Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Prostate Cancer (Part 1 of a 2-Part Series)

Thursday, February 17, 2022

7:00 PM – 9:00 PM PT

Faculty

Neeraj Agarwal, MD
Himisha Beltran, MD
Fred Saad, MD
A Oliver Sartor, MD

Moderator

Alan H Bryce, MD

RTP RESEARCH TO PRACTICE

Faculty

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

Himisha Beltran, MD
Associate Professor of Medicine
Lank Center for Genitourinary Oncology
and the Division of Molecular and Cellular
Oncology
Director of Translational Research
Medical Oncology
Dana-Farber Cancer Institute
Boston, Massachusetts

Fred Saad, MD
Professor and Chairman of Urology
Director of GU Oncology
Raymond Garneau Chair in Prostate Cancer
University of Montreal Hospital Center (CHUM)
Montréal, Québec

A Oliver Sartor, MD
Laborde Professor for Cancer Research
Medical Director, Tulane Cancer Center
Associate Dean for Oncology
Tulane Medical School
New Orleans, Louisiana

Moderator

Alan H Bryce, MD
Chair, Division of Hematology and Medical Oncology
Chair, Genitourinary Disease Group
Mayo Clinic
Phoenix, Arizona

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TO PRACTICE

Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Bladder Cancer (Part 2 of a 2-Part Series)

Friday, February 18, 2022

6:30 PM – 8:00 PM PT

Faculty

Shilpa Gupta, MD
Daniel P Petrylak, MD
Guru Sonpavde, MD

Moderator

Sumanta Kumar Pal, MD

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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.

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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**

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Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Prostate Cancer (Part 1 of a 2-Part Series)

Thursday, February 17, 2022

7:00 PM – 9:00 PM PT

Faculty

Neeraj Agarwal, MD
Himisha Beltran, MD
Fred Saad, MD
A Oliver Sartor, MD

Moderator

Alan H Bryce, MD

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Agenda

Module 1 – Optimal Use of Hormonal Therapy in Nonmetastatic Prostate Cancer (PC) and Metastatic Hormone-Sensitive Disease — Dr Saad

Module 2 – Selection and Sequencing of Therapy for Patients with Metastatic CRPC (mCRPC) — Dr Sartor

Module 3 – Integration of PARP Inhibitors into the Current Management of mCRPC — Dr Beltran

Module 4 – Available Data with, Ongoing Investigation of and Potential Future Role of PARP Inhibitor-Based Combinations — Dr Bryce

Module 5 – Novel Investigational Strategies for Patients with PC — Dr Agarwal

Prostate Cancer Survey Respondents

Neeraj Agarwal, MD

Andrew J Armstrong, MD, ScM

Tomasz M Beer, MD

Himisha Beltran, MD

Alan H Bryce, MD

Heather H Cheng, MD, PhD

Nancy Ann Dawson, MD

Tanya B Dorff, MD

Robert Dreicer, MD, MS

Karim Fizazi, MD, PhD

Petros Grivas, MD, PhD

Maha Hussain, MD, FACP, FASCO

Sumanta Kumar Pal, MD

Daniel P Petrylak, MD

Fred Saad, MD

A Oliver Sartor, MD

Susan F Slovin, MD, PhD

Matthew R Smith, MD, PhD

Evan Y Yu, MD

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MODULE 1: Optimal Use of Hormonal Therapy in Nonmetastatic Prostate Cancer (PC) and Metastatic Hormone-Sensitive Disease — Dr Saad

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Optimal Use of Hormonal Therapy in Nonmetastatic Prostate Cancer (PC) and Metastatic Hormone-Sensitive Disease

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

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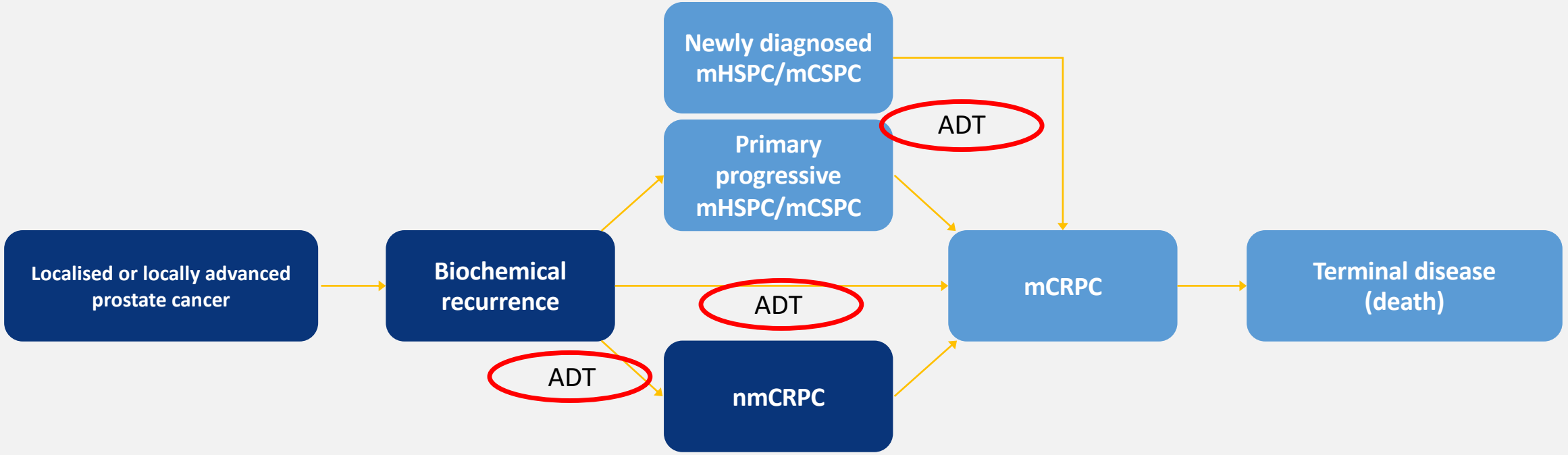
Dr Saad — Disclosures

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

The prostate cancer landscape



1. Tannock IF *et al. N Engl J Med* 2004; 351:1502–12. **2.** Ryan CJ *et al. Lancet Oncol* 2015;16:152–60. **3.** Rathkopf DE *et al. Eur Urol* 2014;66:815–25. **4.** Beer TM *et al. Eur Urol* 2017;71:151–4.
5. Armstrong AJ *et al. Cancer* 2017;123:2303–11. **6.** de Bono JS *et al. Lancet* 2010;376:1147–54. **7.** Hoskin P *et al. Lancet Oncol* 2014;15:1397-406.

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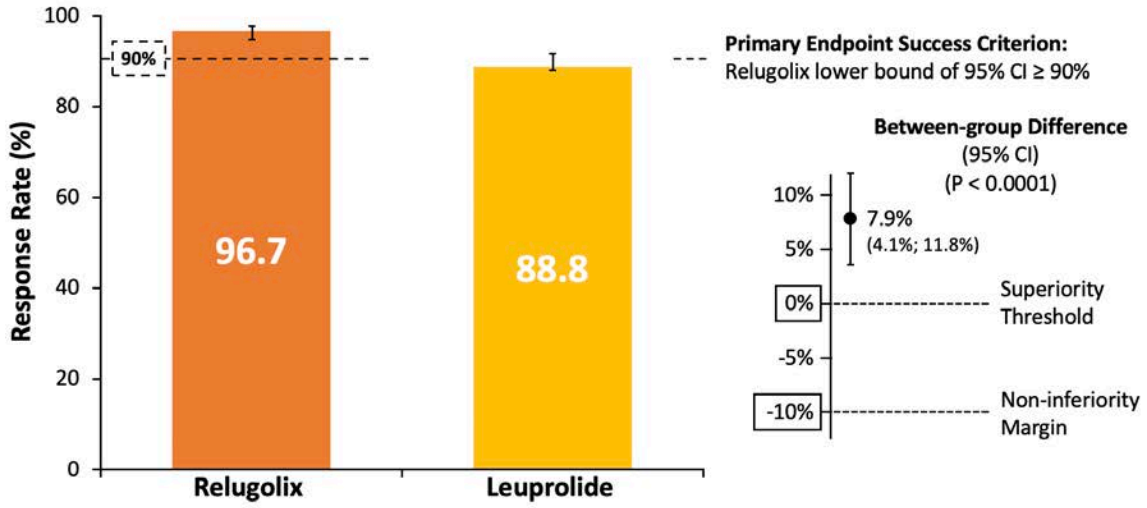
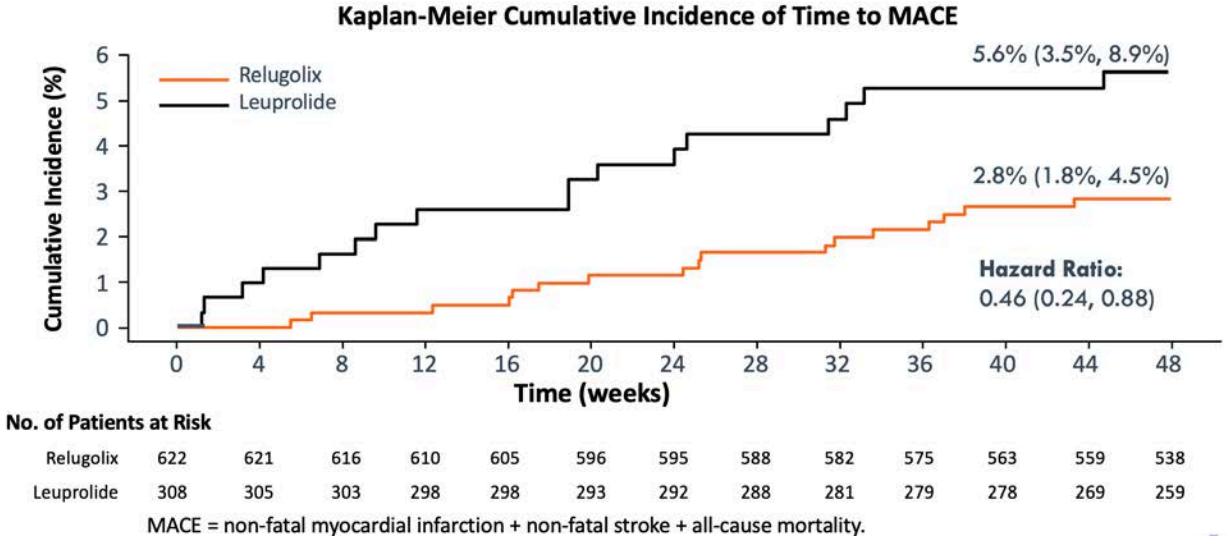
What's new in ADT: Oral antagonist

Primary Endpoint – Sustained Castration
Key Secondary Endpoint – Non-inferiority to Leuprolide



54% Reduction in Risk of Major Adverse Cardiovascular Events (MACE)



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

Shore N, Saad F et al. NEJM 2020 Jun 4;382(23):2187-2196

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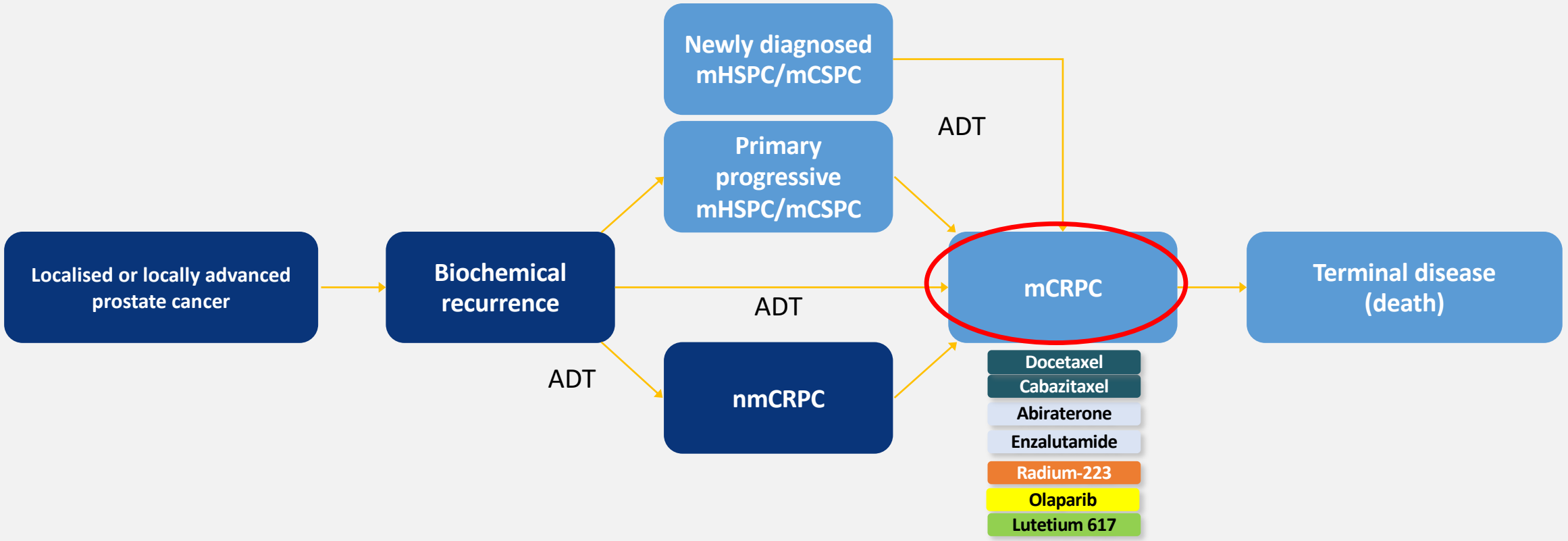
The prostate cancer landscape



Median survival improvement of 2.5-4.5 months

1. Tannock IF *et al. N Engl J Med* 2004; 351:1502–12. **2.** Ryan CJ *et al. Lancet Oncol* 2015;16:152–60. **3.** Rathkopf DE *et al. Eur Urol* 2014;66:815–25. **4.** Beer TM *et al. Eur Urol* 2017;71:151–4.
5. Armstrong AJ *et al. Cancer* 2017;123:2303–11. **6.** de Bono JS *et al. Lancet* 2010;376:1147–54. **7.** Hoskin P *et al. Lancet Oncol* 2014;15:1397-406.

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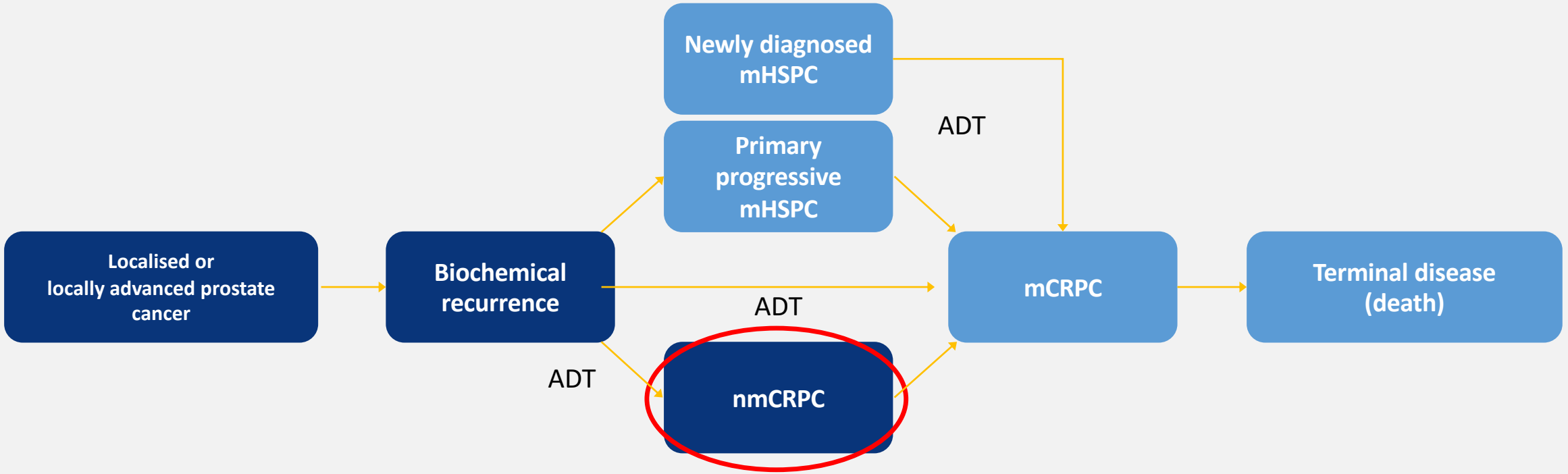
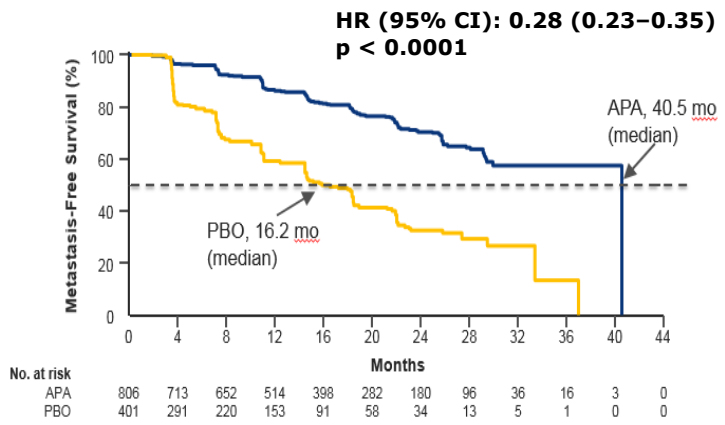
Non-Metastatic CRPC: On conventional imaging



Primary Endpoint: Metastases Free Survival

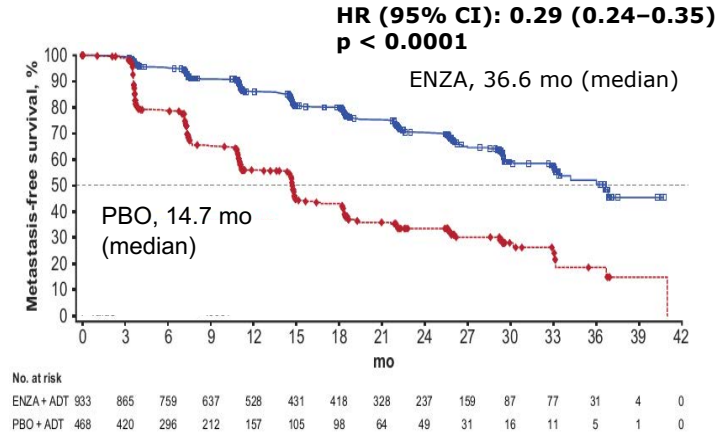
In nmCRPC patients with PSADT ≤ 10 months

SPARTAN (Apalutamide)



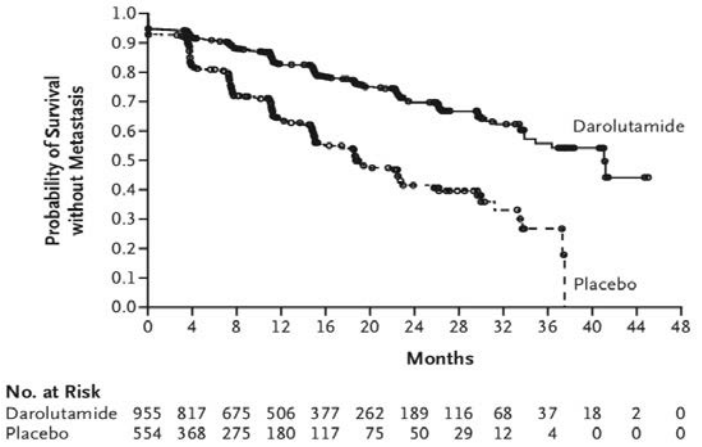
- 72% reduction of metastases or death
- 40.5 m vs PBO 16.2 m
- **24-month additional MFS**

PROSPER (Enzalutamide)



- 71% reduction of metastases or death
- 36.6 m vs 14.7 m
- **22-month additional MFS**

ARAMIS (Darolutamide)



- 59% reduction of metastases or death
- 40.4 m vs 18.4 m
- **22-month additional MFS**

1. Smith MR, *et al. N Engl J Med*. 2018;378:1408-18. **2.** Hussain M, *et al. N Engl J Med.* 2018;378:2465-74. **3.** Fizazi K, *et al. N Engl J Med.* 2019;doi: 10.1056/NEJMoa1815761.

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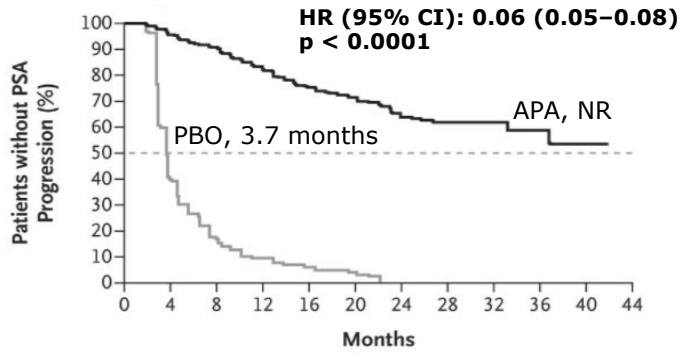
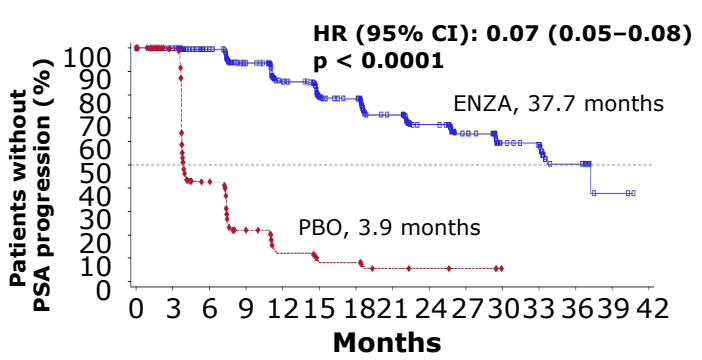
Time to PSA progression (resistance)

SPARTAN[1] (APA)



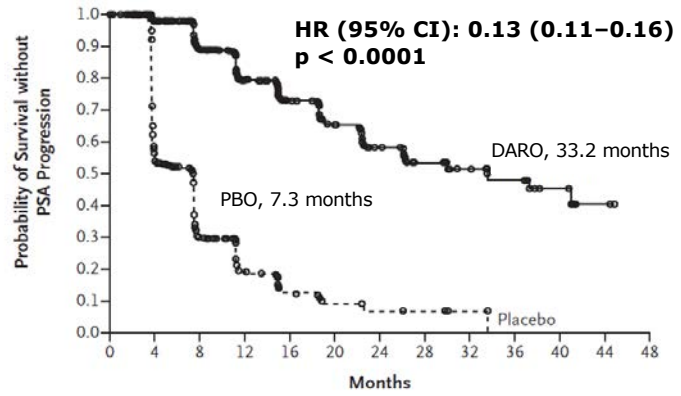
- 94% risk reduction in PSA progression
- TTPP: PBO 3.9 vs APA NR months

PROSPER[2] (ENZA)



- 93% risk reduction in PSA progression
- TTPP: PBO 3.9 vs ENZA 37.2 months

ARAMIS[3] (DARO)



- 87% risk reduction in PSA progression
- TTPP: PBO 7.3 vs DARO 33.2 months

Resistance to therapy much longer than in mCRPC

1. Smith MR, *et al. N Engl J Med.* 2018;378:1408-18. **2.** Hussain M, *et al. N Engl J Med.* 2018;378:2465-74. **3.** Fizazi K, *et al. N Engl J Med.* 2019 Feb 14 [Epub ahead of print].

