Current and Future Management Paradigms for Metastatic Castration-Resistant Prostate Cancer

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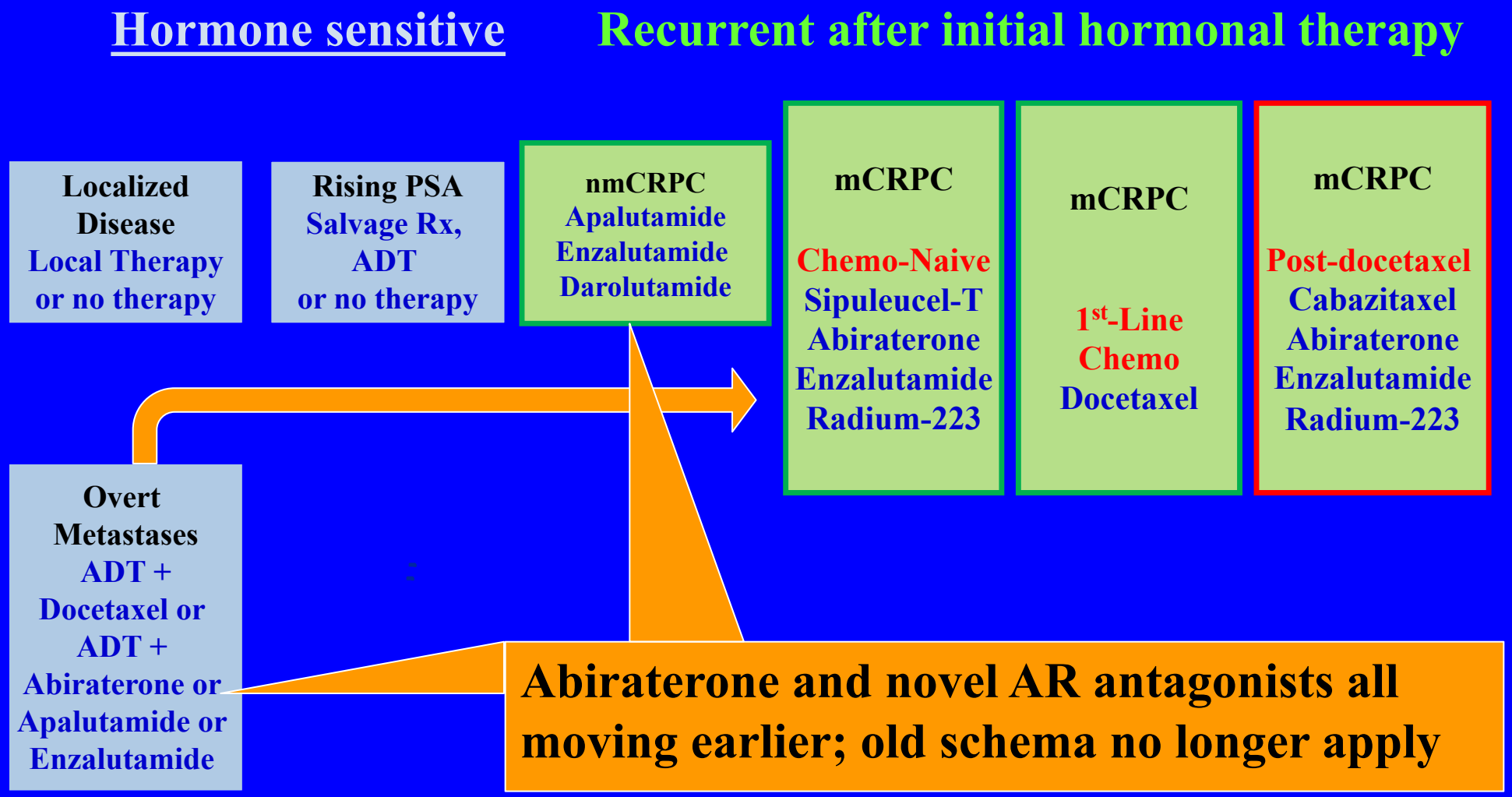
Prostate Cancer Clinical States: Older paradigms disrupted by recent advances

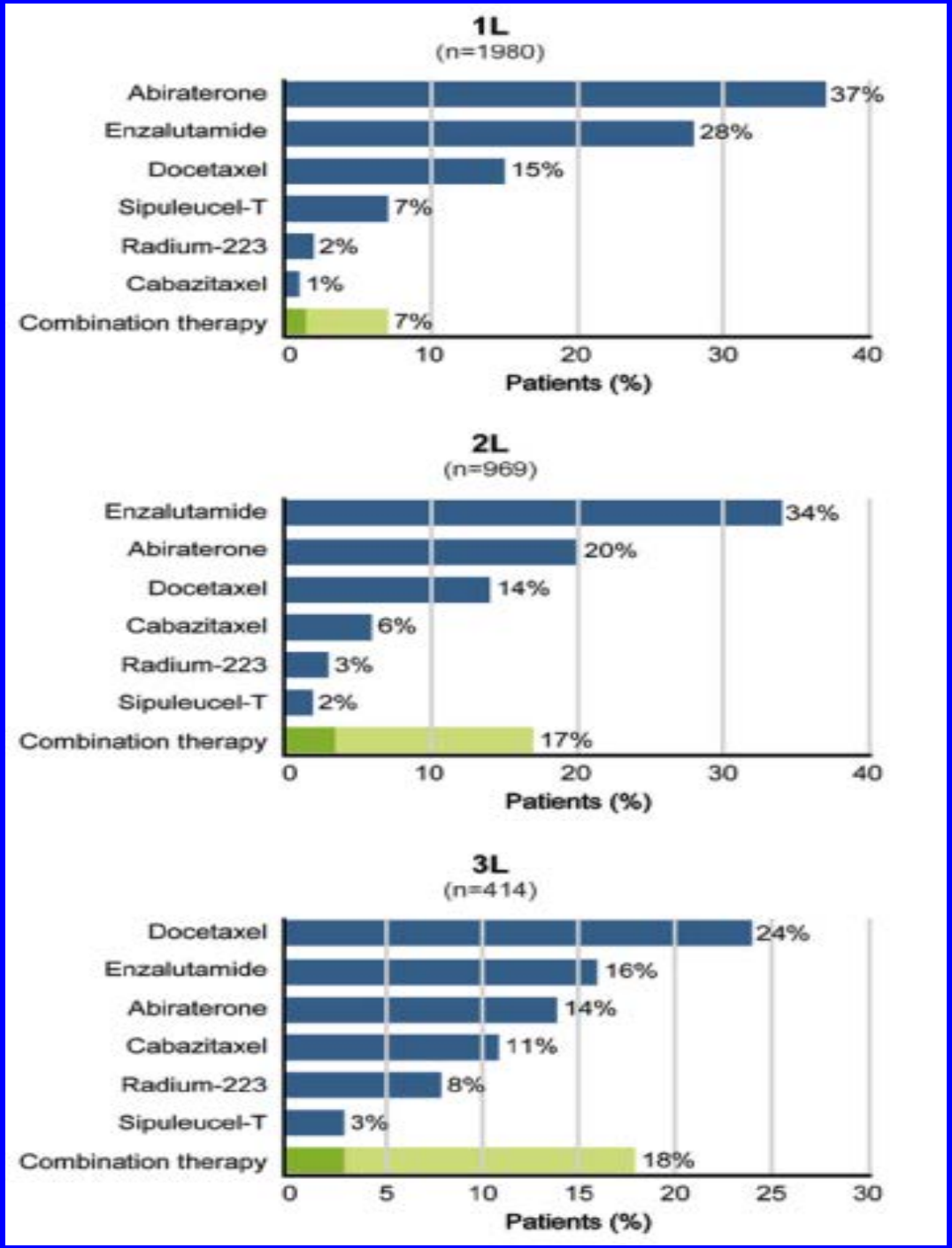


Courtesy of A Oliver Sartor, MD

Do we understand optimal sequences of therapy?

A little bit….

