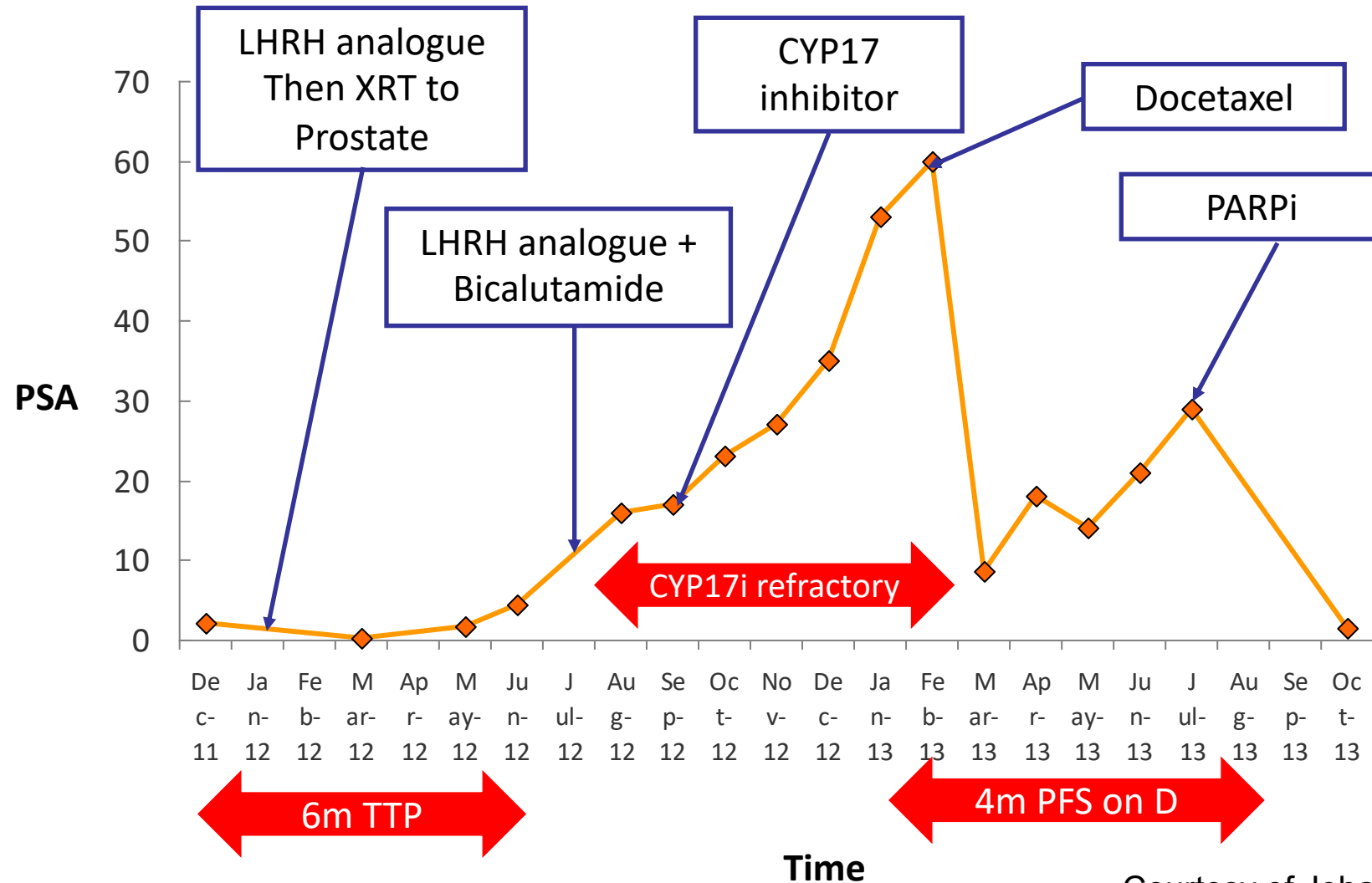
Case Presentation – Prof de Bono: A 70-year-old man with mCRPC and Somatic Cell Biallelic BRCA2 loss

One of our first responders

- 70 year old patient with no family history
 - Acute urinary retention in Dec 2011
- Staging: T4 tumor with extension into bladder base, pelvic nodes and metastatic bone disease
- Biopsy confirmed adenocarcinoma of prostate with Gleason score of 4 + 5 (9) in 10/10 cores, up to 80% core involvement

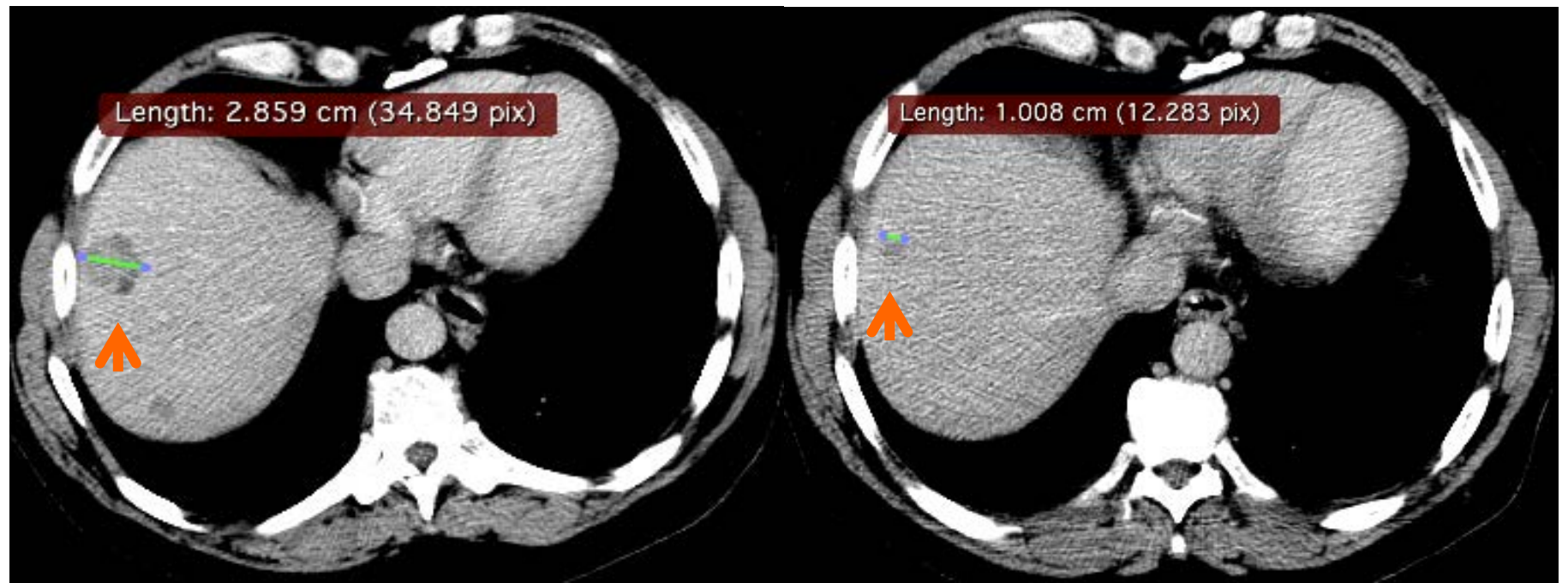
Case Presentation – Prof de Bono: A 70-year-old man with mCRPC and Somatic Cell Biallelic BRCA2 loss (continued)

Detailed case study: TOPARP responder



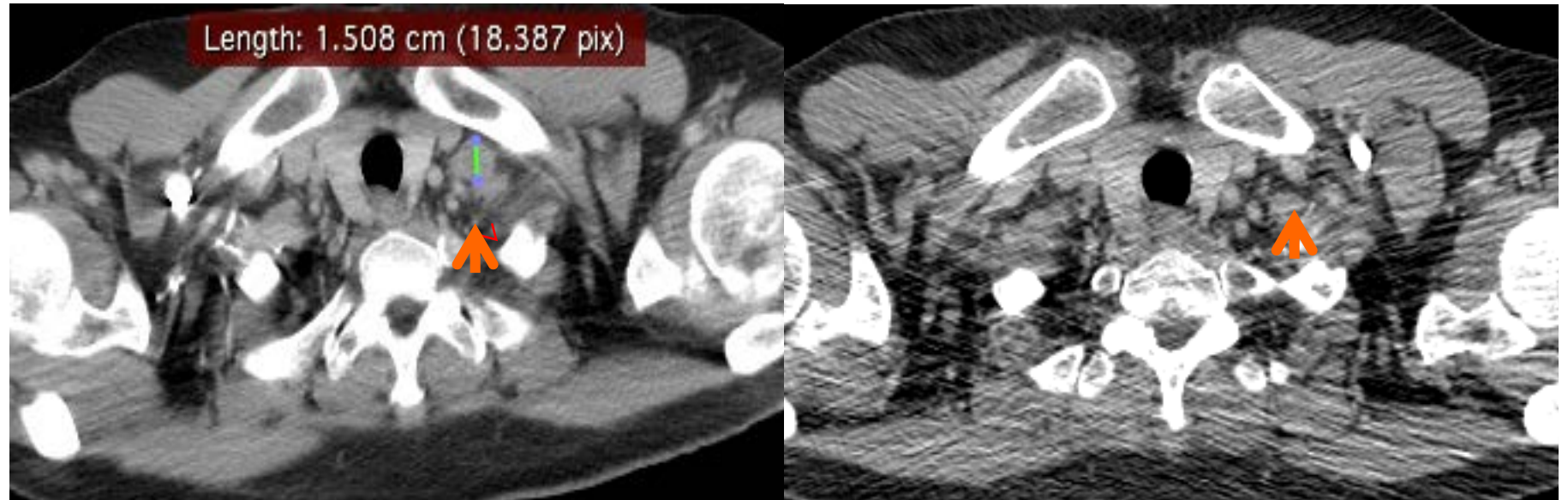
Courtesy of Johann de Bono, MBChB, MSc, PhD

**Case Presentation –
Prof de Bono: A 70-year-
old man with mCRPC and
Somatic Cell Biallelic
BRCA2 loss (continued)**



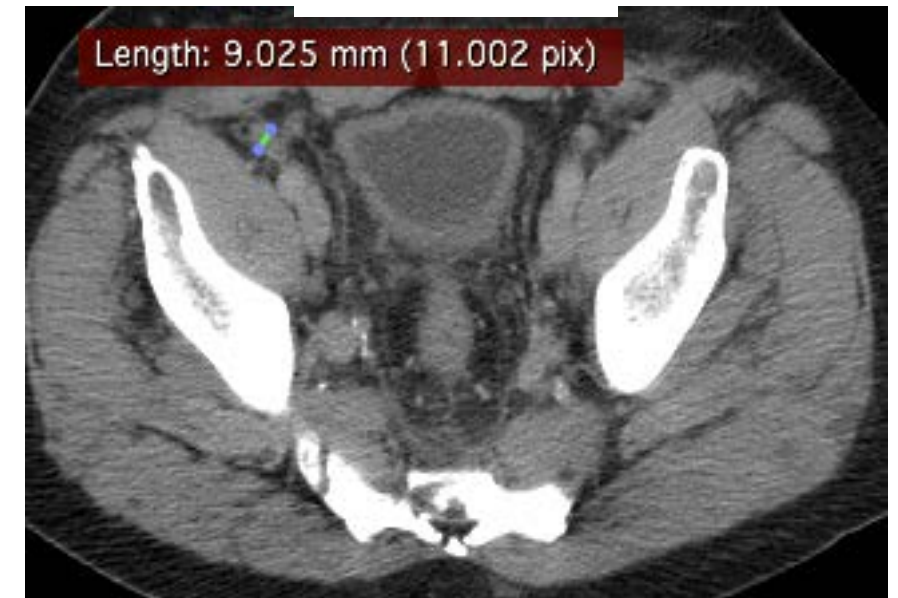
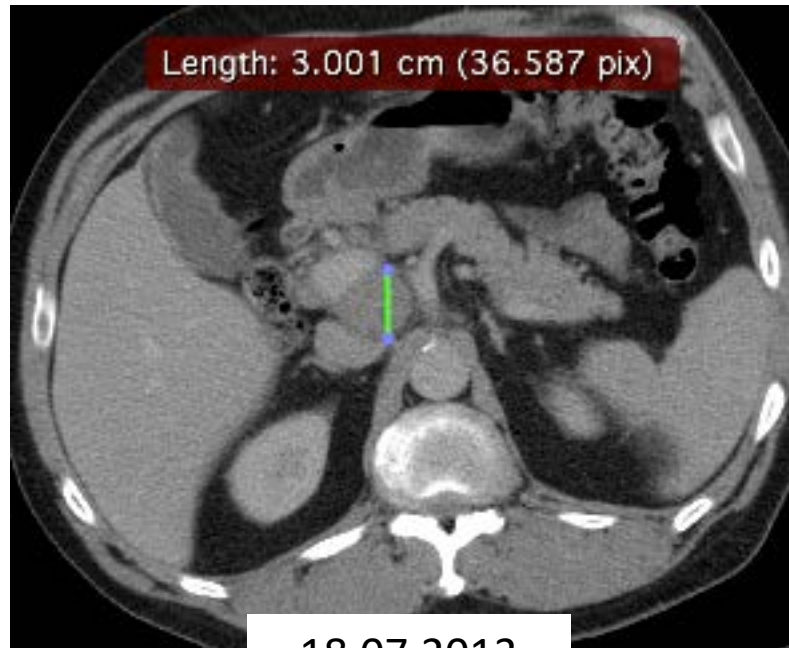
18.07.2013

14.10.2013



Courtesy of Johann de Bono, MBChB, MSc, PhD

**Case Presentation –
Prof de Bono: A 70-year-
old man with mCRPC and
Somatic Cell Biallelic
BRCA2 loss (continued)**



Response in portacaval (top row) and right external iliac nodes (bottom row)
A similar trend was seen at all nodal disease sites (supraclavicular, retroperitoneal, pelvic, sigmoid mesentery)

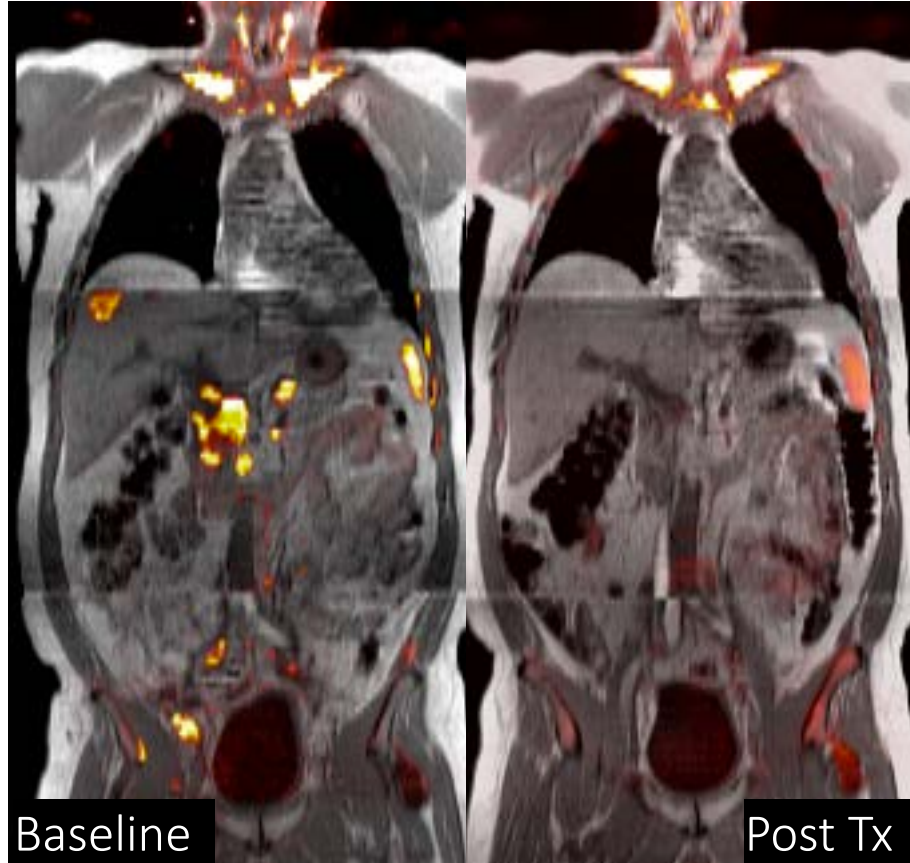
Courtesy of Johann de Bono, MBChB, MSc, PhD

