Castration resistant prostate cancer: What is the optimal approach?

!7th Annual CCC Conference

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David I. Quinn

MBBS (Hons) PhD FRACP FACP

Associate Professor of Medicine

Chief, Section of GU Medical Oncology

Division of Medical Oncology

Medical Director, Norris Cancer Hospital and Clinics

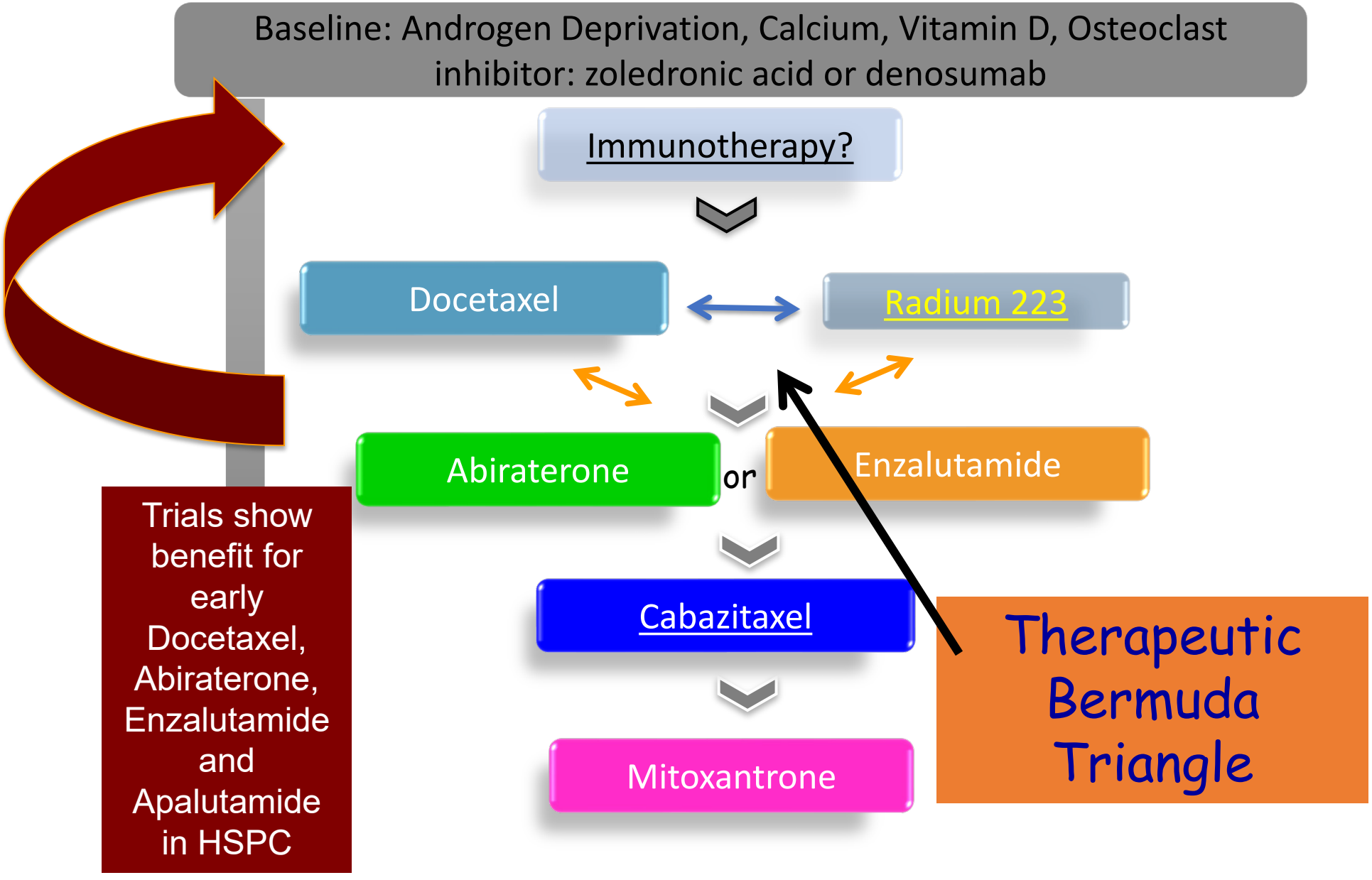
Kenneth J. Norris Comprehensive Cancer Center

Keck School of Medicine at

University of Southern California

diquinn@med.usc.edu

Preferred Therapeutic Sequencing For Metastatic CRPC possible changes for 2019



NON-METASTATIC CRPC: METASTASES FREE SURVIVAL /OVERALL SURVIVAL

INCLUSION CRITERIA:

Pathologically confirmed adenocarcinoma of the prostate

PSA doubling time ≤ 10 months

ECOG 0-1

CT or MRI c/a/p and radionucleotide bone scan without evidence of metastatic disease, or pelvic lymph nodes <2cm (cN1)

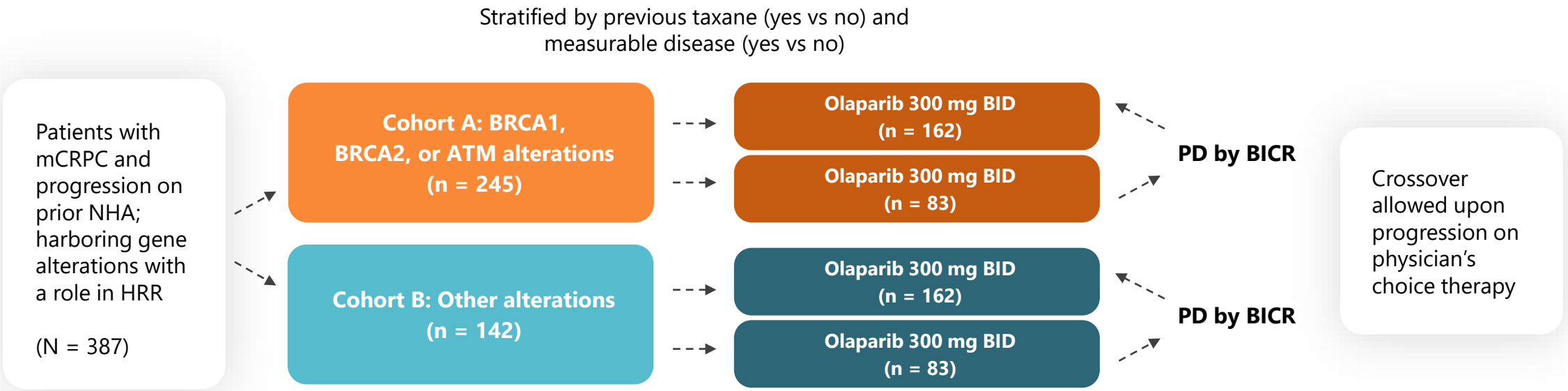
Very similar data for 3 agents. M_0 CRPC: ATRA: pick one!

DRUG	TRIAL	MFS (MOS)	OS	REFERENCE
Enzalutamide	PROSPER	36.6 vs 14.7 HR-0.29	HR-0.73	Husain, NEJM 2018
Apalutamide	SPARTAN	40.5 va 16.2 HR-0.28	HR-0.75	Smith, NEJM 2018
Darolutamide	ARAMIS	40.4 vs 18.4 HR-0.41	HR-0.69	Fizazi NEJM 2019

mCRPC: PLETHORA OF AGENTS

DRUG	TRIAL	COMPARATOR	PATIENT POPULATION	OS (MOS)	HR	REFERENCE
Abiraterone	COU- AA 301	Placebo/prednisone	Post docetaxel	15.8 vs 11.2=4.6	0.74	Fizazi, Lancet Oncology 2012
Abiraterone	COU-AA 302	Placebo/prednisone	Pre Docetaxel	34.7 vs 30.3=4.4	0.81	Ryan, Lancet Oncology 2015
Enzalutamide	AFFIRM	Placebo	Post Docetaxel	18.4 vs 13.6=3.8	0.63	Scher NEJM 2012
Enzalutamide	PREVAIL	Placebo	Pre Docetaxel	32.4 vs 30.2=2.2	0.71	Beer NEJM 2014
Sipuleucel-T	IMPACT	Placebo	Pre/Post Docetaxel	25.8 vs 21.7=4.1	0.78	Kantoff NEJM 2010
Docetaxel*	TAX327	Mitoxantrone	Docetaxel naive	19.2 vs 17.8=2.5	0.76	Barthold J Clin Oncol 2008
Cabazitaxel	TROPIC	Mitoxantrone	Post Docetaxel	15.1 vs 12.7=2.4	0.70	deBono Lancet 2010
Radium 223	ALSYMCA	Placebo	Pre/Post Docetaxel	14 vs 11.2=3.6	0.70	Parker NEJM 2013
Olaparaib	**ProFound**	**NHA2**	**Pre/post docetaxel**	**19.1 vs 14.7=4.4**	**0.69**	**deBono NEJM 2020**

PHASE III PROFOUND: OLAPARIB VS PHYSICIAN'S CHOICE IN PROGRESSING METASTATIC CRPC WITH DDR



*Enzalutamide 160 mg QD or abiraterone acetate 100 mg QD plus prednisone 5 mg BID.