Courtesy of A Oliver Sartor, MD



Real world evidence on treatment sequences for mCRPC

George et al.
Clin Genitourinary Cancer
18:284-94, 2020

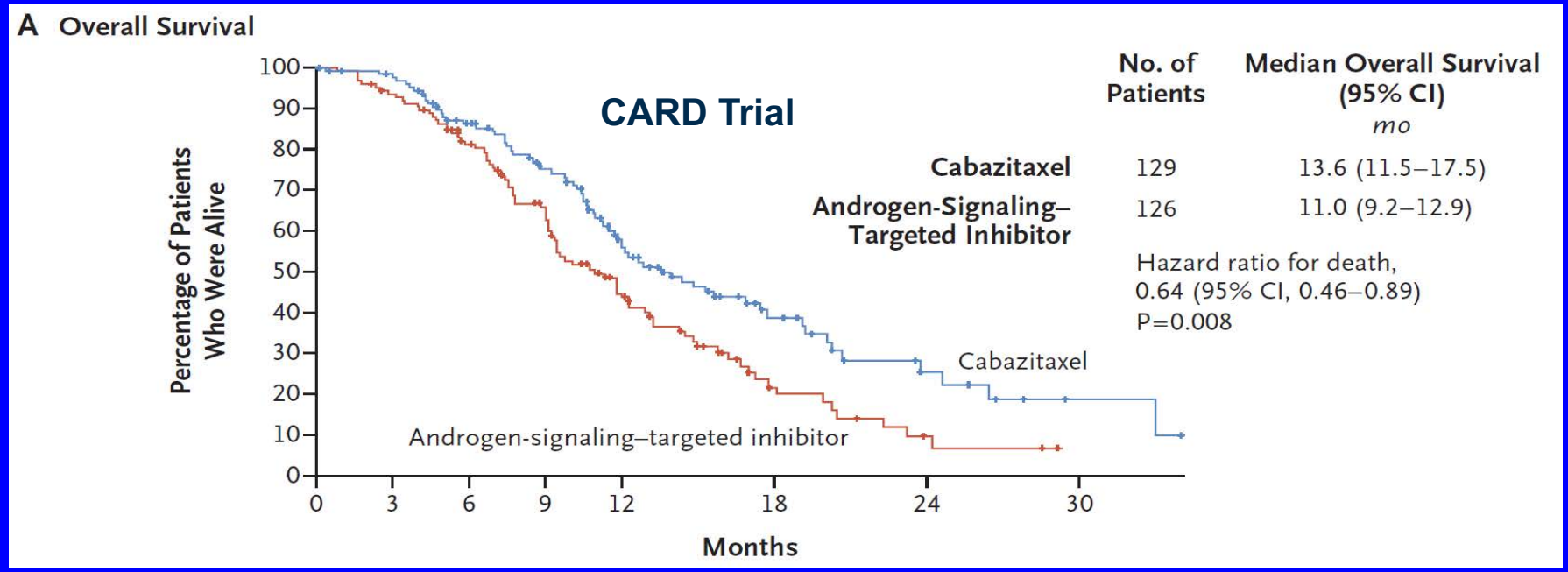
Courtesy of A Oliver Sartor, MD

Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer

R. de Wit, J. de Bo… ing, G. Kramer, J.-C. Eymard, A… verrisdóttir, C. Theodore, S. … ud-Ricouard, and D. Castellano, for the CARD Investigators*

Post-abiraterone and or enzalutamide and docetaxel

N Engl J Med 2019;381:2506-18



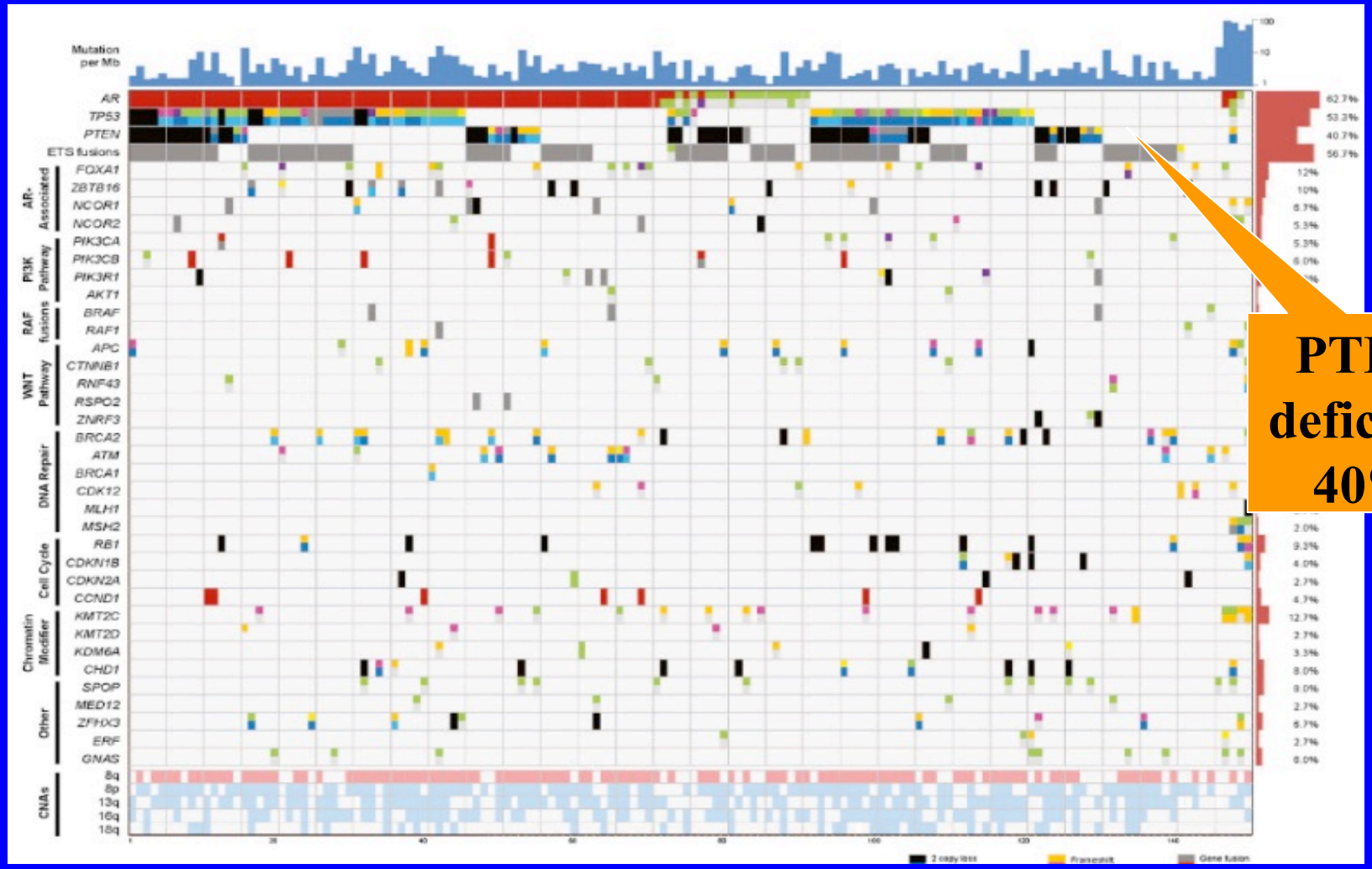
Courtesy of A Oliver Sartor, MD

Are there therapeutic combinations that deserve to be used as standard of care?

NOT YET but lots of interesting concepts are being explored

Courtesy of A Oliver Sartor, MD

Challenges: mCRPC is a heterogeneous group of diseases

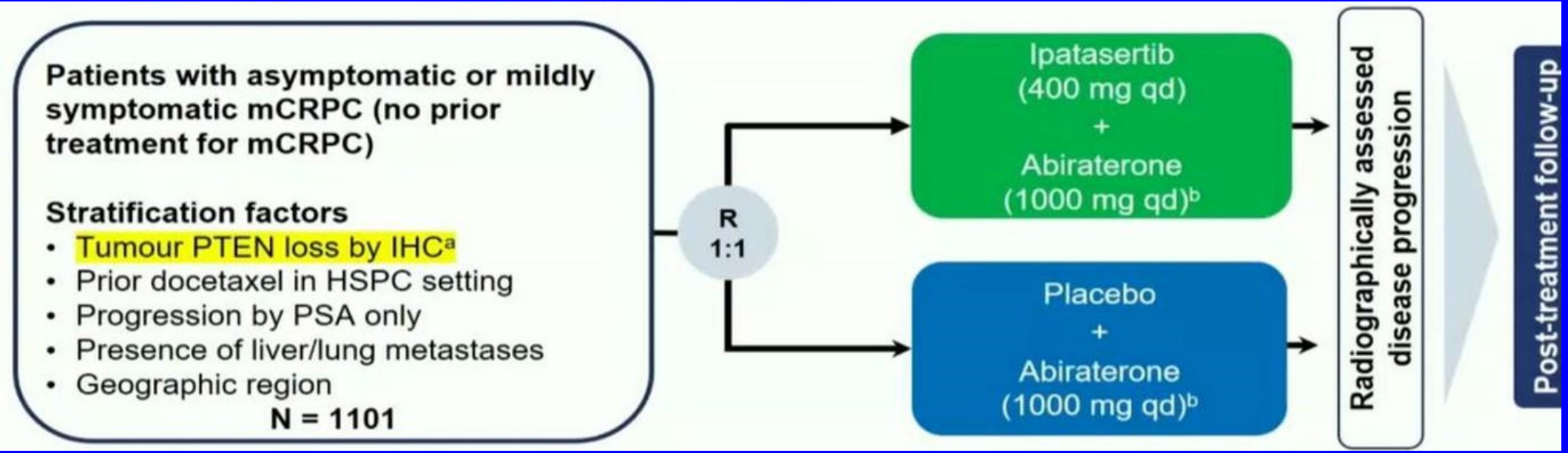


Robinson et al. Cell 161:1215, 2015

Courtesy of A Oliver Sartor, MD

IPATential150: Phase 3 study of ipatasertib plus abiraterone vs placebo plus abiraterone in mCRPC