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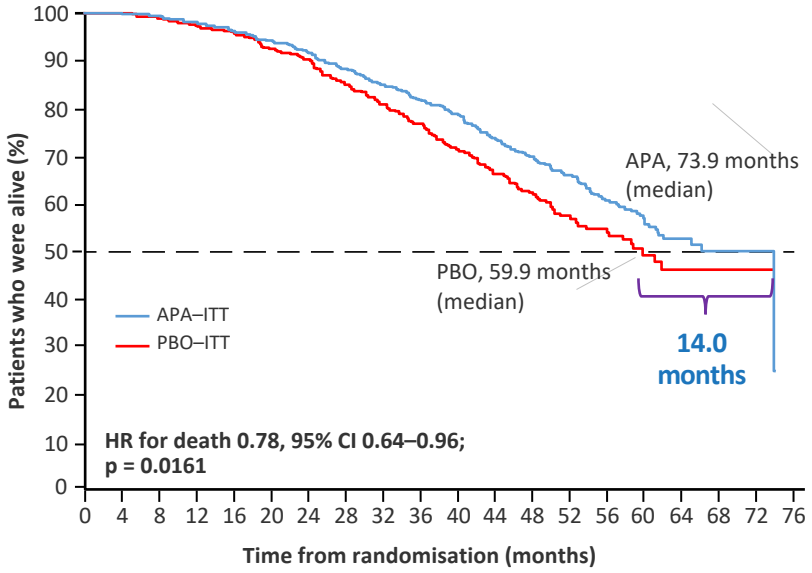
Final Overall Survival

SPARTAN[1]

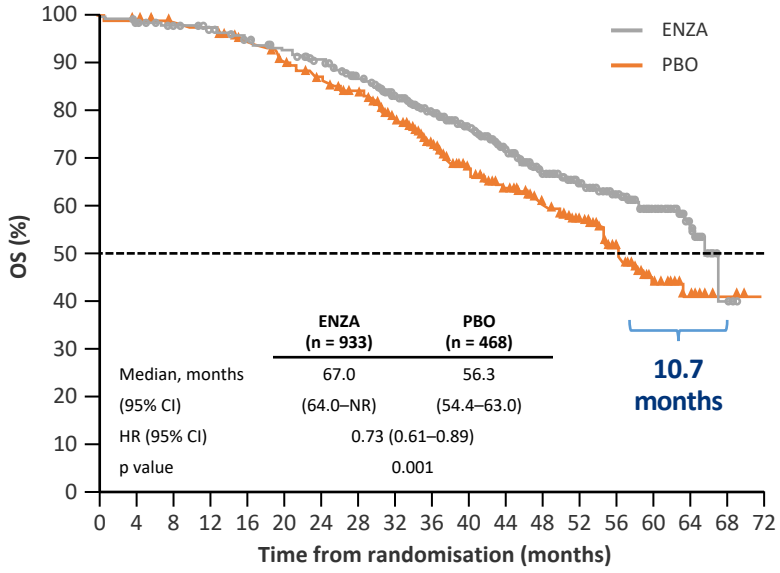


No. of patients at risk

APA	806	791	774	758	739	717	691	658	625	593	558	499	376	269	181	100	47	19	4	0
PBO	401	392	385	373	358	339	328	306	286	263	240	204	156	114	82	38	21	6	2	0

- OS events:
- APA 274 (34%) and PBO 154 (38%)

PROSPER[2]

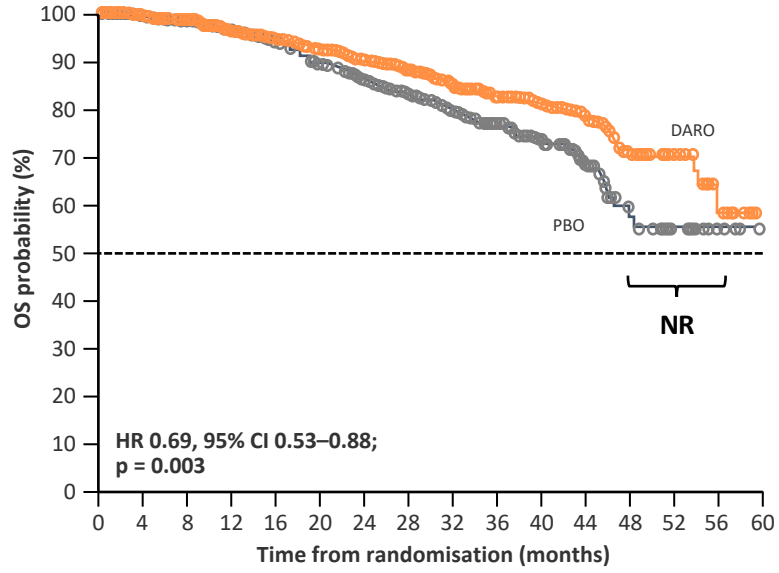


No. of patients at risk

ENZA	933	926	910	897	874	850	822	782	700	608	517	424	327	244	169	89	33	4	0	
PBO	468	467	459	444	428	404	381	363	321	274	219	177	140	106	64	30	16	3	0	

- OS events:
- ENZA 288 (31%) and PBO 178 (38%)

ARAMIS[3]



No. of patients at risk

DARO	955	932	908	863	816	771	680	549	425	293	214	129	69	37	12	0
PBO	554	530	497	460	432	394	333	261	182	130	93	54	28	16	4	0

- OS events:
- DARO 148 (15%) and PBO 106 (19%).

2-3x greater than in mCRPC

1. Smith M, Saad F, Chowdhury S et al. Eur Urol. 2021 Jan;79(1):150-158. 2. Sternberg CN, Fizazi K, Saad F, et al. N Engl J Med 3. Fizazi K et al., N Engl J Med; 2020, 383:1040-1049

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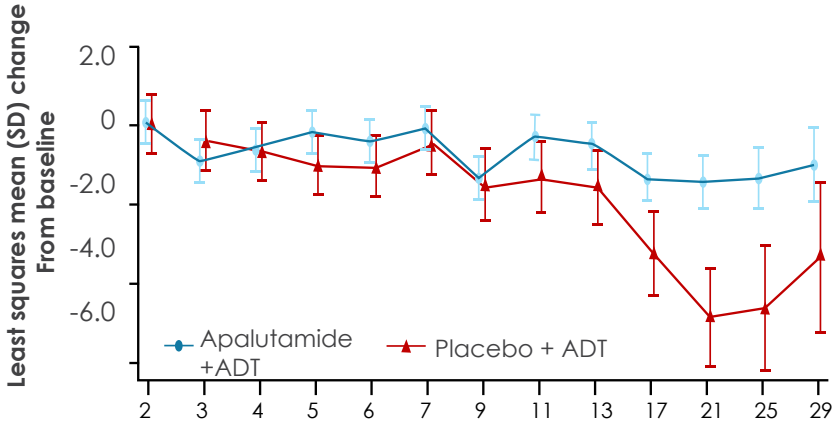
Health-Related QoL is Maintained

SPARTAN

FACT-P total score (treatment difference in least squares mean change from baseline)

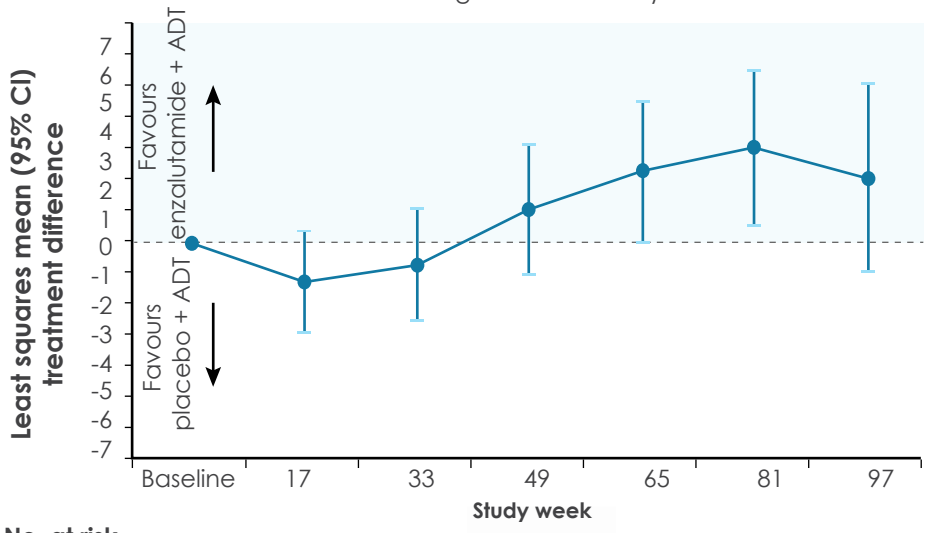


No. of patients in each cycle

APA + ADT	787	769	750	732	707	689	657	631	598	486	373	274	179
PBO + ADT	390	382	376	358	339	289	276	255	208	181	99	62	44

PROSPER

FACT-P total score (treatment difference in least squares mean change from baseline)

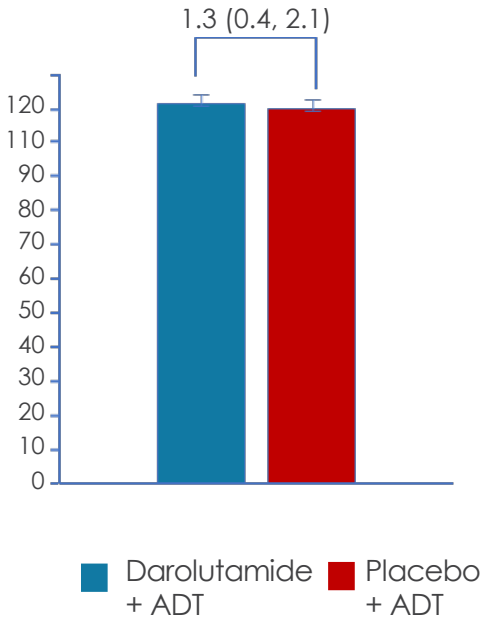


No. at risk

ENZA + ADT	...	815	718	621	522	427	354
PBO + ADT	...	403	329	239	183	139	90

ARAMIS

FACT-P total score (difference with placebo)



Saad F, et al. *Lancet Oncol* 2018;19:1404-1416;
Tombal B, et al. *Lancet Oncol* 2019;20:556-559;
Fizazi K, et al. *N Engl J Med* 2019;380:1235-1246. [Epub ahead of print](Supplement Appendix)

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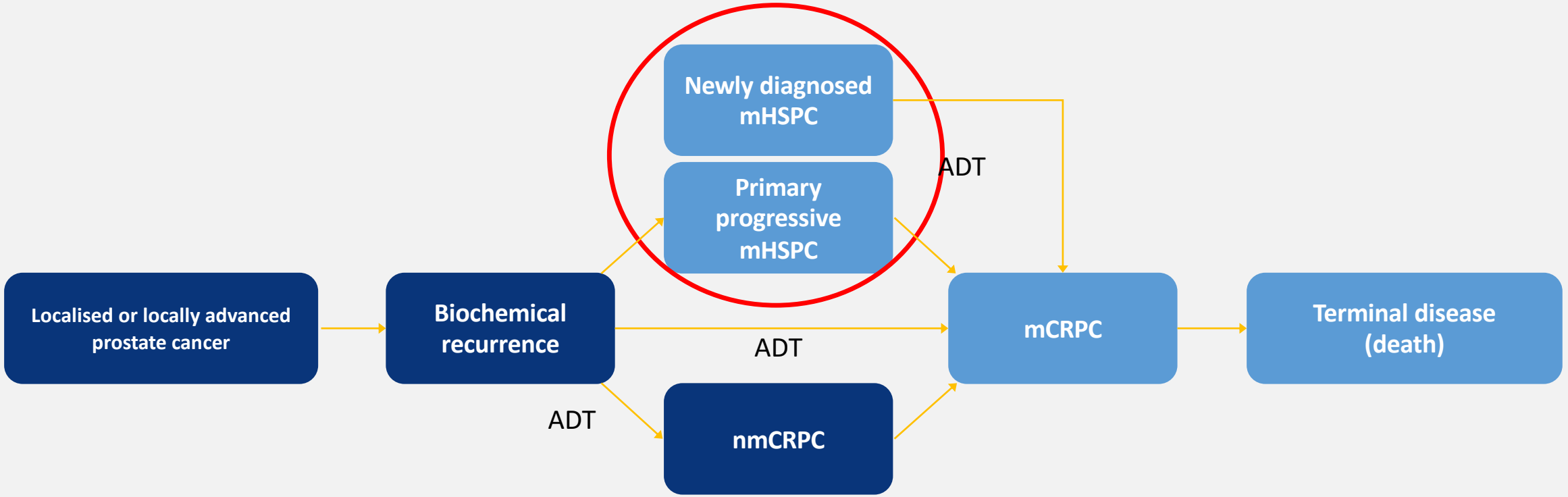
The prostate cancer landscape



Almost all will progress to mCRPC and die of prostate cancer

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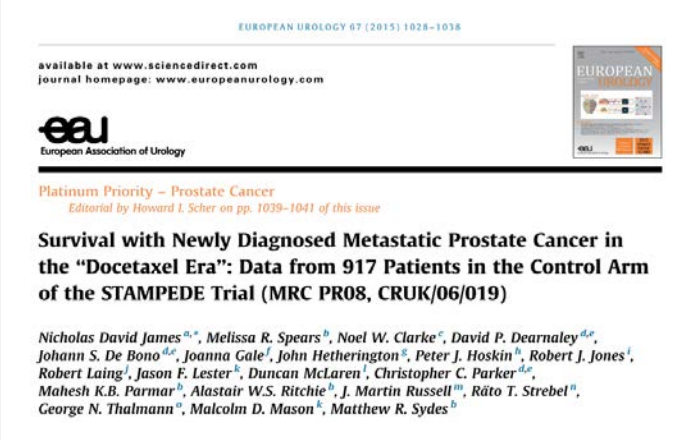
STAMPEDE control arm (ADT)

FFS and OS



EUROPEAN UROLOGY 67 (2015) 1028–1038

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Prostate Cancer

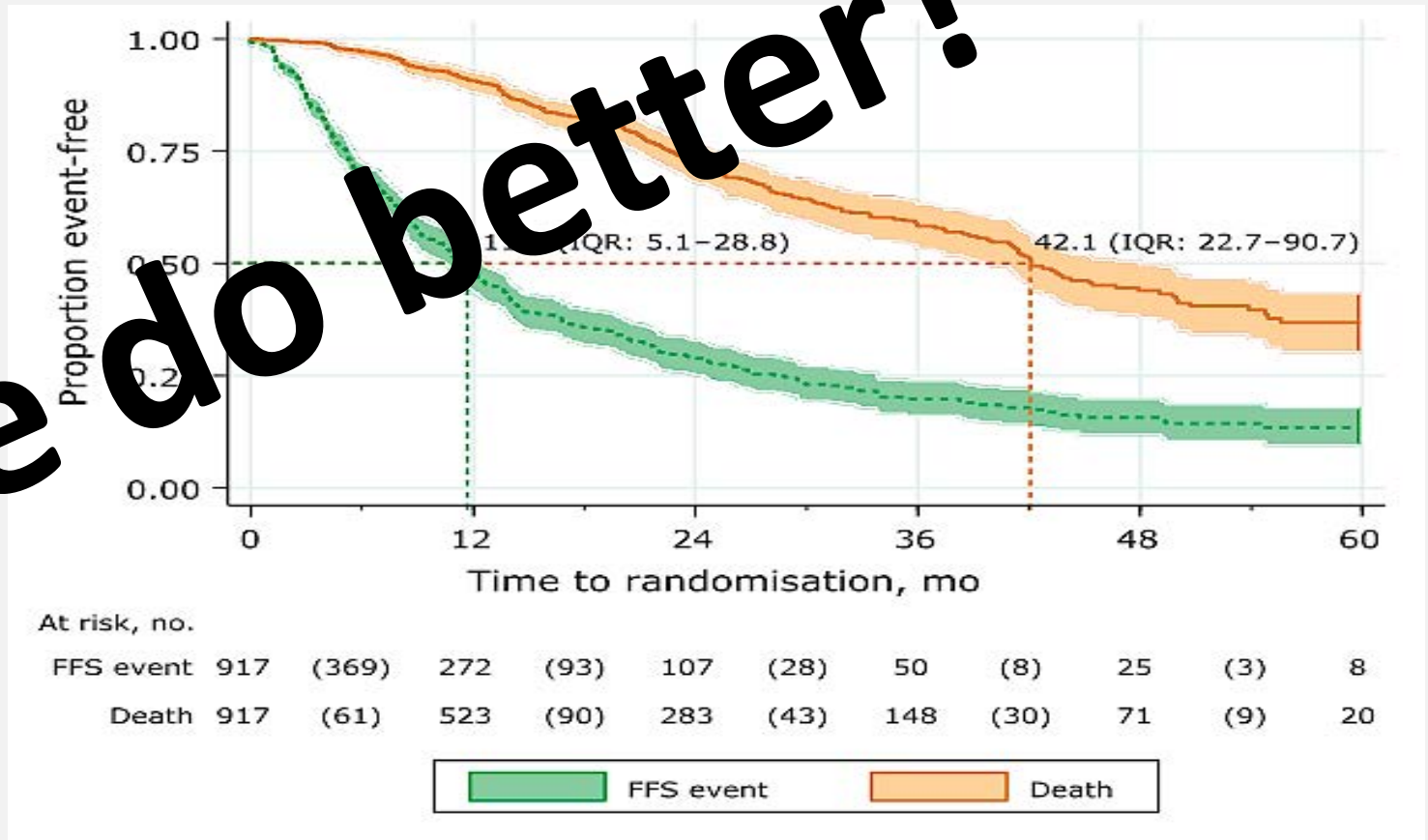
Editorial by Howard I. Scher on pp. 1039–1041 of this issue

Survival with Newly Diagnosed Metastatic Prostate Cancer in the "Docetaxel Era": Data from 917 Patients in the Control Arm of the STAMPEDE Trial (MRC PR08, CRUK/06/019)

Nicholas David James[a,], Melissa R. Spears[b], Noel W. Clarke[c], David P. Dearnaley[d,e], Johann S. De Bono[d,e], Joanna Gale[f], John Hetherington[g], Peter J. Hoskin[h], Robert J. Jones[i], Robert Laing[j], Jason F. Lester[k], Duncan McLaren[l], Christopher C. Parker[d,e], Mahesh K.B. Parmar[b], Alastair W.S. Ritchie[b], J. Martin Russell[m], Răto T. Strebel[n], George N. Thalmann[o], Malcolm D. Mason[k], Matthew R. Sydes[b]*

- 917 men with newly diagnosed metastatic PCa treated with ADT only (control arm)

Can we do better?



James ND et al. *Eur Urol*. 2015;67:1028-38.