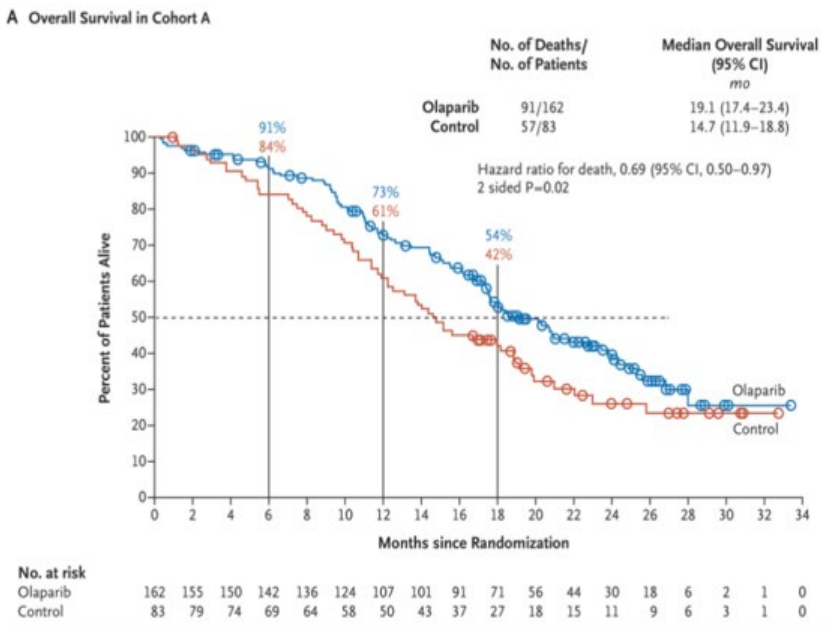
†BRCA1/2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RA51D, or RAD54L.

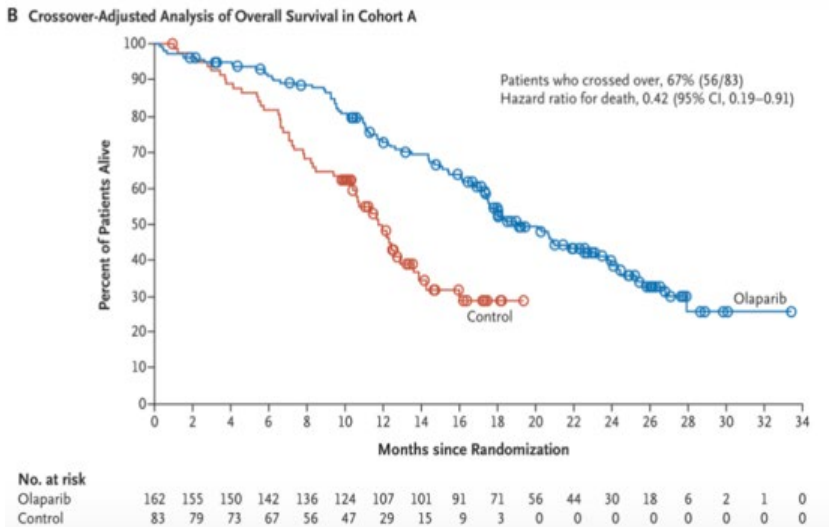
Primary endpoint: radiographic PFS in Cohort A using RECIST 1.1 and PCWG3 by BICR

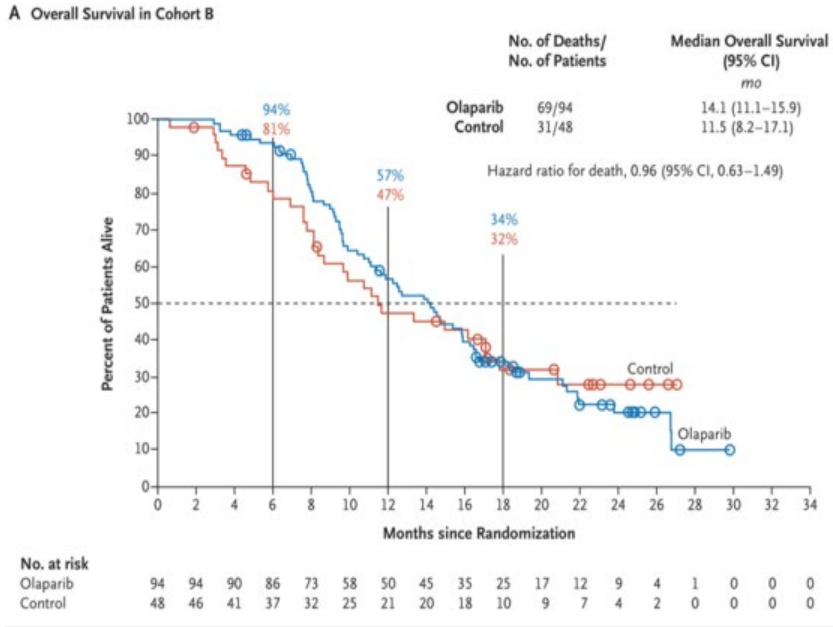
Secondary endpoints: radiographic PFS in both cohorts, confirmed radiographic ORR in Cohort A, time to pain progression in Cohort A, OS in Cohort A

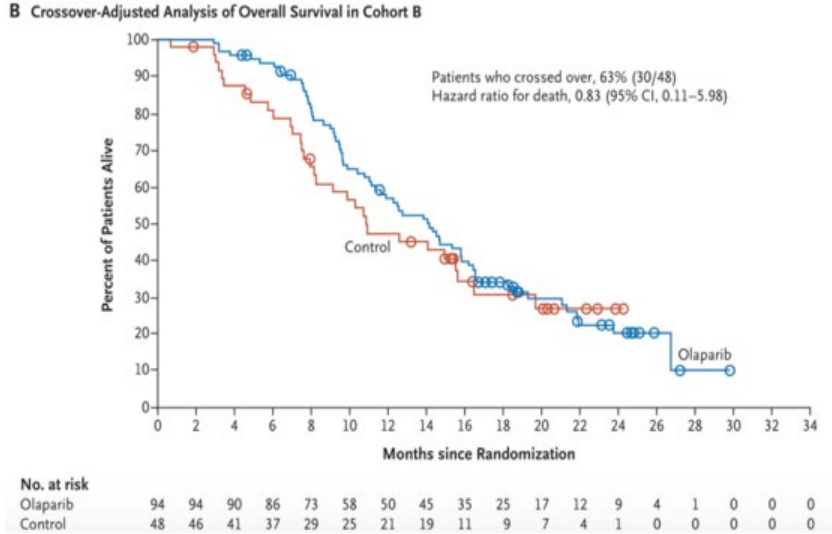
Hussain. NEJM 2020; de Bono. NEJM. 2020;382:2091.