IPATential150 phase 3 trial design



- **Co-primary endpoints:** investigator-assessed rPFS (PCWG3 criteria) in ITT and PTEN-loss (by IHC) populations
- **Secondary endpoints included:** OS, time to pain progression, time to initiation of chemotherapy, ORR, investigator-assessed rPFS in PTEN-loss (by NGS) population

NGS. Next generation sequencing; PCWG3, Prostate Cancer Working Group 3; R, randomised
[a] PTEN loss was defined as a minimum of 50% of the specimen's tumor area with no detectable PTEN staining (by Ventana IHC assay using SP218 antibody).
[b] Abiraterone (1000 mg qd) plus prednisone/prednisolone (5 mg bid).

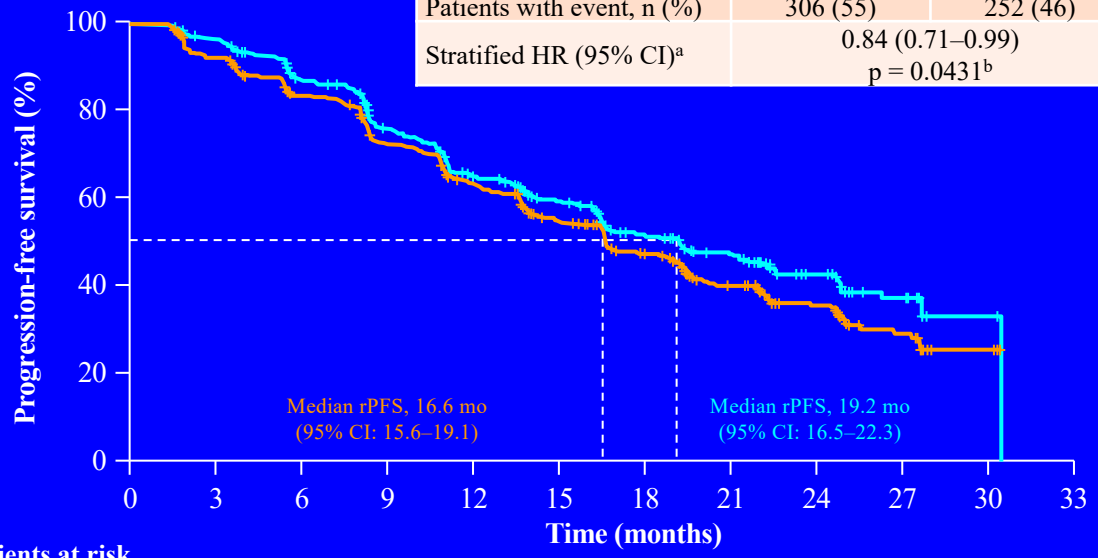
de Bono JS, et al. Oral presentation at ESMO 2020; abstract LBA4.

Courtesy of A Oliver Sartor, MD

IPATential150: rPFS with ipatasertib plus abiraterone compared with placebo plus abiraterone

ITT population: not statistically significant

	Pbo + abi n = 261	Ipat + abi n = 260
Patients with event, n (%)	306 (55)	252 (46)
Stratified HR (95% CI)[a]	0.84 (0.71–0.99) p = 0.0431[b]	

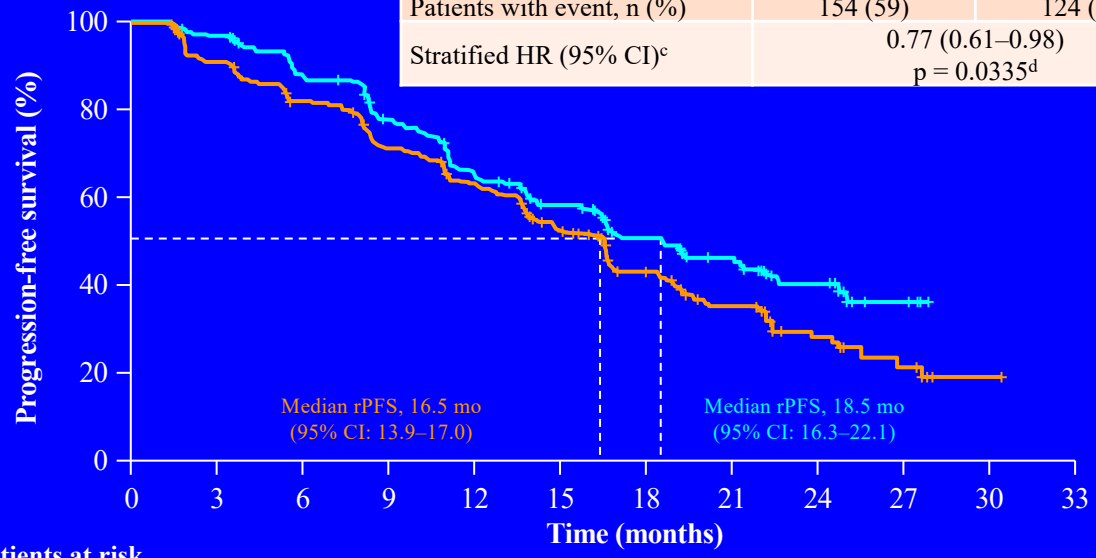


Patients at risk

Pbo + abi	554	501	443	377	322	237	165	98	60	29	5
Ipat + abi	547	495	436	368	310	239	158	103	53	26	2

Patients with PTEN-loss (by IHC): rPFS improved with Ipat + abi compared to PBO + abi

	Pbo + abi n = 261	Ipat + abi n = 260
Patients with event, n (%)	154 (59)	124 (48)
Stratified HR (95% CI)[c]	0.77 (0.61–0.98) p = 0.0335[d]	



Patients at risk

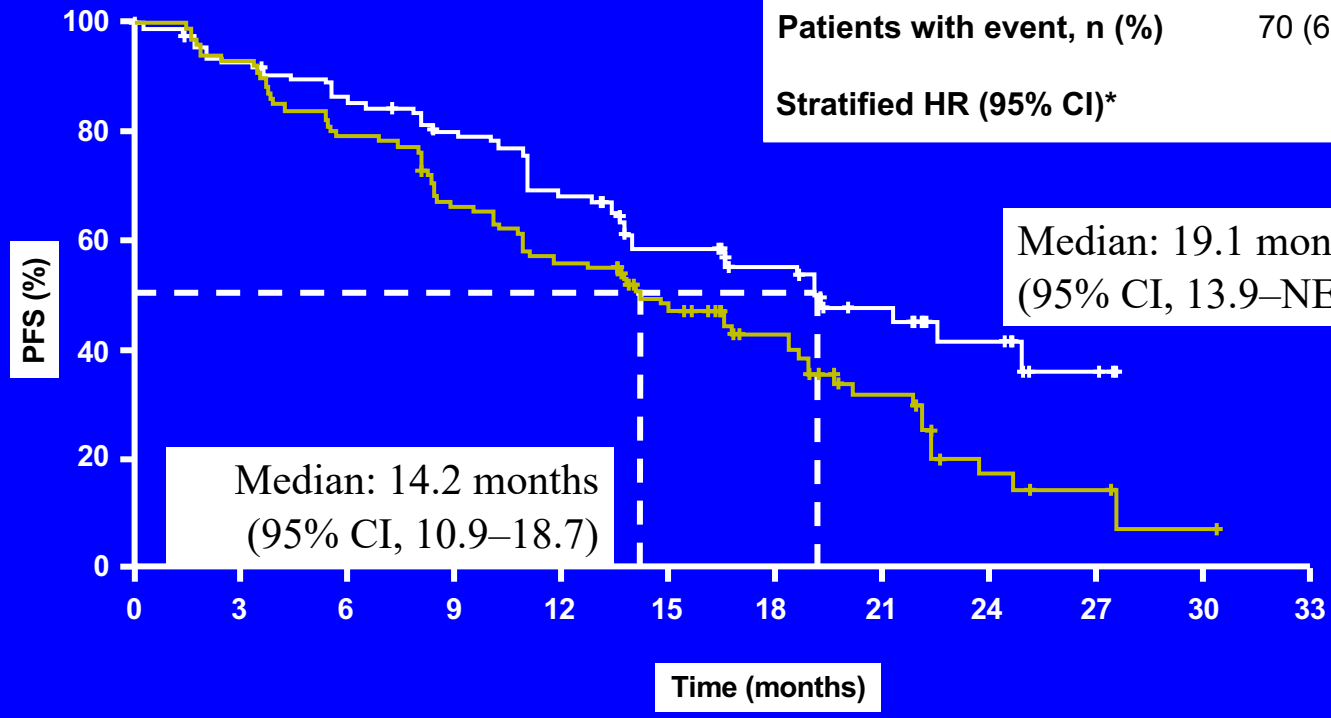
Pbo + abi	261	233	206	175	151	105	71	41	22	10	3
Ipat + abi	260	238	211	182	149	113	72	48	25	12	