**Case Presentation –
Prof de Bono: A 70-
year-old man with
mCRPC and Somatic
Cell Biallelic BRCA2
loss (continued)**

Fused MRI DWI - Anatomical

Pre-Treatment

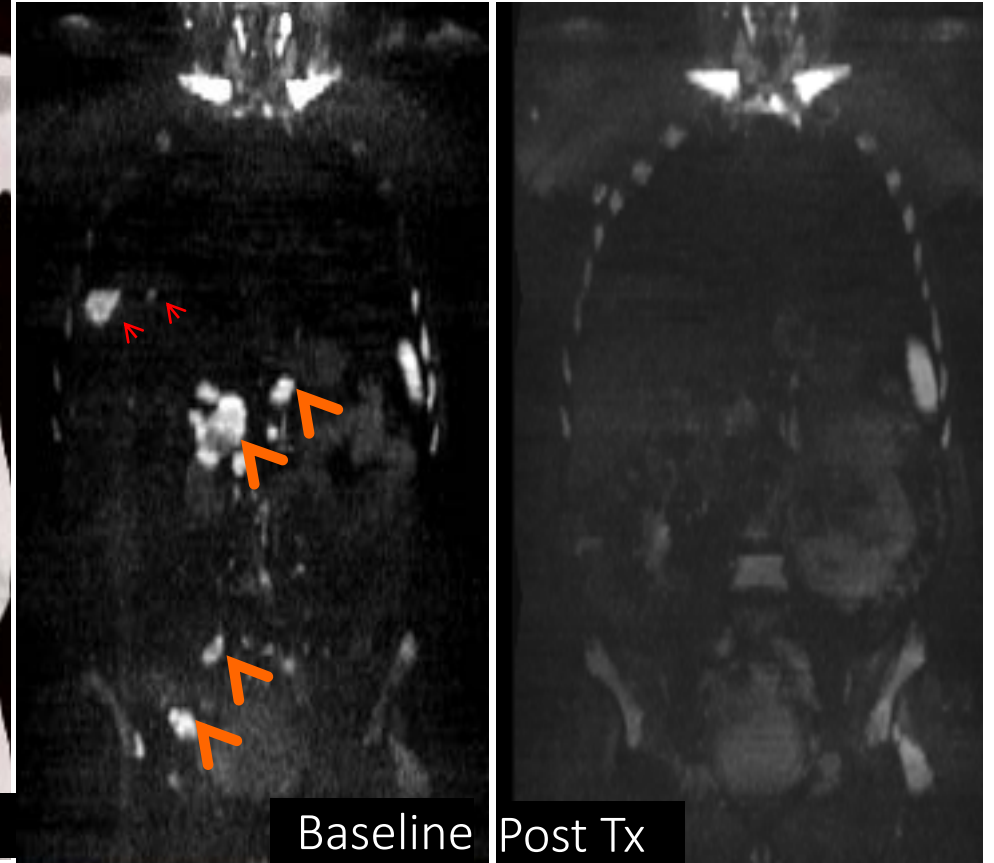
Post-Treatment



Whole Body MRI DWI – b 900

Pre-Treatment

Post-Treatment

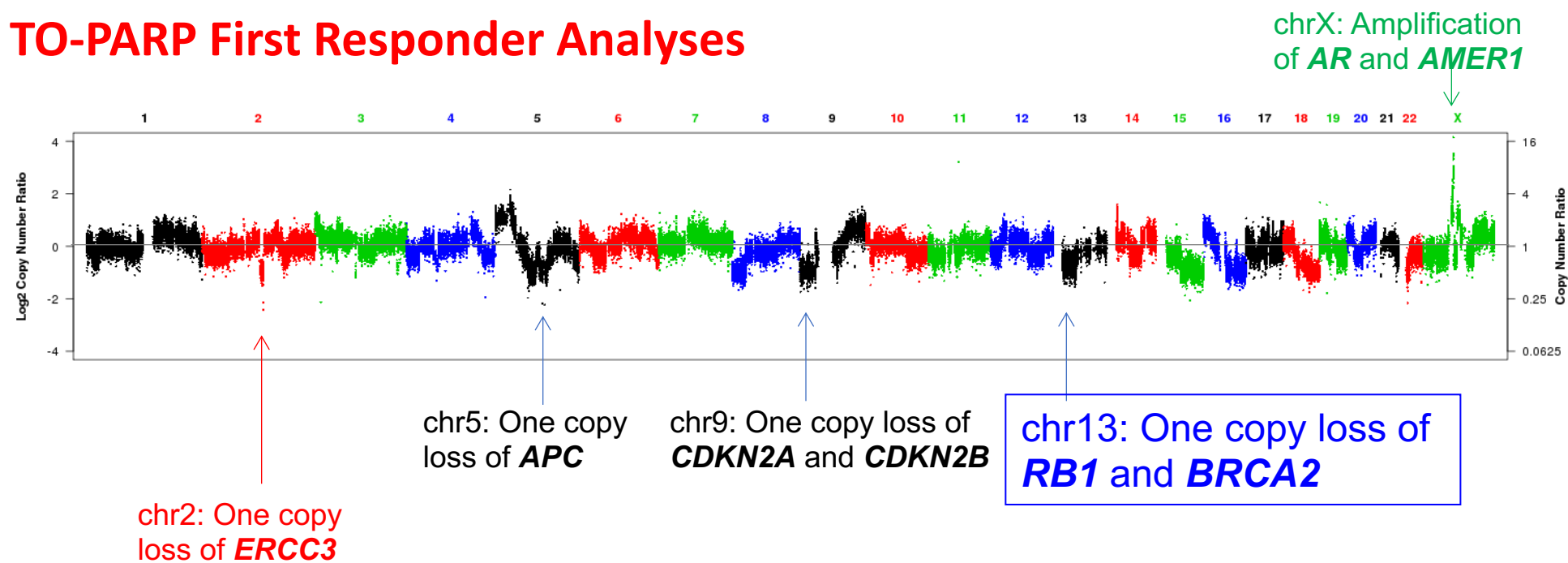


Whole Body MRI showing almost complete resolution of the liver metastases (red arrow), retroperitoneal and pelvic lymph nodes (yellow arrows) after 12 weeks.

(The signal in the clavicles is artifactual; signal in the spleen is normal.)

Case Presentation – Prof de Bono: A 70-year-old man with mCRPC and Somatic Cell Biallelic BRCA2 loss (continued)

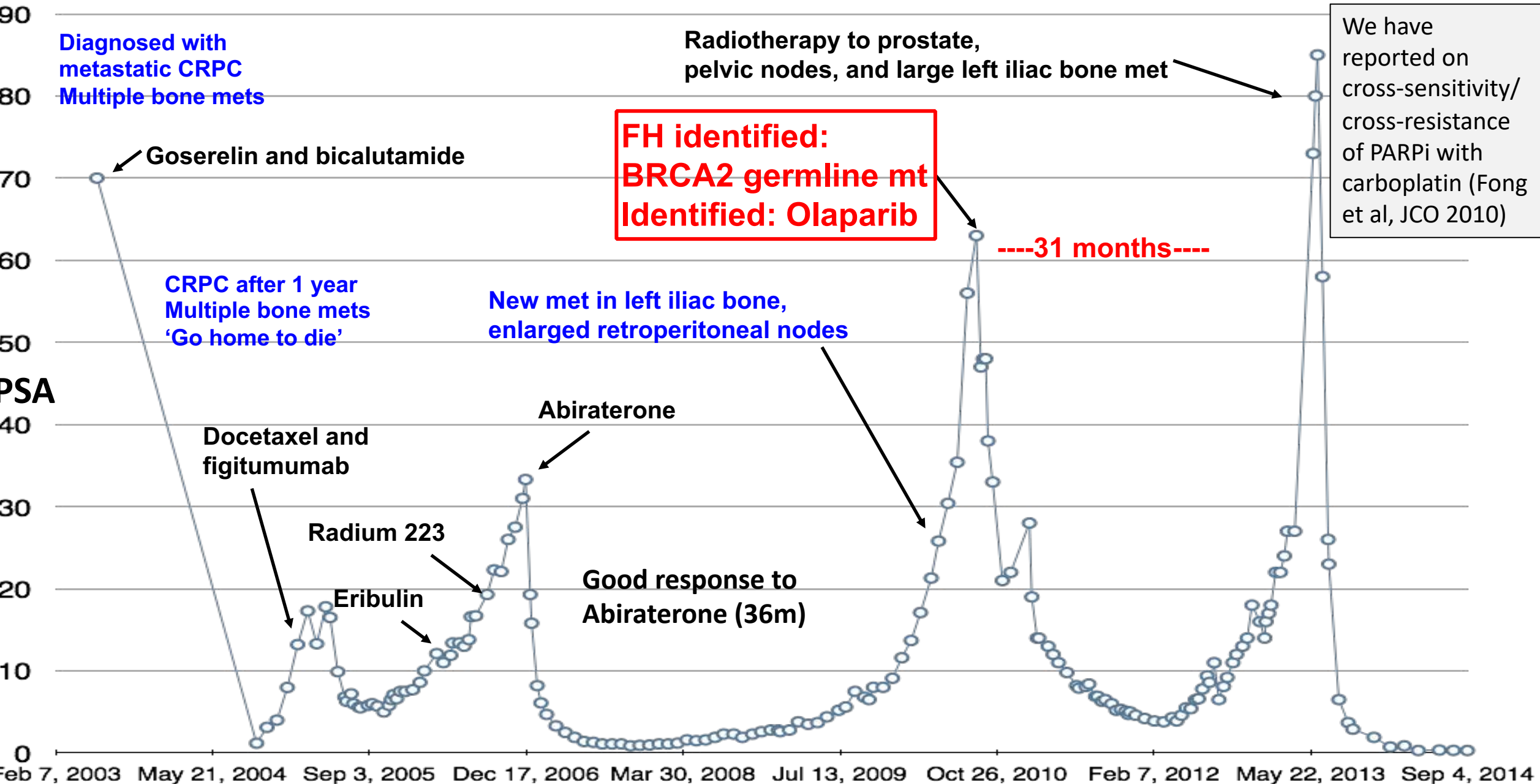
SU2C TO-PARP First Responder Analyses



Gene	ExonicFunc	Chr	Start	End	Ref	Obs	Var reads/ Total reads	Normal
BRCA2	frameshift substitution	13	32954225	32954252	CCATCTTGTTCTGAG GTGGACCTAATAG	CA	8/16	0/57

Somatic Cell Biallelic BRCA2 loss

Case Presentation – Prof de Bono: A 65-year-old man with mCRPC and a germline BRCA2 mutation



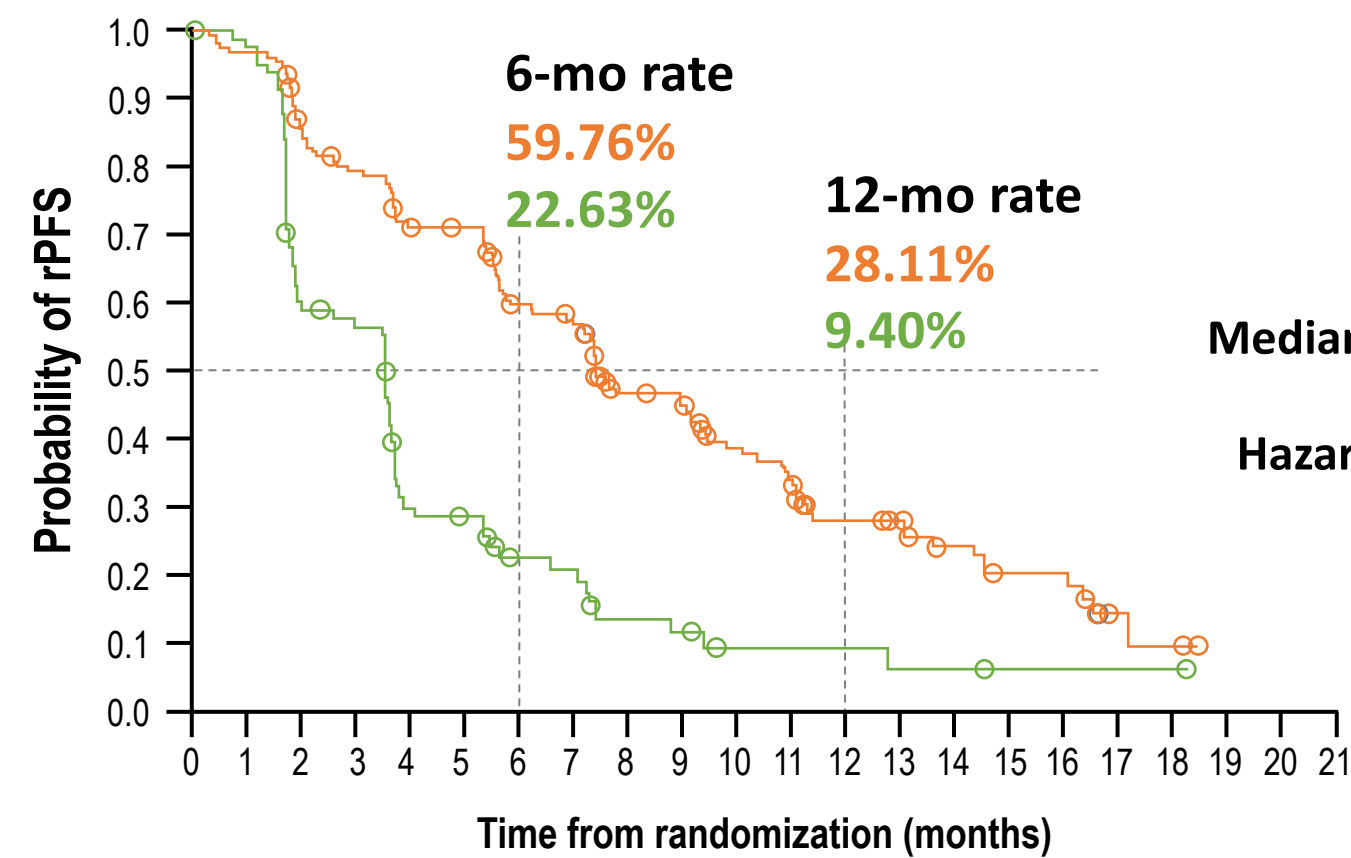
Time →

Courtesy of Johann de Bono, MBChB, MSc, PhD

Primary endpoint

PROfound Trial

rPFS BY BICR IN PATIENTS WITH ALTERATIONS IN *BRCA1*, *BRCA2*, OR *ATM* (COHORT A)



No. at risk

162	149	126	116	102	101	82	77	56	53	42	37	26	24	18	11	11	3	2	0	0	0
83	79	47	44	22	20	13	12	7	6	3	3	3	2	2	1	1	1	1	0	0	0