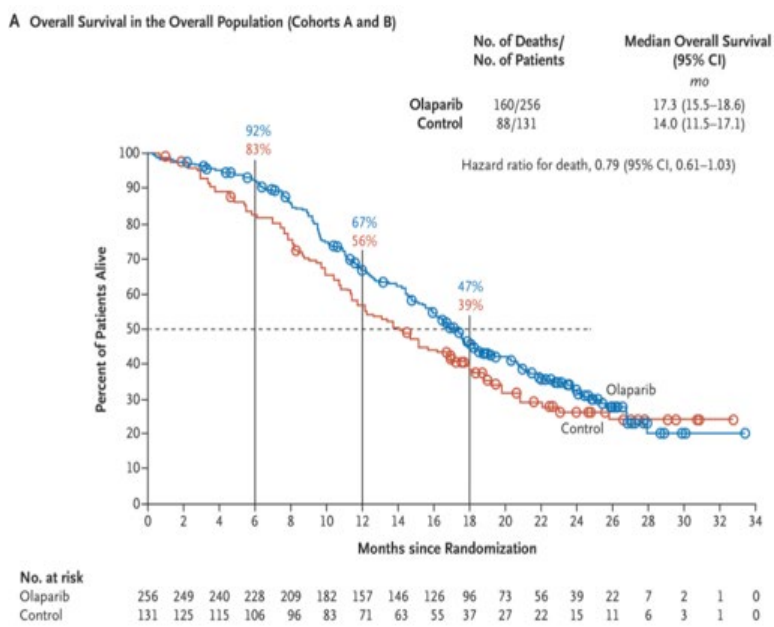
PROFOUND OS: COHORT A/B/OVERALL

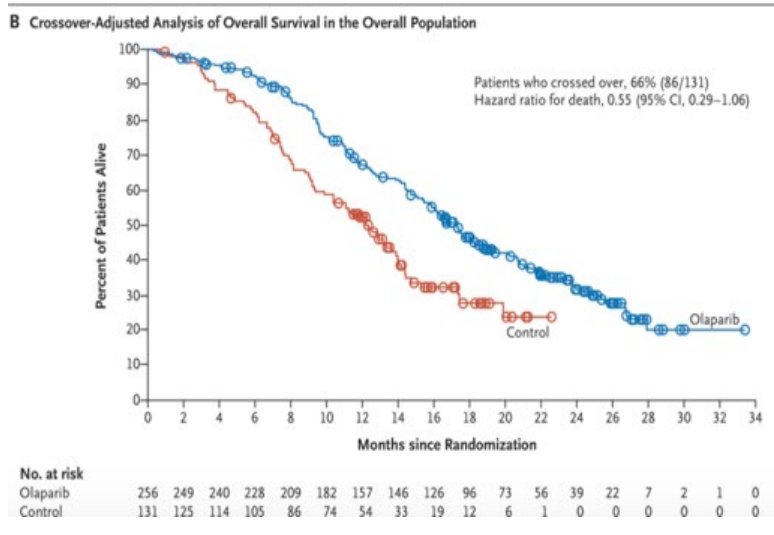




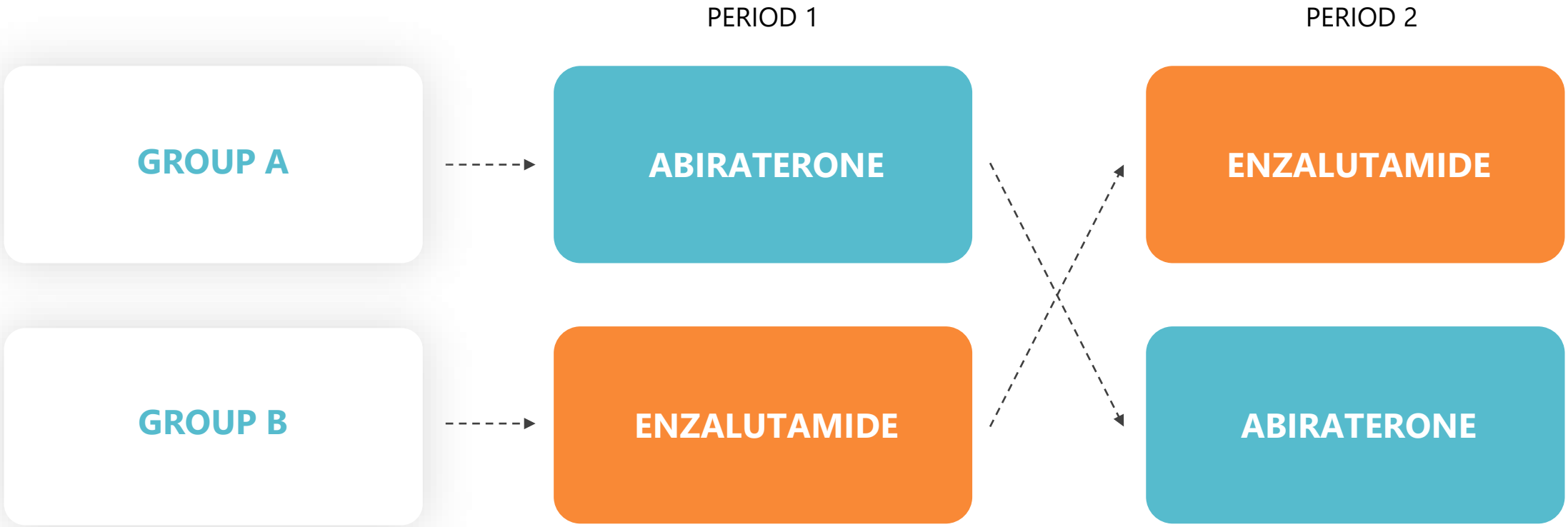








SEQUENCE OF ARTA IN MCRPC

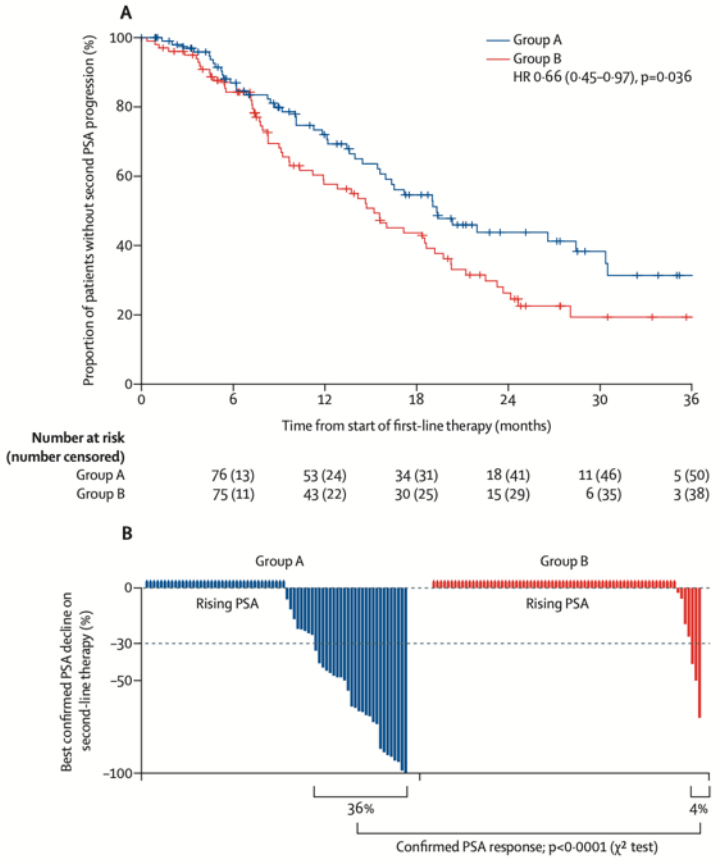


Primary Endpoint:
bPFS2

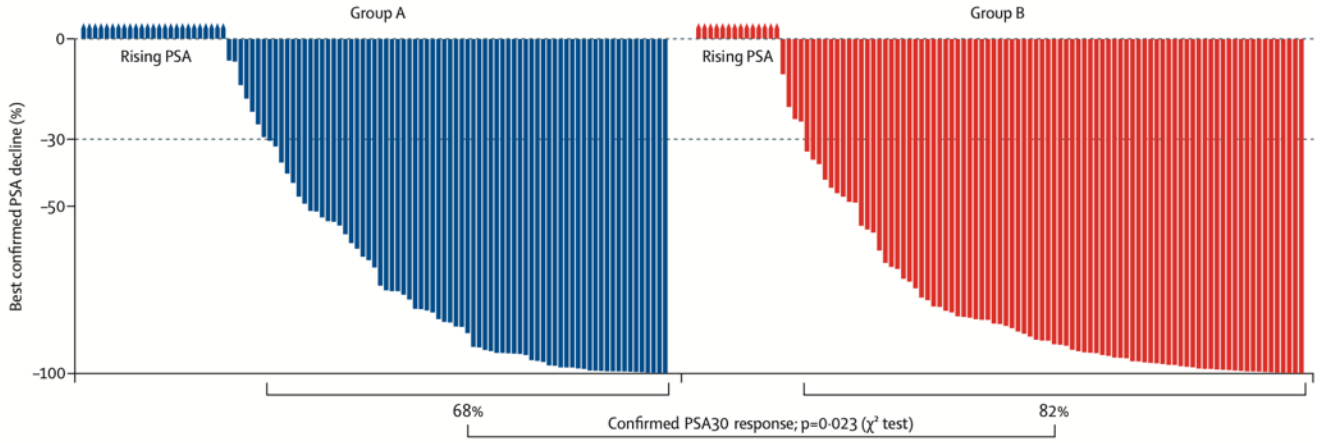
Secondary Endpoint:
PSA $_{50}$ at Cross over