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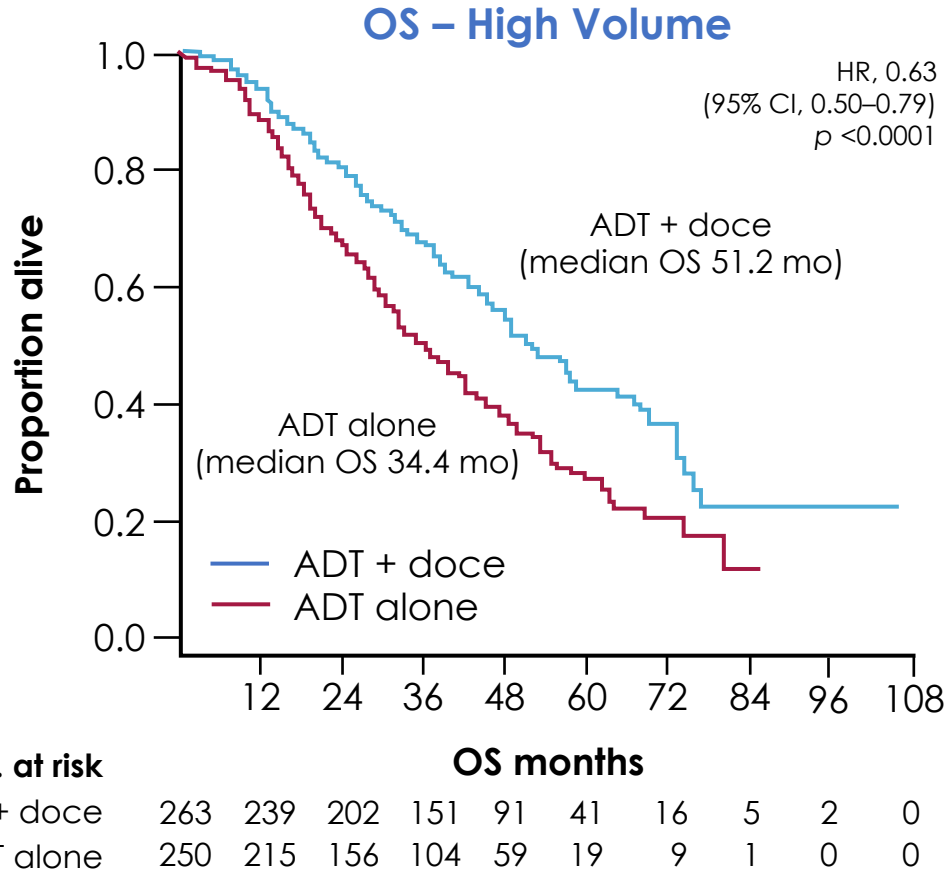
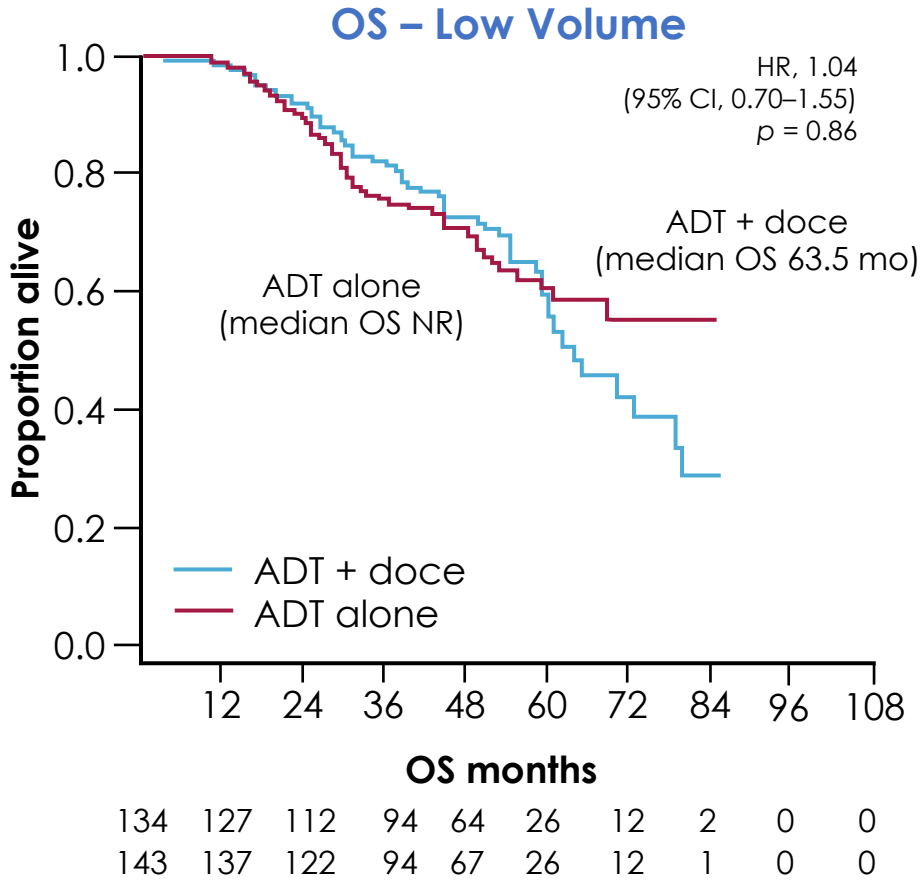
CHAARTED: Docetaxel in mHSPC



16.8 months



0 months

Kyriakopoulos CE, et al. *J Clin Oncol* 2018;36:1080-1087.

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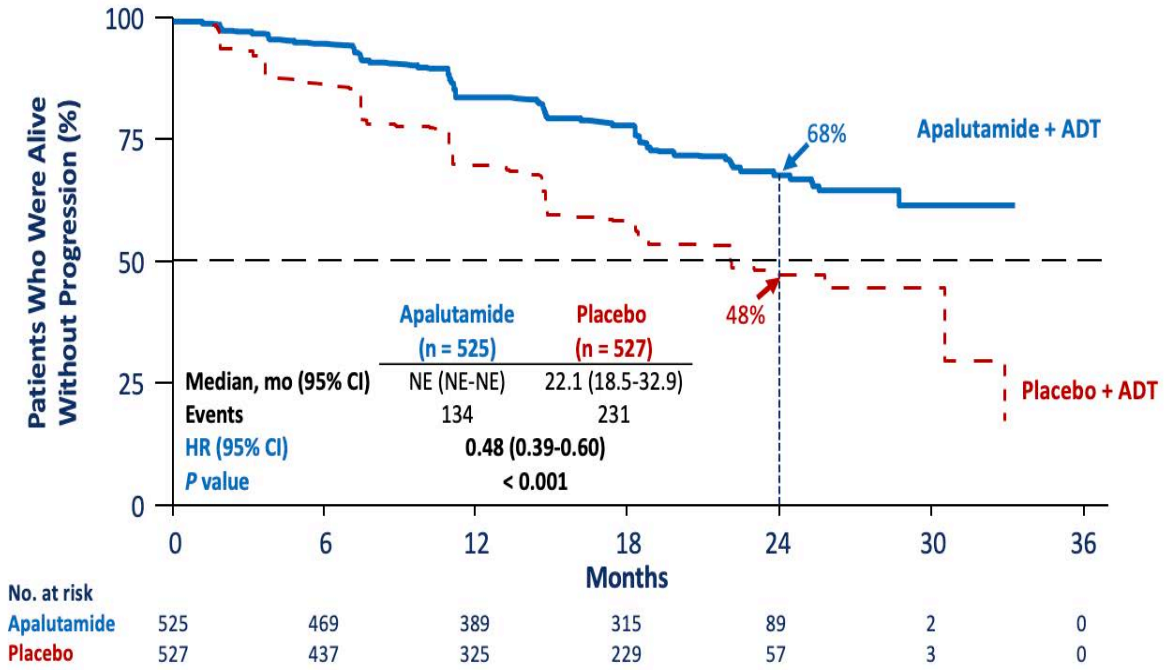
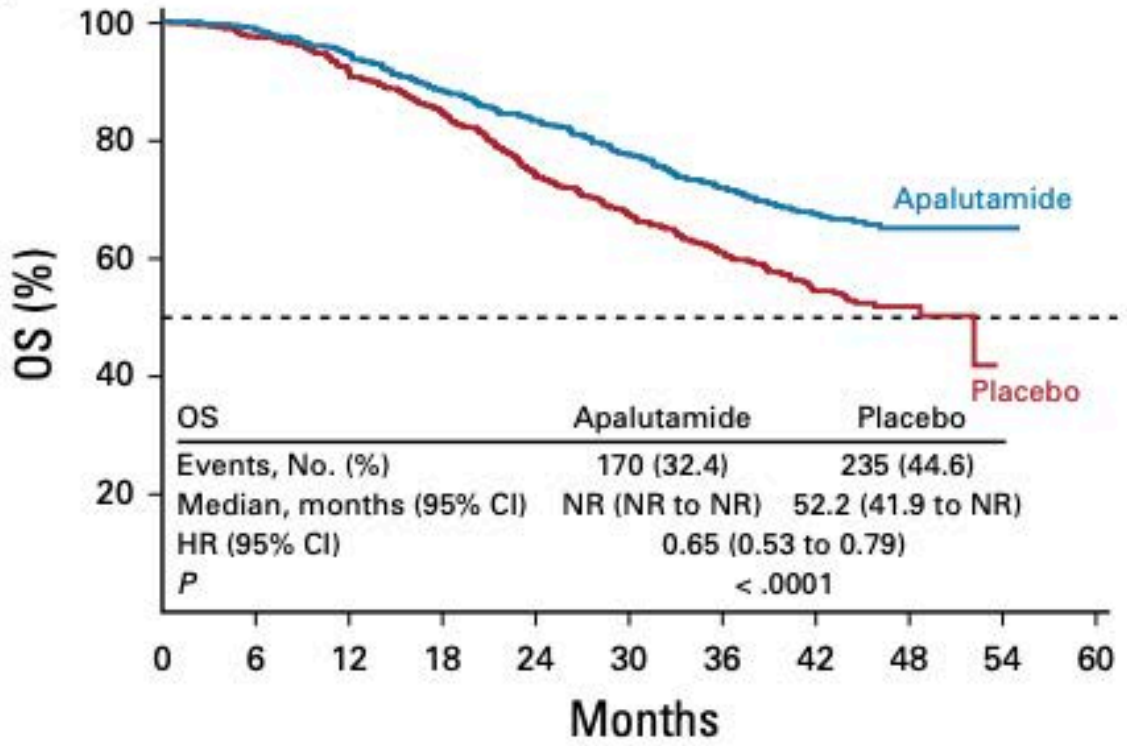
TITAN: Apalutamide in all-comers mCSPC

Progression free survival



Overall survival



Disease volume	High	0.68 (0.50-0.92)	69/325	97/335
	Low	0.67 (0.34-1.32)	14/200	20/192

Chi K et al. N Engl J Med. 2019 Jul 4;381(1):13-24. Chi K et al. J Clin Oncol 2021 Apr 29;JCO2003488.

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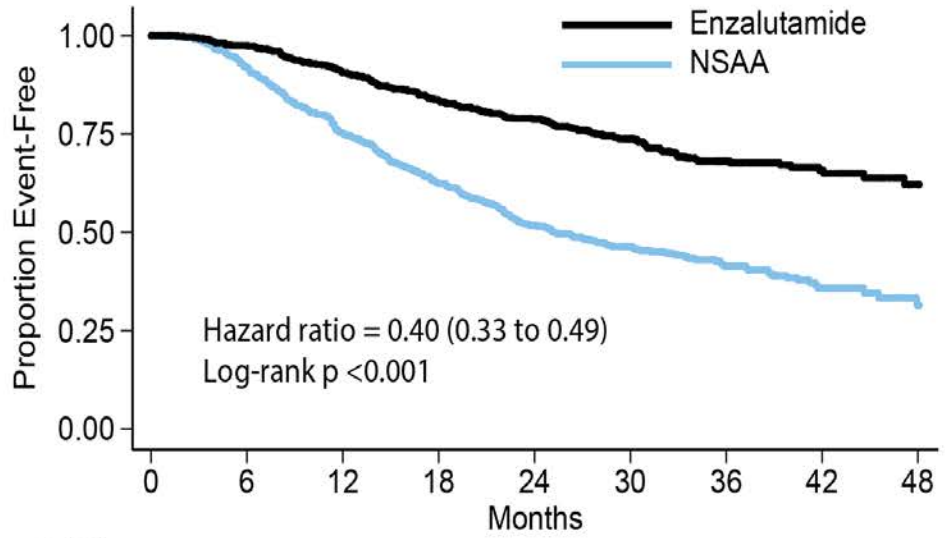
ENZAMET: Enzalutamide in all-comers

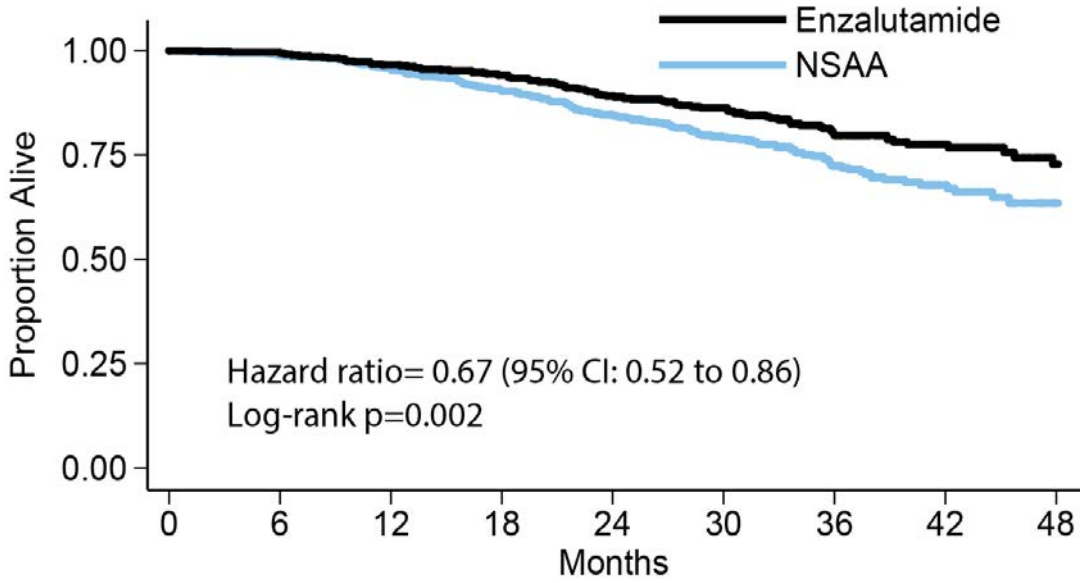
Progression free survival



Number at risk

NSAA	562	512	418	346	272	182	96	50	17
Enzalutamide	563	547	507	468	424	284	156	84	36

Overall survival



Number at risk

NSAA	562	551	531	501	452	311	174	86	32
Enzalutamide	563	558	541	527	480	340	189	106	45

Davis, I et al. Engl J Med. 2019 Jul 11;381(2):121-131.

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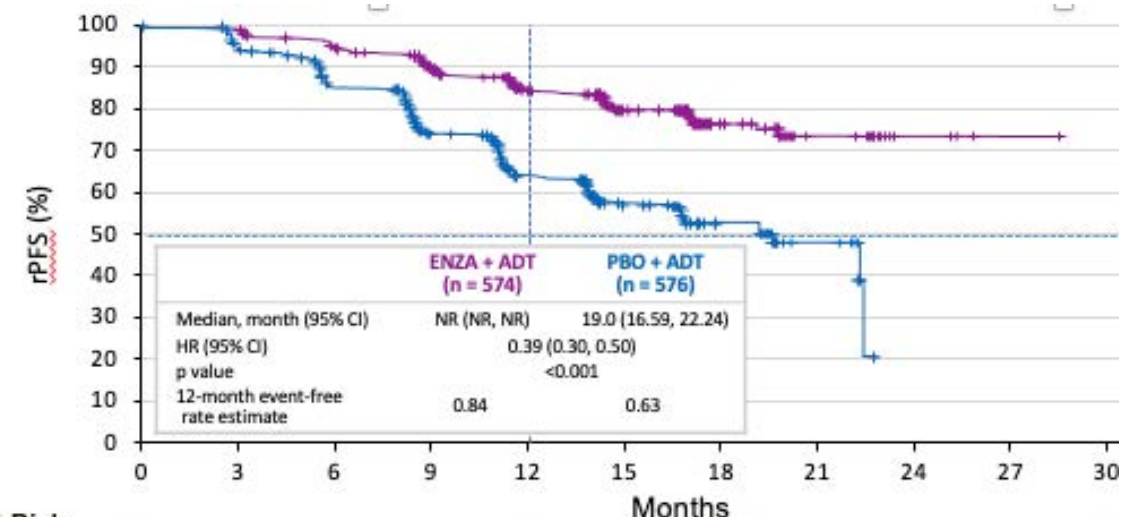
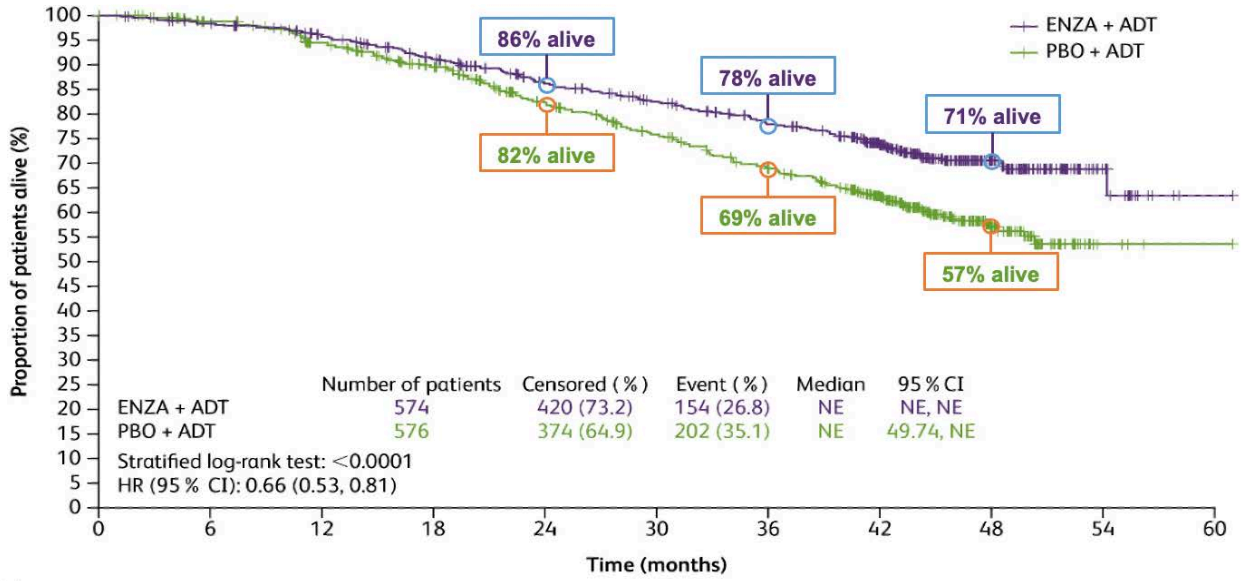
ARCHES: Enzalutamide in all-comers mCSPC

Progression free survival



Overall survival



Low volume of disease	220 (35)/203 (46)	NR/NR	0.66 (0.43, 1.03)
High volume of disease	354 (119)/373 (156)	NR/45.9	0.66 (0.52, 0.83)

How does docetaxel compare to hormonally based therapy?

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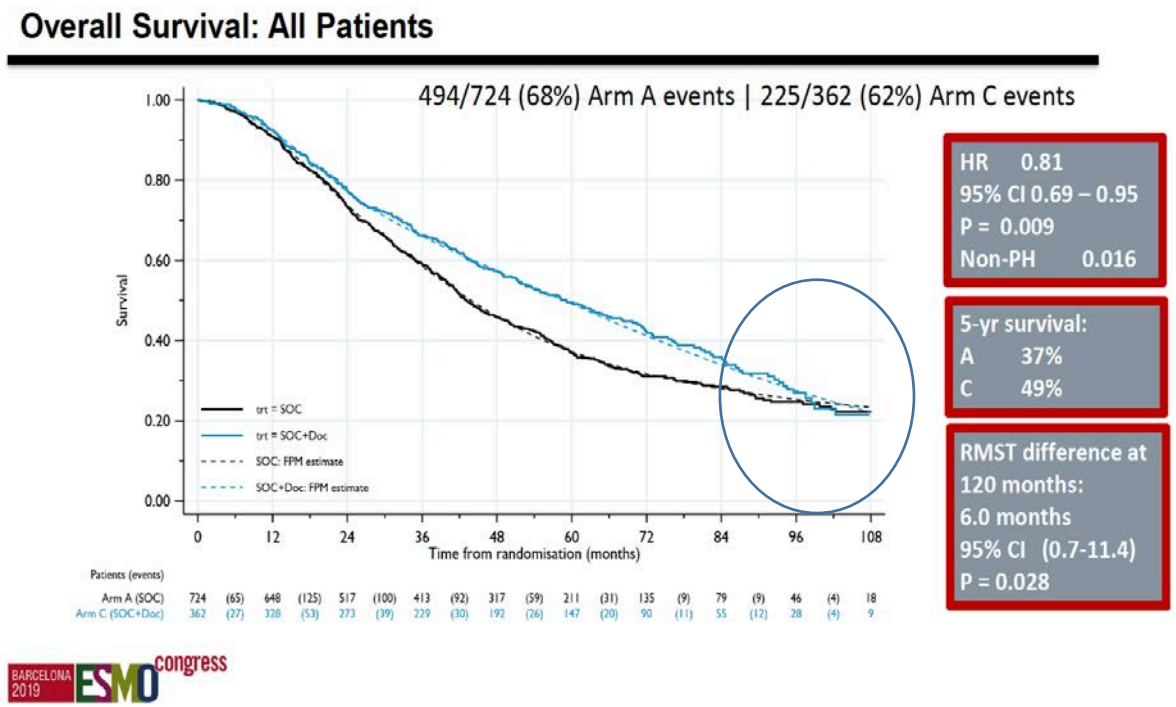
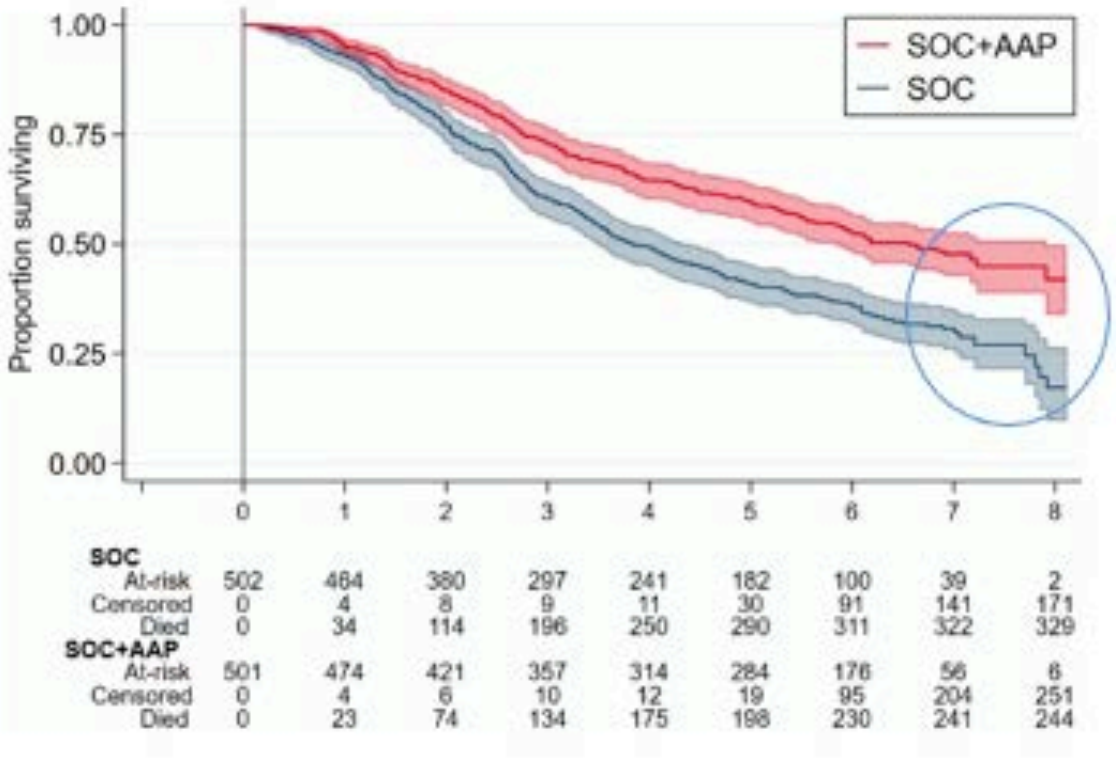
STAMPEDE: Overall Survival in mHSPC

Docetaxel + SOC vs SOC



BARCELONA 2019 ESMO congress

Abiraterone + SOC vs SOC



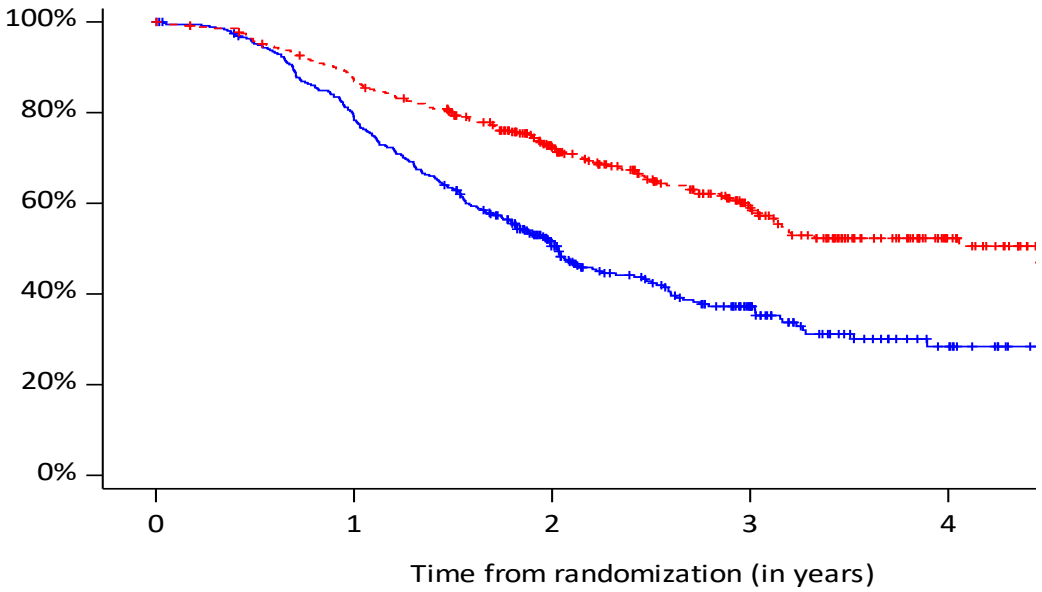
CHUM

Can combinations improve further improve outcome?