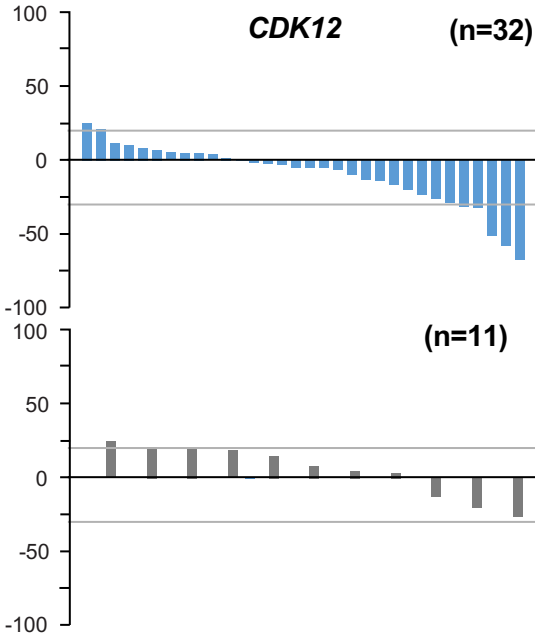
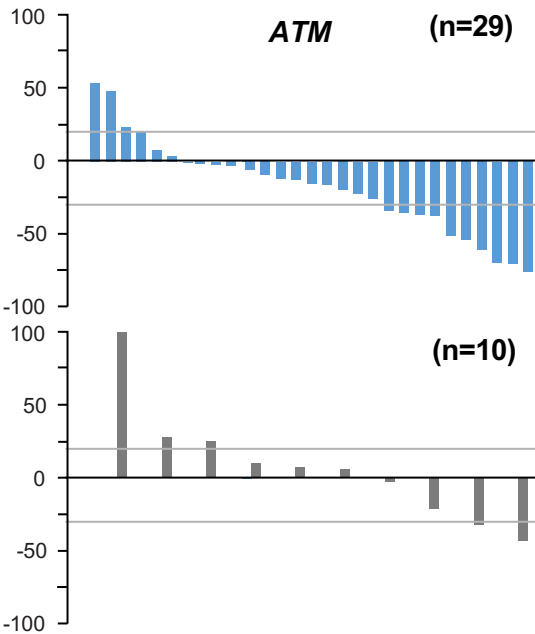
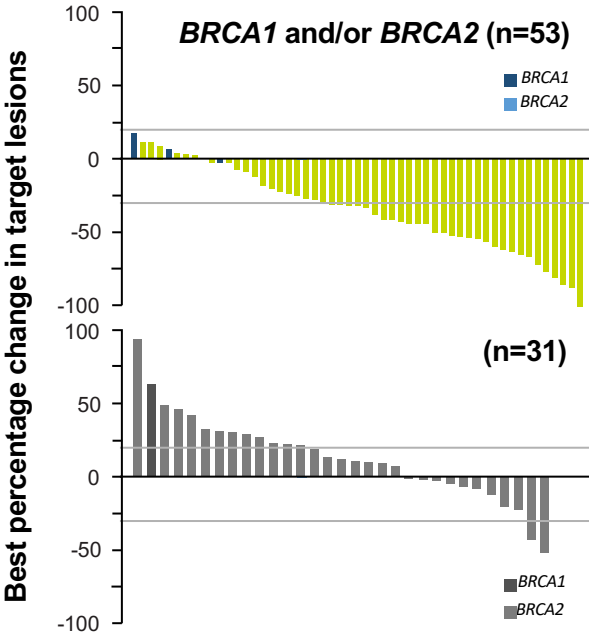
	Olaparib (N=162)	Physician's choice (N=83)
Events (%)	106 (65.4)	68 (81.9)
Median rPFS (months)	7.39	3.55
Hazard ratio (95% CI)	0.34 (0.25, 0.47) P<0.0001	

Olaparib
Physician's choice

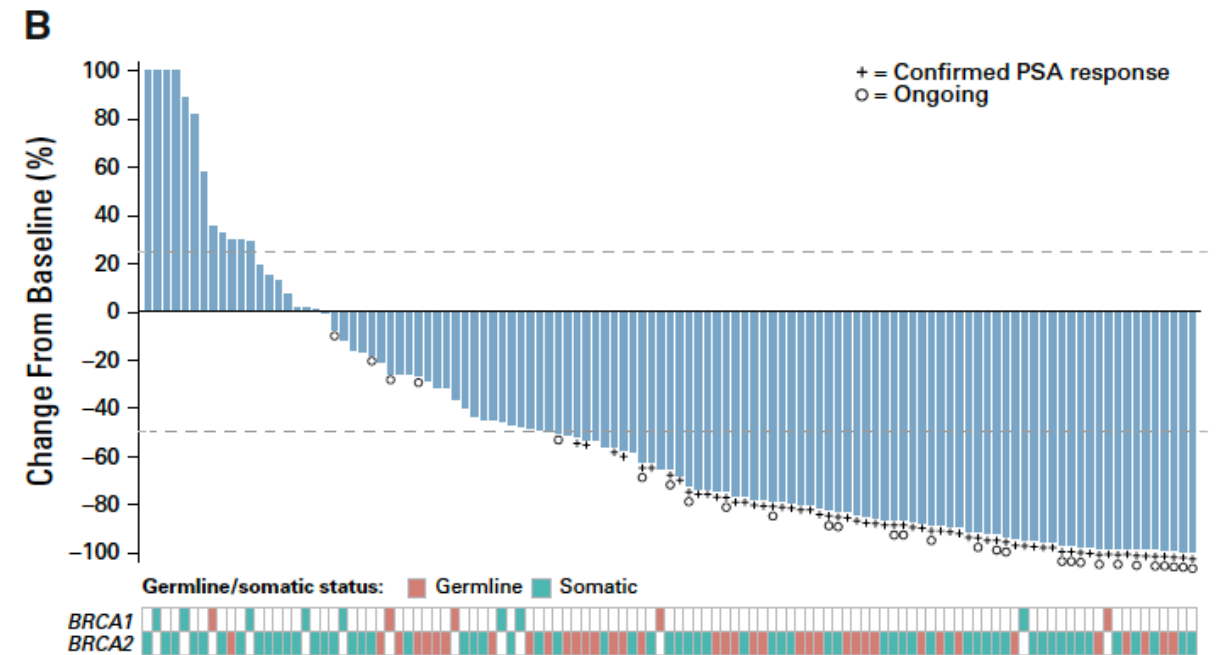
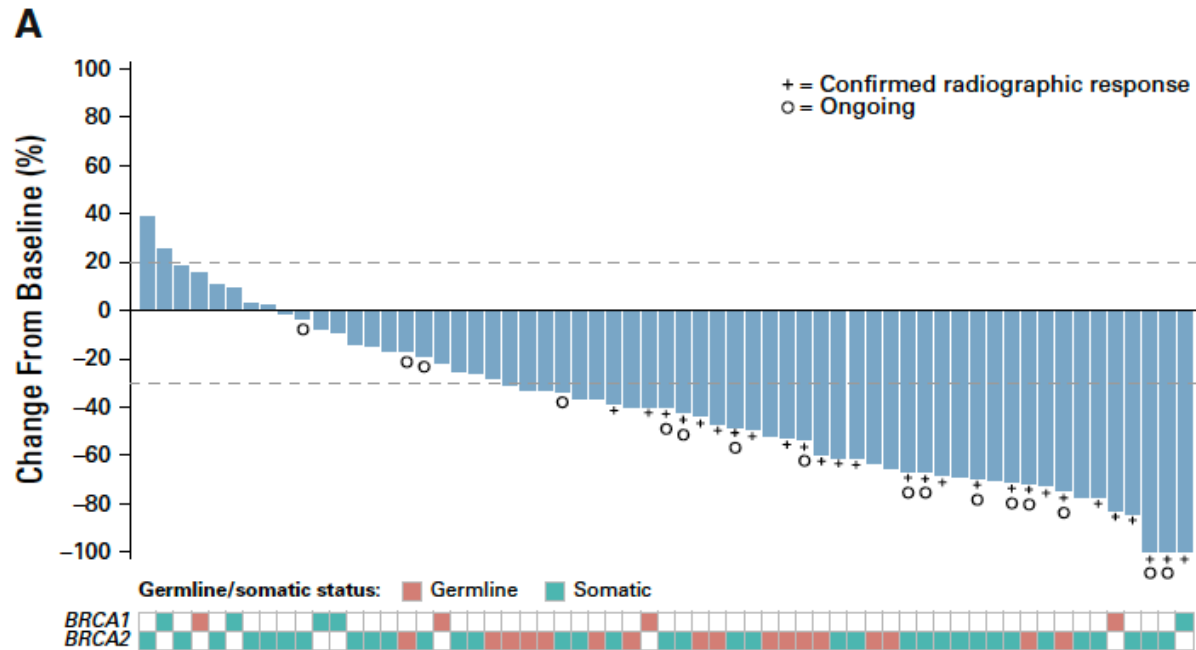
de Bono et al, NEJM 2020

Olaparib antitumor activity in PROfound

		Cohort A		Cohorts A+B		BRCA1 and/or BRCA2		ATM		CDK12	
		Olaparib (N=162)	Control (N=83)	Olaparib (N=256)	Control (N=131)	Olaparib (N=102)	Control (N=58)	Olaparib (N=62)	Control (N=24)	Olaparib (N=61)	Control (N=28)
rPFS	Median, months	7.4	3.6	5.8	3.5	9.8	3.0	5.4	4.7	5.1	2.2
	HR (95% CI)	0.34 (0.25–0.47)		0.49 (0.38–0.63)		0.22 (0.15–0.32)		1.04 (0.61–1.87)		0.74 (0.44–1.31)	
OS	Median OS, months	19.1	14.7	17.3	14.0	20.1	14.4	18.0	15.6	14.1	11.5
	HR (95% CI)	0.69 (0.50–0.97)		0.79 (0.61–1.03)		0.63 (0.42–0.95)		0.93 (0.53–1.75)		0.97 (0.57–1.71)	
ORR	Evaluable patients, n	84	43	138	67	57	33	30	10	34	12
	ORR, %	33.3	2.3	21.7	4.5	43.9	0	10.0	10.0	5.9	0
PSA	Evaluable patients, n	153	77	243	123	94	54	61	22	58	27
	Confirmed response, %	43.1	7.8	30.0	9.8	61.7	0	13.1	22.7	5.2	3.7
CTC	Evaluable patients, n	52	22	78	32	29	17	25	3	14	5
	Conversion, %	55.8	22.7	52.6	21.9	69.0	23.5	40.0	33.3	50.0	40.0



TRITON2: Rucaparib confirmed PARPi antitumor activity in BRCA2 mCRPC



Abida W et al, JCO 2020

Courtesy of Johann de Bono, MBChB, MSc, PhD

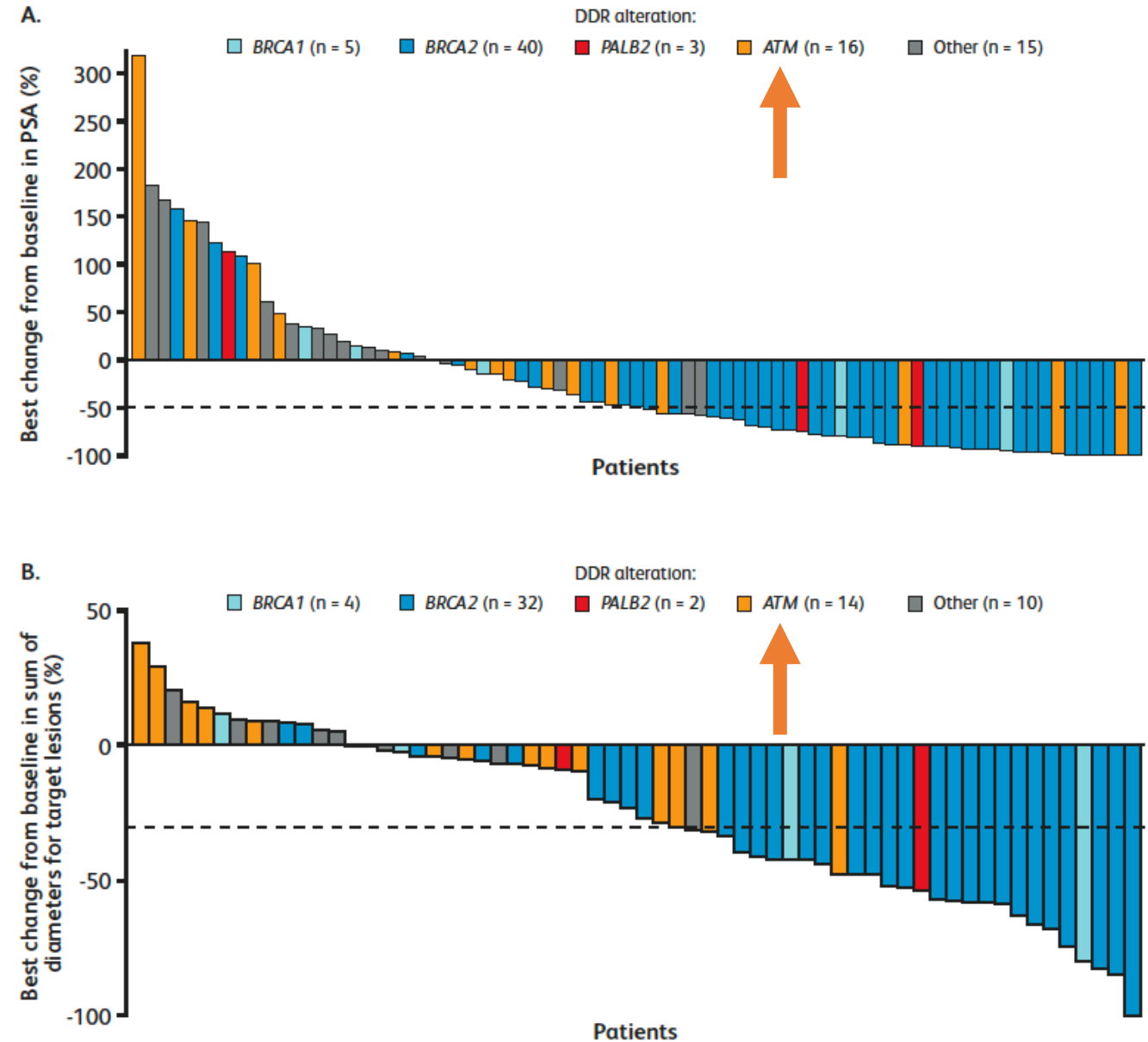
Talazoparib in mCRPC (TALAPRO-1)

BRCA in blue

ATM loss in orange

PALB2 in red

Figure 4. Best Change From Baseline in A. PSA and B. RECIST^a



Courtesy of Johann de Bono, MBChB, MSc, PhD

de Bono et al, in press

^aDDR deficient population includes DDR patients who received treatment for ≥ 16 weeks; for panel A (n = 79) and for panel B (n = 62).
Abbreviations: DDR, DNA damage repair; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors version 1.1.