Khalaf Lancet Oncology 2019

RESULTS : CROSSOVER AND PFS 2



Khalaf Lancet Oncology 2019



bPFS 2: 19.3 vs 15.2 mos; HR- 0.66; P-0.03

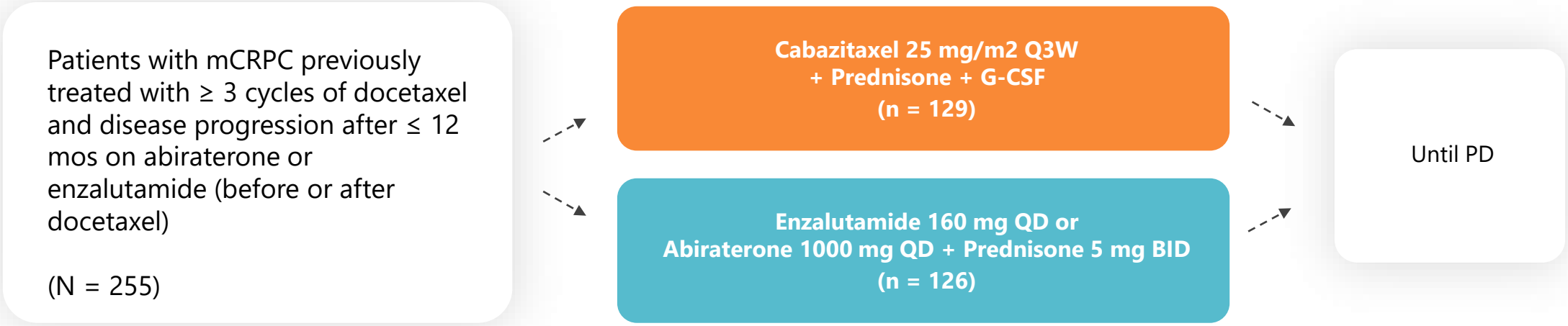
CONCLUSIONS:

abiraterone and enzalutamide have similar PSA $_{50}$ responses in first line setting

However the sequence of abi followed by enza resulted in a better outcome and the PSA $_{50}$ in the second line was low

CARD TRIAL: PHASE IV TRIAL OF CABAZITAXEL VS ABIRATERONE OR ENZALUTAMIDE IN PREVIOUSLY TREATED MCRPC

Stratified by ECOG PS (0/1 vs 2), time to progression of prior alternative ARTA (≤ 6 mos vs > 6-12 mos), timing of prior AR-targeted therapy (before vs after docetaxel)

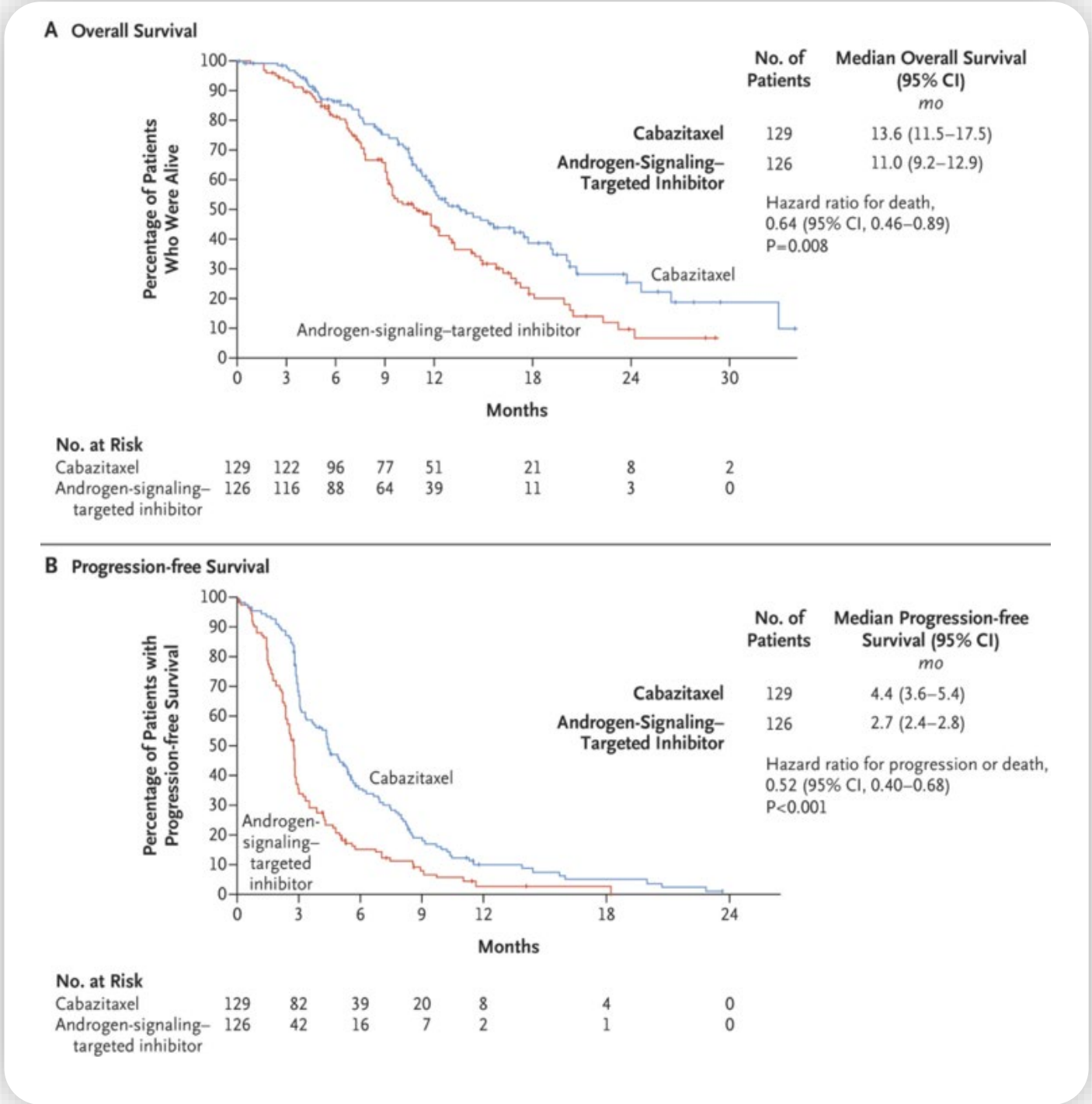


Primary endpoint:
imaging-based PFS

Secondary endpoints:
OS, PFS, PSA response, tumor response, time to SSE, pain response, and safety

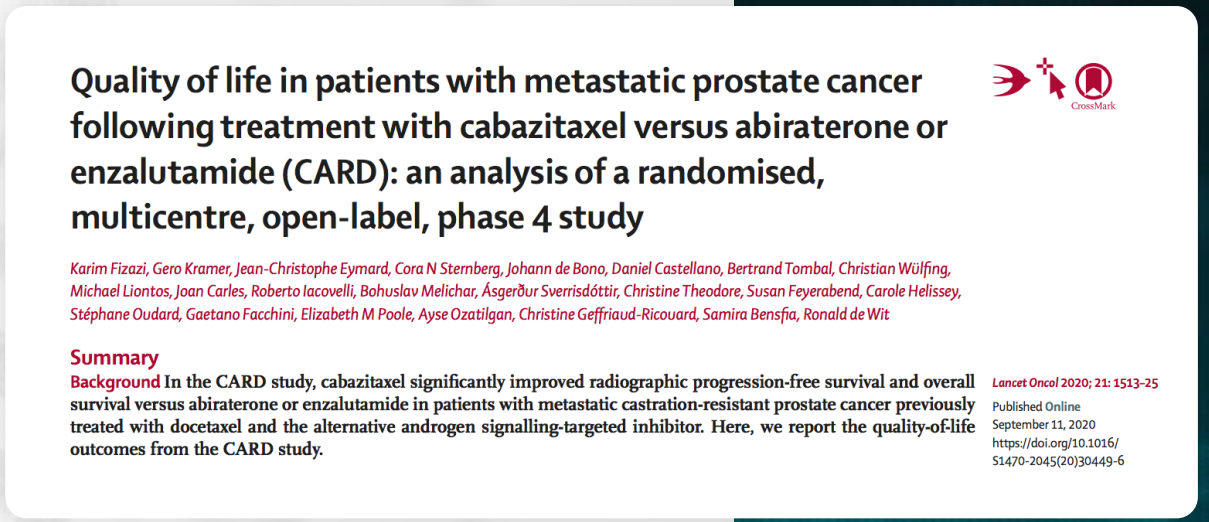
de Wit. NEJM. 2019;381:2506.

CARD: RESULTS



CARD: QUALITY OF LIFE

- In these preplanned analyses, **cabazitaxel significantly improved pain response and prolonged time to pain progression** versus abiraterone or enzalutamide.
- **Cabazitaxel also reduced the probability of developing symptomatic skeletal events,** despite lower use of denosumab or bisphosphonates compared with patients receiving abiraterone or enzalutamide.
- **Cabazitaxel had no deleterious effect on PROs** compared with a second androgen signaling-targeted inhibitor.



Quality of life in patients with metastatic prostate cancer following treatment with cabazitaxel versus abiraterone or enzalutamide (CARD): an analysis of a randomised, multicentre, open-label, phase 4 study

Karim Fizazi, Gero Kramer, Jean-Christophe Eymard, Cora N Sternberg, Johann de Bono, Daniel Castellano, Bertrand Tombal, Christian Wülfing, Michael Liontos, Joan Carles, Roberto Iacovelli, Bohuslav Melichar, Ásgerður Sverrisdóttir, Christine Theodore, Susan Feyerabend, Carole Helissey, Stéphane Oudard, Gaetano Facchini, Elizabeth M Poole, Ayse Ozatilgan, Christine Geffriaud-Ricouard, Samira Bensfia, Ronald de Wit

Summary

Background In the CARD study, cabazitaxel significantly improved radiographic progression-free survival and overall survival versus abiraterone or enzalutamide in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel and the alternative androgen signalling-targeted inhibitor. Here, we report the quality-of-life outcomes from the CARD study.