PEACE-1: mHSPC
ADT + docetaxel +/- abiraterone

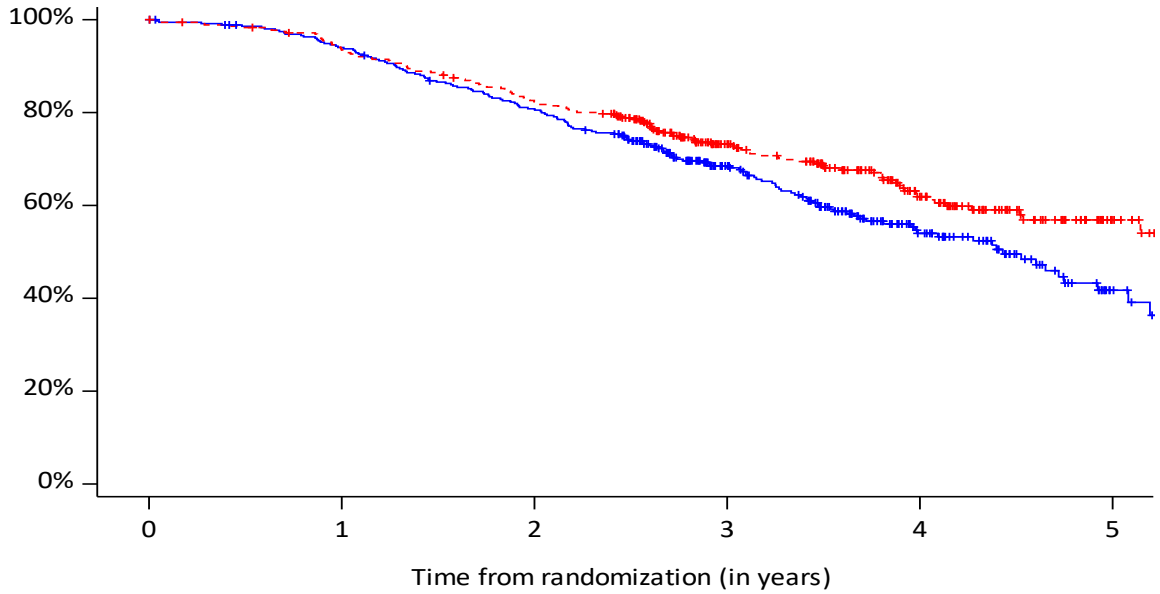
rPFS

	SOC+Abi	SOC
Median, y (95% CI)	4.5 (3.1-NE)	2.0 (1.8-2.3)
Events	139	211
HR (95% CI)*	0.50 (0.40-0.62)	
P value	< 0.0001	



Overall survival

	SOC+Abi	SOC
Median, y (95% CI)	NE (4.5-NE)	4.4 (3.8-4.9)
Events	121	151
HR (95% CI)*	0.75 (0.59-0.95)	
P value	0.017	

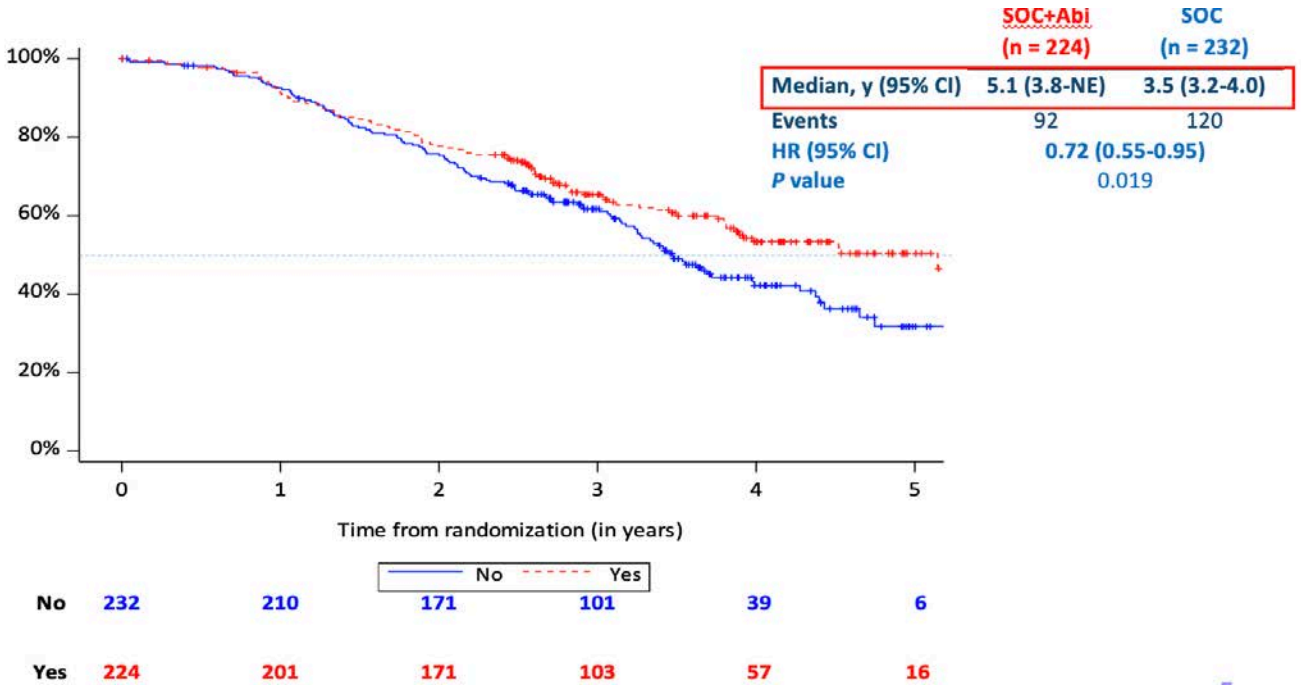


Fizazi K, et al. ESMO 2021

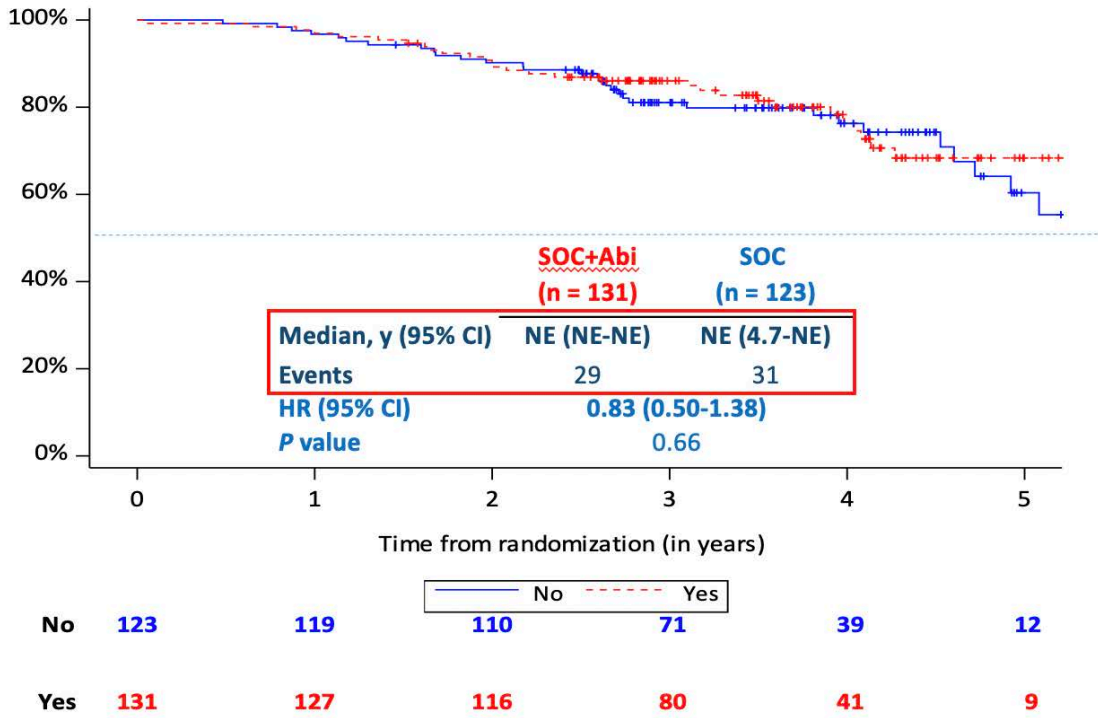
CHUM

PEACE-1: mHSPC
ADT + docetaxel +/- abiraterone

High-volume mHSPC



Low-volume mHSPC



Fizazi K, et al. ESMO 2021

CHUM

Bone Mineral Density in Men with de novo Metastatic Castration-Sensitive Prostate Cancer Treated with or without Abiraterone plus Prednisone in the PEACE-1 Phase 3 Trial

Roubaud G et al.

Genitourinary Cancers Symposium 2022;Abstract 19.

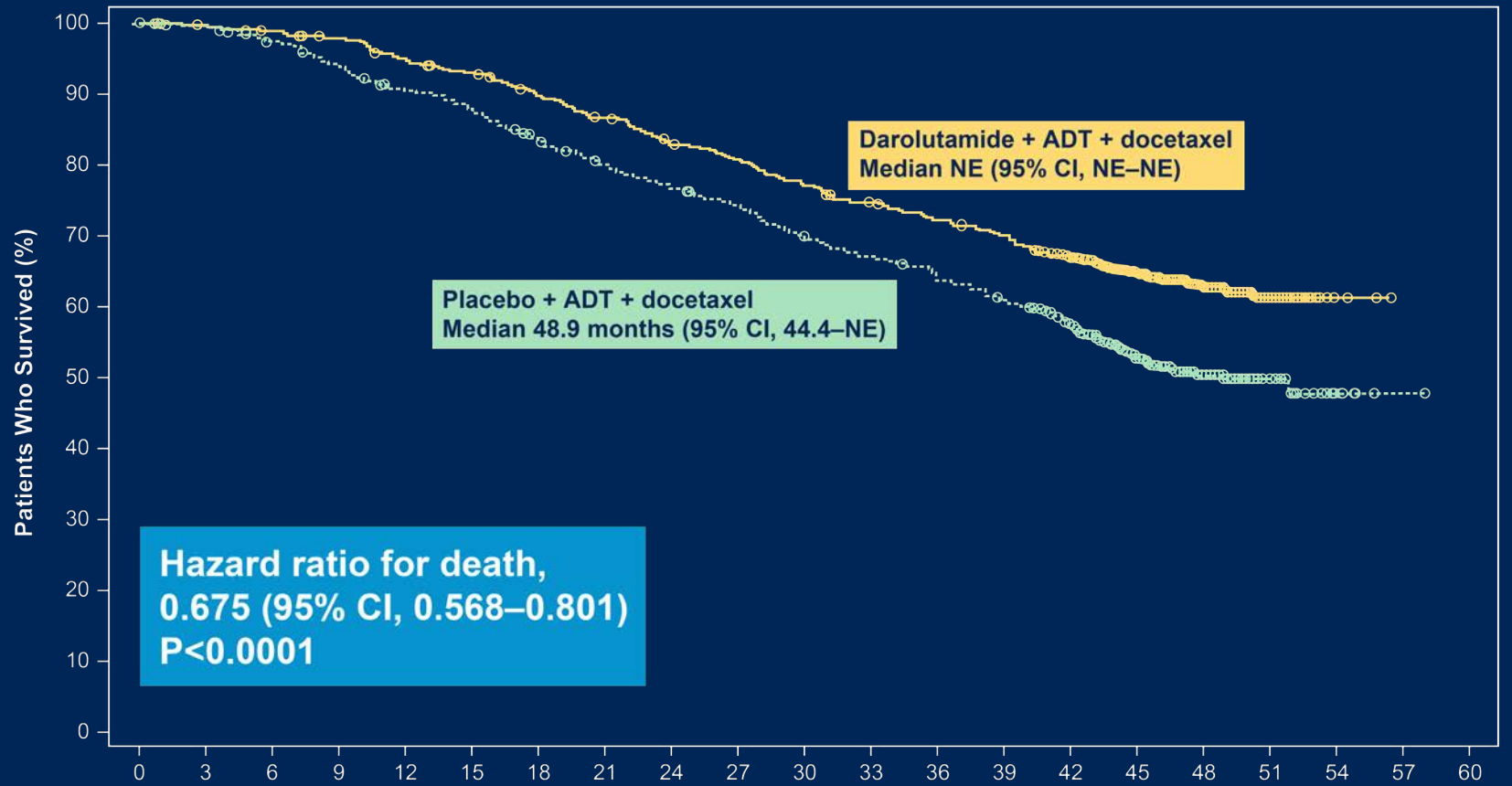
Rapid Abstract Session A: Prostate Cancer

Level 3, Ballroom

Thursday, Feb 17, 2022

7:45 PM – 8:45 PM EST

ARASENS: ADT + docetaxel +/- darolutamide
Primary Endpoint: Overall Survival



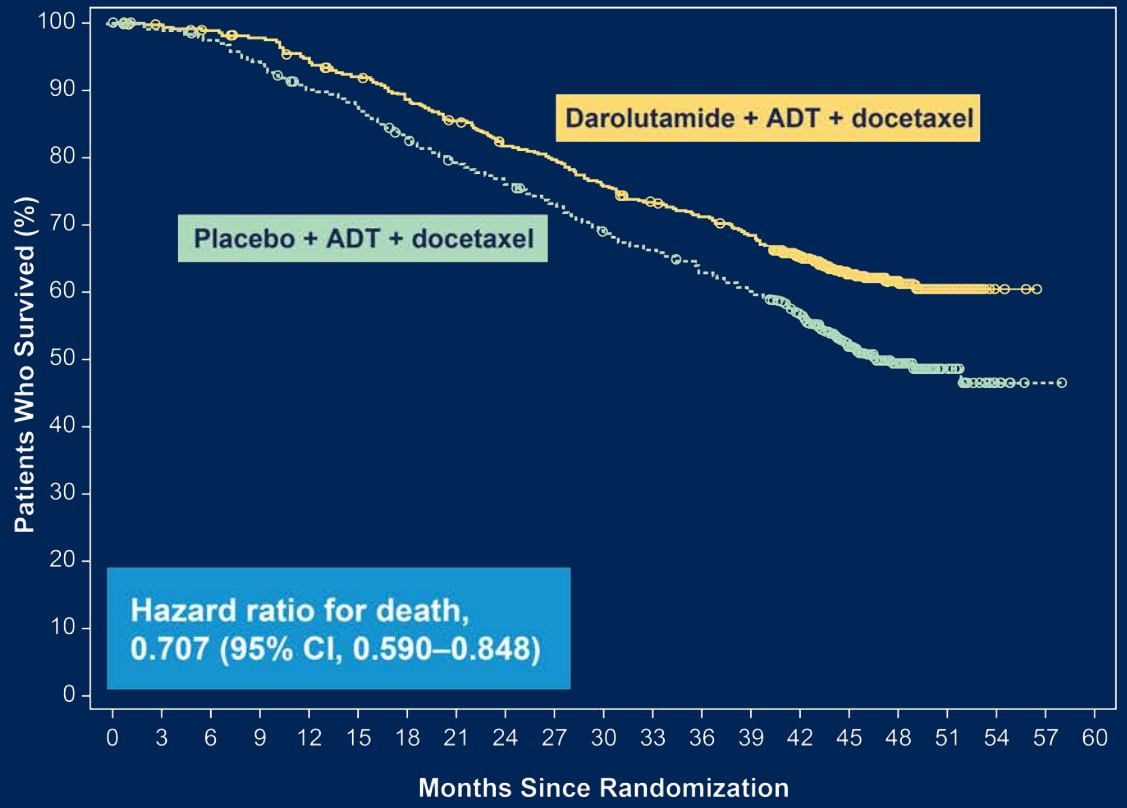
No. at Risk

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

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

ARASENS: ADT + docetaxel +/- darolutamide
Overall Survival By Metastatic Stage at Initial Diagnosis

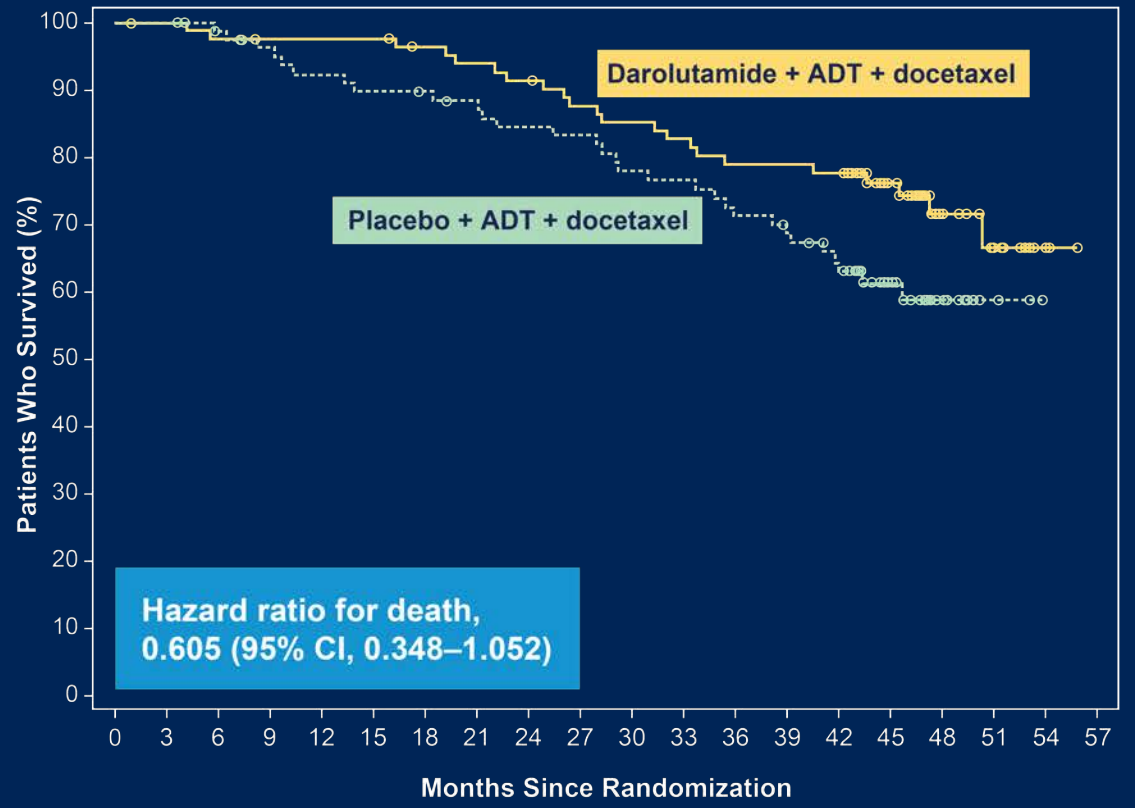
OS in Patients with M1 (*de novo*)



No. at Risk

Darolutamide	558	553	547	539	520	505	485	466	445	433	412	396	383	367	334	220	116	45	7	0	0
Placebo	566	558	546	526	503	490	461	438	420	403	378	362	344	328	292	190	93	33	6	1	0

OS in Patients with M0 (recurrent)