Multiple drug combinations under consideration

- AR signaling inhibitors
 - Abiraterone, apalutamide, enzalutamide
- PSMA targeting radioisotopes
 - PSMA Lutetium
- PD-1/PD-L1 immune checkpoint inhibitors
- Other combinations

Agenda

Module 1: Integration of PARP Inhibitors into the Management of Metastatic Castration-Resistant Prostate Cancer (mCRPC)

- Genomic biology of prostate cancer
- Faculty cases
- PROfound: Olaparib versus AR-targeted therapy in men with HRR mutation-selected mCRPC
- TRITON2: Rucaparib monotherapy for mCRPC previously treated with AR-targeted therapy and a taxane
- TALAPRO-1: Talazoparib in men with DNA damage repair mutations and mCRPC

Module 2: Selection and Sequencing of Therapy in mCRPC

- CARD: Cabazitaxel versus an AR-targeted agent for mCRPC
- OSTRICH: Cabazitaxel versus an AR-targeted agent for patients with poor-prognosis mCRPC
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- VISION: ¹⁷⁷Lu-PSMA-617 for patients with progressive PSMA-positive mCRPC
- COSMIC-021: Cabozantinib with atezolizumab for mCRPC
- Faculty cases

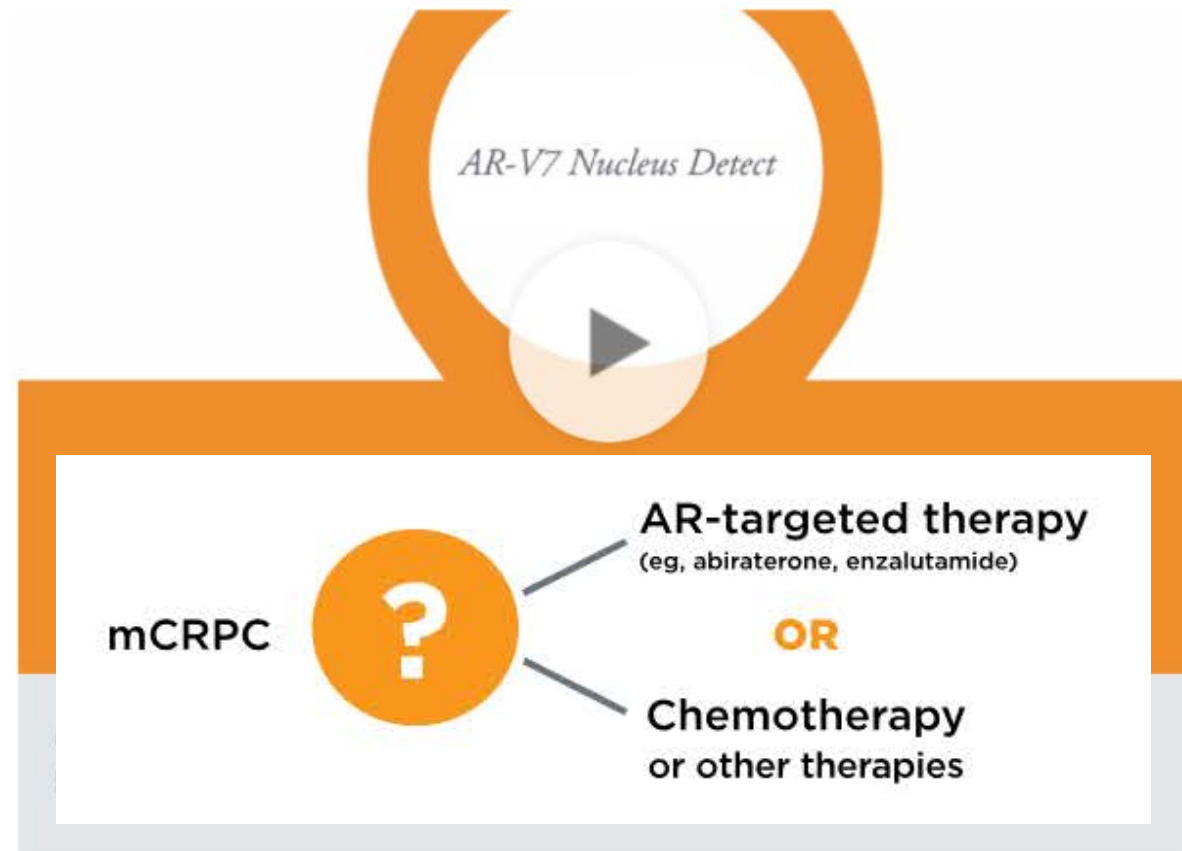
AR-V7

AR-V7 NUCLEUS DETECT

About the AR-V7 Nucleus Detect test

Share    

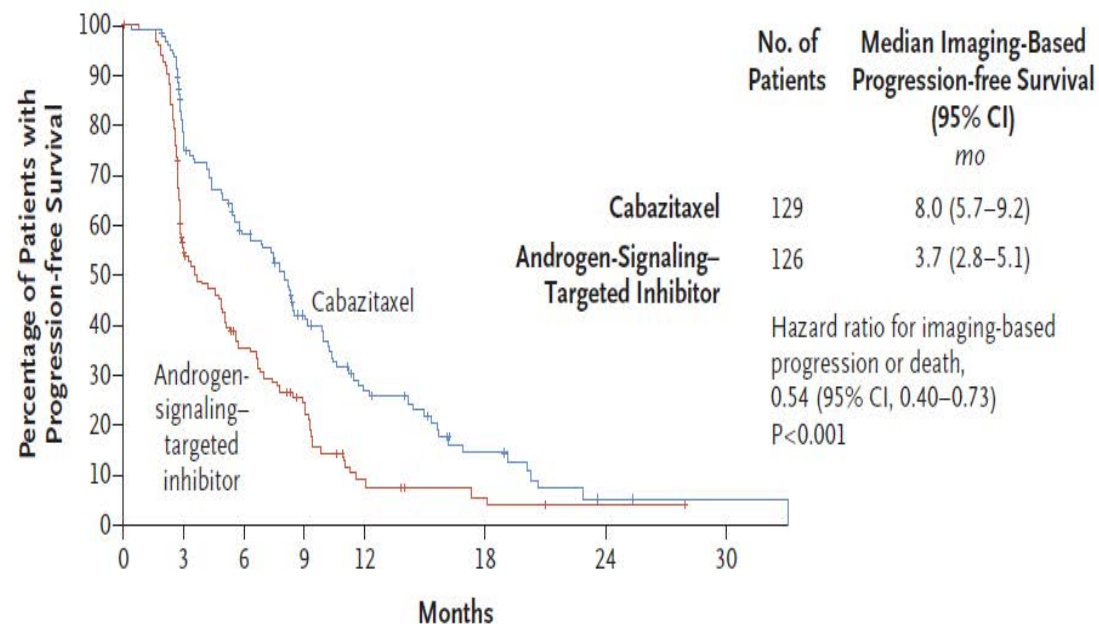
Why Order the AR-V7 Nucleus Detect Test?



Courtesy of Emmanuel S Antonarakis, MD

The CARD trial

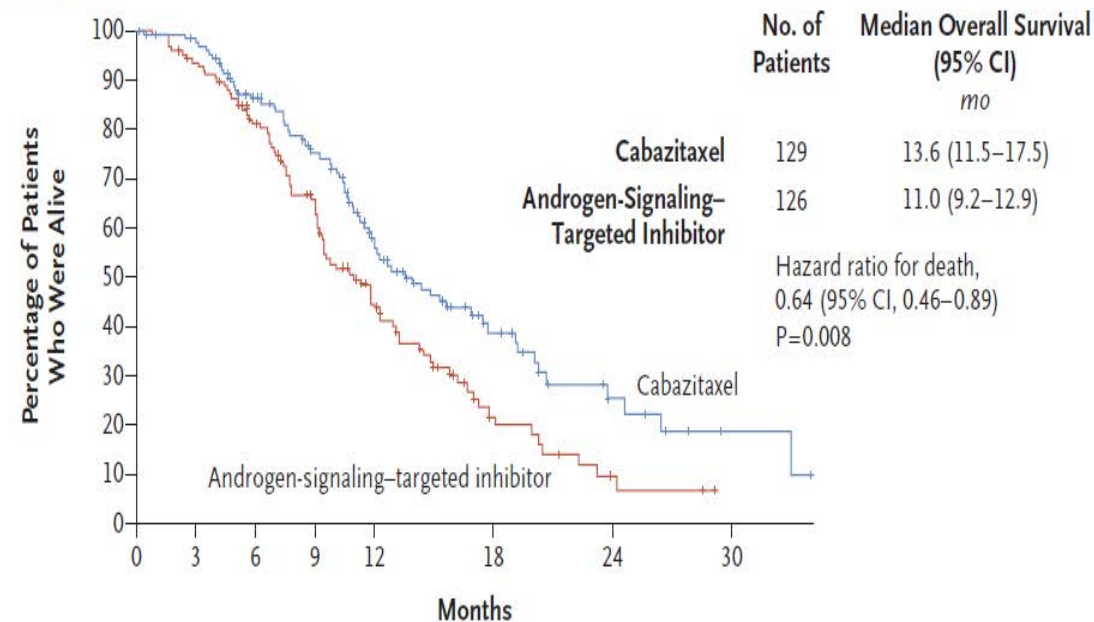
A Imaging-Based Progression-free Survival



No. at Risk

Cabazitaxel	129	91	64	41	23	9	2	1
Androgen-signaling-targeted inhibitor	126	61	36	22	7	3	1	0

A Overall Survival



No. at Risk

Cabazitaxel	129	122	96	77	51	21	8	2
Androgen-signaling-targeted inhibitor	126	116	88	64	39	11	3	0

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

The CARD trial

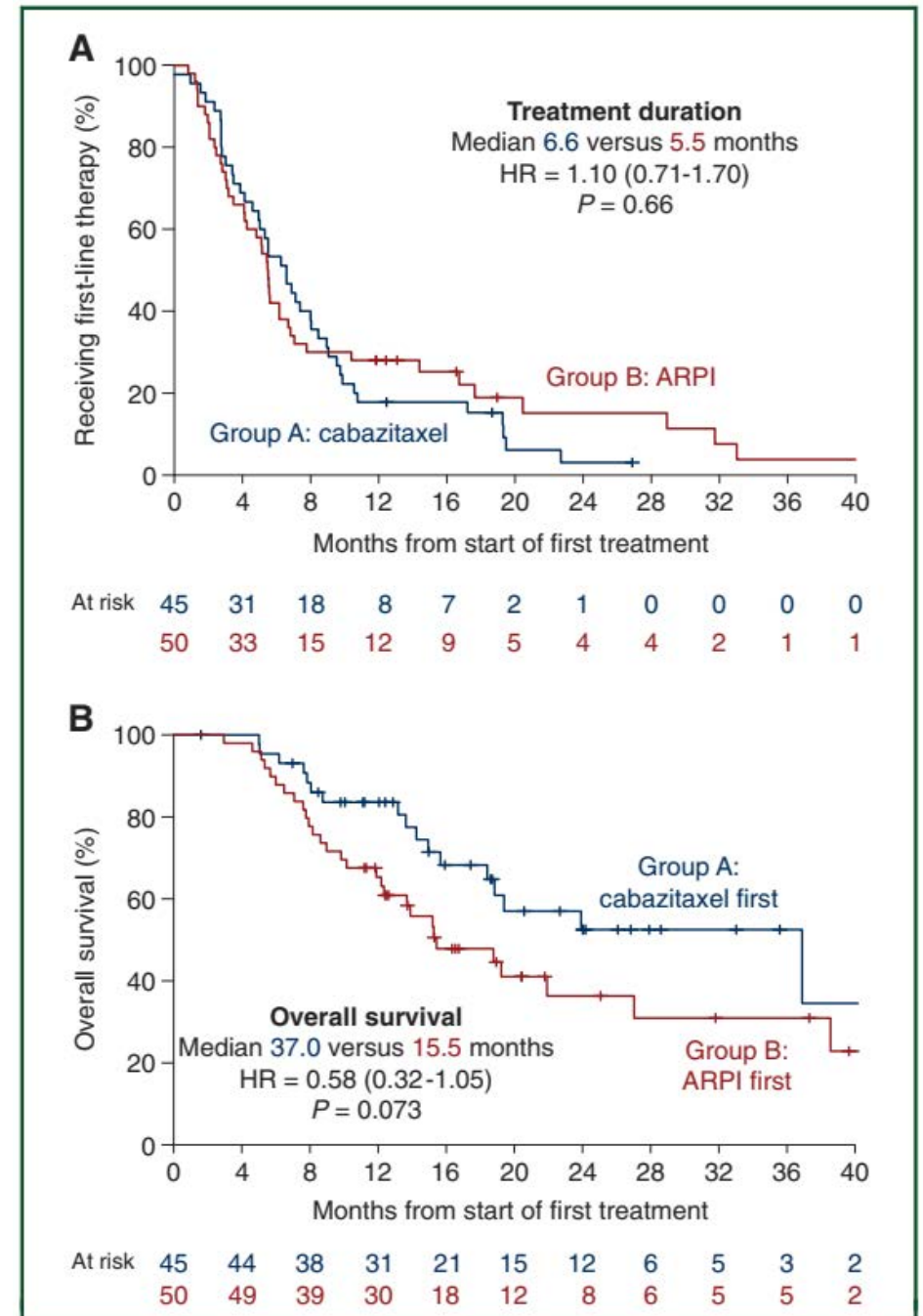
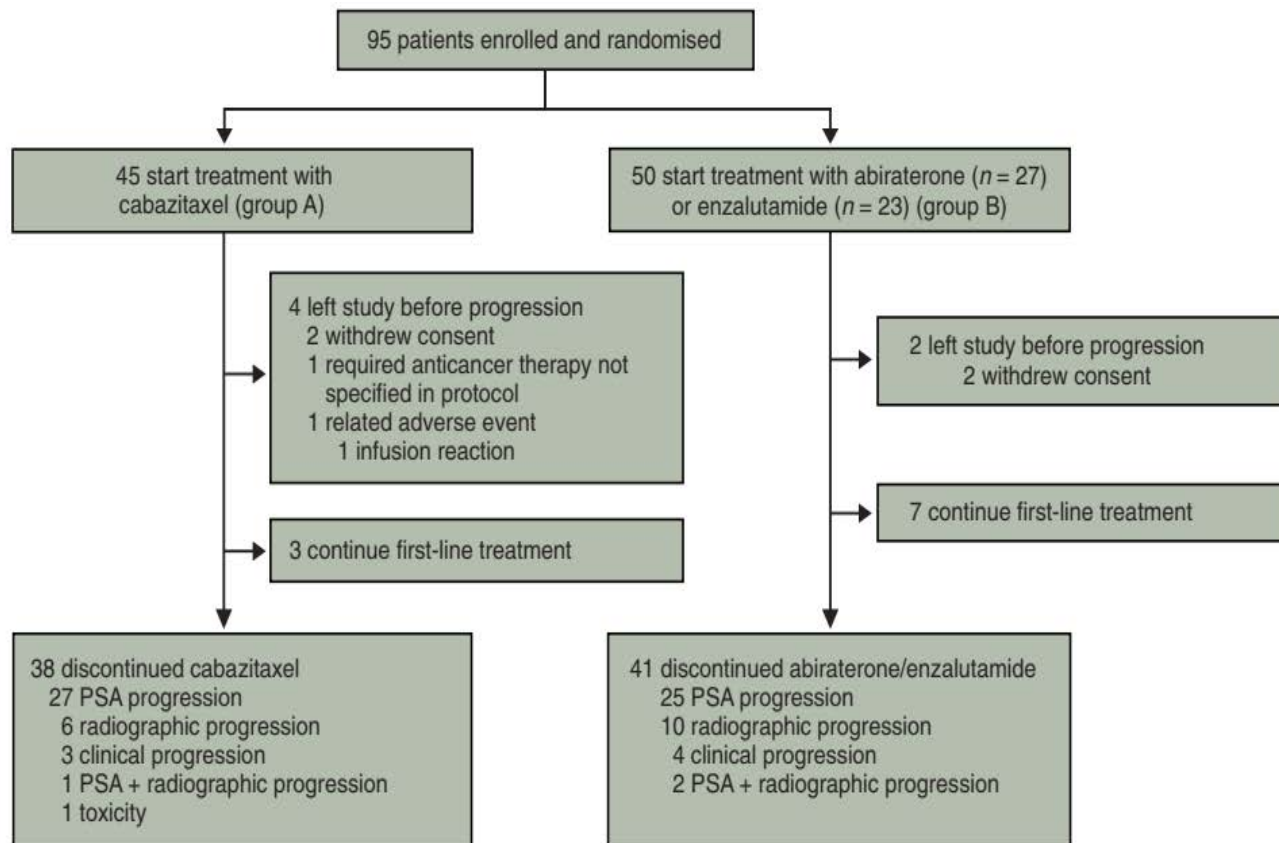
Table 2. Adverse Events (Safety Population).