Lancet Oncol 2020; 21: 1513–25
Published Online
September 11, 2020
https://doi.org/10.1016/
S1470-2045(20)30449-6

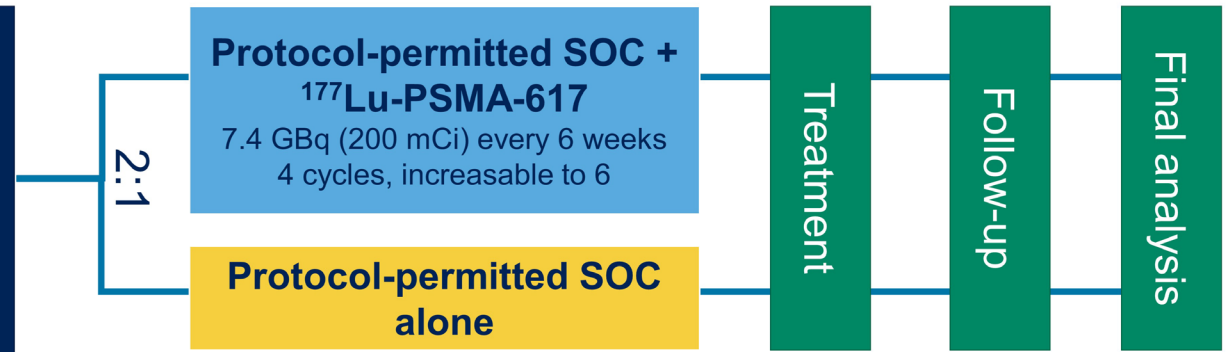
CARD: CONCLUSIONS

- Chemotherapy with cabazitaxel superior to the alternate NHA
- Improved OS, rPFS, bPFS, ORR, pain response
- Improved QOL data favoring cabazitaxel
- Should be offered prior to the 2nd NHA

Open-label study of protocol-permitted standard of care ± ^{177}Lu-PSMA-617 in adults with PSMA-positive mCRPC

Eligible patients

- Previous treatment with <u>both</u>
  - ≥ 1 androgen receptor pathway inhibitor
  - 1 or 2 taxane regimens
- Protocol-permitted standard of care (SOC) planned before randomization
  - Excluding chemotherapy immunotherapy, radium-223, investigational drugs
- ECOG performance status 0–2
- Life expectancy > 6 months
- PSMA-positive mCRPC on PET/CT with ^{68}Ga-PSMA-11



- Rando
  - ECO
  - LDH
  - Live
  - And inhib

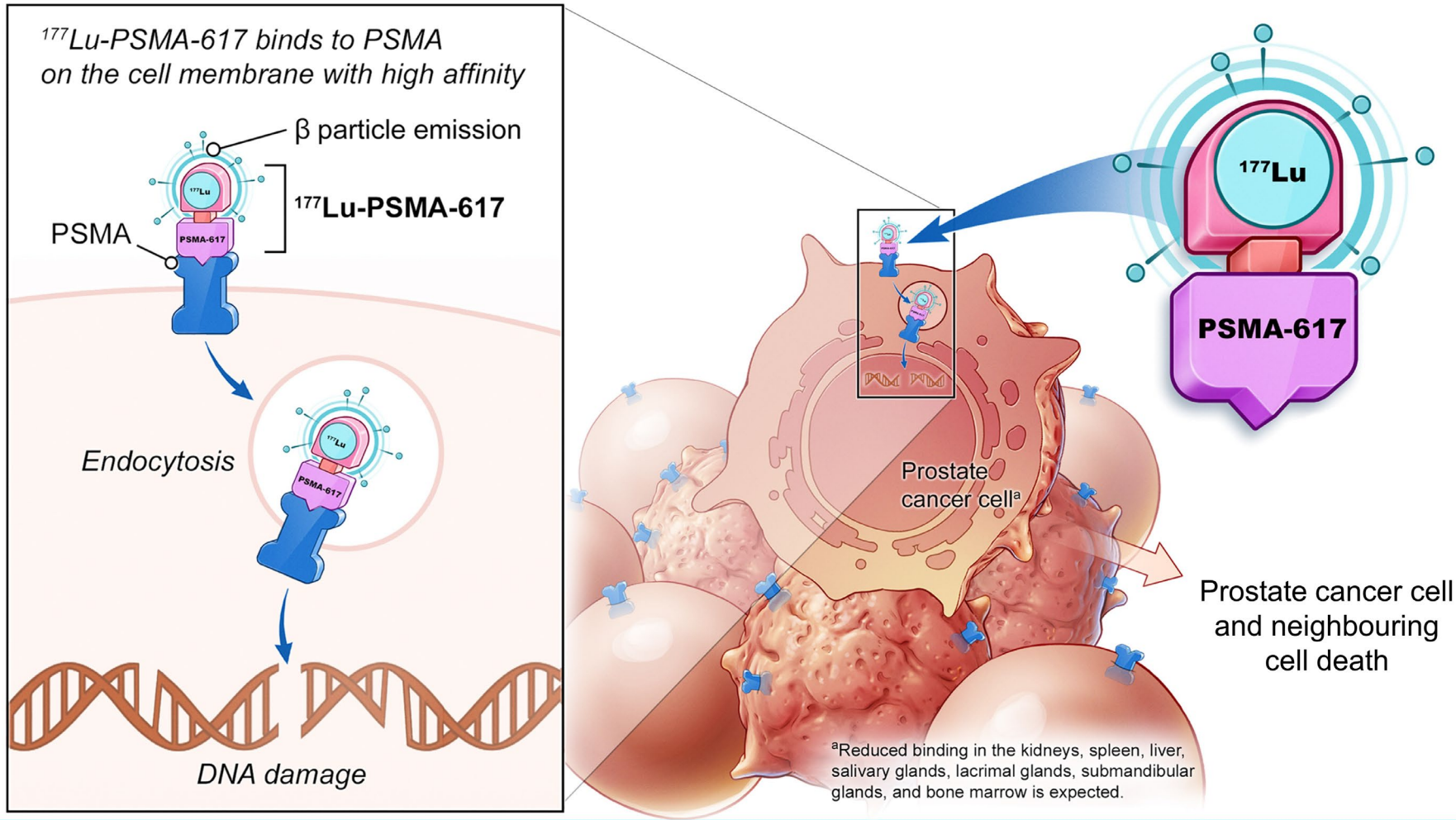
2021 ASCO ANNUAL MEETING

Phase 3 study of ^{177}Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION)

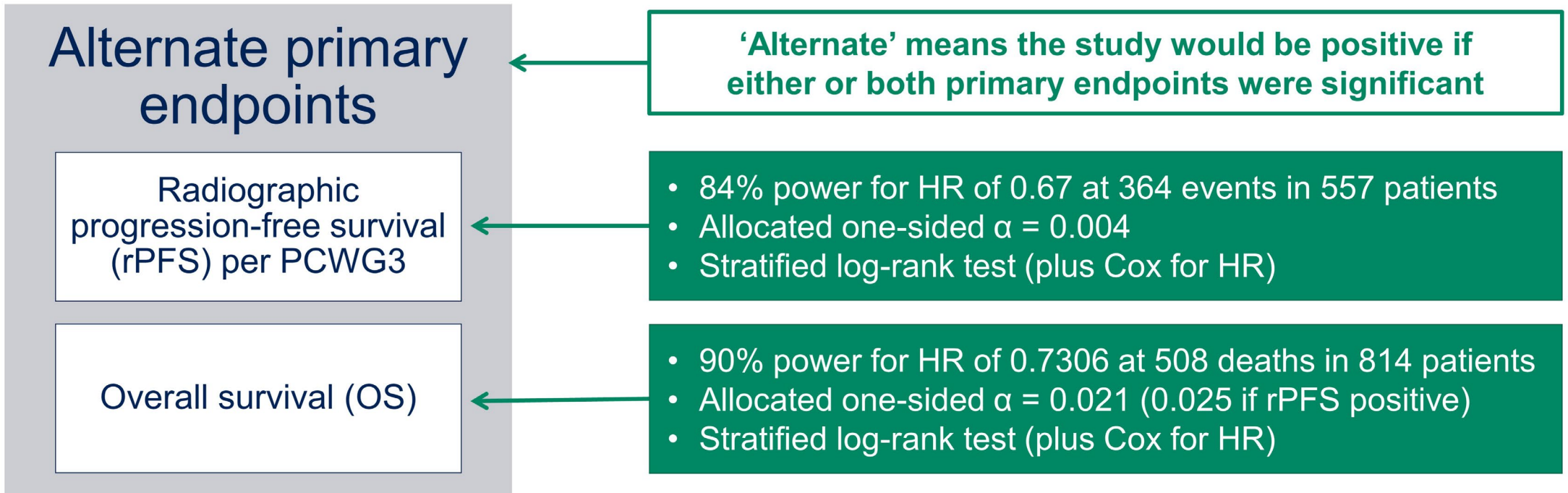
Presenter: Michael J. Morris, Memorial Sloan Kettering Cancer Center