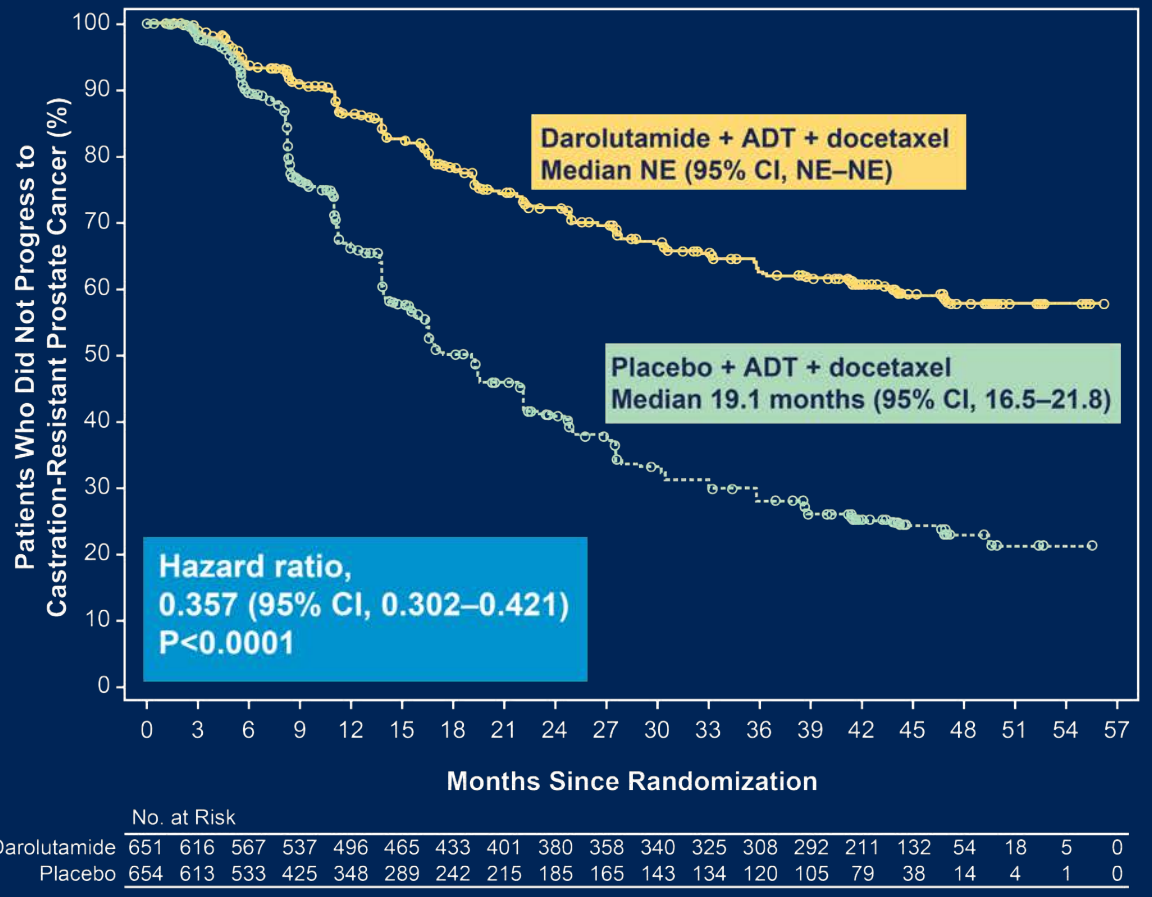


No. at Risk

Darolutamide	86	85	83	81	81	81	78	76	74	70	68	66	63	63	62	43	20	11	2	0
Placebo	82	82	78	75	72	70	69	67	64	63	59	58	54	51	45	26	12	4	0	0

ARASENS: ADT + docetaxel +/- darolutamide
Key Secondary Endpoints

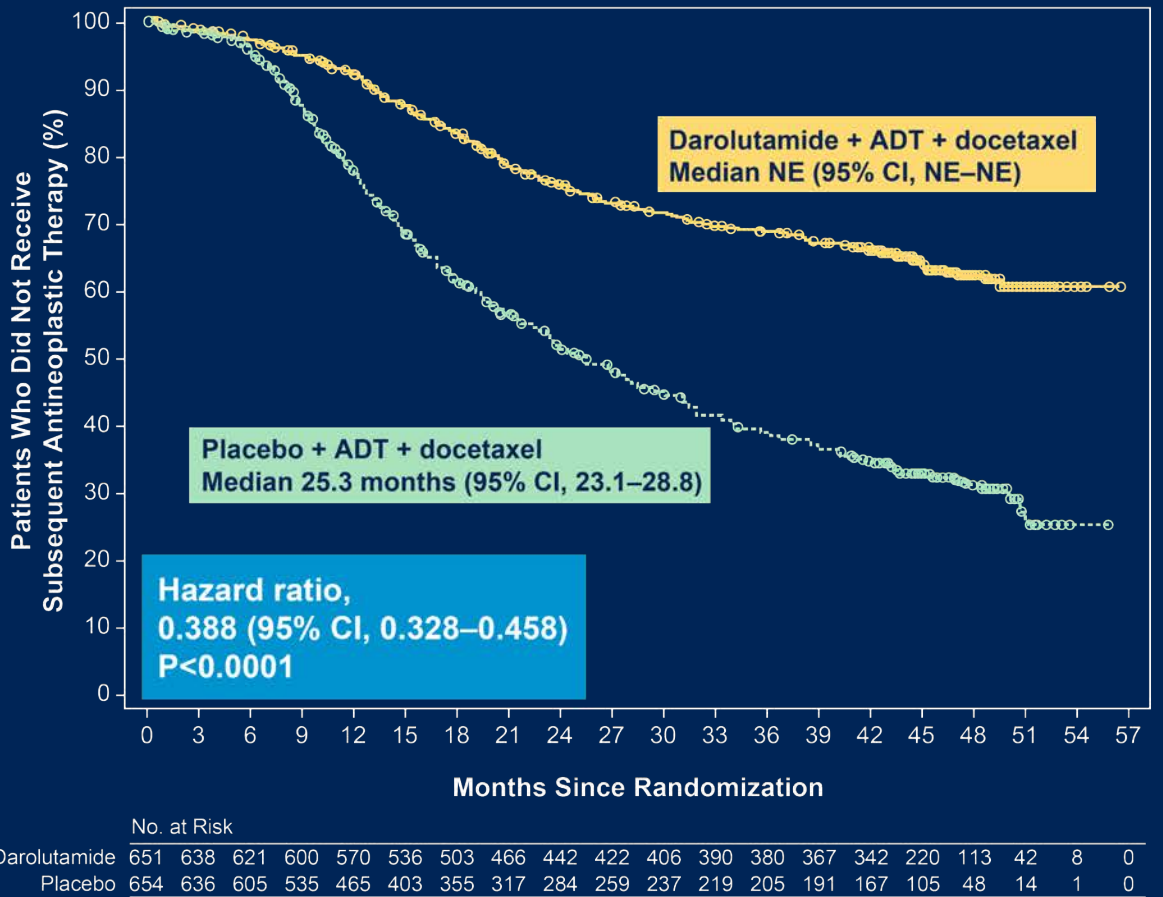
Time to CRPC



No. at Risk

Darolutamide	651	616	567	537	496	465	433	401	380	358	340	325	308	292	211	132	54	18	5	0
Placebo	654	613	533	425	348	289	242	215	185	165	143	134	120	105	79	38	14	4	1	0

Time to First Subsequent Antineoplastic Therapy

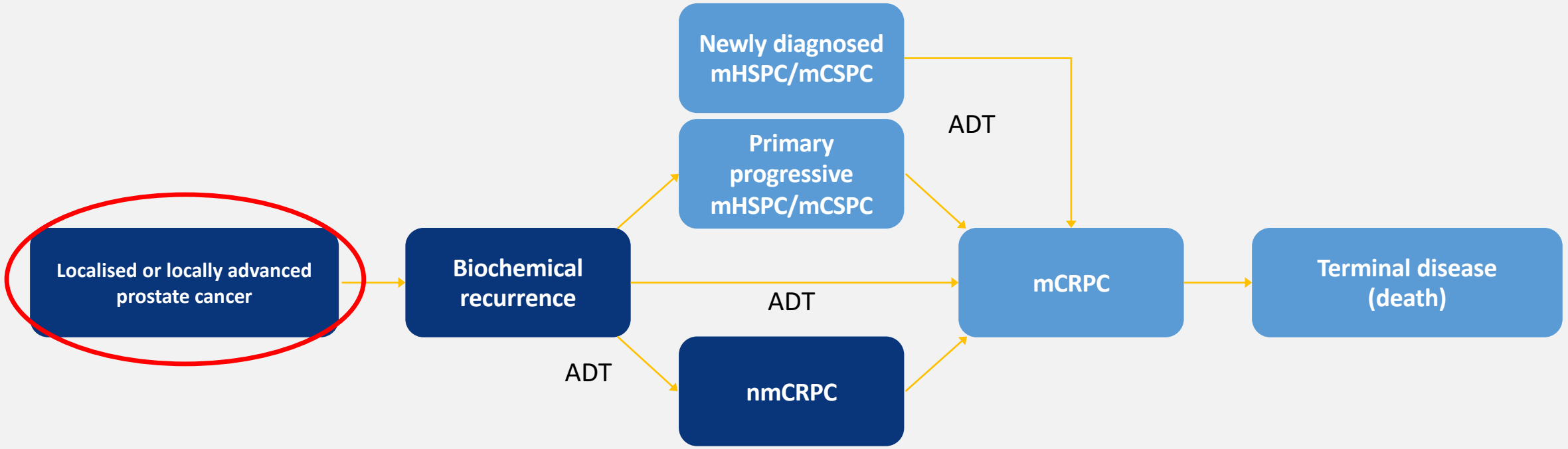


No. at Risk

Darolutamide	651	638	621	600	570	536	503	466	442	422	406	390	380	367	342	220	113	42	8	0
Placebo	654	636	605	535	465	403	355	317	284	259	237	219	205	191	167	105	48	14	1	0

*Pain progression was defined by change in the Brief Pain Inventory–Short Form questionnaire worst pain score or initiation of opioid therapy for ≥7 days..

The prostate cancer landscape

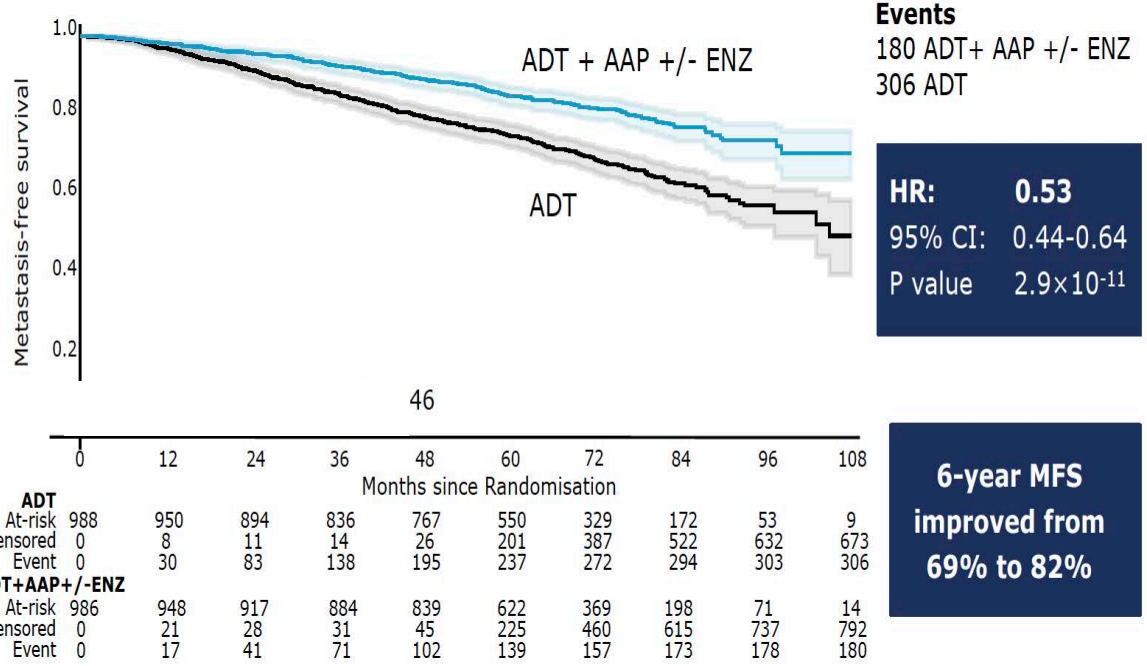


1. Tannock IF *et al. N Engl J Med* 2004; 351:1502–12. **2.** Ryan CJ *et al. Lancet Oncol* 2015;16:152–60. **3.** Rathkopf DE *et al. Eur Urol* 2014;66:815–25. **4.** Beer TM *et al. Eur Urol* 2017;71:151–4.
5. Armstrong AJ *et al. Cancer* 2017;123:2303–11. **6.** de Bono JS *et al. Lancet* 2010;376:1147–54. **7.** Hoskin P *et al. Lancet Oncol* 2014;15:1397-406.

CHUM

Stampede: high risk non metastatic HSPC ADT +/- Abiraterone in M0HSPC

Metastasis-free survival

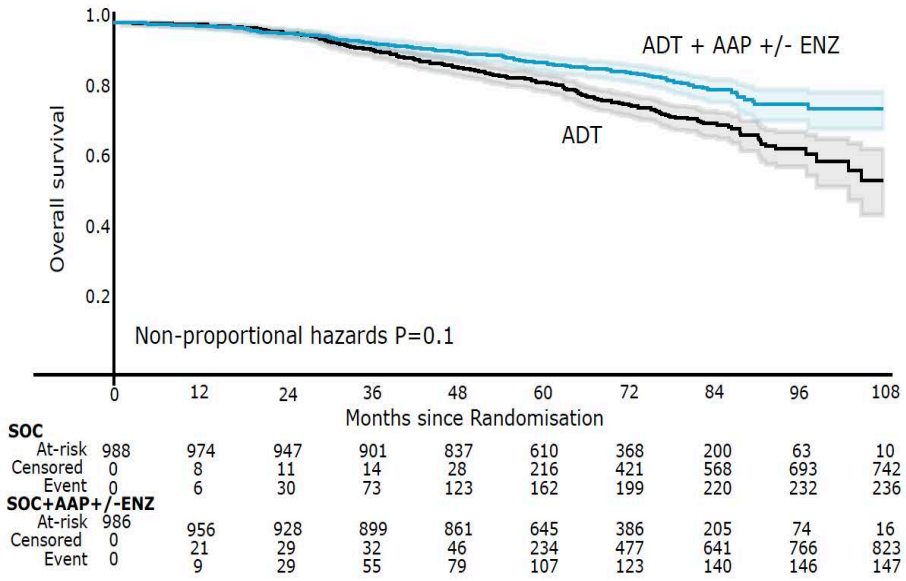


Events
180 ADT+ AAP +/- ENZ
306 ADT

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

6-year MFS improved from 69% to 82%

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}

6-year survival improved from 77% to 86%

Attard G et al. Lancet 2022

CHUM

Conclusions

- Patients with high risk nmCRPC and mCSPC are at high risk of rapid progression to mCRPC and early death
- Treating ALL patients beyond ADT is the new standard of care for mCSPC
  - First generation anti-androgens and CAB are not enough
- Effective agents are now available and should be used in patients with CRPC and CSPC who are destined to suffer and die **OF** prostate cancer
- Benefit of combining NHT with Chemotherapy in mHSPC now confirmed

CHUM

Clinical Investigator Survey Results

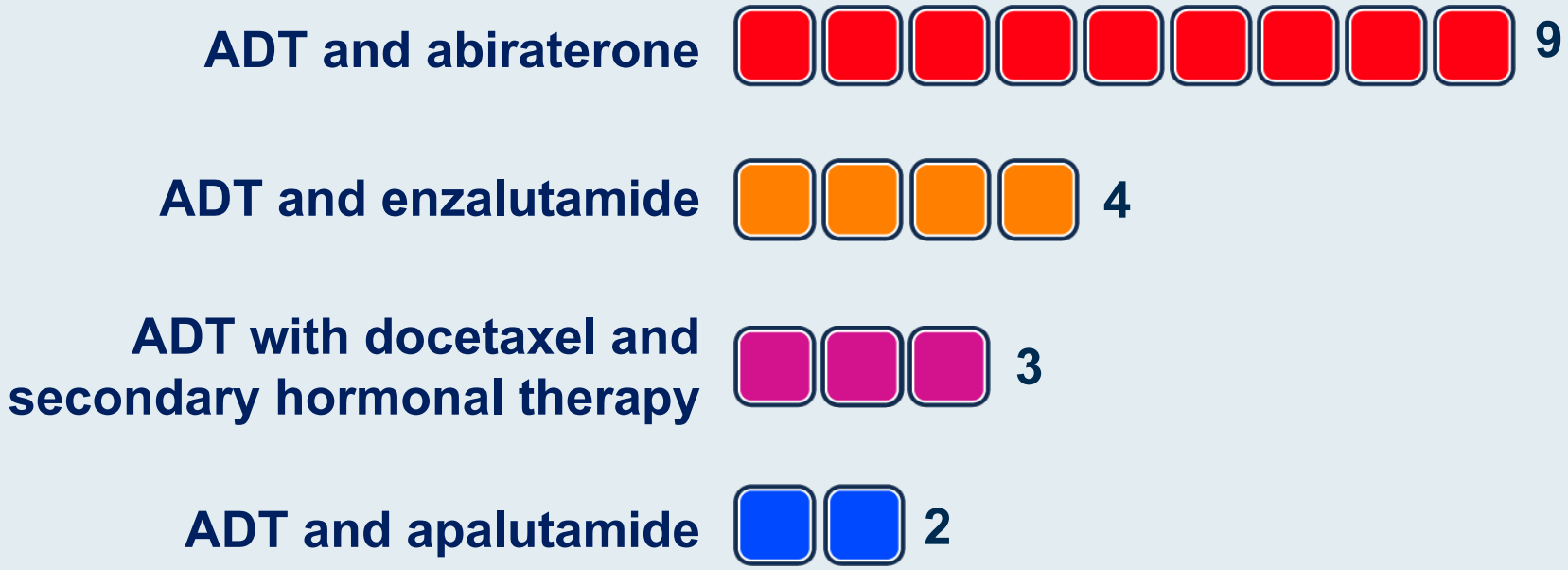
A 65-year-old man s/p RP followed by radiation therapy for PSA-only recurrence (M0) receives an LHRH agonist for further PSA progression. Regulatory and reimbursement issues aside, what would be your most likely treatment recommendation if the patient responded but then experienced PSA progression to a PSA level of 3.4 ng/dL with a doubling time of 10 months?

Survey of genitourinary cancer clinical investigators

For a patient with nonmetastatic castration-resistant prostate cancer (CRPC) for whom you have elected to administer secondary hormonal therapy in combination with ADT, do you prefer a specific agent?

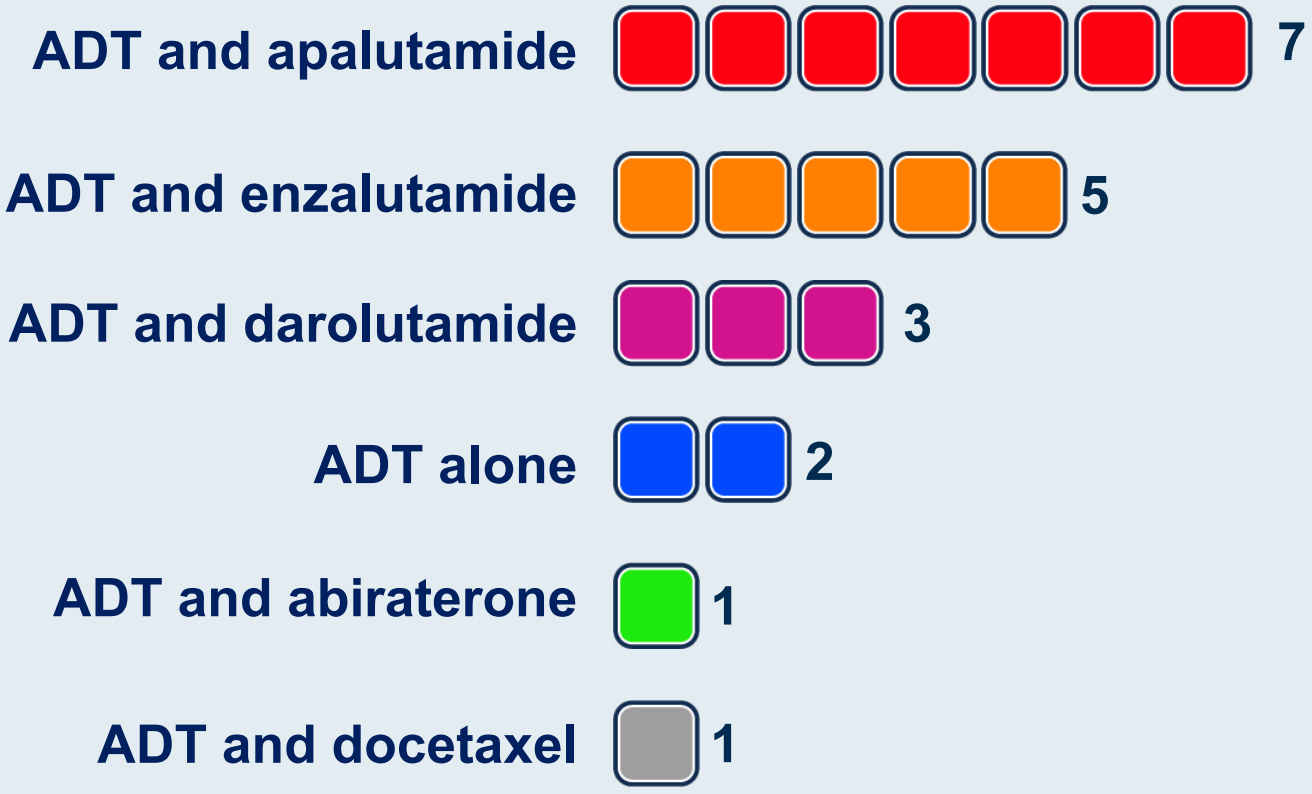
Survey of genitourinary cancer clinical investigators

What systemic therapy would you typically employ for a 65-year-old patient presenting de novo with Gleason 8 prostate cancer and 3 asymptomatic bone metastases?