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)

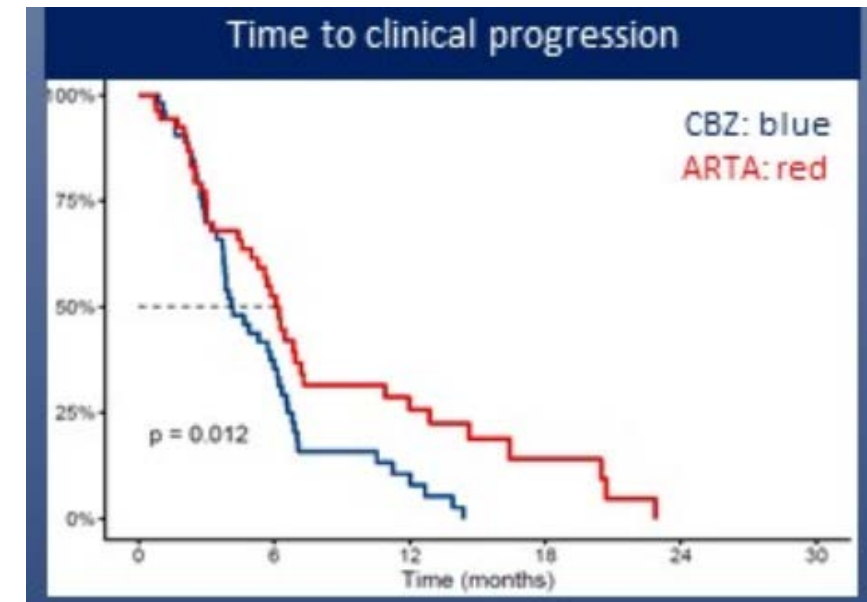
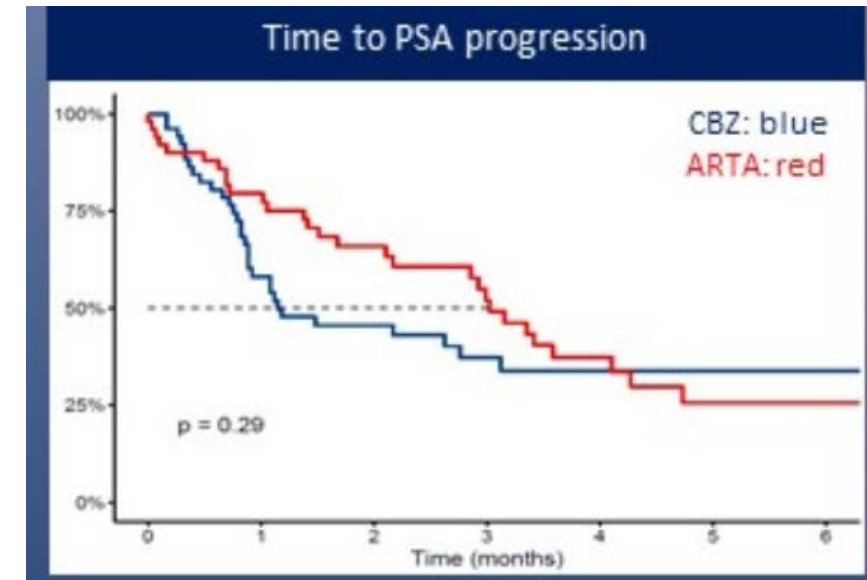
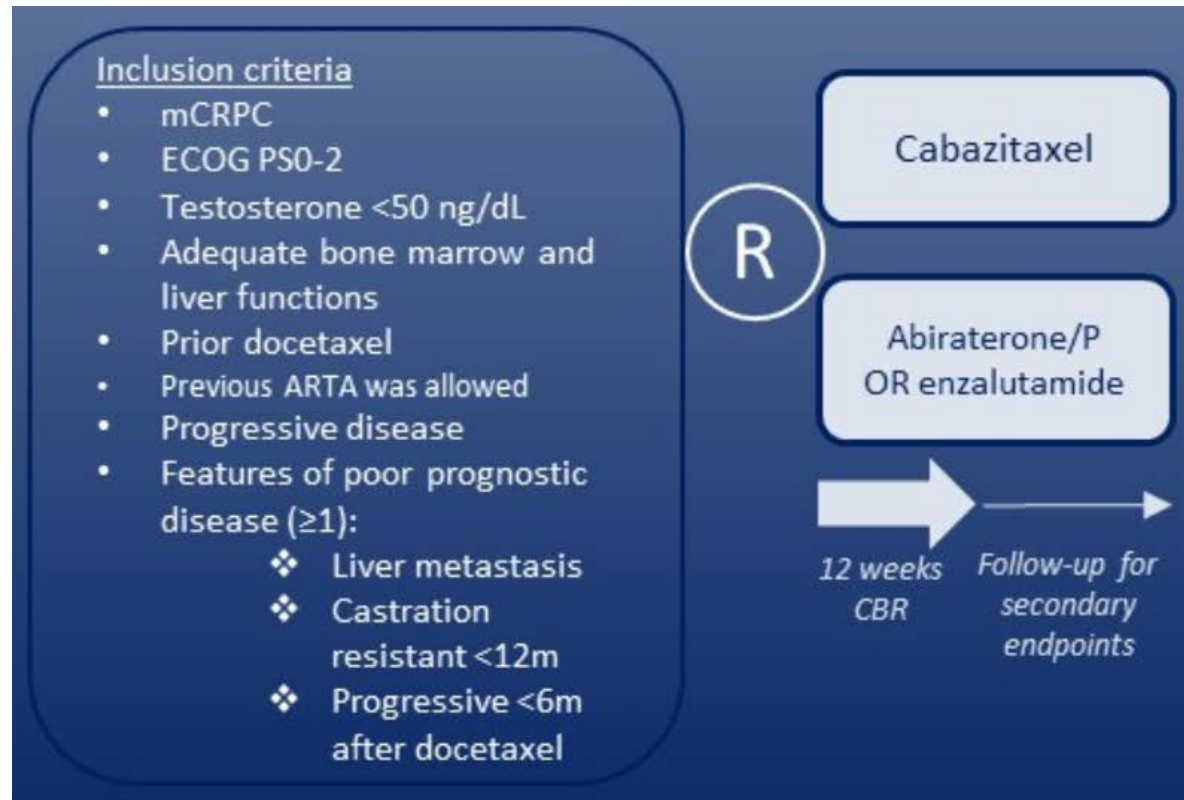
The Canadian trial (Phase II OZM-054 Trial)

Poor prognosis:

liver mets,
CRPC <12 months,
or >3 of 6 (LDH, ECOG, visceral, albumin, ALP, <36 mo from Dx)



The Dutch trial (Phase II OSTRICH Trial)



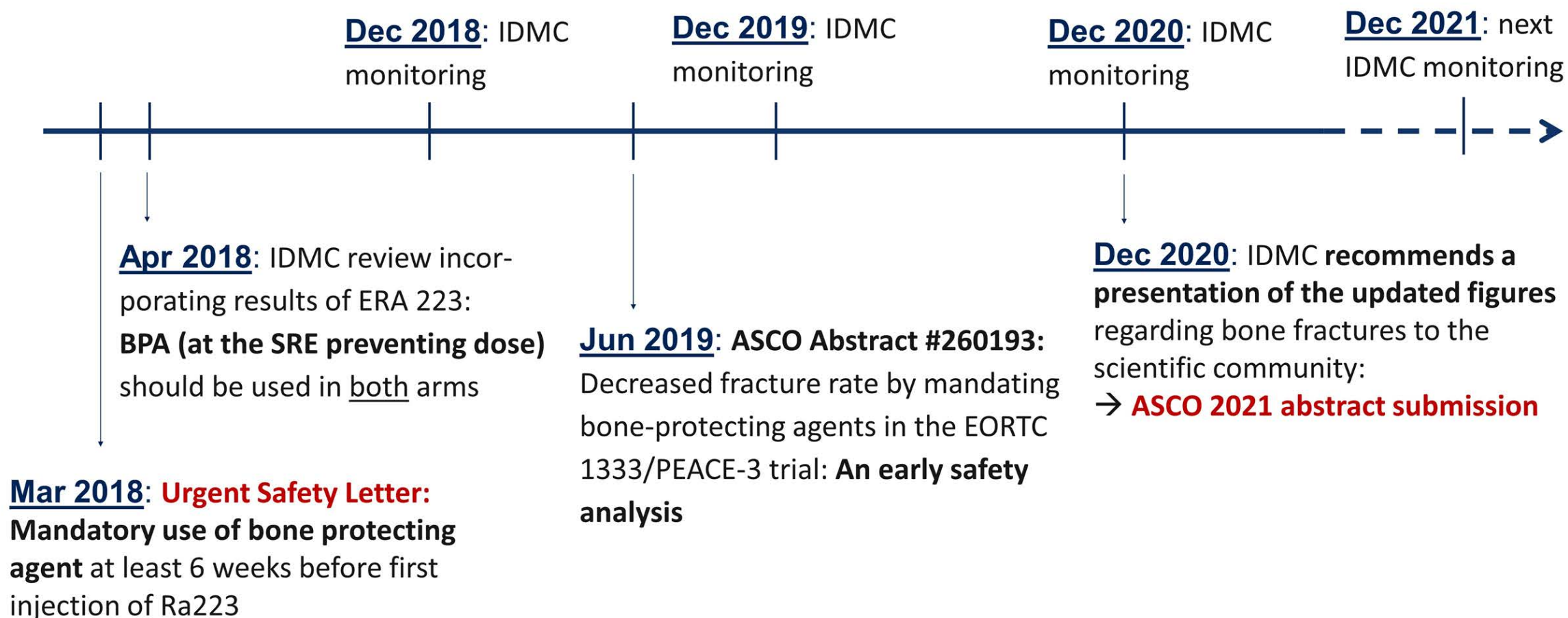
van der Zande K, et al. ASCO 2021; abstract 5059.

Courtesy of Emmanuel S Antonarakis, MD

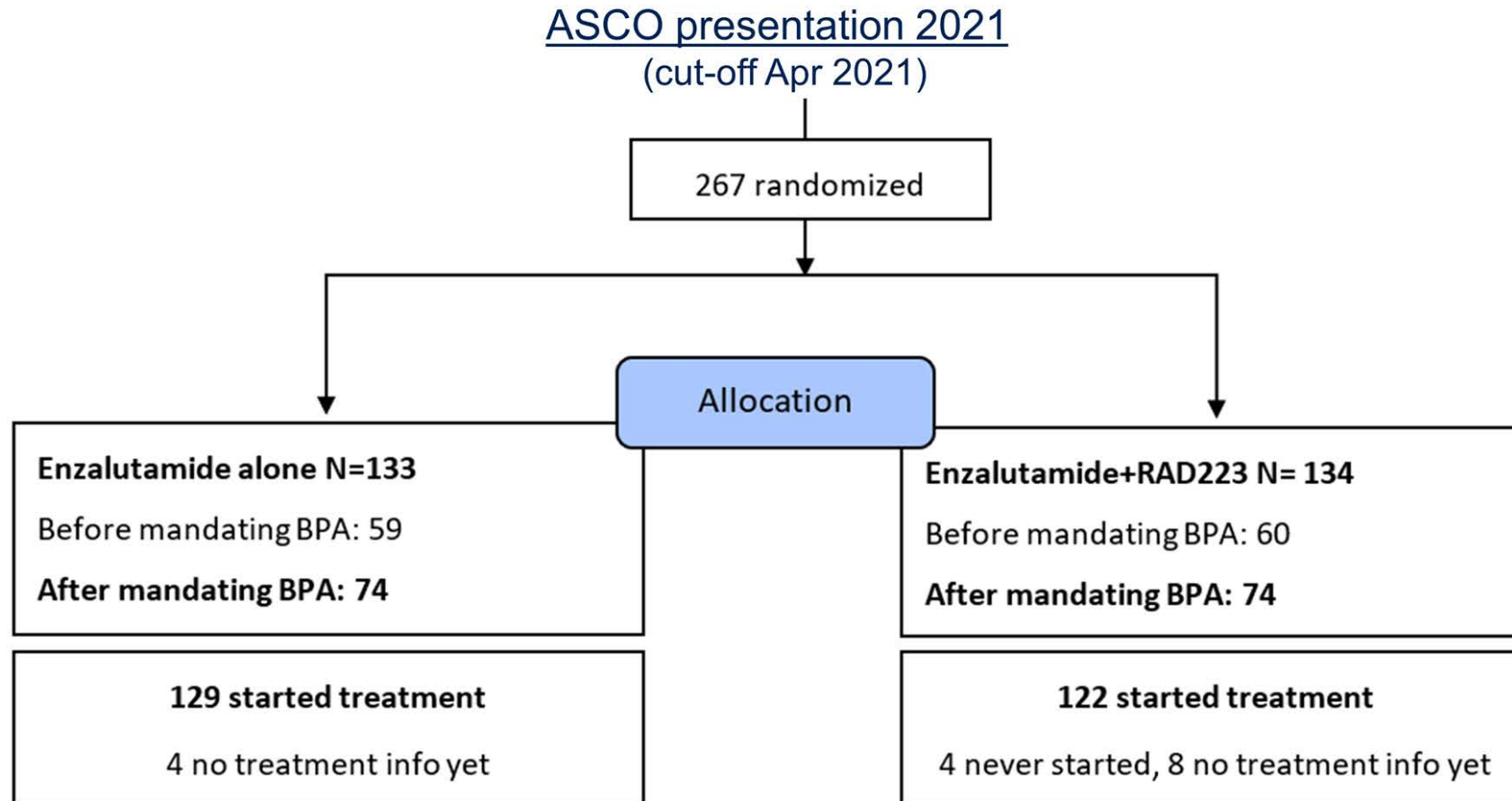
Ideal patient for Radium-223 treatment

- mCRPC with symptomatic bone metastases
- Mild bone pain (1-4/10), but not severe bone pain ($\geq 5/10$)
- 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 $\geq 100K$)
- 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

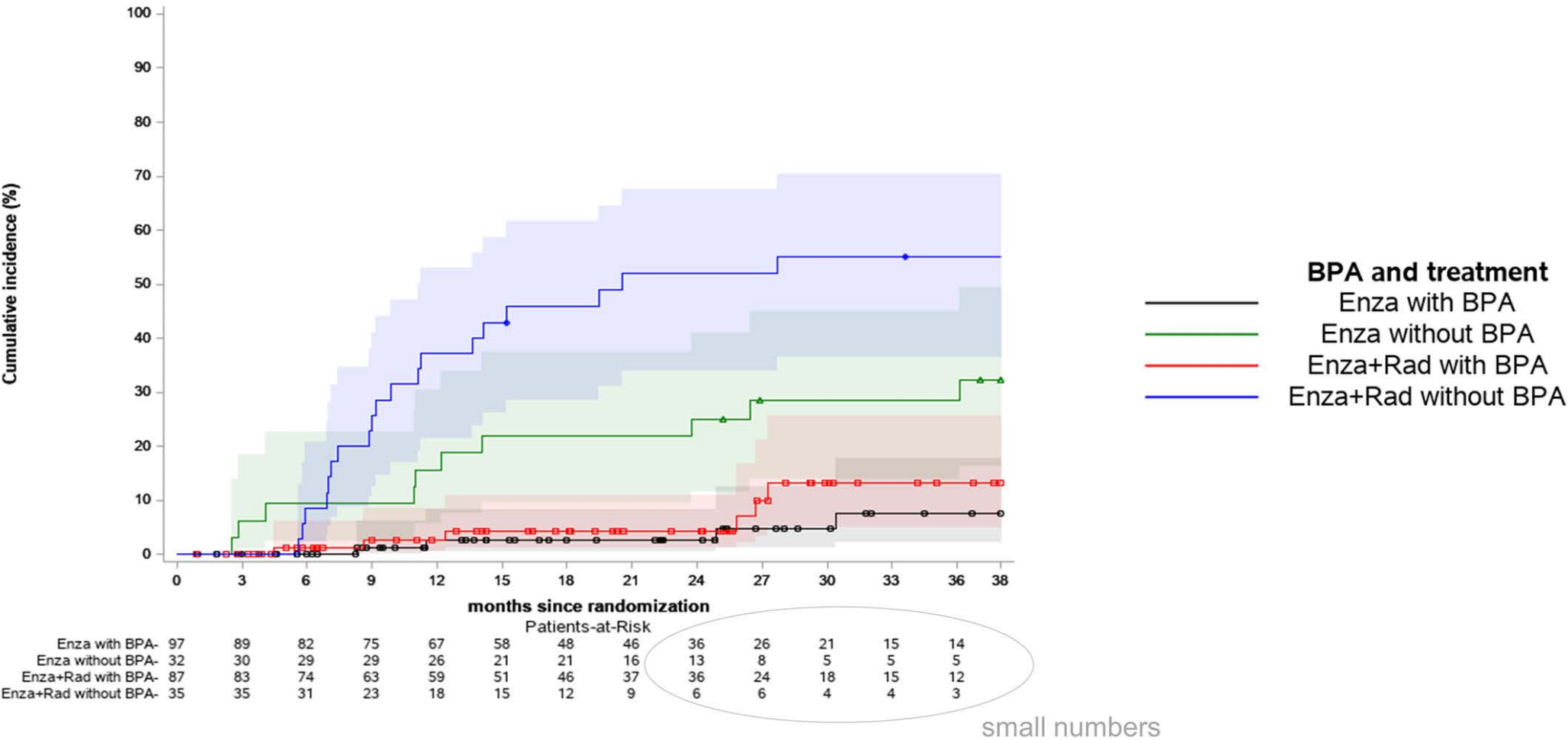
PEACE III: Timelines, impact of ERA 223 and role of IDMC