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

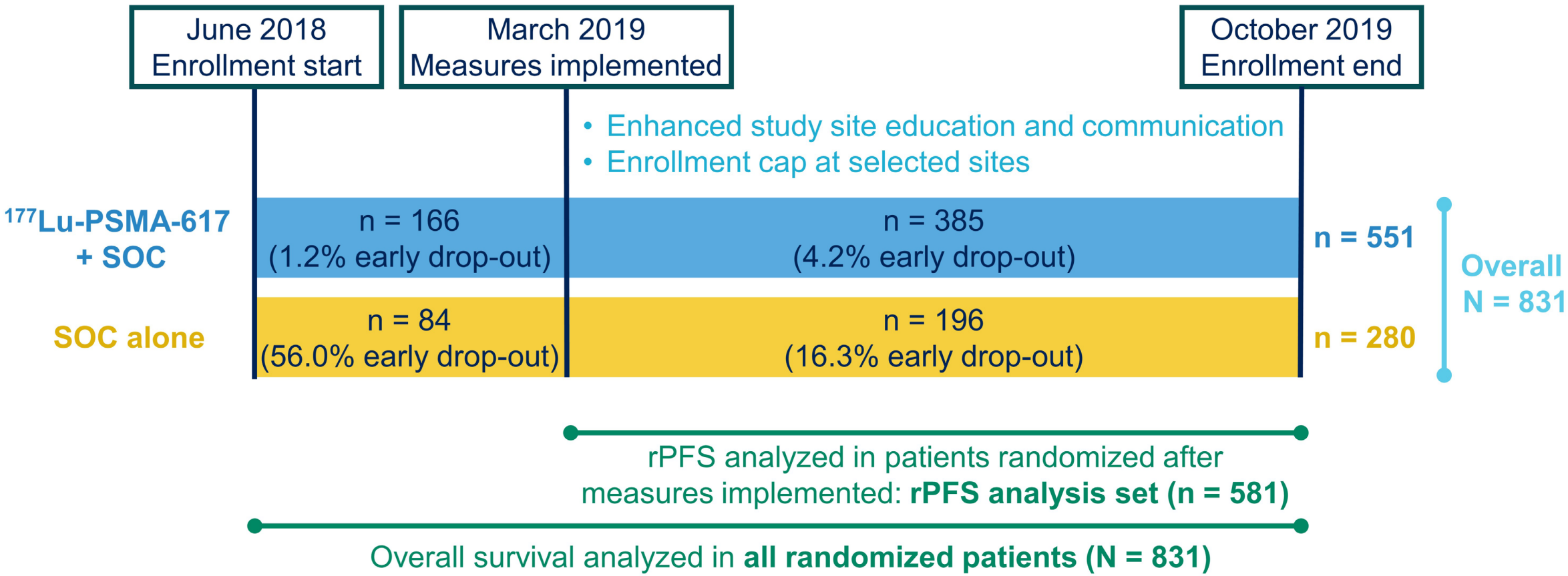
^{177}Lu-PSMA-617 targeted radioligand therapy



Prespecified alternate primary endpoints: alpha allocation, statistical power, and final analyses



To reduce effect of drop-out on radiographic endpoints, primary analyses used different sets



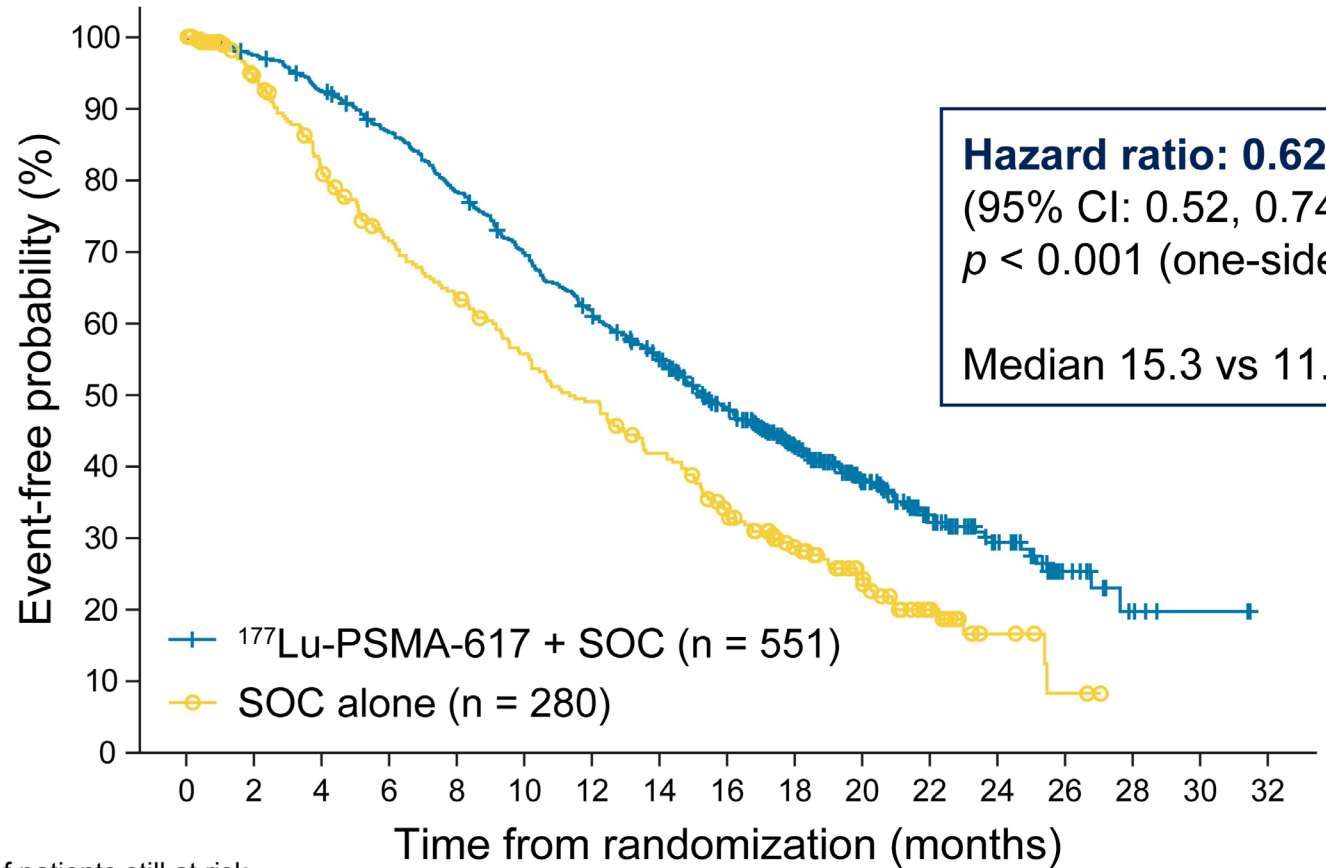
Baseline characteristics were well balanced across treatment arms and the two analysis sets

	rPFS analysis set (n = 581)		All randomized (N = 831)	
	^{177}Lu-PSMA-617 + SOC (n = 385)	SOC alone (n = 196)	^{177}Lu-PSMA-617 + SOC (n = 551)	SOC alone (n = 280)
Age, median (range)	71.0 (52–94)	72.0 (51–89)	70.0 (48–94)	71.5 (40–89)
Race, n (%)				
White	336 (87.3)	166 (84.7)	486 (88.2)	235 (83.9)
Black/African-American	29 (7.5)	14 (7.1)	34 (6.2)	21 (7.5)
Asian	6 (1.6)	9 (4.6)	9 (1.6)	11 (3.9)
ECOG status, n (%)				
0 or 1	352 (91.4)	179 (91.3)	510 (92.6)	258 (92.1)
2	33 (8.6)	17 (8.7)	41 (7.4)	22 (7.9)
Site of disease, n (%)				
Lung	35 (9.1)	20 (10.2)	49 (8.9)	28 (10.0)
Liver	47 (12.2)	26 (13.3)	63 (11.4)	38 (13.6)
Lymph node	193 (50.1)	99 (50.5)	274 (49.7)	141 (50.4)
Bone	351 (91.2)	179 (91.3)	504 (91.5)	256 (91.4)