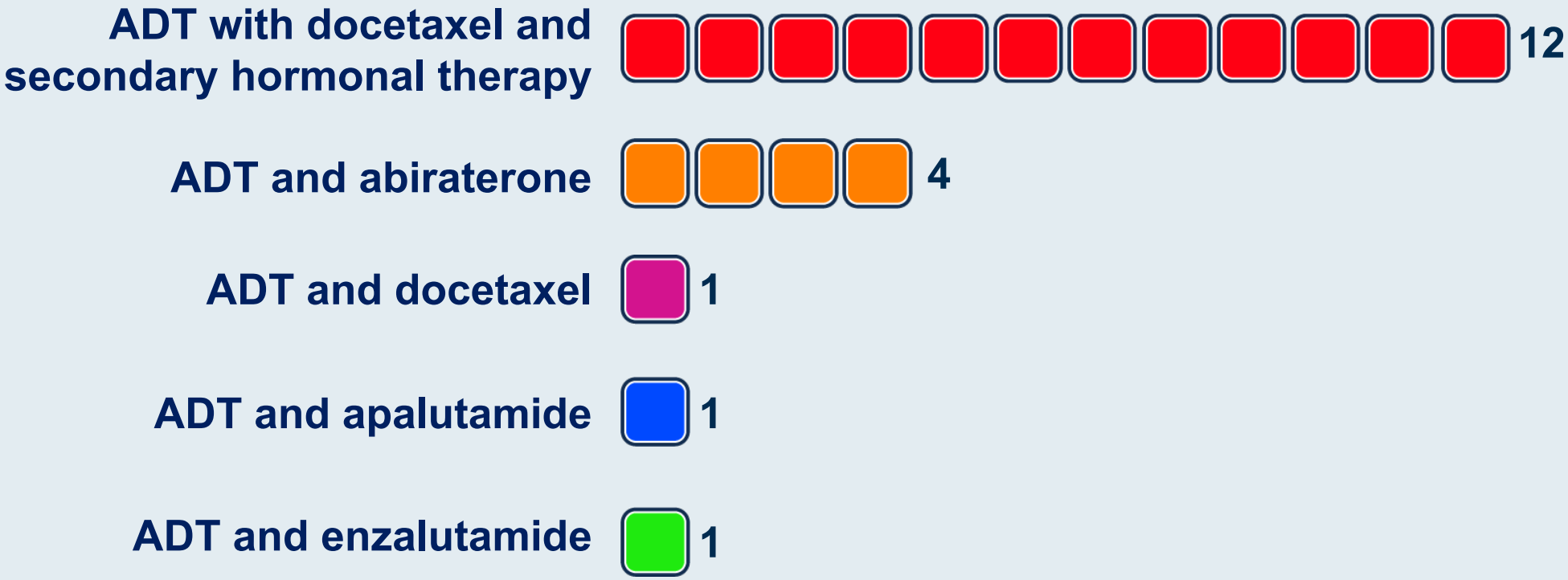
Survey of genitourinary cancer clinical investigators

What systemic therapy would you typically employ for an 80-year-old patient with a history of poorly controlled hypertension presenting de novo with Gleason 8 prostate cancer and 3 asymptomatic bone metastases?



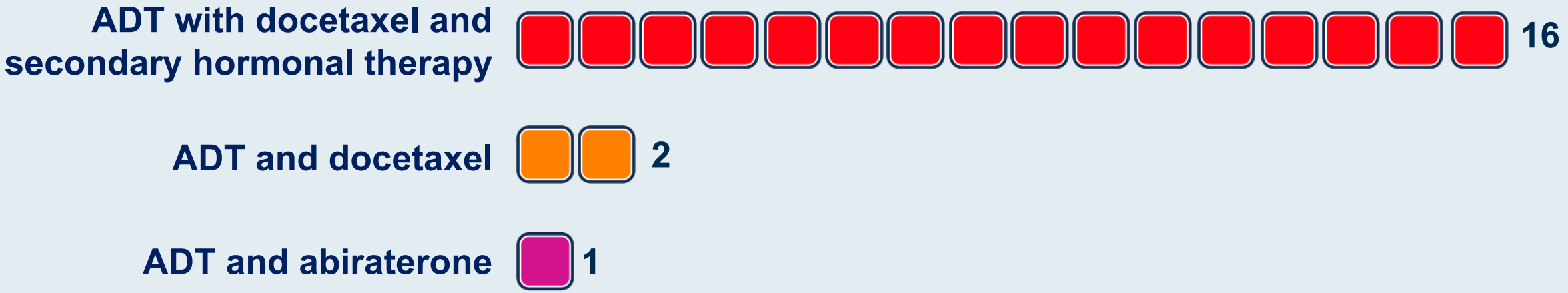
Survey of genitourinary cancer clinical investigators

What systemic therapy would you typically employ for a 65-year-old patient presenting de novo with Gleason 8 prostate cancer and 6 moderately symptomatic bone metastases?



Survey of genitourinary cancer clinical investigators

What systemic therapy would you typically employ for a 65-year-old patient presenting de novo with Gleason 8 prostate cancer and multiple bone and liver metastases?



Survey of genitourinary cancer clinical investigators

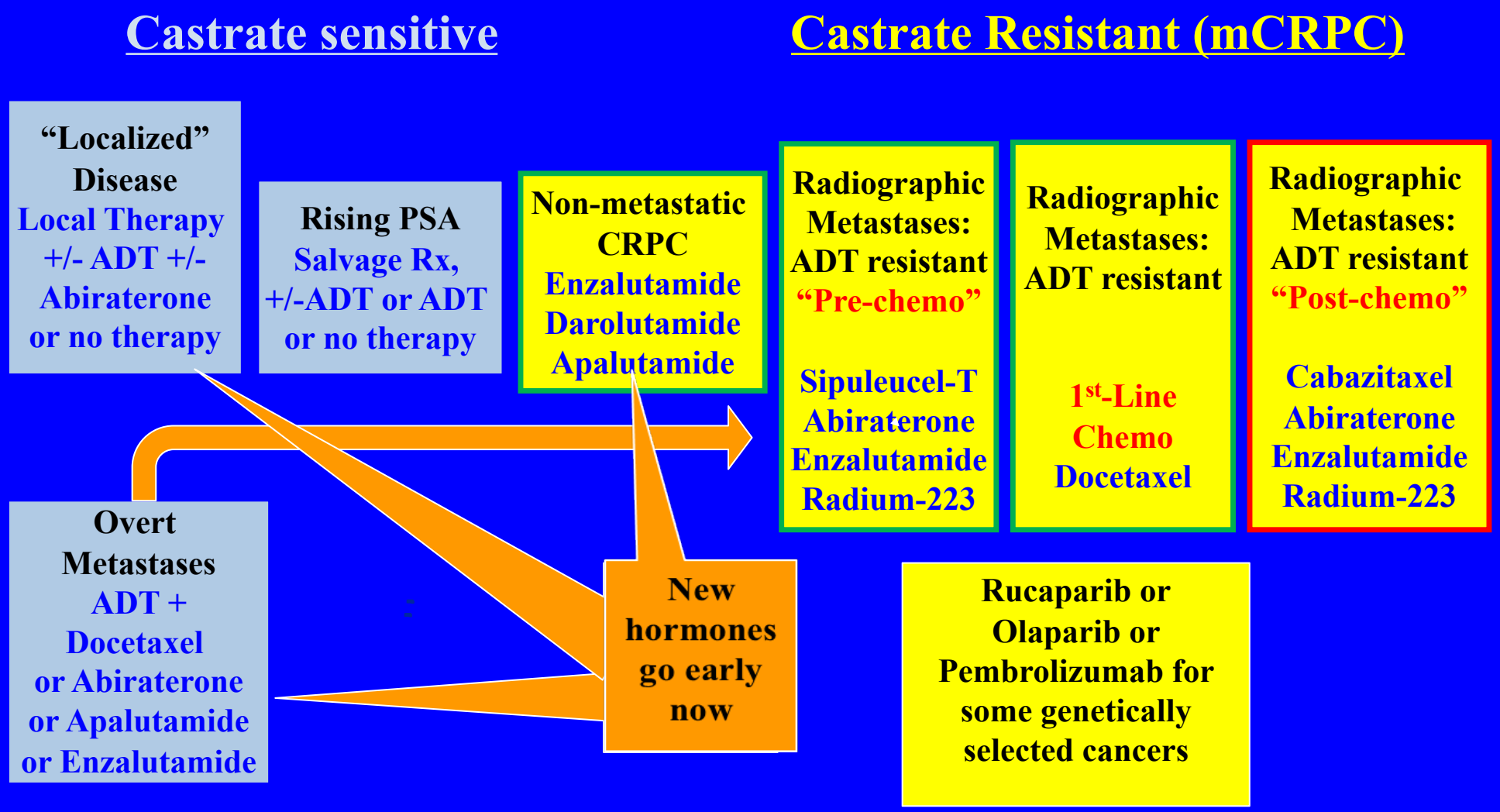
MODULE 2: Selection and Sequencing of Therapy for Patients with Metastatic CRPC (mCRPC) — Dr Sartor

RTP
RESEARCH
TO PRACTICE

Selection and Sequencing of Therapies in Metastatic CRPC

Oliver Sartor, MD
Laborde Professor of Cancer Research
Medical Director Tulane Cancer Center
Departments of Medicine and Urology
Associate Dean for Oncology
Tulane Medical School
New Orleans, Louisiana

Prostate Cancer Clinical States and Standard Therapies Today



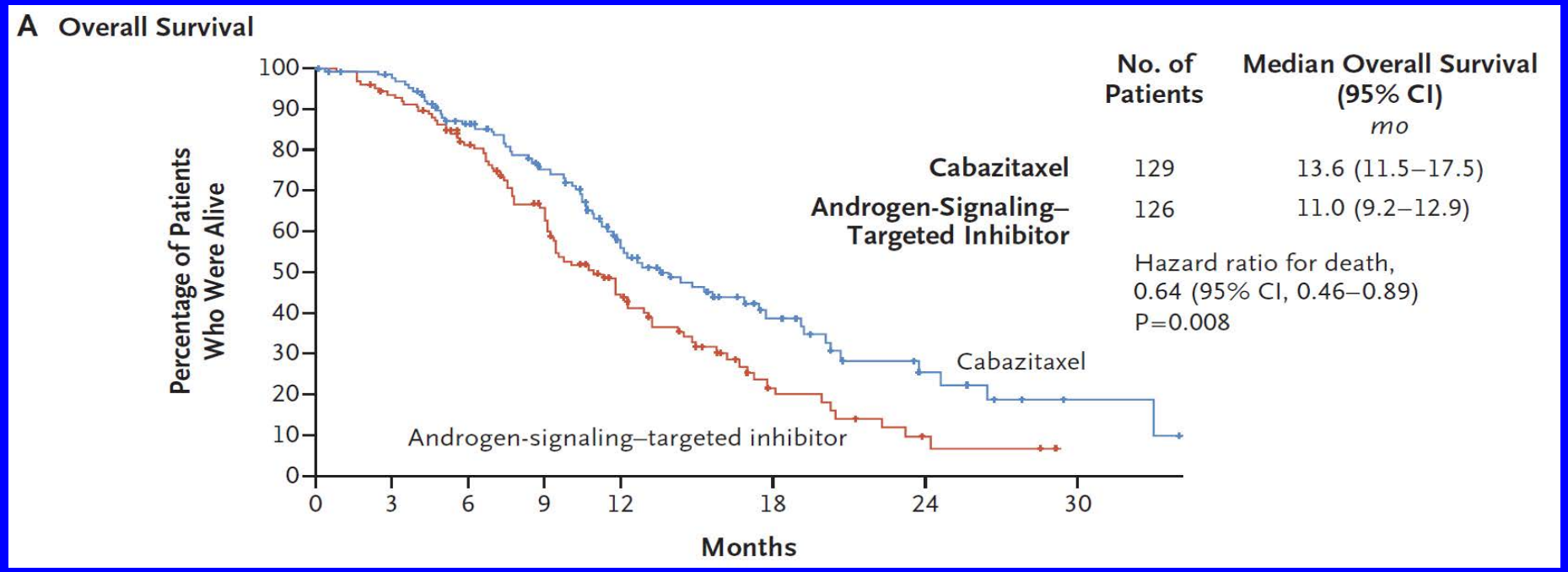
TRIAL	FRONT LINE mCRPC	HR	Survival (months)
TAX 327	Docetaxel/prednisone vs mitoxantrone/prednisone	0.79	19.2 vs 16.3* (2.9 months)
IMPACT	Sipuleucel-T vs Control	0.78	25.8 vs 21.7 (4.1 months
COU-AA-302	Abiraterone/prednisone vs Placebo/prednisone	0.79	35.3 vs. 31.1* (4.2 months)
PREVAIL	Enzalutamide vs Placebo	0.71	35.3 vs. 31.3* (4.0 months)
	POST-DOCETAXEL mCRPC		
TROPIC	Cabazitaxel/prednisone vs mitoxantrone/prednisone	0.70	15.1 vs 12.7 (2.4 months)
COU-AA- 301	Abiraterone/prednisone vs Placebo/prednisone	0.74	15.8 vs 11.2* (4.6 months)
AFFIRM	Enzalutamide vs Placebo	0.63	18.4 vs 13.6 (4.8 months)
	FRONT LINE and POST-DOCETAXEL mCRPC		
ALSYMPCA	Standard of care +/- radium-223	0.70	14.9 vs 11.3* (3.6 months)
	POST-ABI OR -ENZA OR POST-ABI OR -ENZA AND -DOCETAXEL (HRR SUBSET)		
PROfound	Olaparib vs abi/enza second line	0.69	19.1 vs 14.7** (4.4 months)
	Third Line (POST-ABI or -ENZA and POST-DOCETAXEL		
CARD	Cabazitaxel vs abi/enza second line	0.64	13.6 vs 11.0 (2.6 months)
VISION	Standard of care +/- PSMA-617 Lu-177	0.62	15.3 vs 11.3 (4.0 months)

* Mature analysis **BRCA1/BRCA2/ATM subset

Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer

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

N Engl J Med 2019;381:2506-18



A Randomized, Double-Blind, Placebo (PBO)-Controlled, Phase 3b Study of the Efficacy and Safety of Continuing Enzalutamide (ENZA) in Chemotherapy-Naive, Metastatic Castration-Resistant Prostate Cancer (mCRPC) Patients (pts) Treated with Docetaxel (DOC) plus Prednisolone (PDN) Who Have Progressed on ENZA: PRESIDE

Merseburger AS et al.

Genitourinary Cancers Symposium 2022;Abstract 15.

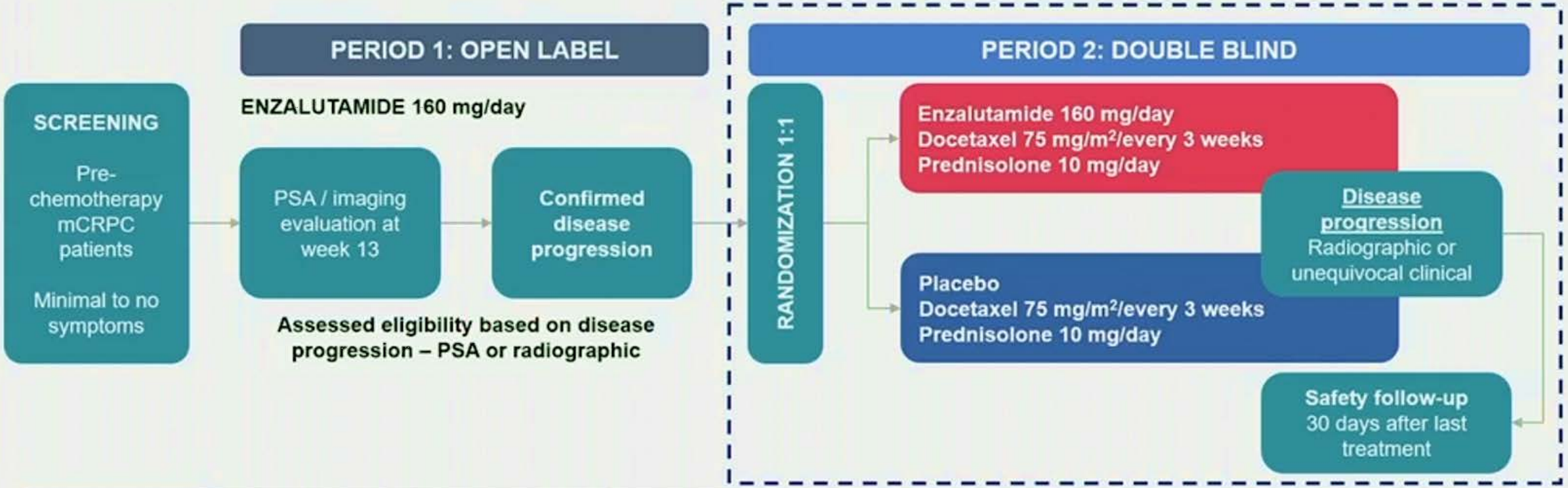
Oral Abstract Session A: Prostate Cancer

Level 3, Ballroom

Thursday, Feb 17, 2022

4:00 PM – 5:30 PM EST

Methods

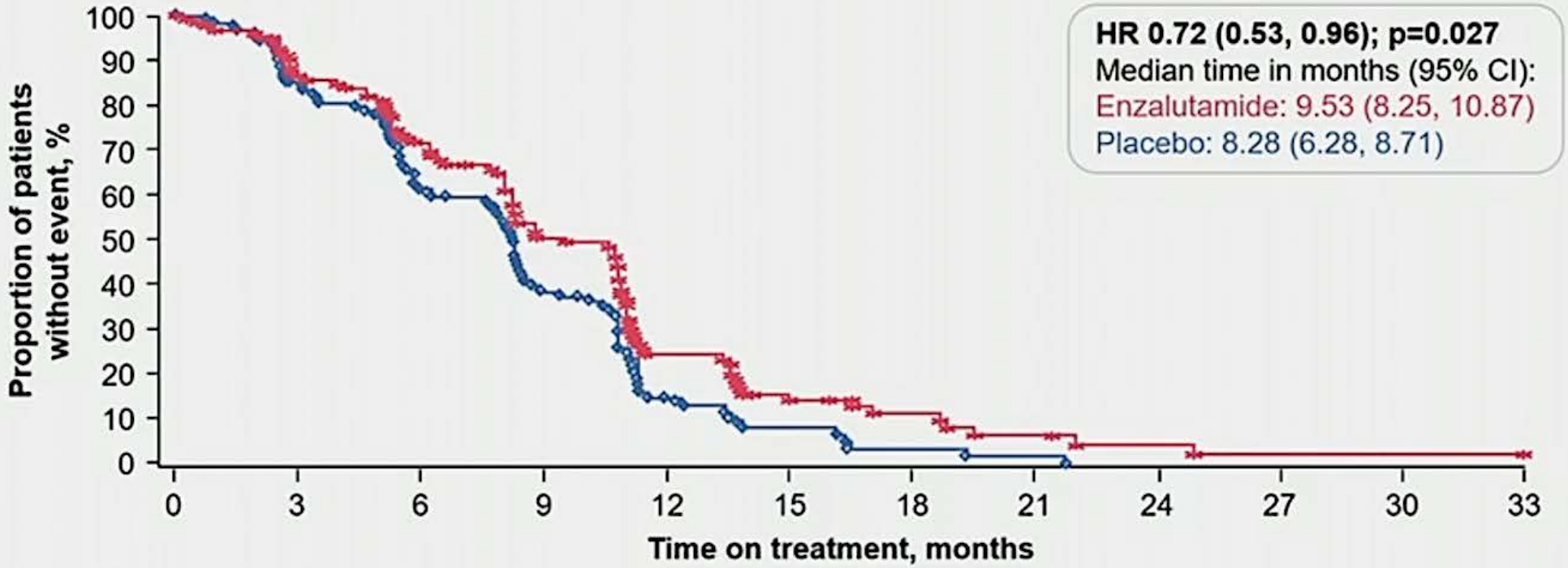


Endpoints

- **Primary endpoint:** PFS
  - Progression in Period 2 was defined as radiographic progression, unequivocal clinical progression, or death on study
- **Secondary endpoints:** time to PSA progression, PSA response, and ORR
- Safety

ORR=objective response rate; PFS=progression-free survival; PSA=prostate-specific antigen.

Primary Endpoint: PFS



Enzalutamide + D + P	136	121	94	74	48	22	12	7	4	2	1	1
Placebo + D + P	135	121	93	63	35	9	5	2	1	0	0	0

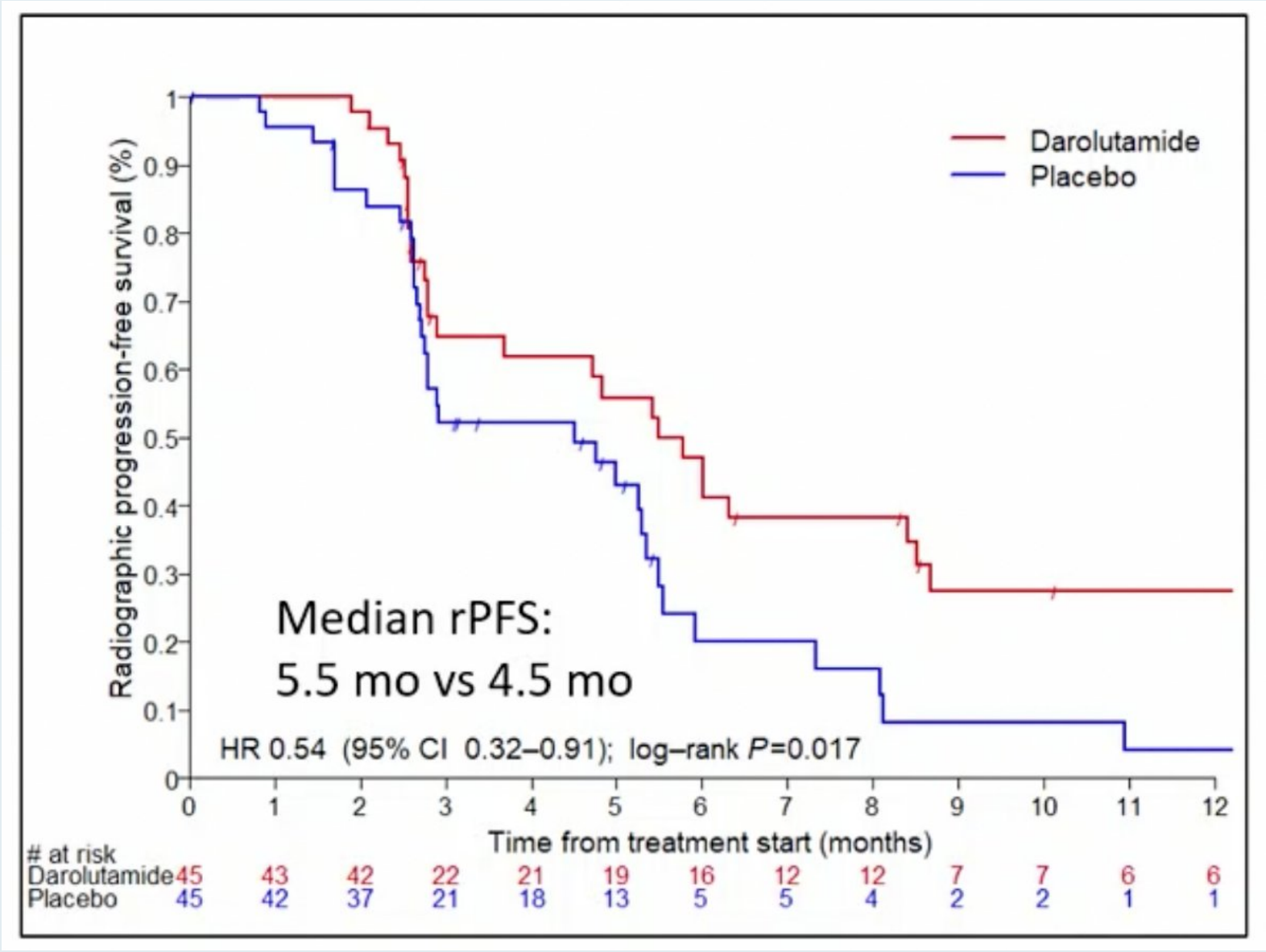
The study met its primary endpoint and enzalutamide plus docetaxel and prednisolone demonstrated a statistically significant reduction in the risk of progression compared with placebo plus docetaxel and prednisolone

CI=confidence interval; D=docetaxel; HR=hazard ratio; P=prednisolone; PFS=progression-free survival.