Updated results of the safety analysis for the EORTC 1333 (PEACE III) trial: Impact of bone protecting agents (BPA) on fracture rates



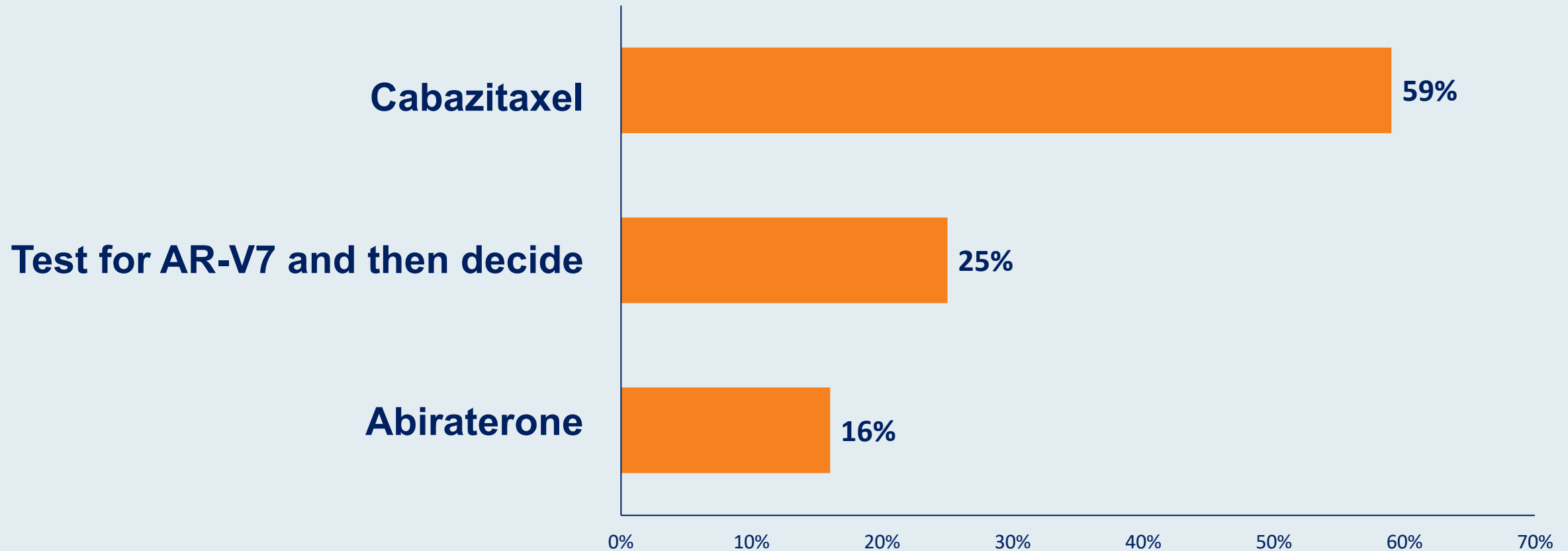
PEACE III: Cumulative incidence of fractures by treatment arm and use of bone protecting agents



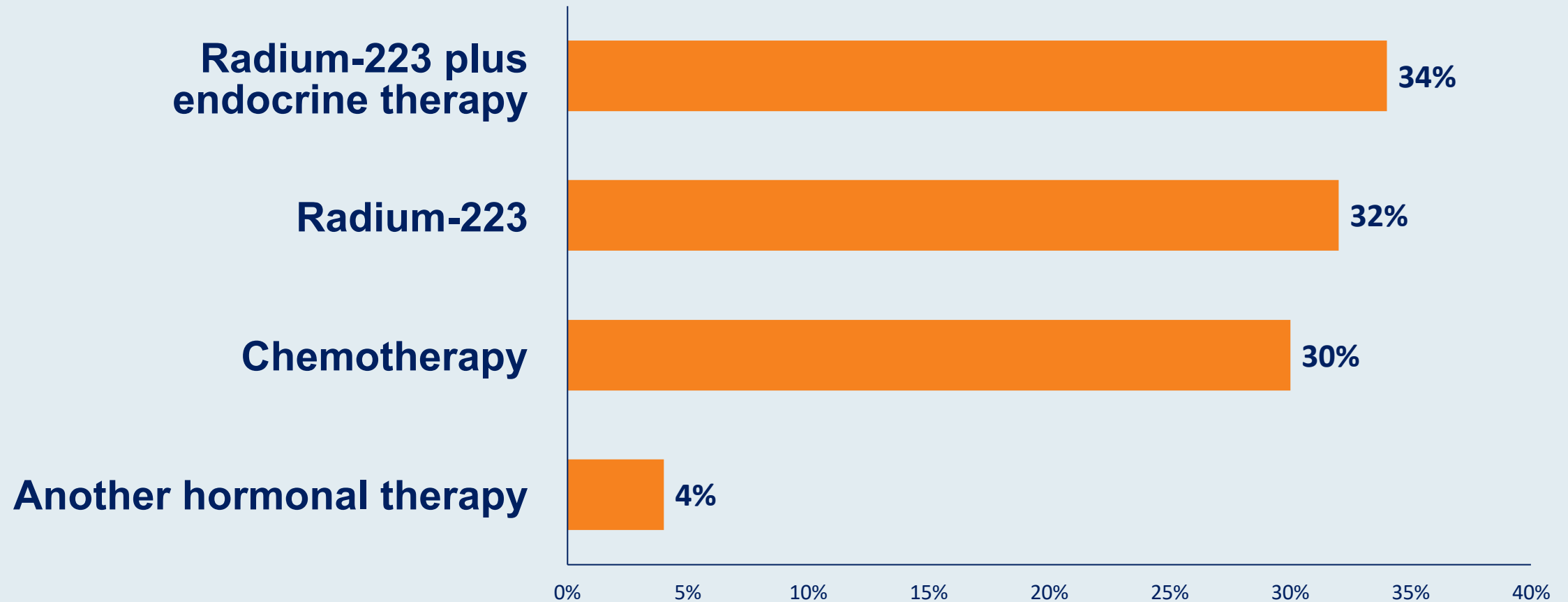
PEACE III: Bone fractures and cumulative incidence – safety population

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)

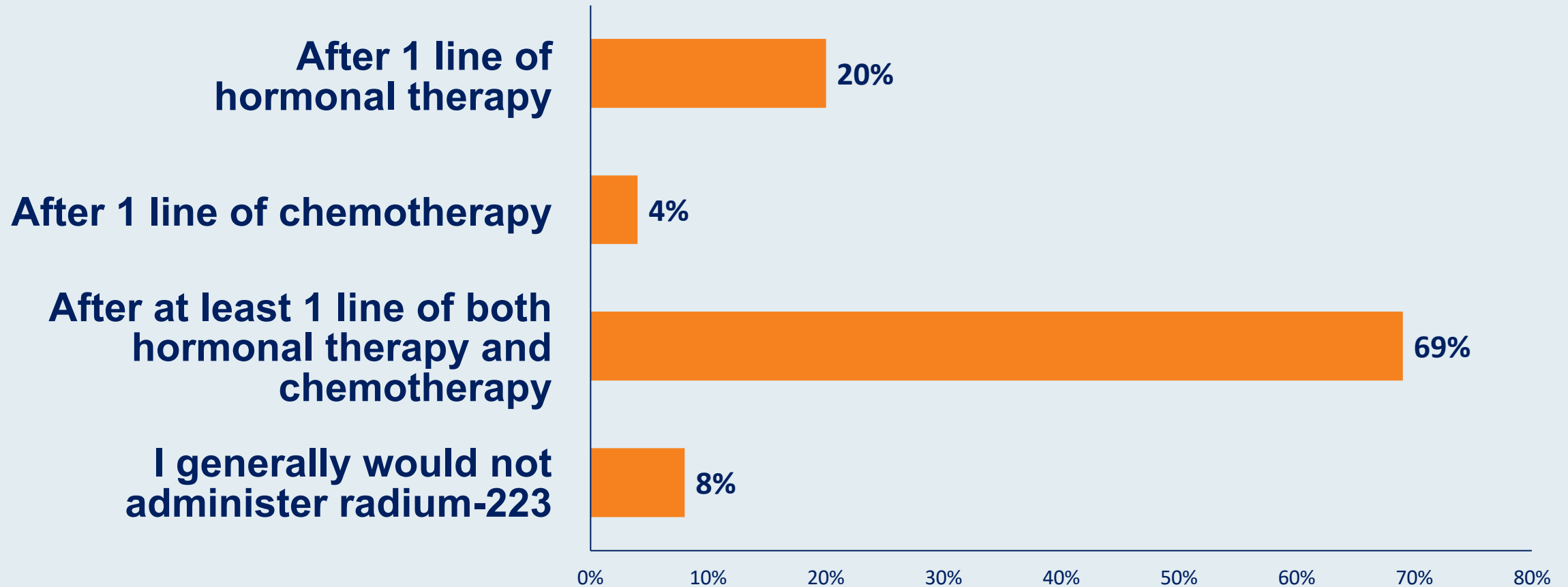
A 65-year-old man presents with minimally symptomatic mPC to the nodes and bone and receives docetaxel and ADT with response followed by disease progression. The patient is started on enzalutamide but experiences further progression after 9 months. What would you recommend?



For a patient with mPC and bone-only metastases who has received prior docetaxel then responds to but develops disease progression on secondary hormonal therapy (eg, enzalutamide, apalutamide, abiraterone), what is your likely next systemic treatment?



At what point, if any, do you generally recommend radium-223 to a patient with bone-only mCRPC?



Case Presentation – Dr Antonarakis: A 62-year-old man with de novo mHSPC

- 62-year-old man, diagnosed with *de novo* mHSPC (bone + liver)
- Prostate biopsy: Gleason 5+4=9
- Liver biopsy: prostate adeno, no NEPC, NGS—somatic *BRCA1*
- No family history of cancer; germline testing negative
- Received ADT + 6x docetaxel; developed mCRPC in 9 mo
- Then received enzalutamide, no response after 3 mo
- Worsening bone mets; liver mets growing again
- Options: olaparib, cabazitaxel
- Started cabazitaxel—PR in liver, and PSA response (ongoing)

Case Presentation – Dr Antonarakis: A 58-year-old man with mCRPC and a germline *ATM* mutation

- 58-year-old man; Gleason 4+3=7 localized prostate cancer
- Family history of male breast cancer in father
- Prostatectomy (pT3b N0 R0); Adjuvant XRT
- Biochemical recurrence, treated with intermittent ADT
- Developed nmCRPC after 2 years; PSADT = 5.8 months
- Received Darolutamide for 18 months
- Developed mets in bones (x3) and RP lymph nodes
- Lymph node biopsy: somatic NGS found *ATM* mutation
- Germline testing confirmed inherited *ATM* mutation

Case Presentation – Dr Antonarakis: A 58-year-old man with mCRPC and a germline *ATM* mutation (continued)

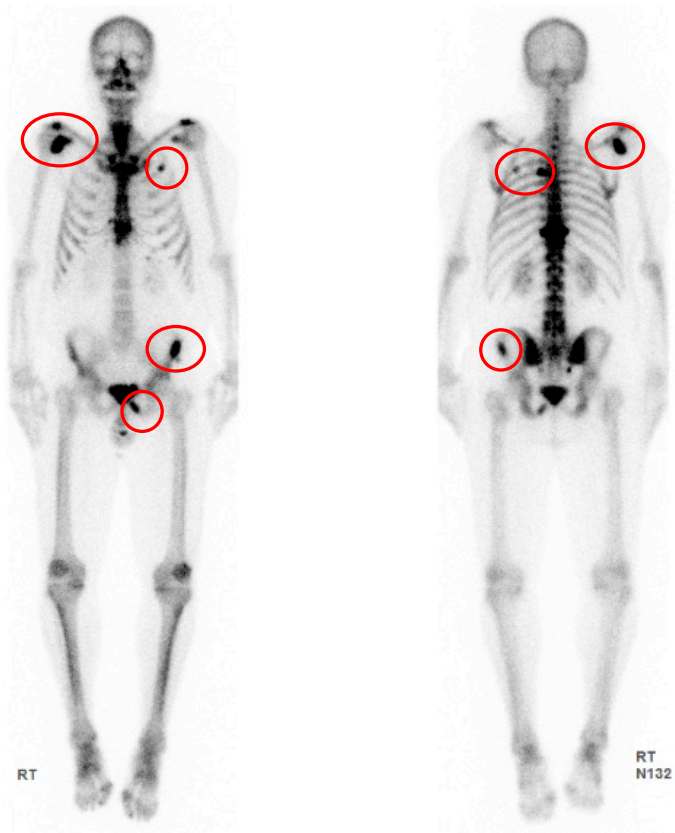
- 58 y/o man; received Daro for nmCRPC; g*ATM* mutation
- Then developed mCRPC (3 bone mets; RP nodes)
- Declined chemo; received Abiraterone (no response)
- Due to g*ATM* mutation, then received Olaparib
- Minor response to Olaparib, with progression after 5 mo
- Now, mCRPC s/p Daro, Abi and Olaparib → symptomatic
- Options: Chemo? Rad-223?

Case Presentation – Dr Antonarakis: A 58-year-old man with mCRPC and a germline ATM mutation (continued)

ATM-mutated Pt who received Radium-223

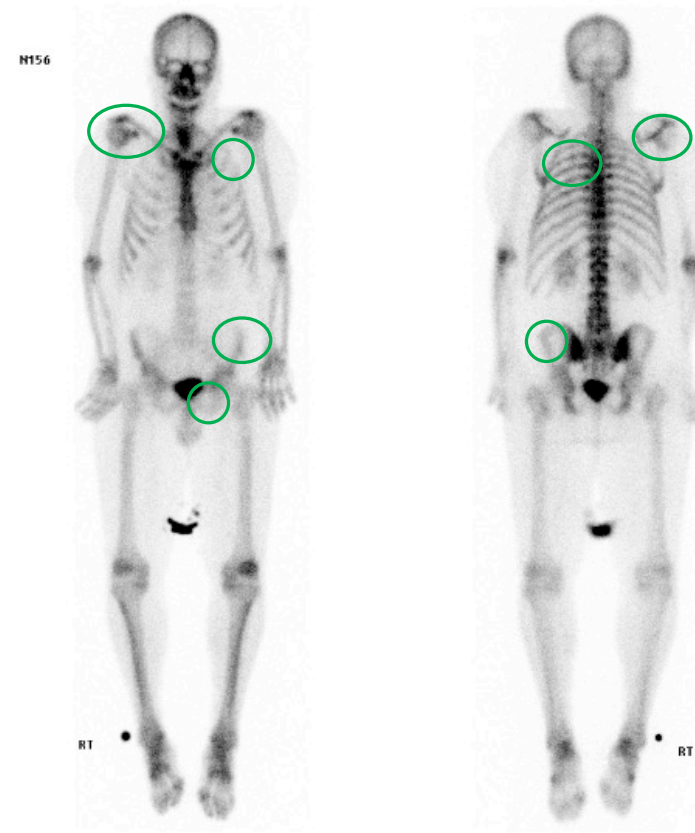
Bone scan (2/23/2019)

- Baseline



Bone scan (8/26/2019)