Primary endpoints: ^{177}Lu-PSMA-617 prolonged OS

Primary analysis

All randomized patients
(N = 831)

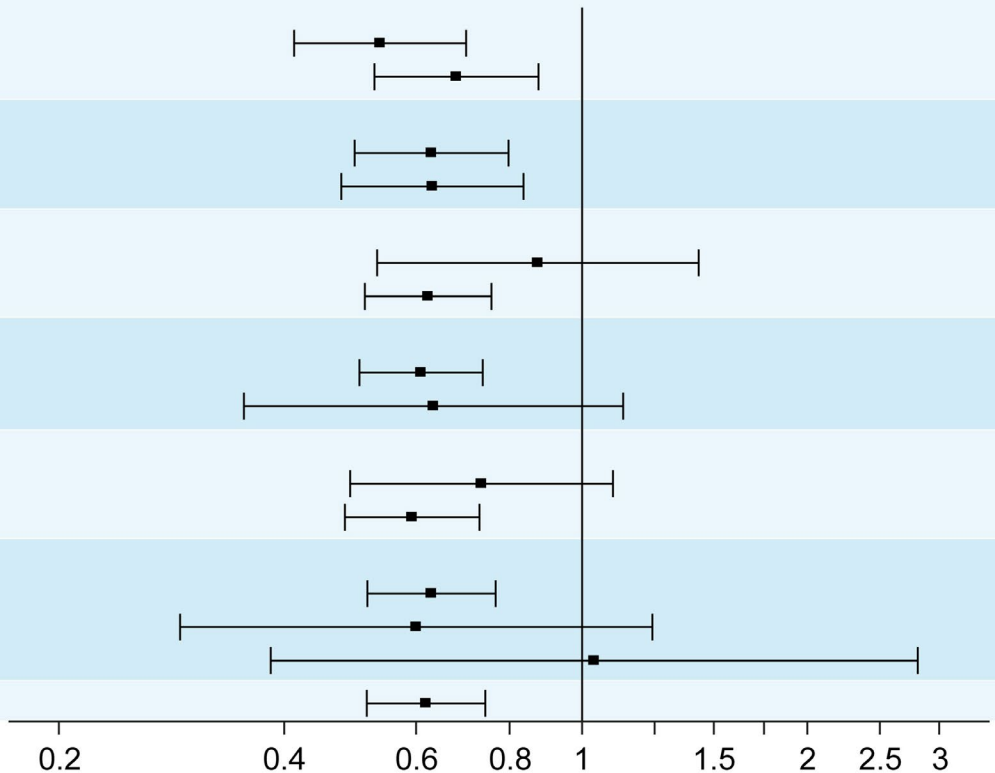


Number of patients still at risk

^{177}Lu-PSMA-617 + SOC	551	535	506	470	425	377	332	289	236	166	112	63	36	15	5	2	0
SOC alone	280	238	203	173	155	133	117	98	73	51	33	16	6	2	0	0	0

Overall survival was generally consistent across prespecified stratification factor subgroups

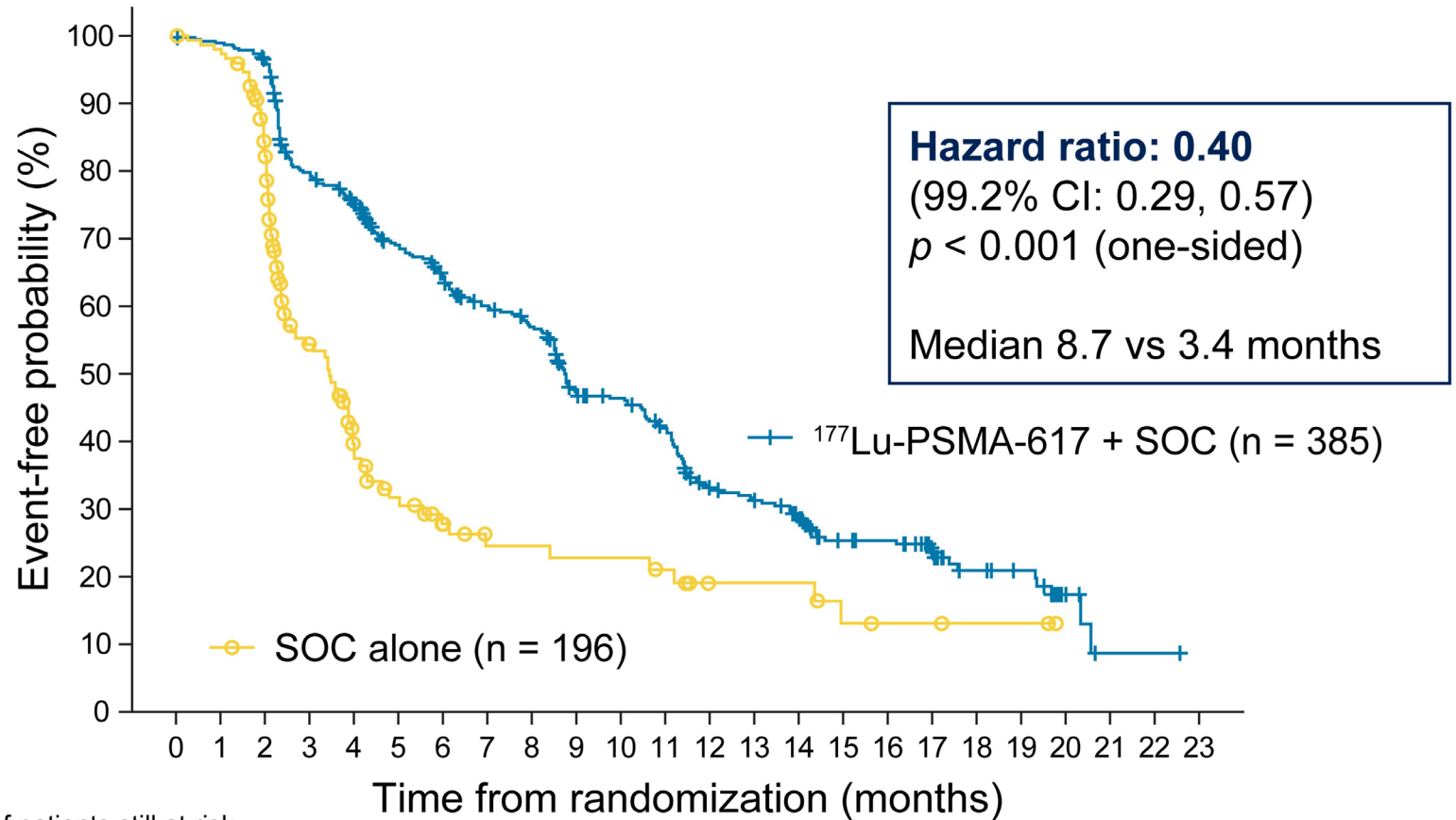
Subgroup	^{177}Lu-PSMA-617 + SOC (n = 551)	SOC alone (n = 280)	Hazard ratio (95% CI)
Androgen receptor pathway inhibitors as part of planned SOC			
Yes	243	146	0.54 (0.41, 0.70)
No	308	134	0.68 (0.53, 0.87)
LDH			
≤ 260 IU/L	368	182	0.63 (0.50, 0.80)
> 260 IU/L	182	97	0.63 (0.48, 0.84)
Liver metastases			
Yes	48	34	0.87 (0.53, 1.43)
No	503	246	0.62 (0.51, 0.76)
ECOG score			
0 or 1	510	258	0.61 (0.50, 0.74)
2	41	22	0.63 (0.35, 1.13)
Age			
< 65 years	145	60	0.73 (0.49, 1.10)
≥ 65 years	406	220	0.59 (0.48, 0.73)
Race			
White	486	235	0.63 (0.52, 0.77)
African American or Black	34	21	0.60 (0.29, 1.24)
Asian	9	11	1.04 (0.38, 2.81)
All patients	551	280	0.62 (0.52, 0.74)