de Bono JS, et al. Oral presentation at ESMO 2020; abstract LBA4.

Courtesy of A Oliver Sartor, MD

rPFS in the NGS-defined PTEN-loss group

	Placebo + abiraterone (n=103)	Ipatasertib + abiraterone (n=105)
Patients with event, n (%)	70 (68)	47 (45)
Stratified HR (95% CI)*	0.65 (0.45–0.95) p=0.0206†	



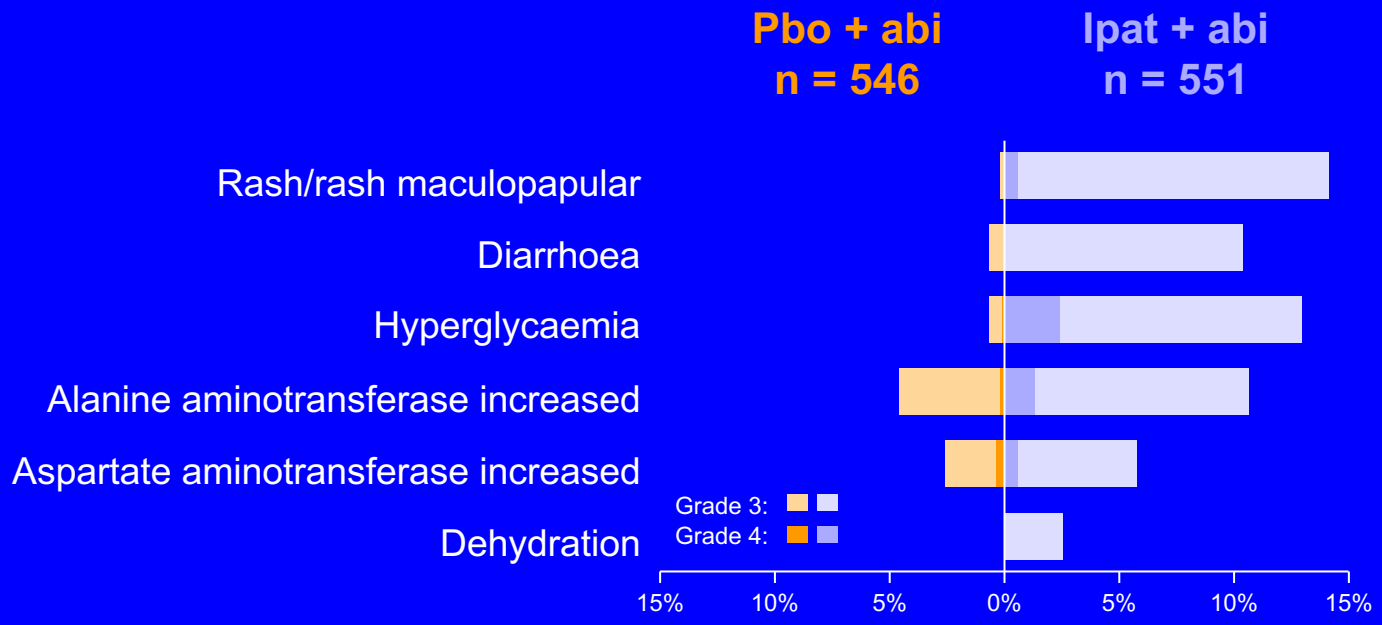
De Bono et al. Oral Presentation ESMO 2020

Courtesy of A Oliver Sartor, MD

IPATential150: Increased toxicity was observed with the addition of ipatasertib to abiraterone

Grade 3 and 4 AEs

≥2% difference between treatment arms



AEs leading to discontinuation or dose reduction

	PBO + abi (n = 546)	Ipat + abi (n = 551)
AEs leading to discontinuation of PBO/Ipat, n (%)	28 (5.1)	116 (21.1)
AEs leading to dose reduction of PBO/Ipat, n (%)	34 (6.2)	220 (39.9)

de Bono JS, et al. Oral presentation at ESMO 2020; abstract LBA4.

Courtesy of A Oliver Sartor, MD

The NEW ENGLAND JOURNAL of MEDICINE

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

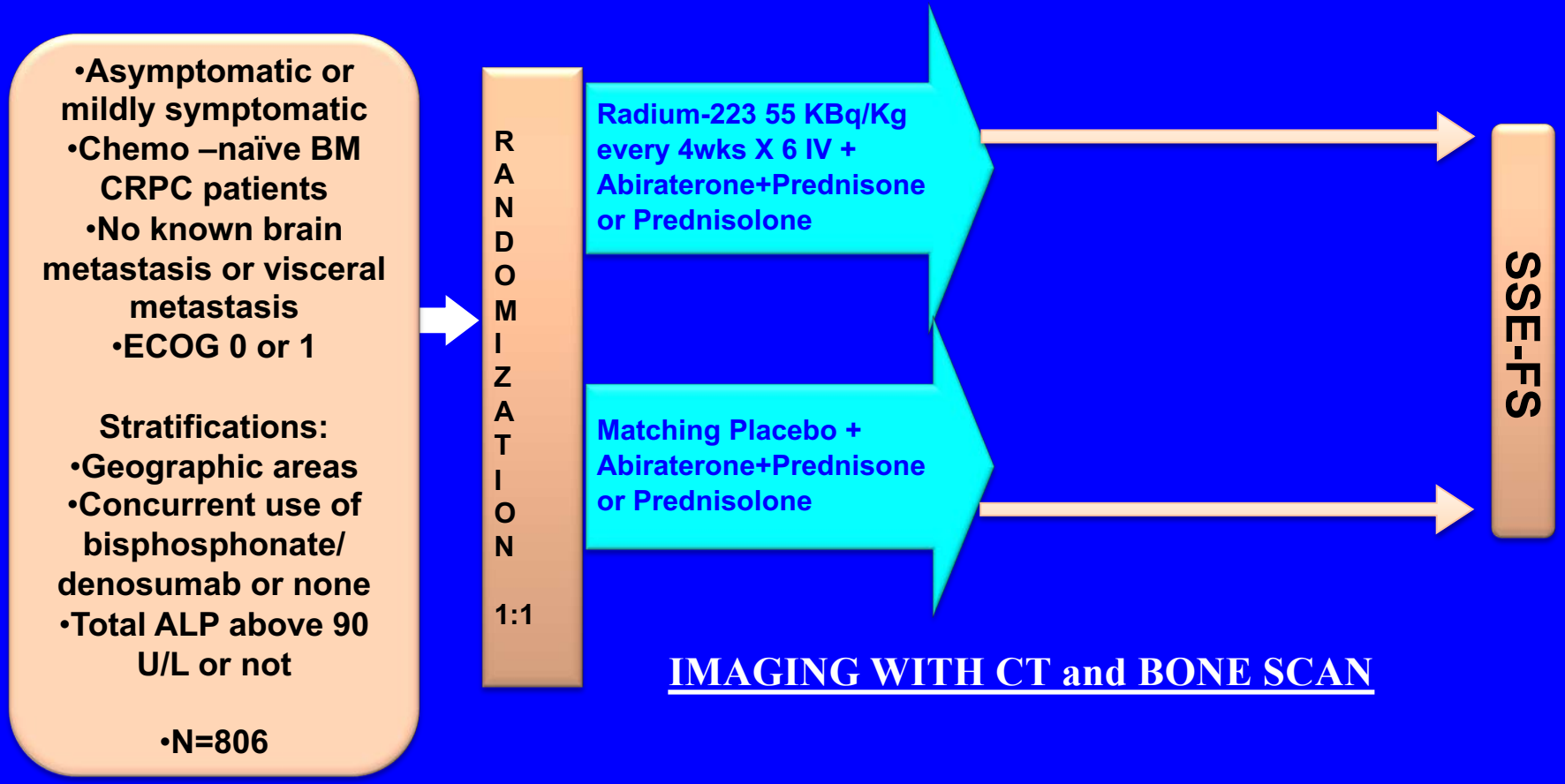
Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