Darolutamide Maintenance in Metastatic Castration Resistant Prostate Cancer (mCRPC) Previously Treated with Novel Hormonal Agents (NHA) and Non-Progressive Disease After Subsequent Treatment with a Taxane: A Randomized Double-Blind Placebo-Controlled Phase II Trial (SAKK 08/16)

Cathomase R al.
ESMO 2021;Abstract LBA26.

SAKK 08/16: Primary Endpoint (rPFS)

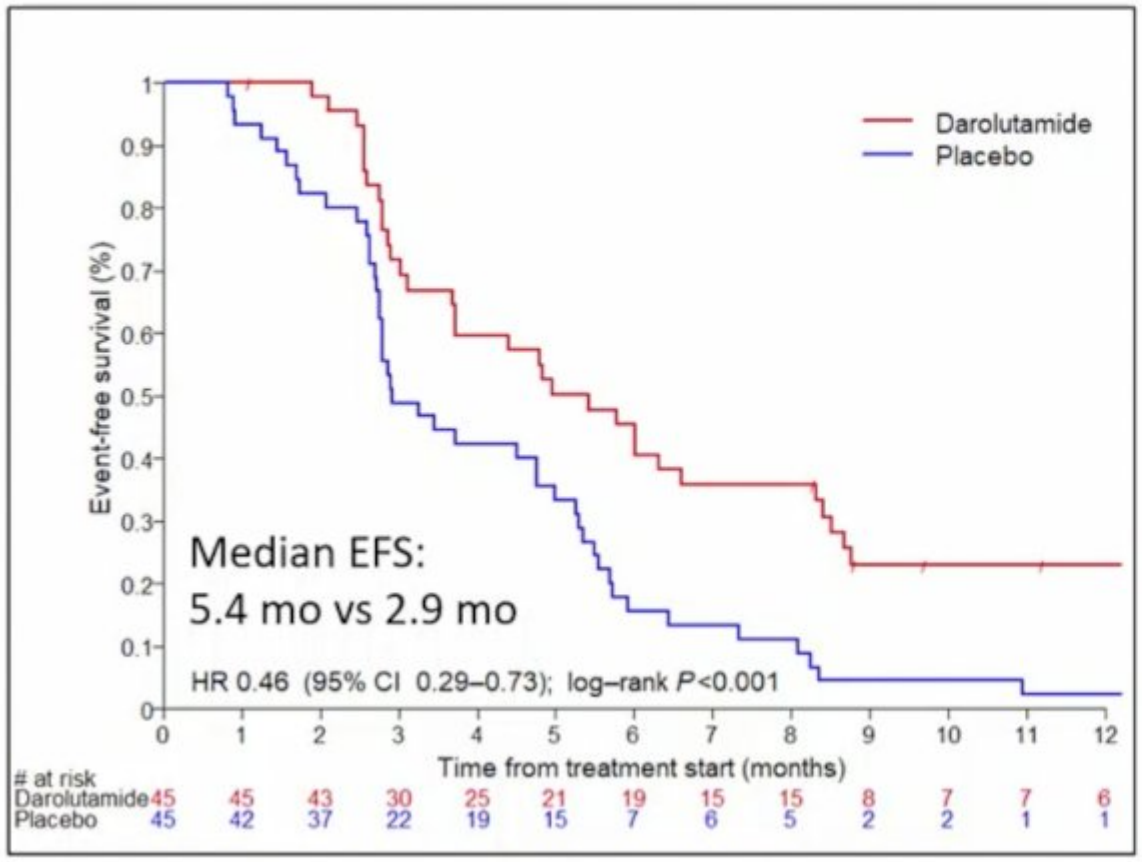


Cathomase R al. ESMO 2021;Abstract LBA26.

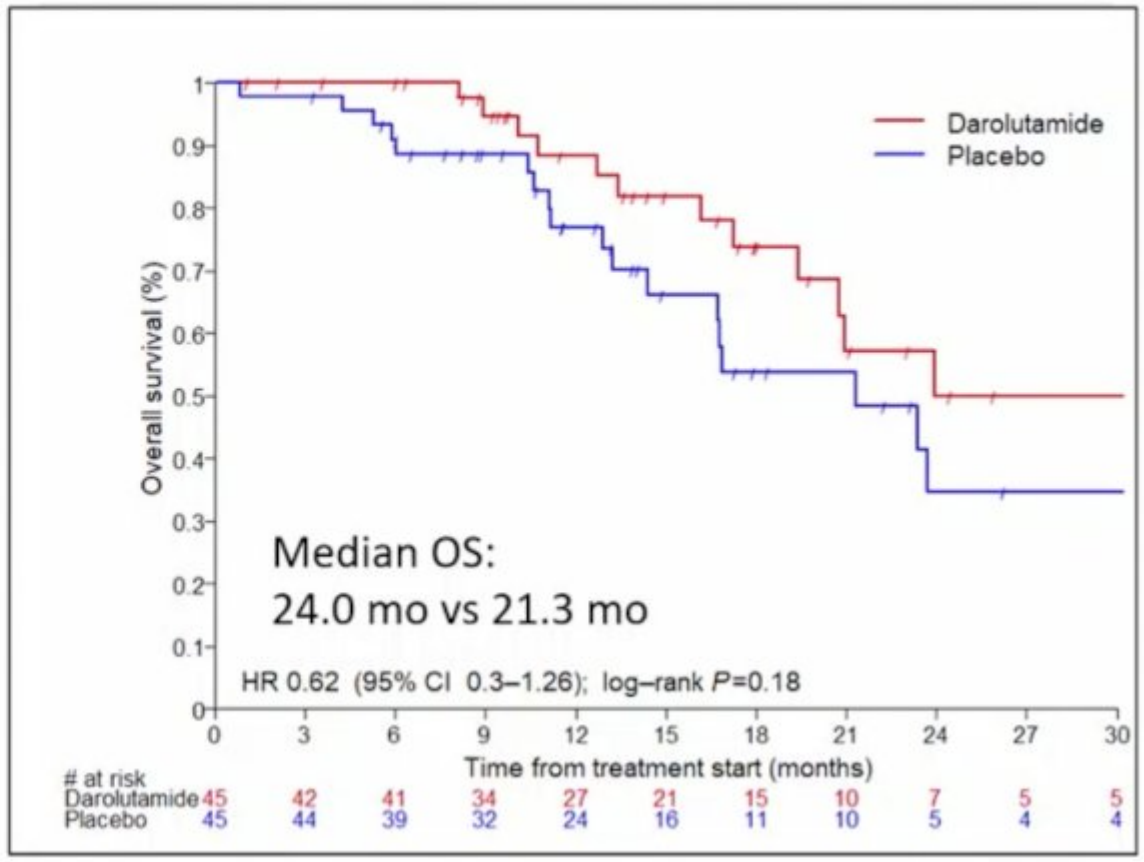
RTP RESEARCH TO PRACTICE

SAKK 08/16: Secondary Endpoints

Secondary endpoint: event-free survival



Secondary endpoint: overall survival



Cathomase R al. ESMO 2021;Abstract LBA26.

RTP RESEARCH TO PRACTICE

2021 ASCO ANNUAL MEETING

Abstract 5002

EORTC Genito-Urinary Cancers Group
The future of cancer therapy

DECREASED FRACTURE RATE BY MANDATING BONE PROTECTING AGENTS IN THE EORTC 1333/PEACE-3 TRIAL COMBINING RA-223 WITH ENZALUTAMIDE VERSUS ENZALUTAMIDE ALONE: AN UPDATED SAFETY ANALYSIS

Silke GILLESSEN, Ananya CHOUDHURY, Alejo RODRIGUEZ-VIDA, Franco NOLE, Enrique GALLARDO, Thierry Andre ROUMEGUERE, Gedske DAUGAARD, Yohann LORIOT, Fred SAAD, Raymond S. McDERMOTT, Anouk NEVEN, Beatrice FOURNIER, Bertrand F. TOMBAL

For EORTC GUCG, CUOG, UNICANCER and Cancer Trials Ireland

CUOG

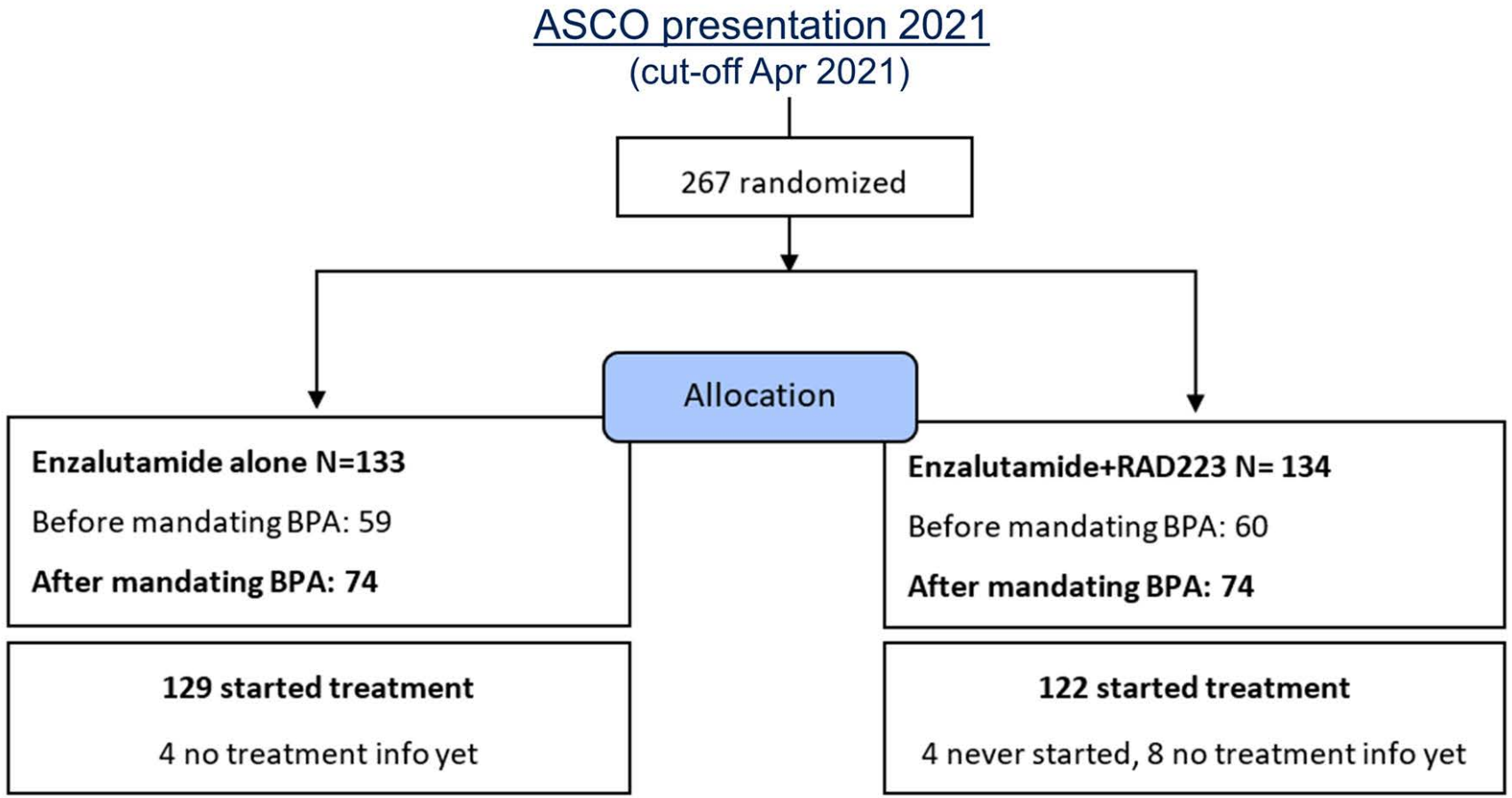
GETUG

unicancer

cancer trials ireland

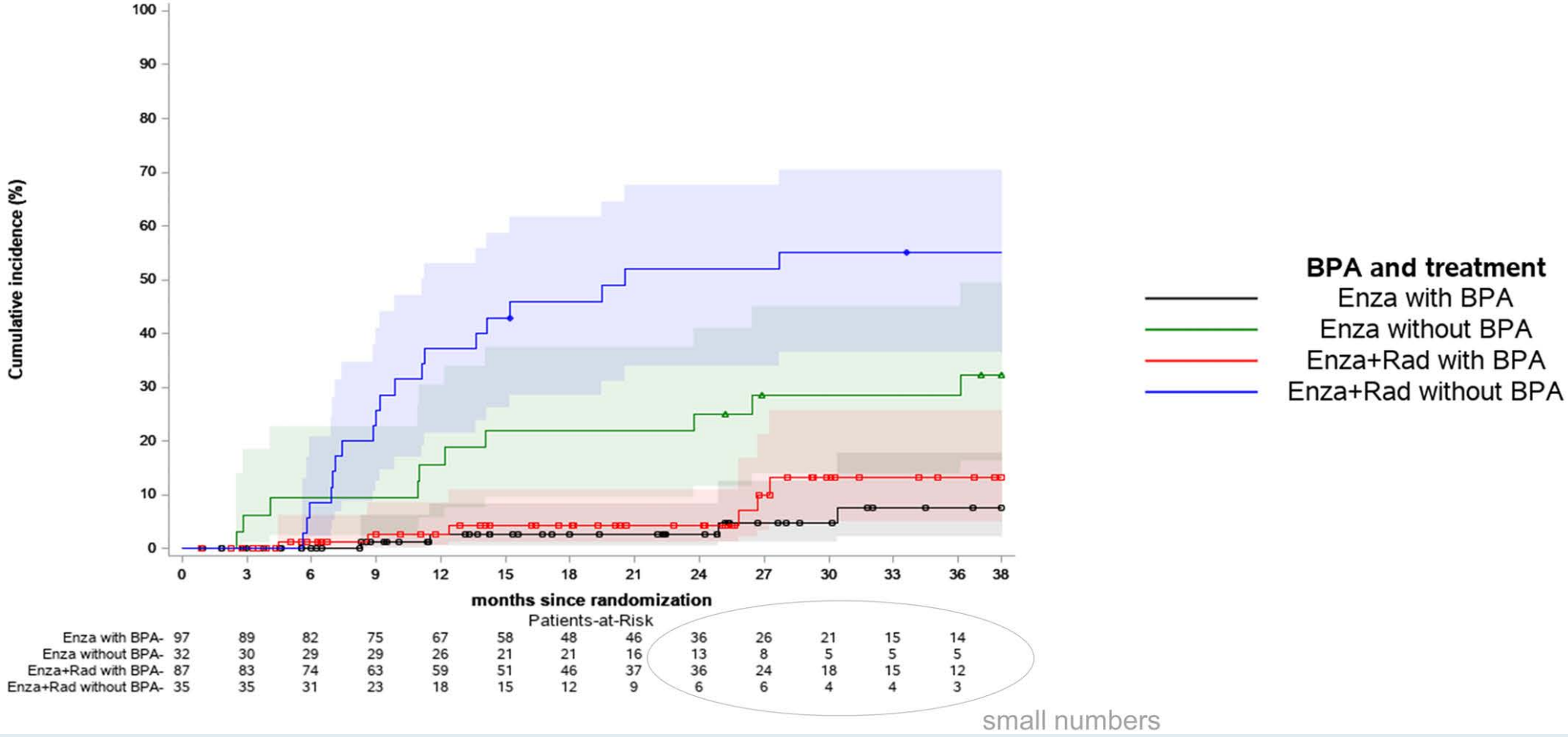
RTP RESEARCH TO PRACTICE

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



Gillessen S et al. ASCO 2021; Abstract 5002.

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



Gillessen S et al. ASCO 2021; Abstract 5002.

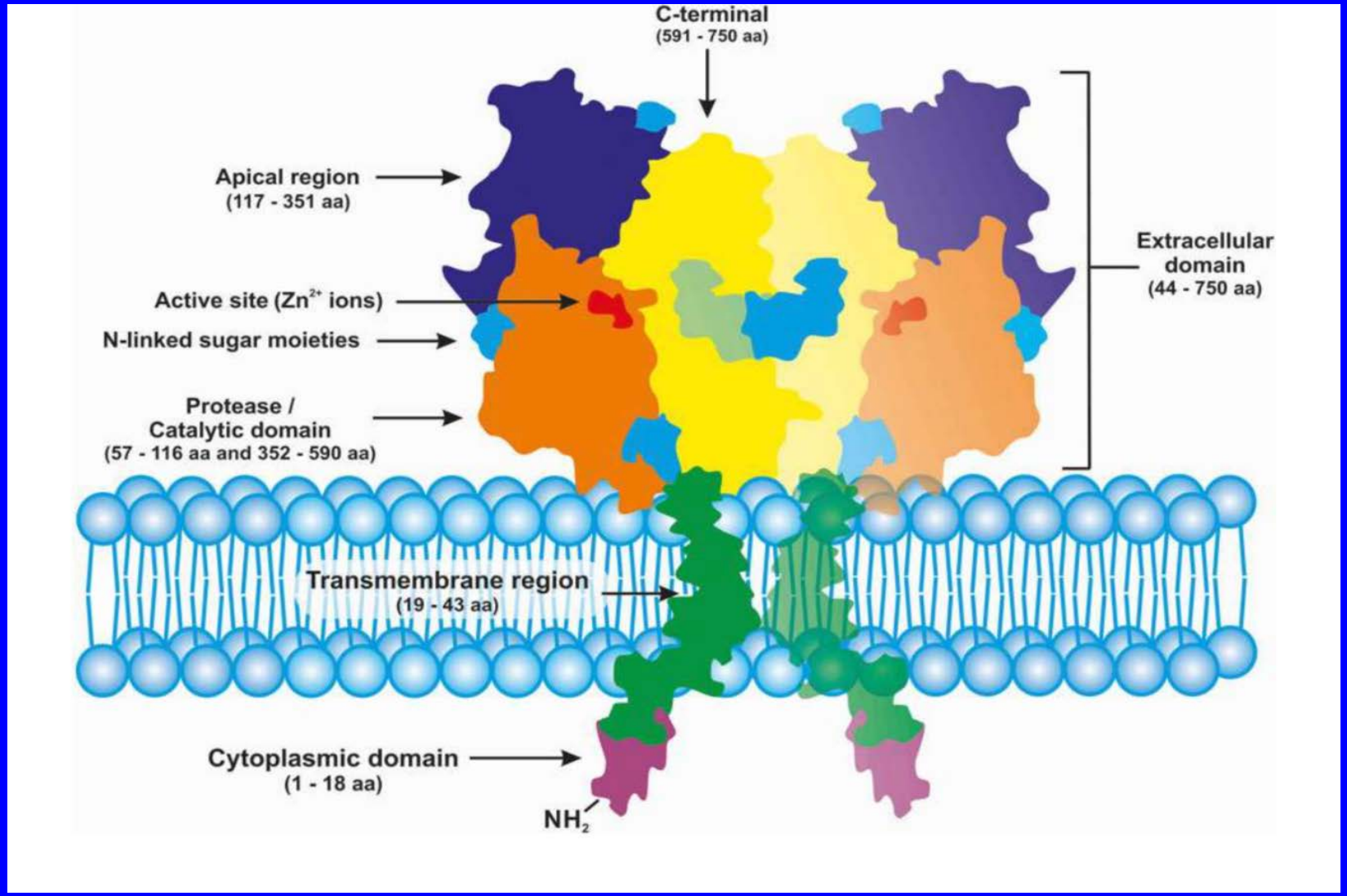
PEACE III: Bone fractures and cumulative incidence – safety population

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)

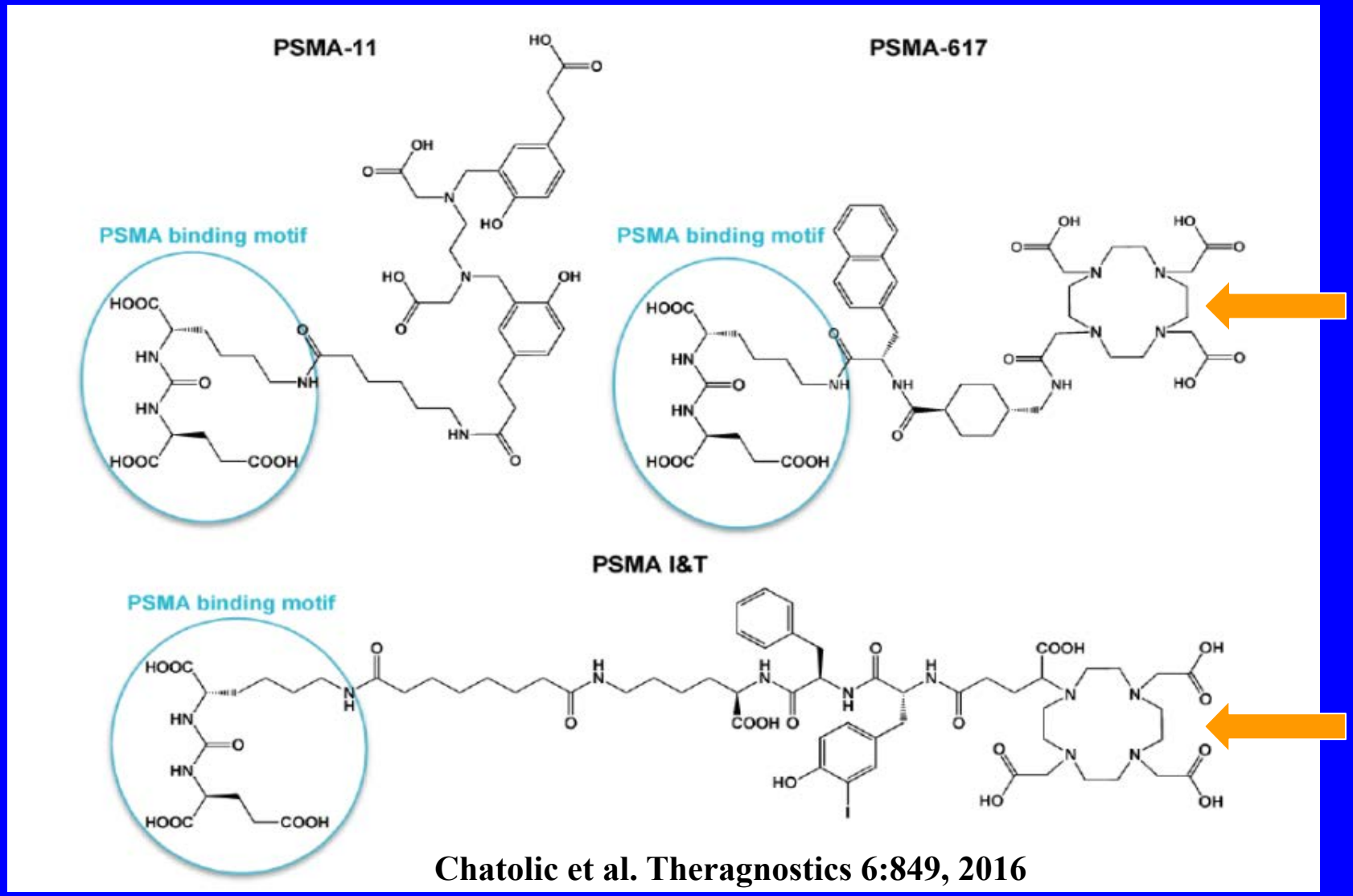
Gillessen S et al. ASCO 2021; Abstract 5002.