Primary endpoints: ^{177}Lu-PSMA-617 improved rPFS

Primary analysis

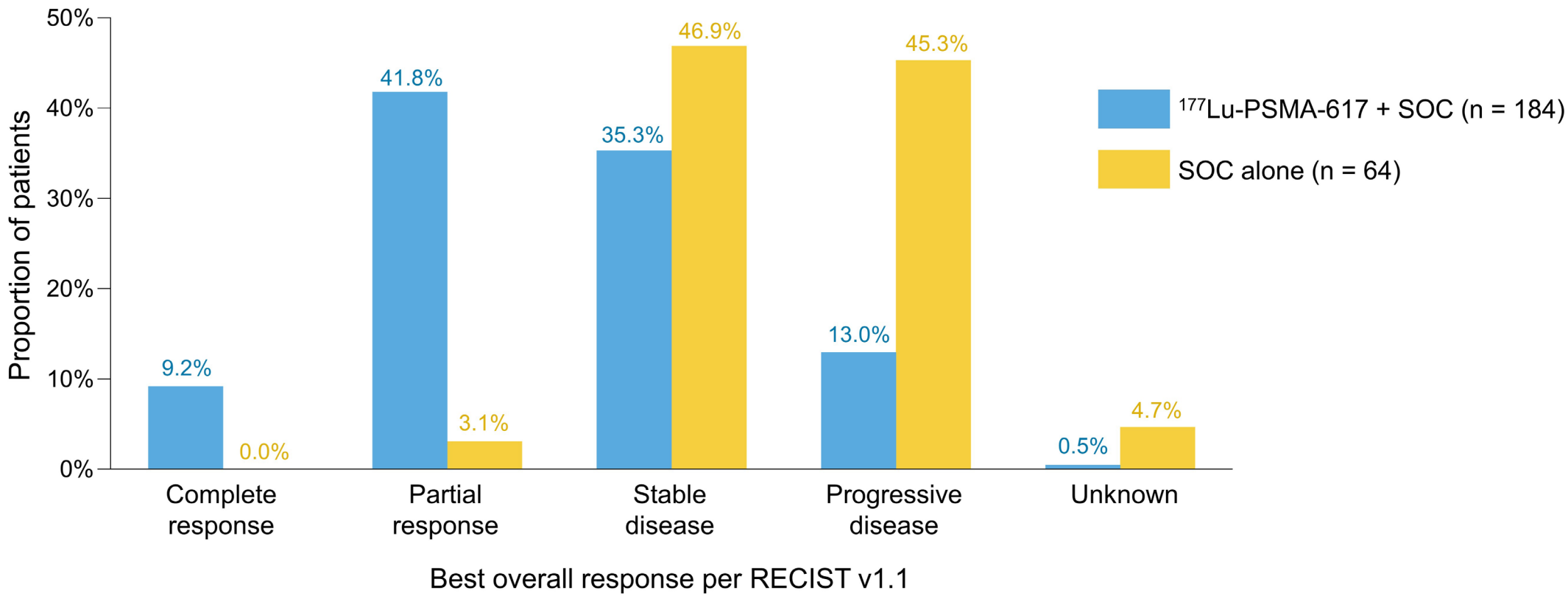
rPFS analysis set (n = 581)



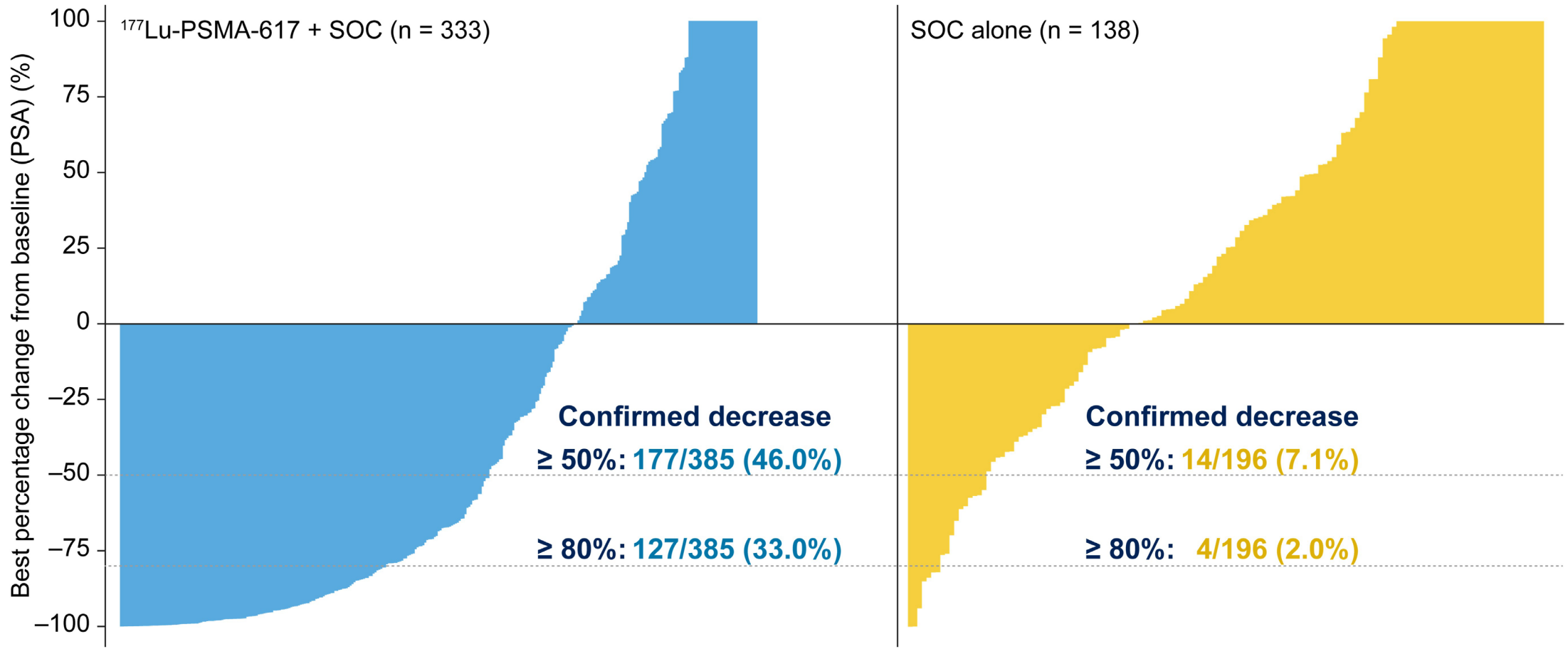
Number of patients still at risk

^{177}Lu-PSMA-617 + SOC	385	373	362	292	272	235	215	194	182	146	137	121	88	83	71	51	49	37	21	18	6	1	1	0
SOC alone	196	146	119	58	36	26	19	14	14	13	13	11	7	7	7	4	3	3	2	2	0	0	0	0

Secondary endpoint: RECIST v1.1 responses favored the ^{177}Lu-PSMA-617 arm in patients with measurable disease



Secondary endpoint: PSA responses favored the ^{177}Lu-PSMA-617 arm among evaluable patients



Higher rate of drug-related treatment-emergent adverse events with addition of ^{177}Lu-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)

VISION study conclusions

- Adding ^{177}Lu-PSMA-617 to safely combinable standard of care in patients with mCRPC after androgen receptor pathway inhibition and chemotherapy
    - Extended overall survival
    - Delayed radiographic disease progression
- ^{177}Lu-PSMA-617 was well tolerated
- These findings warrant adoption of ^{177}Lu-PSMA-617 as a new treatment option in patients with mCRPC

TheraP: OVERVIEW

^{177}Lu-PSMA-617 **(Lu-PSMA)** is a radiolabelled small molecule that delivers **therapeutic β-radiation to PSMA-expressing tumours**

Encouraging efficacy and safety of Lu-PSMA has been observed in prior trials of mCRPC

TheraP is the first randomised study comparing Lu-PSMA to cabazitaxel in men with mCRPC after docetaxel

ELIGIBILITY:

Metastatic castration-resistant prostate cancer post docetaxel suitable for cabazitaxel

PSMA + FDG PET/CT:

SUVmax >20 at a site of disease

Measurable sites SUVmax >10

No discordant FDG+ PSMA-disease

Centrally reviewed

R
1:1

^{177}Lu-PSMA-617
8.5 GBq i.v. q6 weekly
↓ 0.5 GBq/cycle
Up to 6 cycles

Cabazitaxel
20 mg/m^2 i.v. q3 weekly
Up to 10 cycles

SPECT/CT @ 24 h
Suspend Rx if exceptional response; recommence upon progression

Stratified by:

- Disease burden (>20 sites vs ≤20 sites)
- Prior enzalutamide or abiraterone
- Study site

Primary Endpoint

- PSA response (Reduction of ≥50% from baseline)

Key Secondary Endpoints

- PSA PFS, Adverse events

FDG, Fluorodeoxyglucose; LuPSMA, 177Lu-PSMA-617; i.v., intravenous; mCRPC, metastatic castration resistant prostate cancer; PET/CT, Positron emission tomography-computed tomography; PFS, progression free survival; PSA, prostate specific antigen; PSMA, prostate specific membrane antigen; Rx, treatment; SUV, standardised uptake value.

Hofman M, et al. ASCO 2020. Abstract #5500. Oral presentation

CRPC Therapy: where to in 2021?

- **Major decision point in mCRPC: progression on the first ARTA**
- **Screen for DDR – Olaparib or Rucaparib**
- **Sequence for those without DDR**
- **CARD trial supports cabazitaxel chemotherapy over ARTA after a first ARTA**
- **VISION data support Lu177 PSMA 617 represents another active option in patient who have had ARTAs and chemotherapy**

Preferred Therapeutic Sequencing For Metastatic CRPC possible changes for 2021