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

Courtesy of A Oliver Sartor, MD

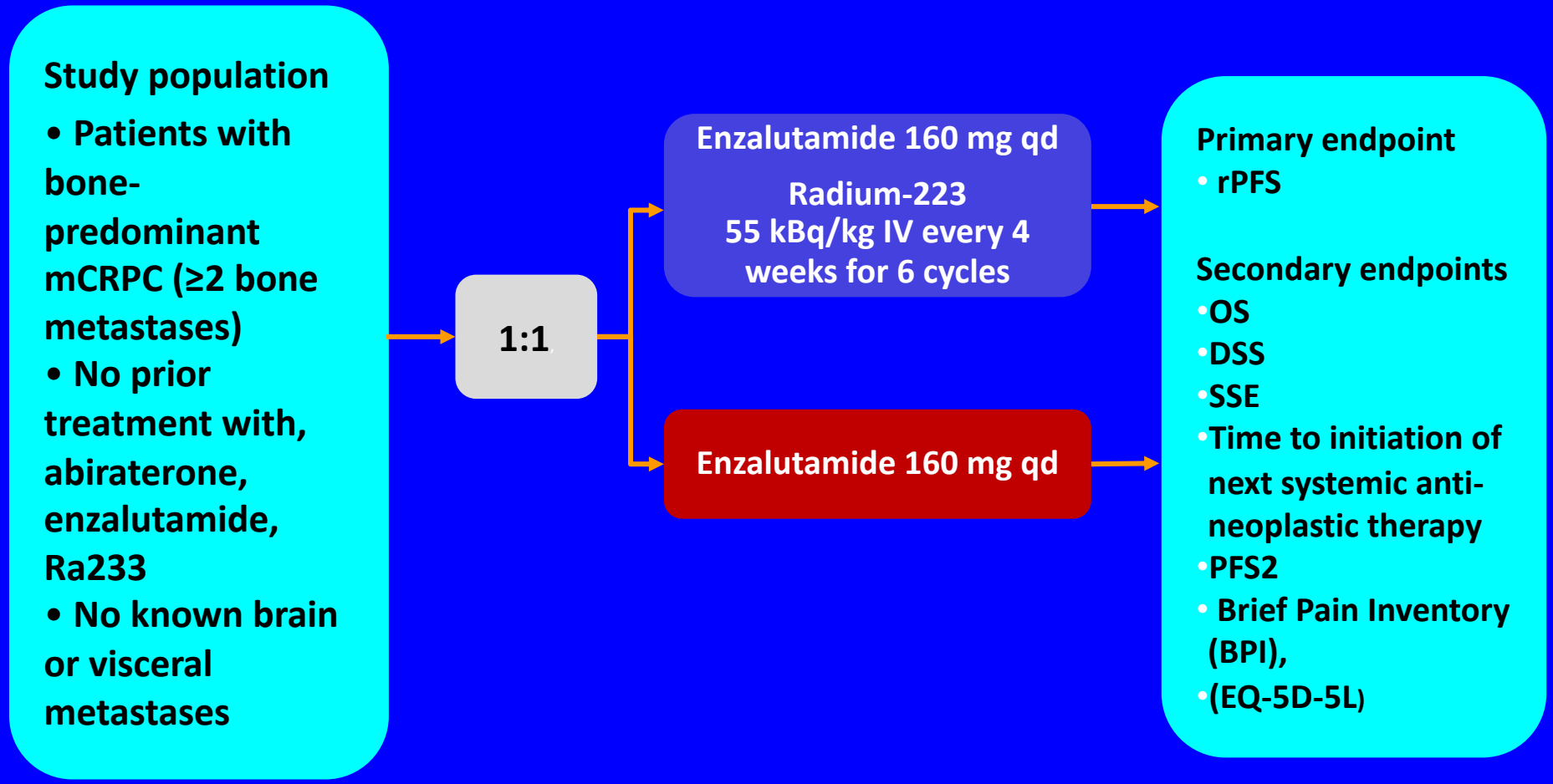
ERA-223: Abiraterone +/- Radium-223

Not successful and high rates of fractures in those without bone protection



Courtesy of A Oliver Sartor, MD

EORTC-1333-GUCG (PEACE III) is ongoing



Courtesy of A Oliver Sartor, MD

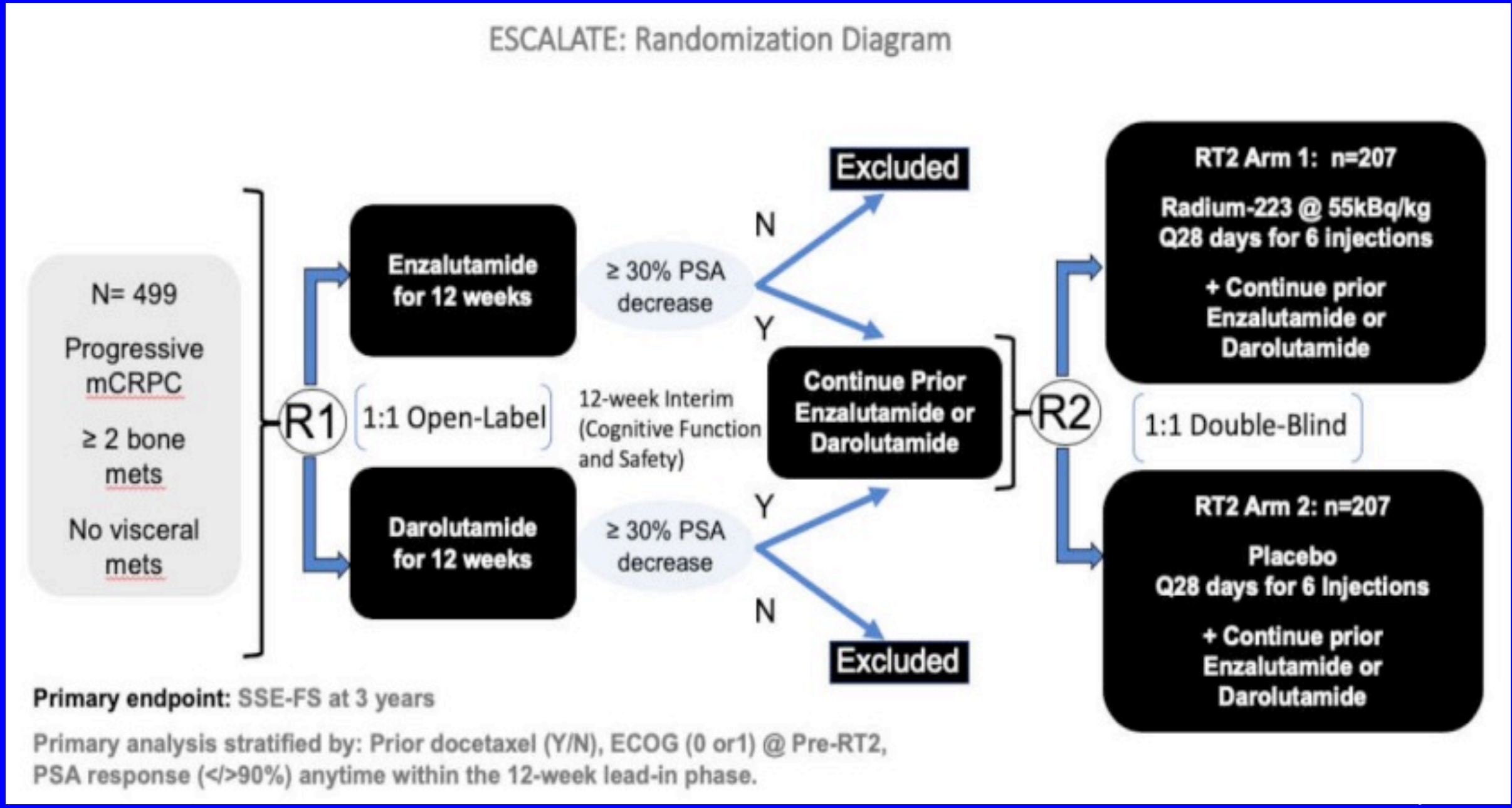
Bone fractures and cumulative incidence safety population of PEACE III:

Huge differences with bone protective agents

Tombal, ASCO 2019, #5007

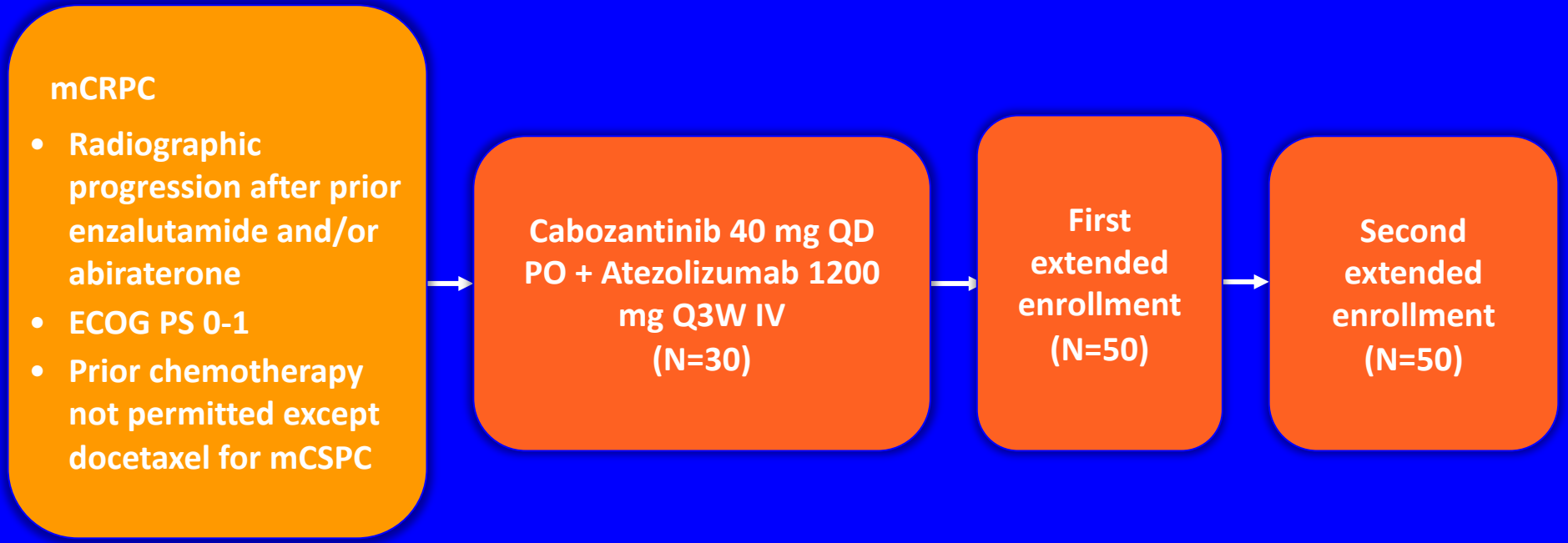
Time point	Treatment and use of bone protecting agents			
	With exposure to BPA		Without exposure to BPA	
	Enza+Rad (N=39)	Enza (N=49)	Enza+Rad (N=37)	Enza (N=35)
	Cum Incidence (95% CI)*	Cum Incidence (95% CI)	Cum Incidence (95% CI)	Cum Incidence (95% CI)
3 months	0 (-)	0 (-)	0 (-)	5.7 (1.0-16.7)
6 months	0 (-)	0 (-)	5.6 (1.0-16.3)	8.8 (2.2-21.0)
9 months	0 (-)	0 (-)	22.6 (10.6-37.3)	8.8 (2.2-21.0)
12 months	**0 (-)**	**0 (-)**	**37.4 (21.8-53.1)**	**12.4 (3.9-26.2)**
15 months	0 (-)	0 (-)	43.6 (26.8-59.3)	16.6 (5.9-32.0)
18 months	0 (-)	0 (-)	43.6 (26.8-59.3)	16.6 (5.9-32.0)

Courtesy of A Oliver Sartor, MD



Courtesy of A Oliver Sartor, MD

COSMIC-021: Study Design of the Expansion for CRPC Cohort 6



Patients receive study treatment as long as they continue to experience clinical benefit as assessed by the investigator or until unacceptable toxicity

Agarwal N, et al. ASCO GU. 2020 (abstr 139)

Courtesy of A Oliver Sartor, MD

Cabozantinib in combination with atezolizumab in patients with metastatic castration-resistant prostate cancer: results of cohort 6 of the COSMIC-021 study

Neeraj Agarwal,[1] Yohann Loriot,[2] Bradley McGregor,[3] Robert Dreicer,[4] Tanya B. Dorff,[5] Benjamin L. Maughan,[1] William Kelly,[6] Lance Pagliaro,[7] Sandy Srinivas,[8] Christian Squillante,[9] Ulka Vaishampayan,[10] Yingjie Liu,[11] Dominic Curran,[11] Toni K. Choueiri,[3] Sumanta Pal[5]

[1]Medical Oncology, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; [2]Gustave Roussy, University of Paris Sud, Villejuif, France; [3]Dana-Farber Cancer Institute, Boston, MA; [4]University of Virginia Cancer Center, Charlottesville, VA; [5]City of Hope, Duarte, CA; [6]Thomas Jefferson University Hospital, Philadelphia, PA; [7]Mayo Clinic, Rochester, MN; [8]Stanford University Medical Center, Palo Alto, CA; [9]MD Anderson Cancer Center at Cooper, Camden, NJ; [10]Karmanos Cancer Center, Detroit, MI; [11]Exelixis, Inc., Alameda, CA

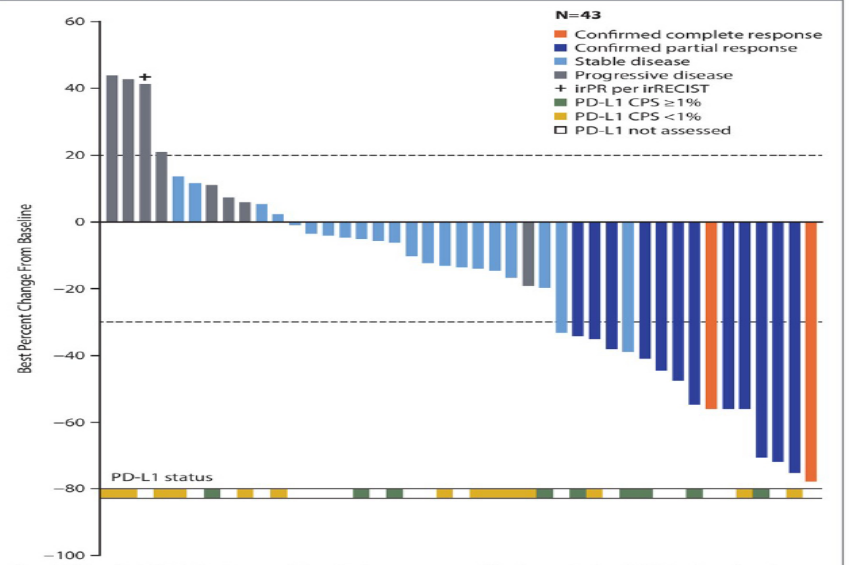
Table 2. Tumor Response per Investigator by RECIST v1.1

	CRPC Cohort (N=44)
Objective response rate (80% CI), %	32 (23–42)
Best overall response, n (%)	
Confirmed complete response	2 (4.5)
Confirmed partial response	12 (27)
Stable disease	21 (48)
Progressive disease	8 (18)*
Missing	1 (2.3)
Disease control rate, n (%)	35 (80)
Duration of objective response, median (range), mo	8.3 (2.8–9.8+)
Time to objective response, median (range), mo	1.6 (1–7)

Disease control rate = complete response + partial response + stable disease
*One patient with progressive disease had a subsequent immune-related partial response per irRECIST.