- After 6 months



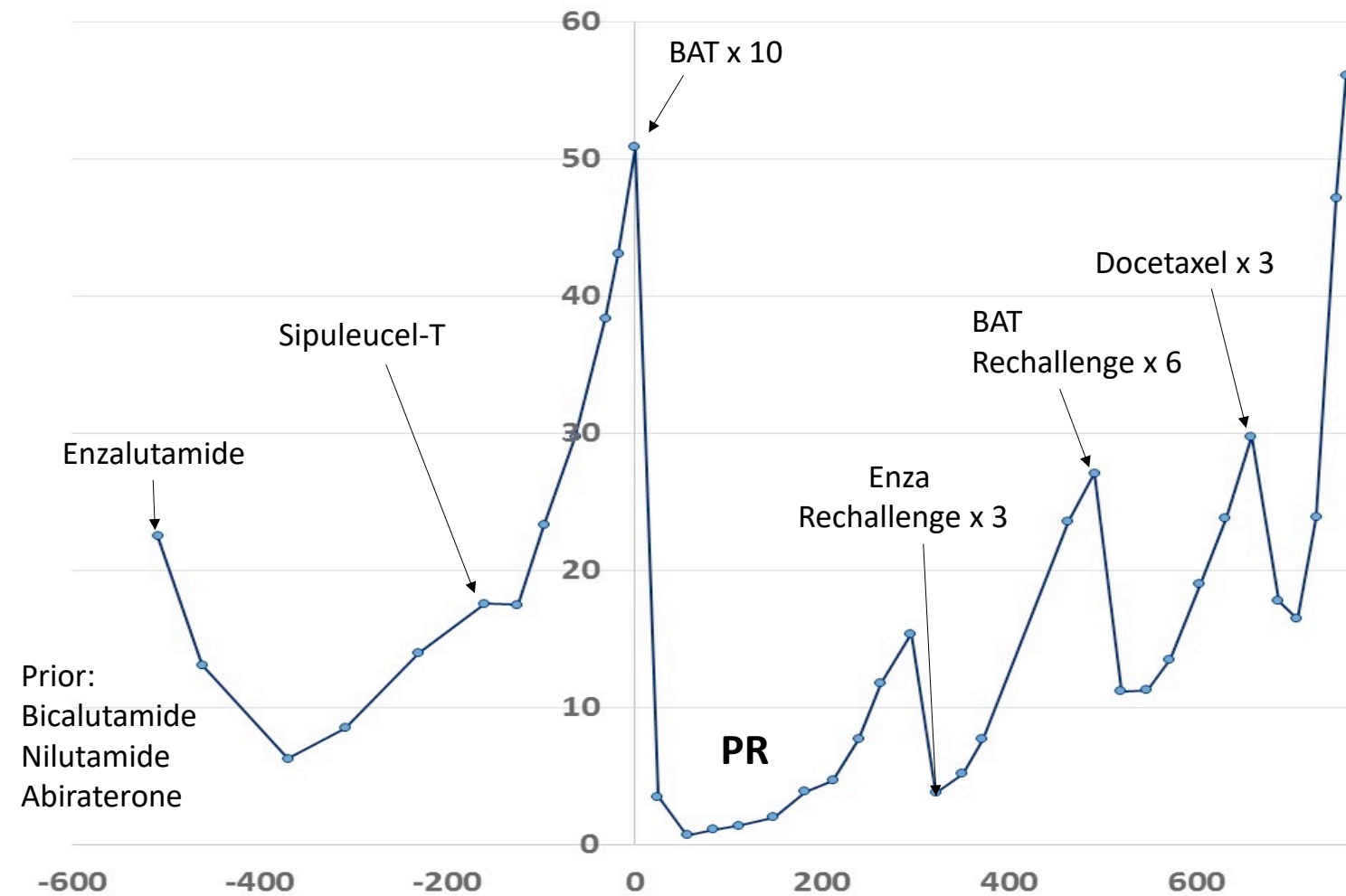
Courtesy of Emmanuel S Antonarakis, MD

Case Presentation – Dr Antonarakis: A 66-year-old man with mCRPC and a TP53 mutation

- 66-year-old man, diagnosed with *de novo* mHSPC (bone mets)
- Prostate biopsy: Gleason 4+4=8
- No family history of cancer
- Received ADT + bicalutamide; developed mCRPC in 2 years
- Then received nilutamide, abiraterone, enzalutamide
- Received sipuleucel-T
- Worsening bone mets; new pelvic adenopathy
- Participated in first clinical trial of BAT

Case Presentation – Dr Antonarakis: A 66-year-old man with mCRPC and a TP53 mutation (continued)

DNMT3A	R882H	Somatic
JAK2	V617F	Somatic
NTRK2	R598C	Somatic
TP53	Y205D	Somatic
TP53	H193L	Somatic
MS-S		



Courtesy of Emmanuel S Antonarakis, MD

Agenda

Module 1: Integration of PARP Inhibitors into the Management of Metastatic Castration-Resistant Prostate Cancer (mCRPC)

- Genomic biology of prostate cancer
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- PROfound: Olaparib versus AR-targeted therapy in men with HRR mutation-selected mCRPC
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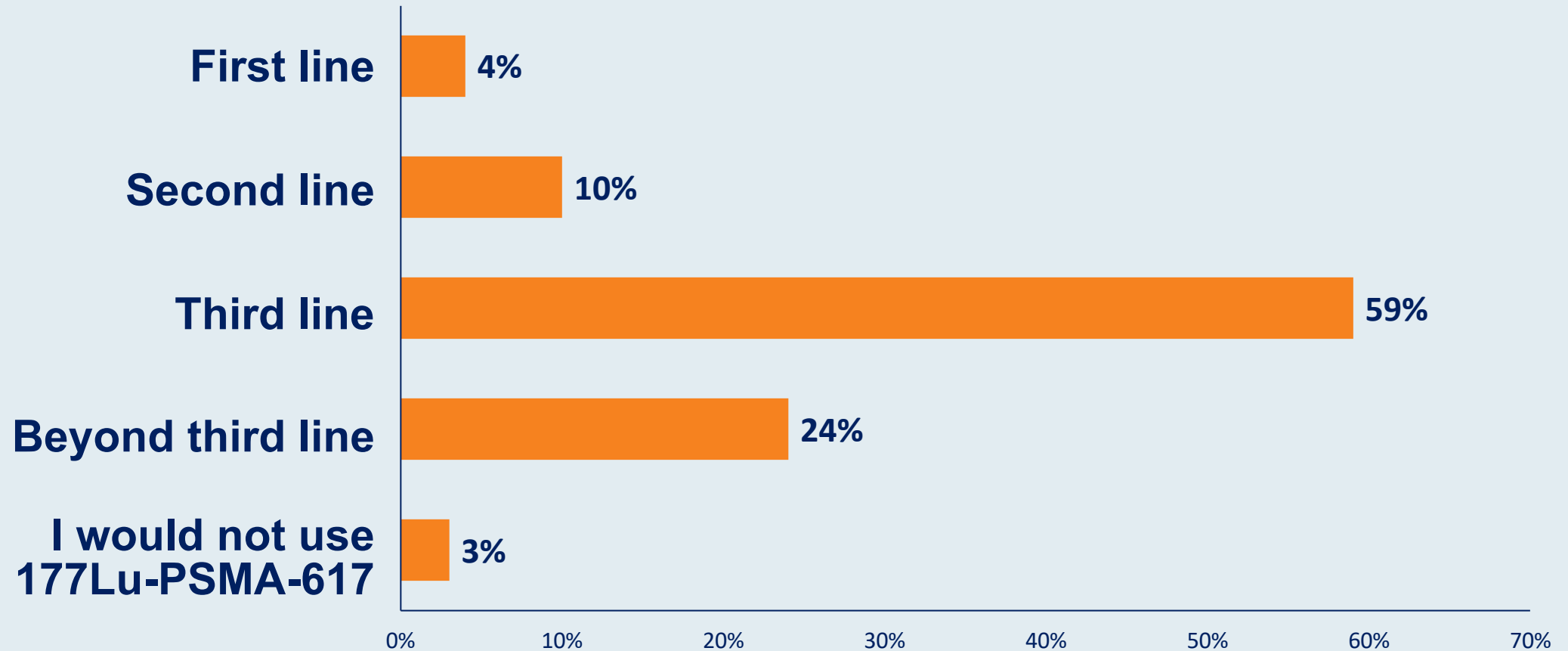
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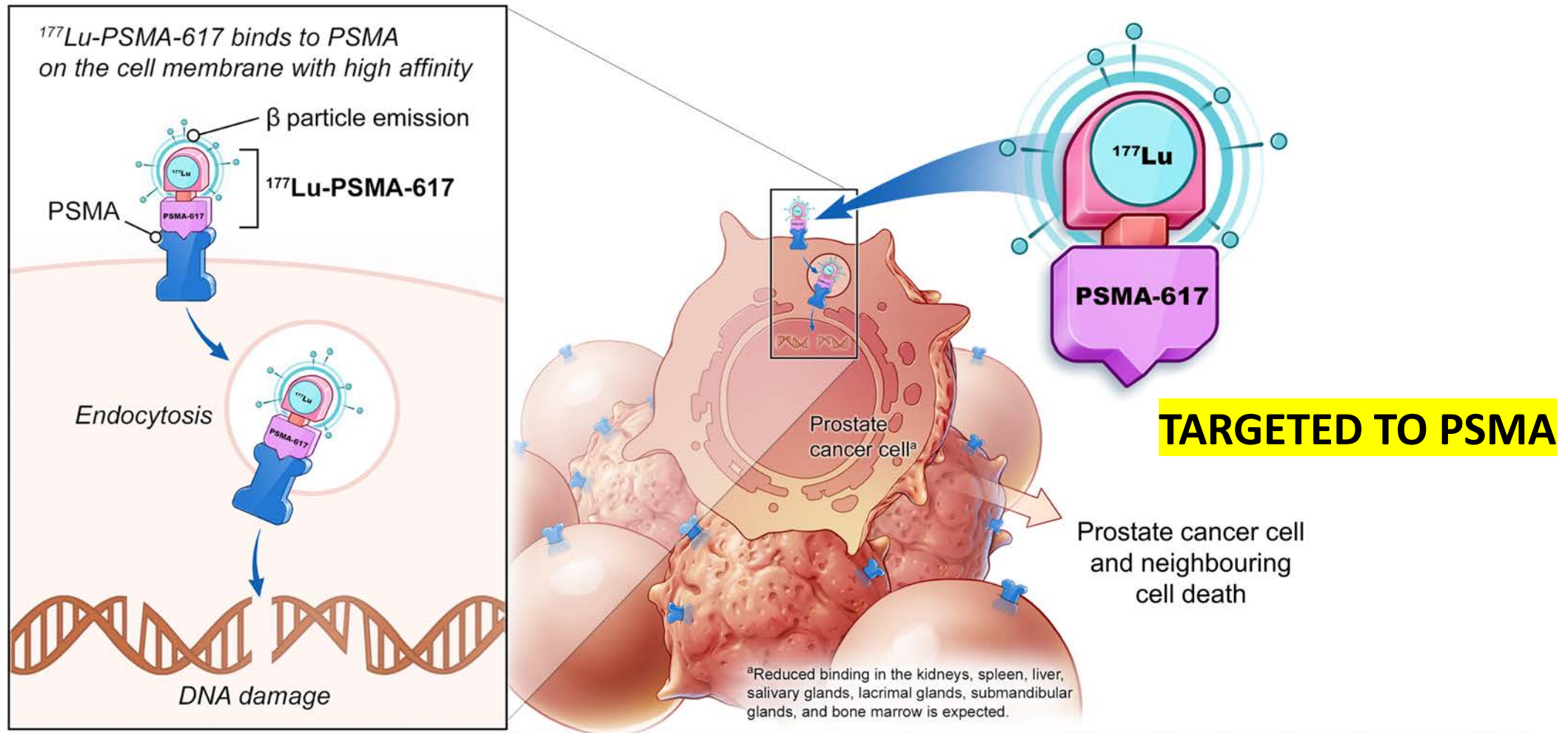
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- VISION: ¹⁷⁷Lu-PSMA-617 for patients with progressive PSMA-positive mCRPC
- COSMIC-021: Cabozantinib with atezolizumab for mCRPC
- Faculty cases

Regulatory and reimbursement issues aside, in what line of therapy would you administer ^{177}Lu -PSMA-617 for patients with mPC?



^{177}Lu -PSMA-617 targeted radioligand therapy



Presented By: Michael J. Morris

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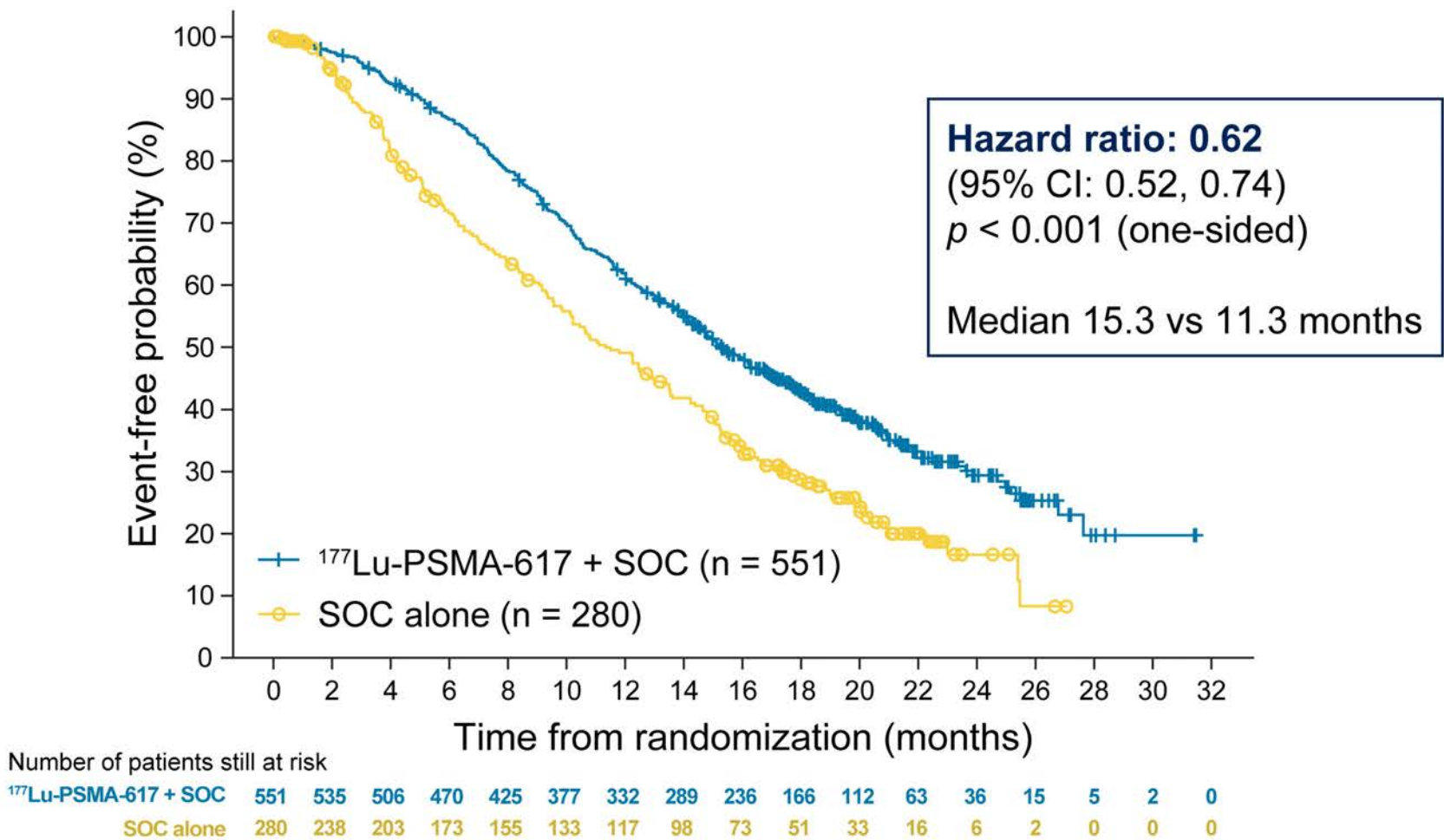
2021 ASCO[®]
ANNUAL MEETING

ADAPTED FROM DR. MORRIS' SLIDES

Courtesy of Julie N Graff, MD

Primary endpoints: ¹⁷⁷Lu-PSMA-617 prolonged OS

Primary analysis
All randomized patients
(N = 831)