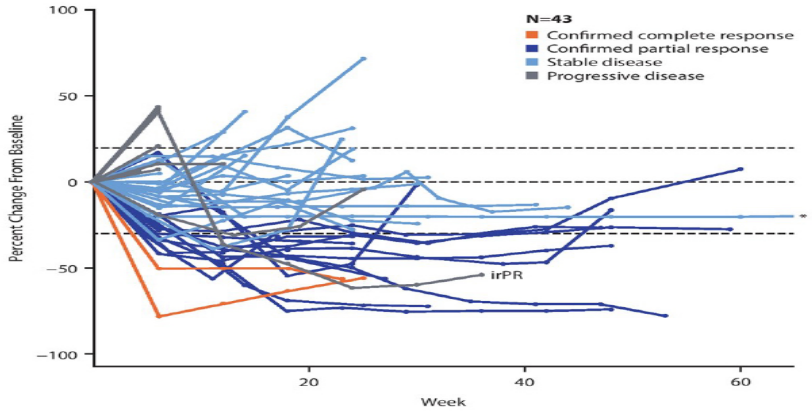
- ORR was 32% among all 44 CRPC patients and 33% among 36 patients with high-risk clinical features (visceral and/or extra-pelvic lymph node metastases)
- The disease control rate among all 44 CRPC patients was 80%

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



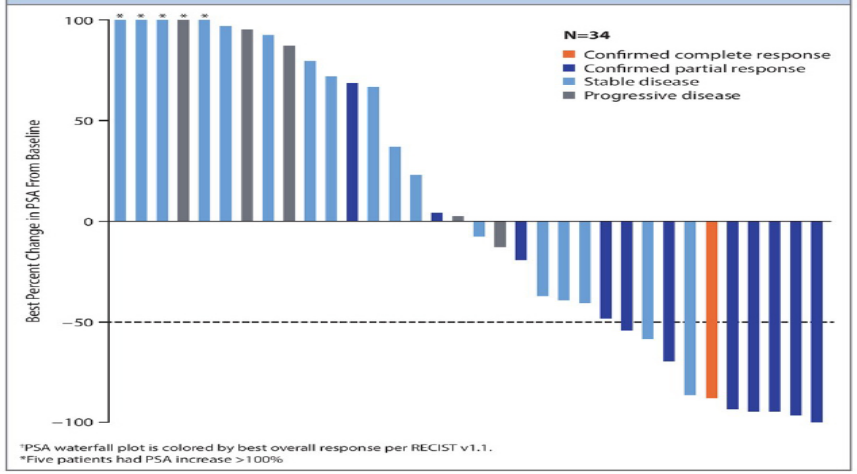
43 out of 44 patients had at least one post-baseline tumor assessment. The two patients with CRs had lymph node metastases as target lesions; one patient (notated above) had an irPR per irRECIST with a reduction in target lesions from baseline of ~60% after initial PD (see **Figure 6** for imaging). PD-L1 status is shown for patients with known PD-L1 status; analysis of PD-L1 is ongoing.

Figure 4. Change in Sum of Target Lesions Over Time per Investigator by RECIST v1.1



43 out of 44 patients had at least one post-baseline tumor assessment.
*Reduction in target lesions from baseline of -20% was continuing as of week 75.

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



†PSA waterfall plot is colored by best overall response per RECIST v1.1.
*Five patients had PSA increase >100%

Agarwal N et al. ASCO 2020;Abstract 139.

Courtesy of A Oliver Sartor, MD

CONTACT-02 is a global, multicenter, randomized, phase 3, open-label study that plans to enroll approximately 580 patients at 250 sites.

Patients will be randomized 1:1 to the experimental arm of cabozantinib in combination with atezolizumab and the control arm of a second novel hormonal therapy (either abiraterone/prednisone or enzalutamide).

The co-primary endpoints of the trial are PFS and OS. Additional endpoints include objective response rate, PSA response, and duration of response.

Courtesy of A Oliver Sartor, MD

What else is new?

Courtesy of A Oliver Sartor, MD

High Dose Testosterone and Resensitization to Subsequent Hormonal Agents:

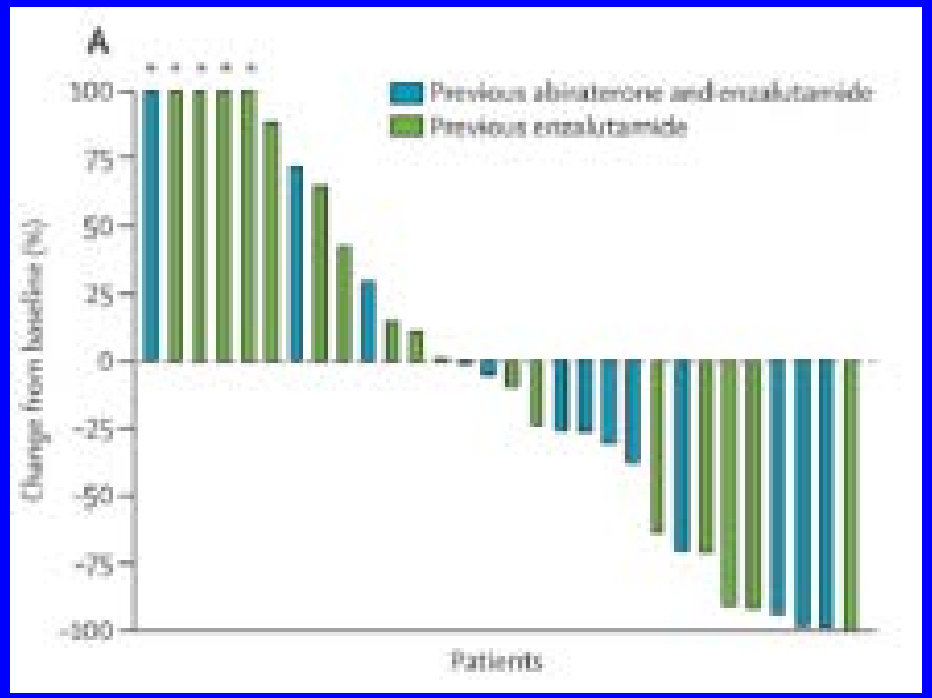
Disrupting Paradigms

Courtesy of A Oliver Sartor, MD

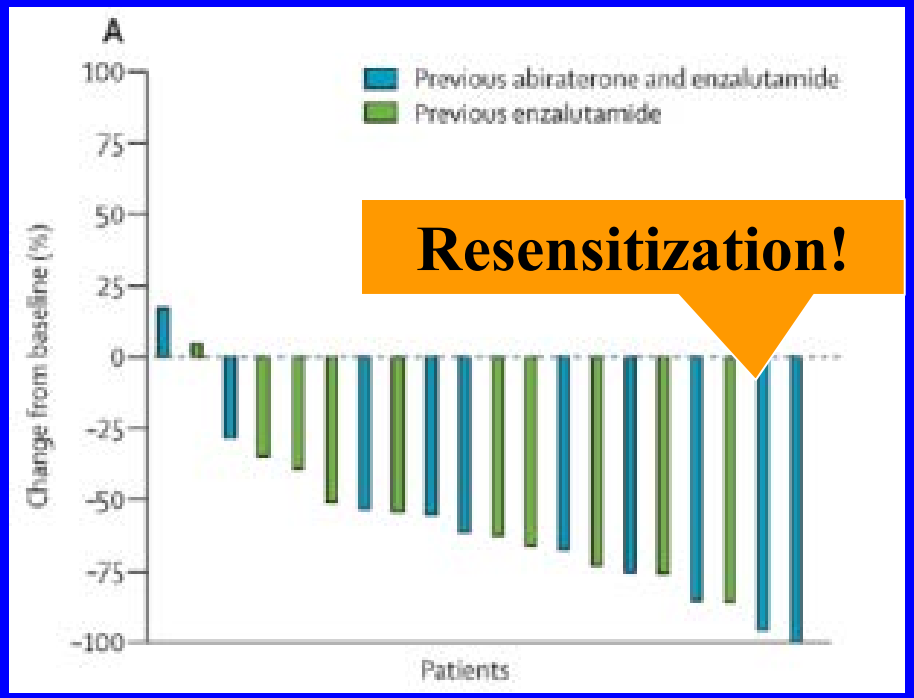
Bipolar androgen therapy in men with metastatic castration-resistant prostate cancer after progression on enzalutamide: an open-label, phase 2, multicohort study

Benjamin A Teply, MD, Hao Wang, PhD, Brandon Luber, MS, Rana Sullivan, RN, Irina Rifkind, RN, Ashley Bruns, RN, Avery Spitz, RN, Morgan DeCarli, BS, Victoria Sinibaldi, CRNP, Caroline F Pratz, CRNP, Changxue Lu, PhD, John L Silberstein, MHS, Jun Luo, PhD, Michael T Schweizer, MD, Prof Charles G Drake, MD, Prof Michael A Carducci, MD, Channing J Paller, MD, Emmanuel S Antonarakis, MD, Prof Mario A Eisenberger, MD, and Prof Samuel R Denmeade, MD

Lancet Oncol. 2018 January ; 19(1): 76–86.