Presented By: Michael J. Morris

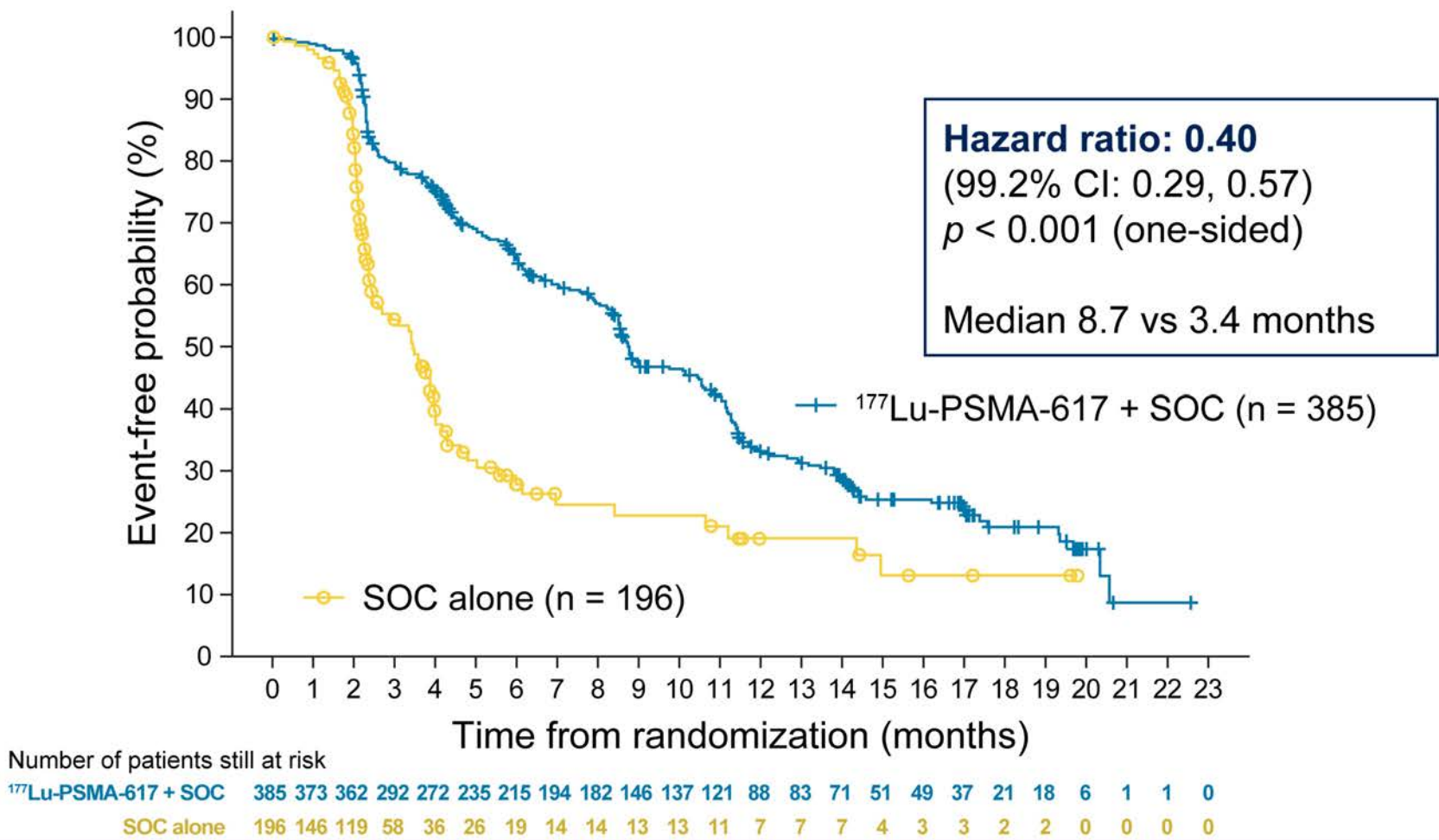
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Primary endpoints: ¹⁷⁷Lu-PSMA-617 improved rPFS

Primary analysis

rPFS analysis set (n = 581)



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ANNUAL MEETING

Higher rate of drug-related treatment-emergent adverse events with addition of ¹⁷⁷Lu-PSMA-617 to SOC

Patients, n (%)	All grades		Grade 3–5	
	¹⁷⁷ Lu-PSMA-617 + SOC (n = 529)	SOC alone (n = 205)	¹⁷⁷ Lu-PSMA-617 + SOC (n = 529)	SOC alone (n = 205)
Any TEAE	451 (85.3)	59 (28.8)	150 (28.4)	8 (3.9)
Serious	49 (9.3)	5 (2.4)	43 (8.1)	5 (2.4)
Grade 5	–	–	5 (0.9)	0 (0.0)

Treatment-emergent adverse events grouped as topics of interest: no unexpected or concerning safety signals

Patients, n (%)	All grades		Grade 3–5	
	¹⁷⁷ Lu-PSMA-617 + SOC (n = 529)	SOC alone (n = 205)	¹⁷⁷ Lu-PSMA-617 + SOC (n = 529)	SOC alone (n = 205)
Fatigue	260 (49.1)	60 (29.3)	37 (7.0)	5 (2.4)
Bone marrow suppression	251 (47.4)	36 (17.6)	124 (23.4)	14 (6.8)
Leukopenia	66 (12.5)	4 (2.0)	13 (2.5)	1 (0.5)
Lymphopenia	75 (14.2)	8 (3.9)	41 (7.8)	1 (0.5)
Anemia	168 (31.8)	27 (13.2)	68 (12.9)	10 (4.9)
Thrombocytopenia	91 (17.2)	9 (4.4)	42 (7.9)	2 (1.0)
Dry mouth	208 (39.3)	2 (1.0)	0 (0.0)	0 (0.0)
Nausea and vomiting	208 (39.3)	35 (17.1)	8 (1.5)	1 (0.5)
Renal effects	46 (8.7)	12 (5.9)	18 (3.4)	6 (2.9)
Second primary malignancies	11 (2.1)	2 (1.0)	4 (0.8)	1 (0.5)
Intracranial hemorrhage	7 (1.3)	3 (1.5)	5 (0.9)	2 (1.0)

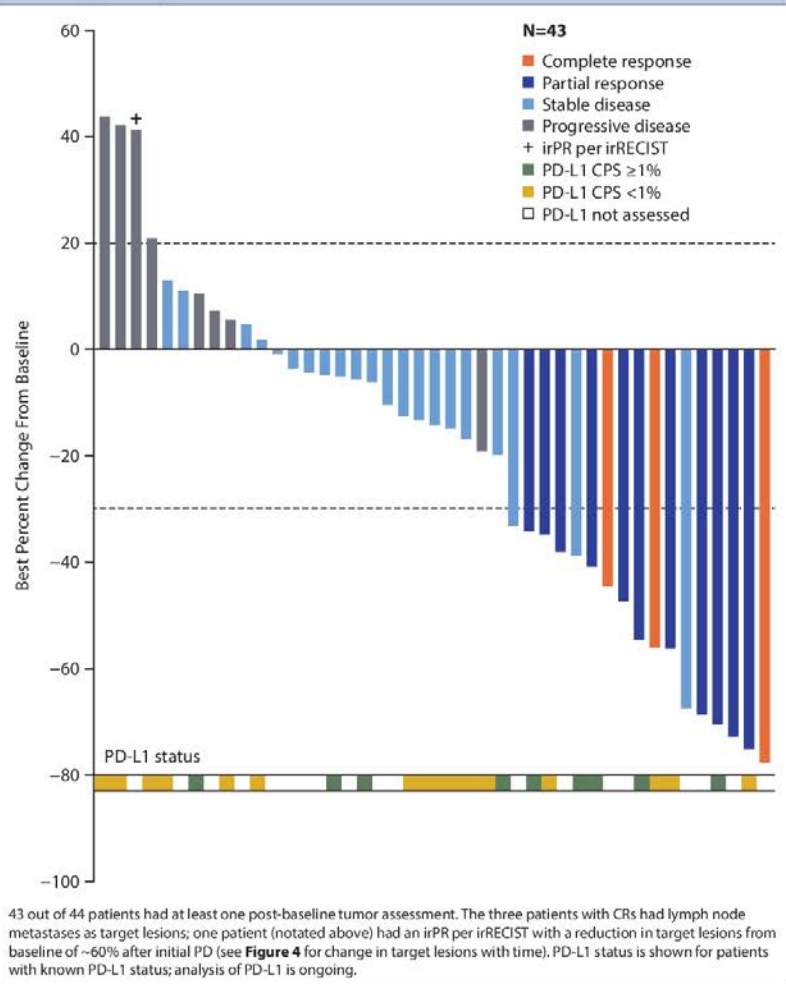
Immune Checkpoint Inhibitors in mCRPC

Therapy	Disease State	Disease Response
Pembrolizumab monotherapy ^a	Post-chemotherapy	ORR 9% PSA RR 14%
Pembrolizumab + enzalutamide ^b	Pre-chemotherapy progressing on enzalutamide	ORR 12% PSA RR 14%
Atezolizumab + enzalutamide ^c	Pre- and post-chemotherapy, s/p abiraterone	ORR 14% PSA RR 26%
Atezolizumab + cabozantinib ^d	Pre-chemotherapy s/p enzalutamide or abiraterone	ORR 34% PSA RR 29%

^aJCO 2020: 38(5) 395-405. ^bPresented at the 2021 ASCO Annual Meeting – Virtual; June 4-8, 2021. ^cSweeney C. AACR 2020. IMbassador250. ^dAgarwal ASCO 2020. COSMIC-021

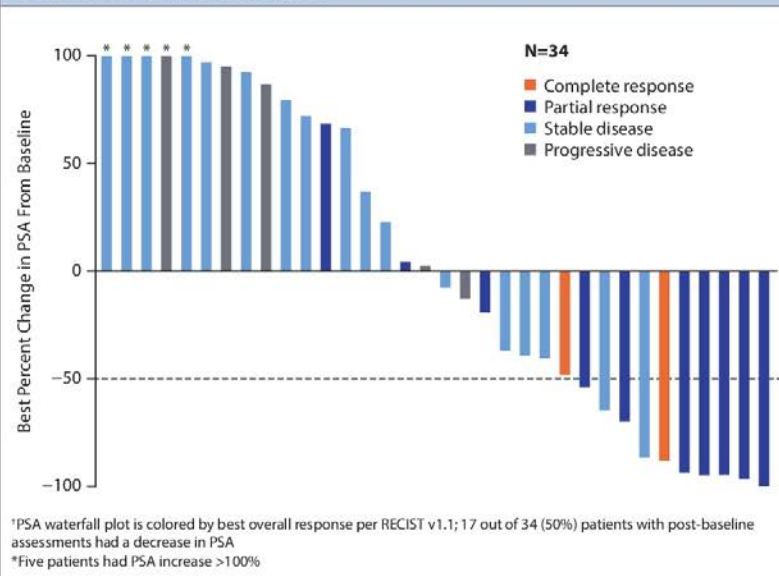
COSMIC-021: Cabozantinib plus Atezolizumab for mCRPC

Figure 3. Best Change From Baseline in Sum of Target Lesions per Investigator by RECIST v1.1



- Preliminary data do not suggest an association between PD-L1 expression and antitumor activity

Figure 5. Best Change in PSA From Baseline in Patients With at Least One Post-Baseline Evaluation[†]

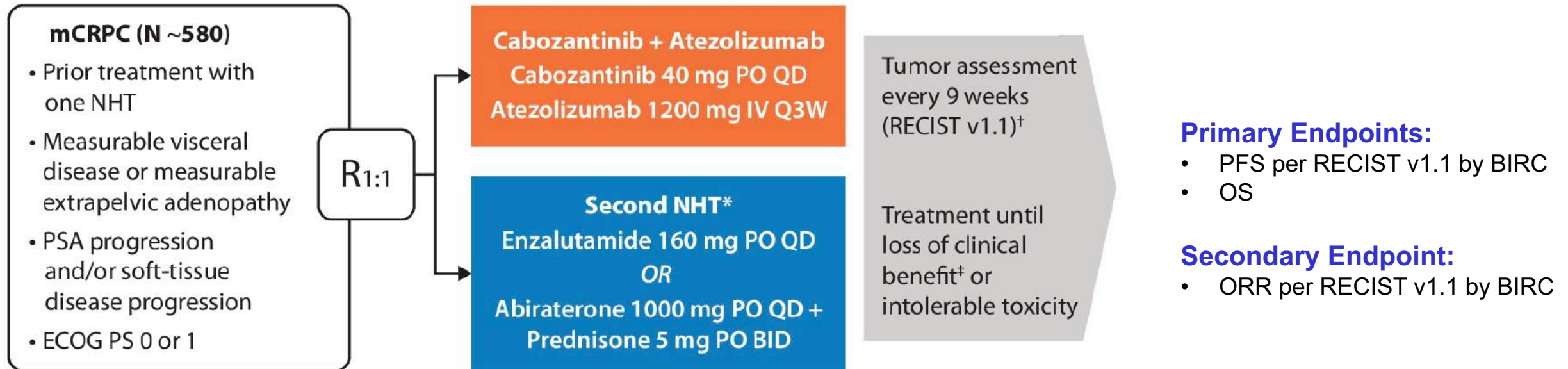


- In 12 patients with objective responses per RECIST v1.1 with at least one post-baseline PSA evaluation, 8 (67%) had a PSA decrease $\geq 50\%$

Table 3. Safety Summary

	CRPC Cohort (N=44)
Patients on study treatment at data cut-off, n (%)	11 (25)
Median duration of exposure, months (range)	6.9 (1–18)
Treatment-related grade 3/4 AEs, n (%)	26 (59)
Immune-related grade 3/4 AEs, n (%)	4 (9.1)
Treatment-related grade 5 AEs,* n (%)	1 (2.3)
AEs leading to cabozantinib dose reductions, n (%)	19 (43)
AEs unrelated to disease progression leading to both cabozantinib and atezolizumab discontinuation, [†] n (%)	4 (9.1)
At each level of summarization, a patient was counted once for the most severe event if the patient reported one or more events. *One grade 5 AE of dehydration occurred in a 90-year-old patient with a 6-month history of failure to thrive before study entry. [†] Not necessarily discontinued at the same time.	

CONTACT-02: Phase III Trial Schema



Stratification

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

*Second NHT must differ from previous NHT taken

[†]Tumor assessment (RECIST v1.1) every 9 weeks for the first 28 weeks then every 12 weeks thereafter

[‡]Patients may be treated beyond progression if there is a clinical benefit in the opinion of the investigator

Case Presentation – Dr Graff: A 57-year-old man with mCRPC and no actionable mutations

A 57 yo man diagnosed with metastatic prostate cancer with 5 bone tumors and a liver tumor. He is in good health other than the cancer. His initial treatment included ADT + docetaxel x 10 cycles followed by abiraterone/prednisone. Sequencing of his tumor does not show any actionable mutations. After 18 months, his PSA begins to slowly climb. His imaging studies do not show any changes.

What is an appropriate next step?

1. Continue current therapy until there is clear radiographic progression
2. Add Radium-223 to the abiraterone/prednisone
3. Start PSMA-Lu-177

Case Presentation – Dr Graff: An 82-year-old man with mCRPC and widespread bone metastases

An 82 yo man with metastatic castration-sensitive prostate cancer. He received androgen-deprivation therapy monotherapy, but then he developed a new liver metastatic tumor. He was switched to docetaxel chemotherapy x 10 cycles + ADT. He complains of new hip pain and is found to have widespread bone progression.

Which of the following is appropriate?

1. Radium-223
2. PSMA-Lu-177
3. Radium-223 + abiraterone-prednisone
4. Abiraterone-prednisone

A Conversation with the Investigators: Bladder Cancer

**Wednesday, July 21, 2021
5:00 PM – 6:00 PM ET**

Faculty

**Petros Grivas, MD, PhD
Daniel P Petrylak, MD
Arlene Siefker-Radtke, MD**

Moderator

Neil Love, MD

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 2 to 3 business days.