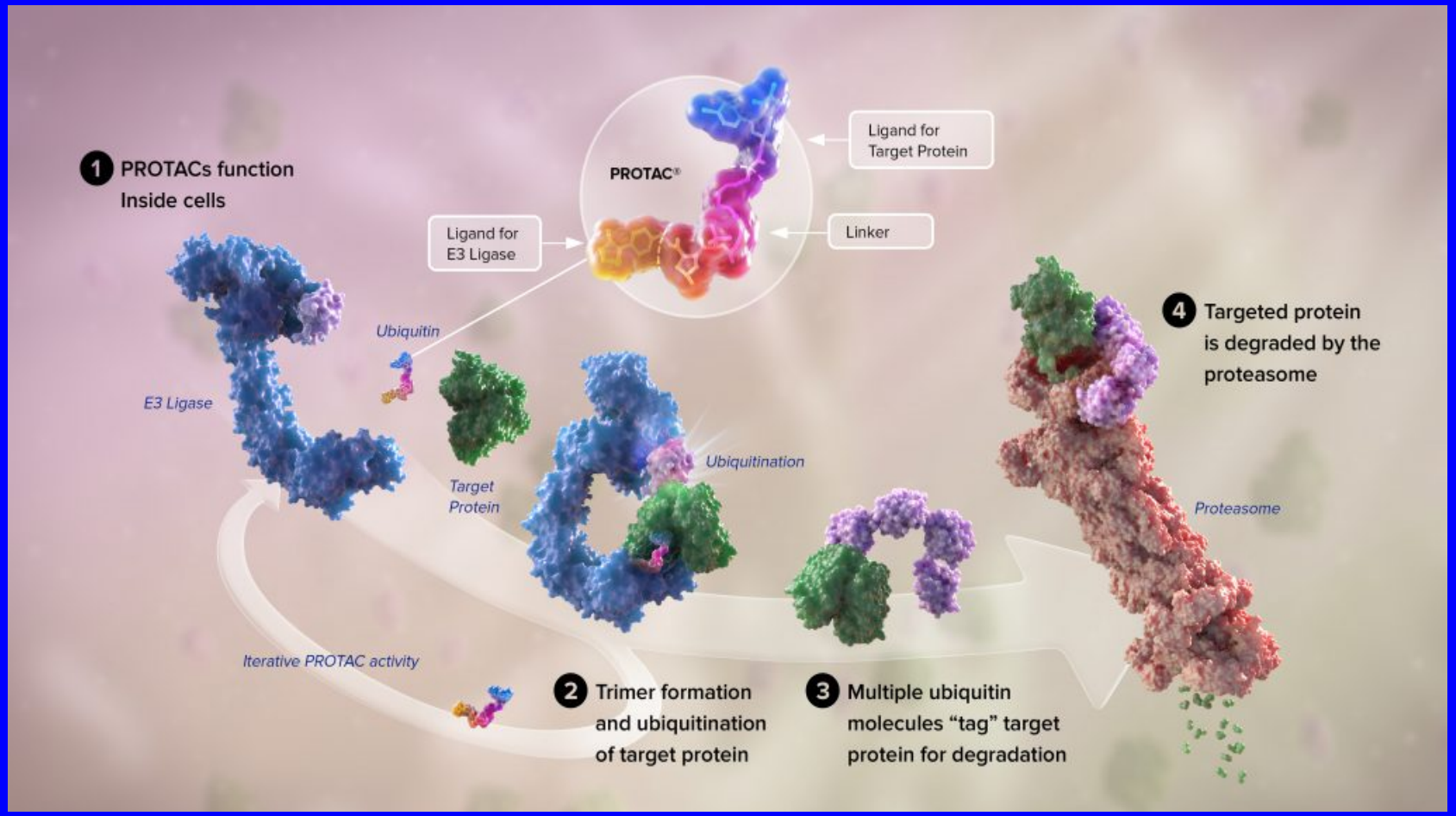
BAT



Enzalutamide post-BAT

Courtesy of A Oliver Sartor, MD

Targeted AR Degradation…..PROTAC



Courtesy of A Oliver Sartor, MD

PROTAC: Selected biomarker data

Petrylak et al. ASCO 2020 #3500

AR biomarker status and best % PSA change in patients at ≥140 mg (excludes DLT patient; N=12)[1]

AR Status:	AR-V7	Wildtype Amplif.	Wildtype	Wildtype Amplif.	AR-V7	L702H T878S W742C	L702H	Wildtype	Wildtype	T878A Amplif. AR-V7	T878A H875Y	T878A H875Y

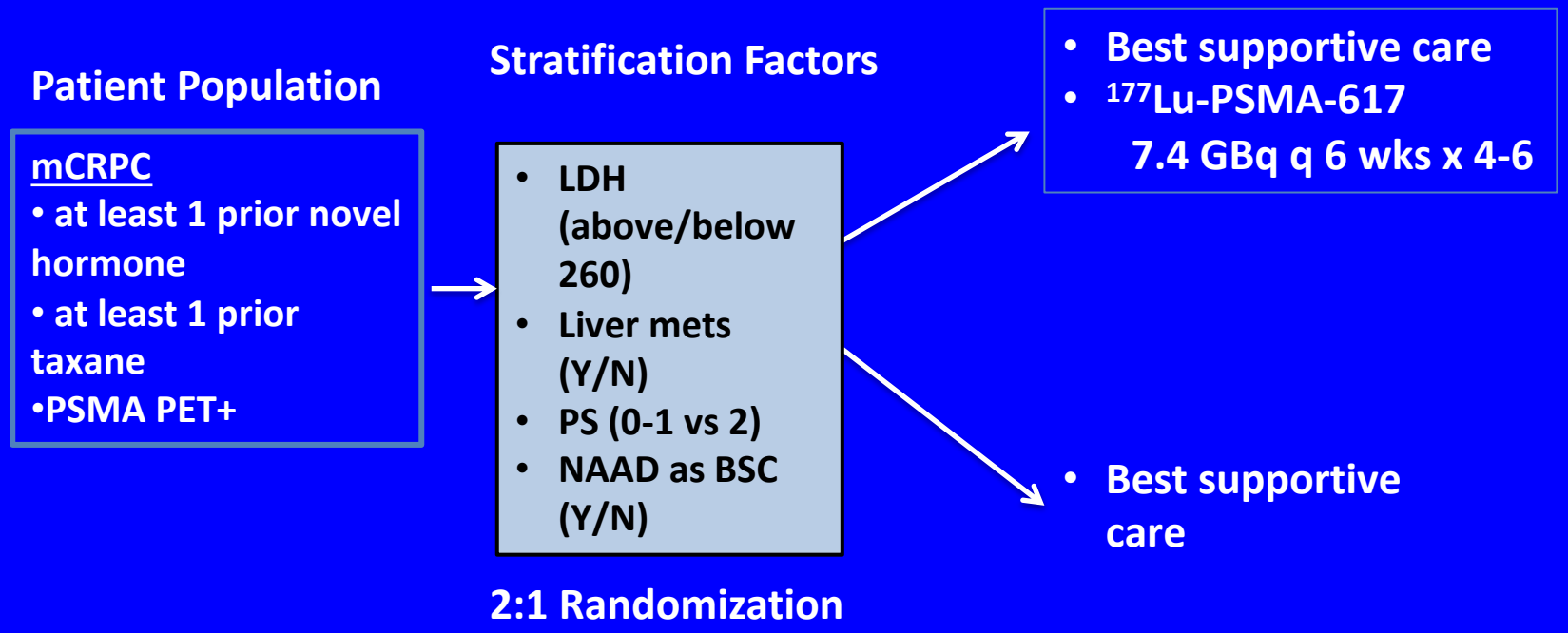
[1]One patient discontinued after 2 weeks due to DLT associated with rosuvastatin; AR status based on assays from Epic Sciences, Foundation Medicine (RUO), and OHSU/KDL

ARVINAS

30

Courtesy of A Oliver Sartor, MD

VISION: PSMA-Lu-177 Pivotal Phase III Trial Using PSMA-Imaging as a Biomarker



N=750
Alternative 1° endpoint:
rPFS or OS

PIs: Sartor and Krause

Courtesy of A Oliver Sartor, MD

THE END

Courtesy of A Oliver Sartor, MD