PSMA

Image from O'Driscott C et al, Br J Pharm 2016



PSMA binding molecules can be linked to therapeutic agents such as ^{177}Lu or ^{225}Ac



Chatolic et al. Theragnostics 6:849, 2016

The NEW ENGLAND JOURNAL of MEDICINE

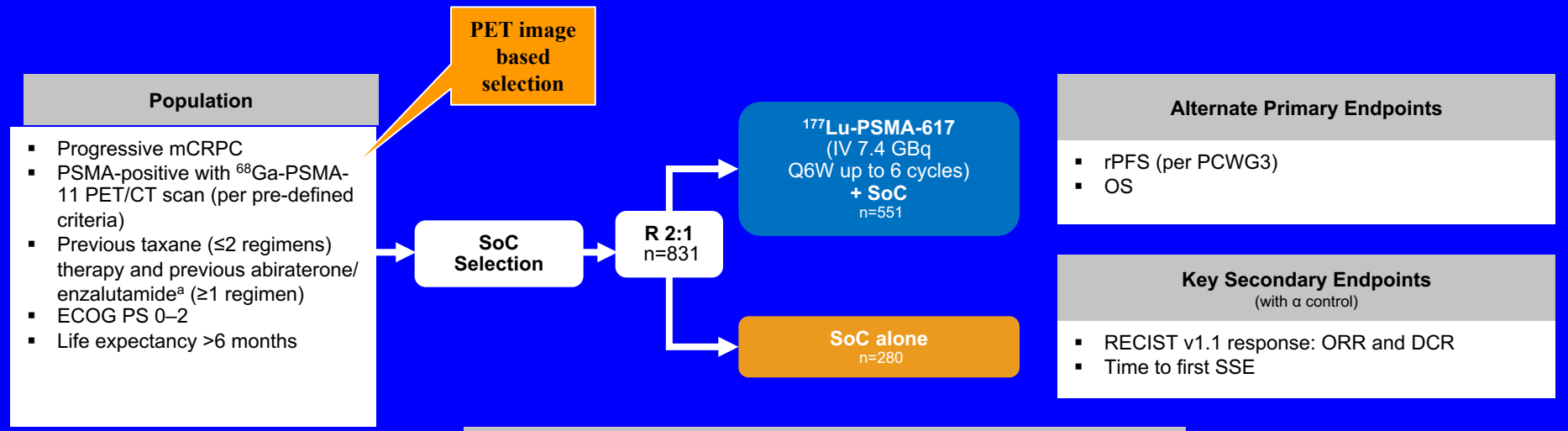
ORIGINAL ARTICLE

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

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

Print Version
Sept 16, 2021

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

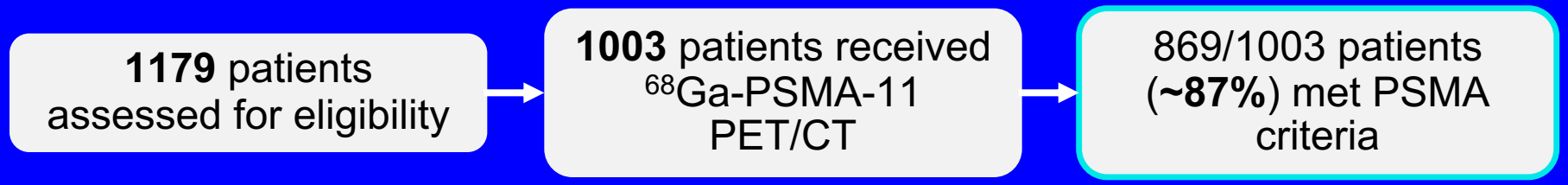


[a] Other ARPIs, including apalutamide and darolutamide, were allowed as prior therapy in VISION.

ARPI, androgen receptor pathway inhibitor; CT, computed tomography; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, lactate dehydrogenase; mCRPC, metastatic castration-resistant prostate cancer; ORR, overall response rate; OS, overall survival; PCWG3, Prostate Cancer Working Group 3; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; R, randomized; RECIST, Response Evaluation Criteria In Solid Tumours; rPFS, radiographic progression-free survival; SoC, standard of care; SSE, symptomatic skeletal event; Q6W, every 6 weeks.

1. Sartor O, et al. N Engl J Med. 2021; doi: 10.1056/NEJMoa2107322. Online ahead of print.

VISION: Image based biomarker used for patient selection



Pre-specified criteria for PSMA positivity

- ≥ 1 PSMA-positive metastatic lesion
  - PSMA PET imaging ligand uptake ≥ liver
- No PSMA PET negative lesion in viscera ≥1 cm
- No PSMA PET negative lymph node ≥2.5 cm

CT, computed tomography; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.

Sartor O, et al. N Engl J Med. 2021; doi: 10.1056/NEJMoa2107322. Online ahead of print.

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

Sartor et al. NEJM 385:1091-1103, 2021

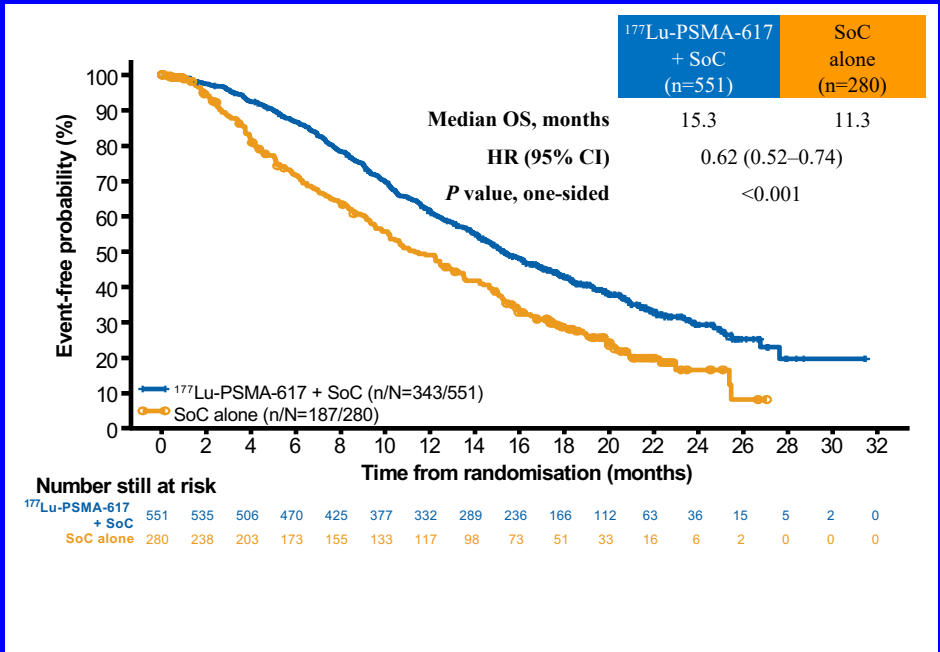
Characteristic	Analysis Set for Imaging-Based Progression-free Survival (N=581)		All Patients Who Underwent Randomization (N=831)	
	^{177}Lu-PSMA-617 plus Standard Care (N=385)	Standard Care Alone (N=196)	^{177}Lu-PSMA-617 plus Standard Care (N=551)	Standard Care Alone (N=280)
Previous prostatectomy — no. (%)¶	159 (41.3)	82 (41.8)	240 (43.6)	130 (46.4)
Previous androgen-receptor–pathway inhibitor — no. (%)‖				
One regimen	213 (55.3)	98 (50.0)	298 (54.1)	128 (45.7)
Two regimens	150 (39.0)	86 (43.9)	213 (38.7)	128 (45.7)
More than two regimens	22 (5.7)	12 (6.1)	40 (7.3)	24 (8.6)
Previous taxane therapy — no. (%)**				
One regimen	207 (53.8)	102 (52.0)	325 (59.0)	156 (55.7)
Two regimens	173 (44.9)	92 (46.9)	220 (39.9)	122 (43.6)
Docetaxel	377 (97.9)	191 (97.4)	534 (96.9)	273 (97.5)
Cabazitaxel	161 (41.8)	84 (42.9)	209 (37.9)	107 (38.2)

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

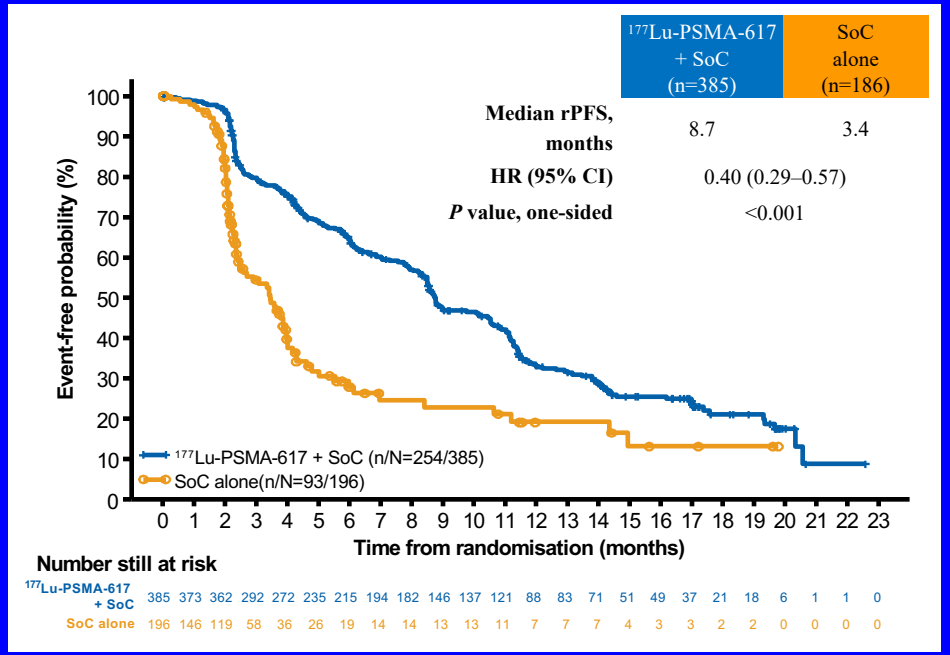
Sartor et al. NEJM 385:1091-1103, 2021

VISION met both primary endpoints of OS and rPFS

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



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



Note: OS positive (HR 0.63) in rPFS subset and rPFS positive (HR 0.43) in OS subset

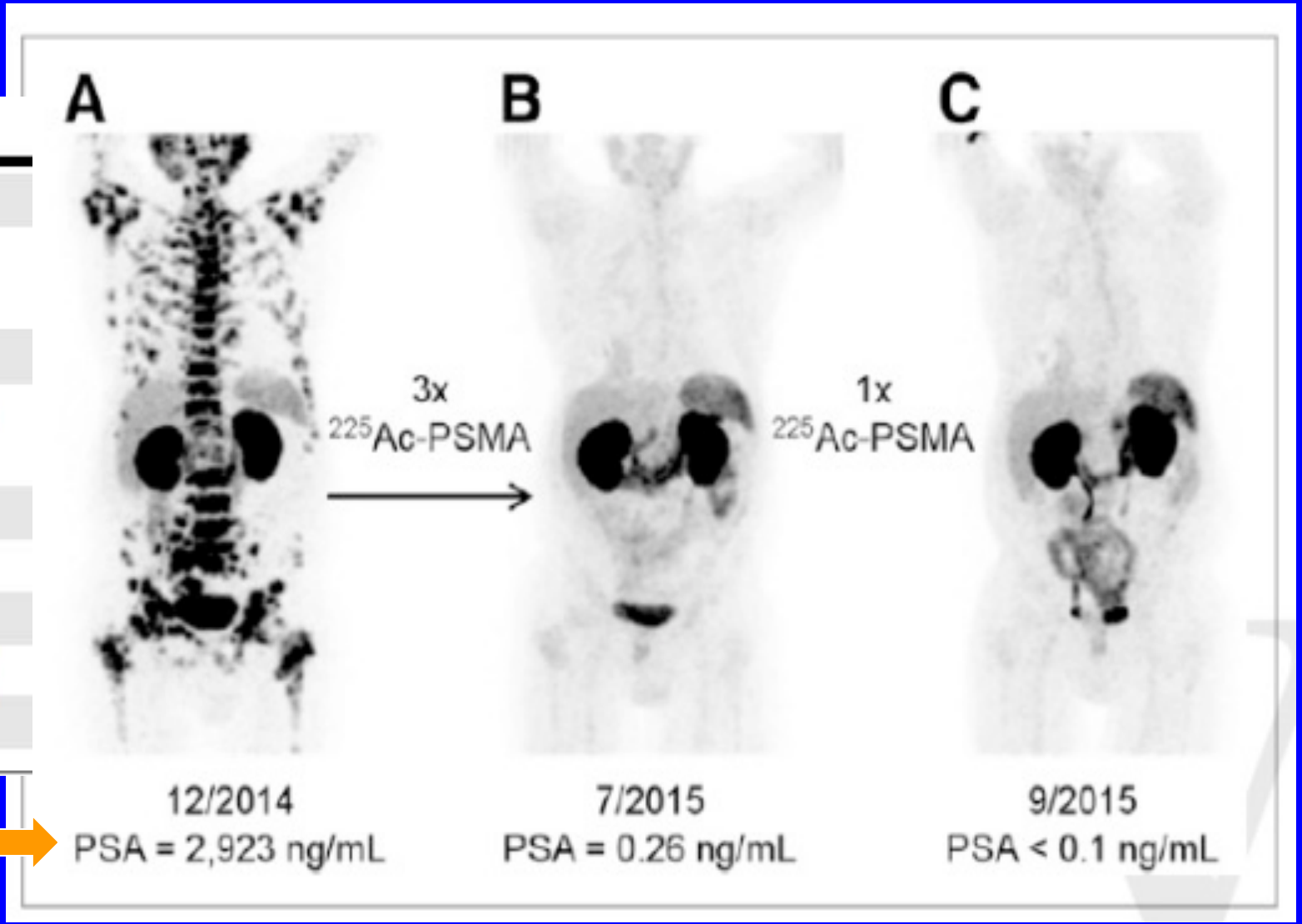
VISION: ^{177}Lu-PSMA-617 pivotal Phase III trial

TEAEs occurring in ≥5% of patients[b], n (%)	Safety Set (N=734)[a]			
	All Grades		Grade 3–5[c]	
	^{177}Lu-PSMA-617 + SoC (n=529)	SoC alone (n=205)	^{177}Lu-PSMA-617 + SoC (n=529)	SoC alone (n=205)
Fatigue	228 (43.1)	47 (22.9)	31 (5.9)	3 (1.5)
Dry mouth	205 (38.8)	1 (0.5)	0	0
Nausea	187 (35.3)	34 (16.6)	7 (1.3)	1 (0.5)
Anaemia	168 (31.8)	27 (13.2)	68 (12.9)	10 (4.9)
Back pain	124 (23.4)	30 (14.6)	17 (3.2)	7 (3.4)
Arthralgia	118 (22.3)	26 (12.7)	6 (1.1)	1 (0.5)
Decreased appetite	112 (21.2)	30 (14.6)	10 (1.9)	1 (0.5)
Constipation	107 (20.2)	23 (11.2)	6 (1.1)	1 (0.5)
Diarrhea	100 (18.9)	6 (2.9)	4 (0.8)	1 (0.5)
Vomiting	100 (18.9)	13 (6.3)	5 (0.9)	1 (0.5)
Thrombocytopaenia	91 (17.2)	9 (4.4)	42 (7.9)	2 (1.0)
Lymphopaenia	75 (14.2)	8 (3.9)	41 (7.8)	1 (0.5)
Leukopaenia	66 (12.5)	4 (2.0)	13 (2.5)	1 (0.5)

Radio-conjugates: PSMA targeted alpha emitters (Actinium-225) as 9th line treatment

Kratochwil et a. J Nuc Med 57: 1-4, 2016

Patient A
Leuprorelin
Zoledronate
Docetaxel (50 cycles)
Carmustine/epirubicin in hyperthermia
Abiraterone
Enzalutamide
^{223}Ra (6 cycles)
Abiraterone reexposition
Estramustine

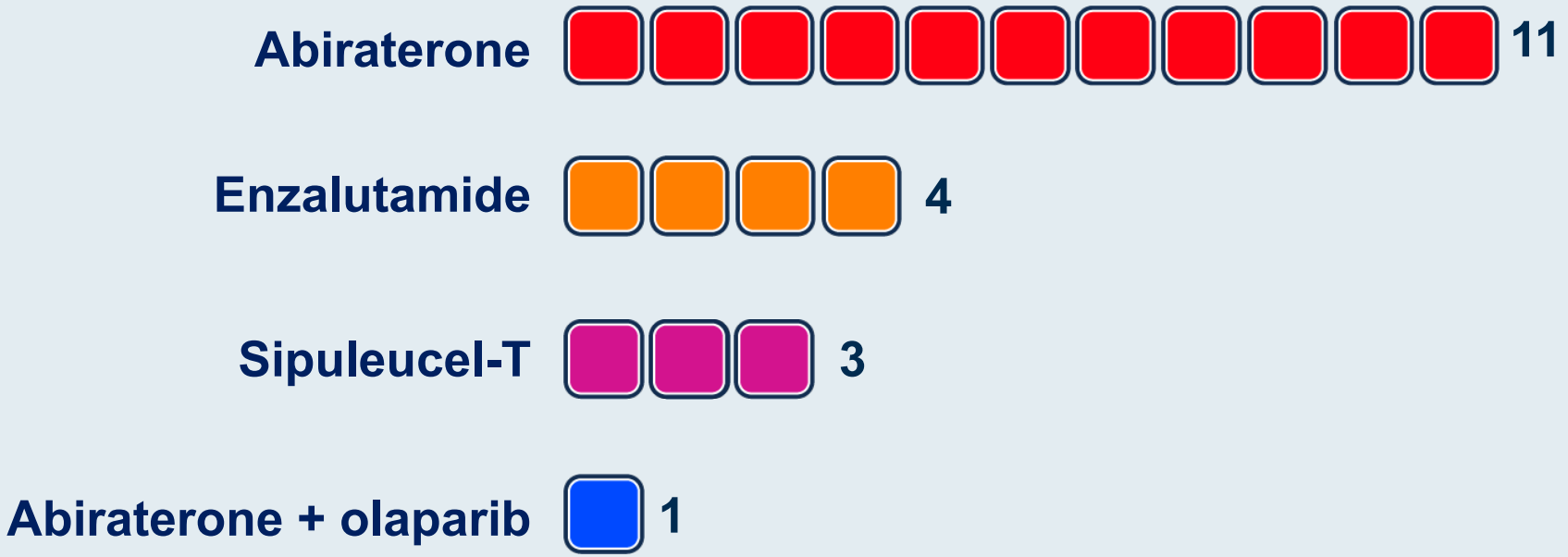


Conclusions

- Selection and sequencing of therapies depends on a number of factors, including prior therapies and genetics
  - More therapies are moving toward the “front” and those early choices have significant “downstream” effects
- Precision medicine is the wave of the future BUT there are multiple limitations of tissue-based biomarkers
  - Imaging as a predictive biomarker is incredibly important and “precision medicine” needs to explore this new paradigm faster
- The pace of progress is faster today than ever before…..

Clinical Investigator Survey Results

A 65-year-old man receiving ADT for M0 disease after RP is found to have asymptomatic bone metastases. Genetic testing is negative for homologous recombination repair (HRR) mutations. Regulatory and reimbursement issues aside, what systemic treatment would you most likely recommend?

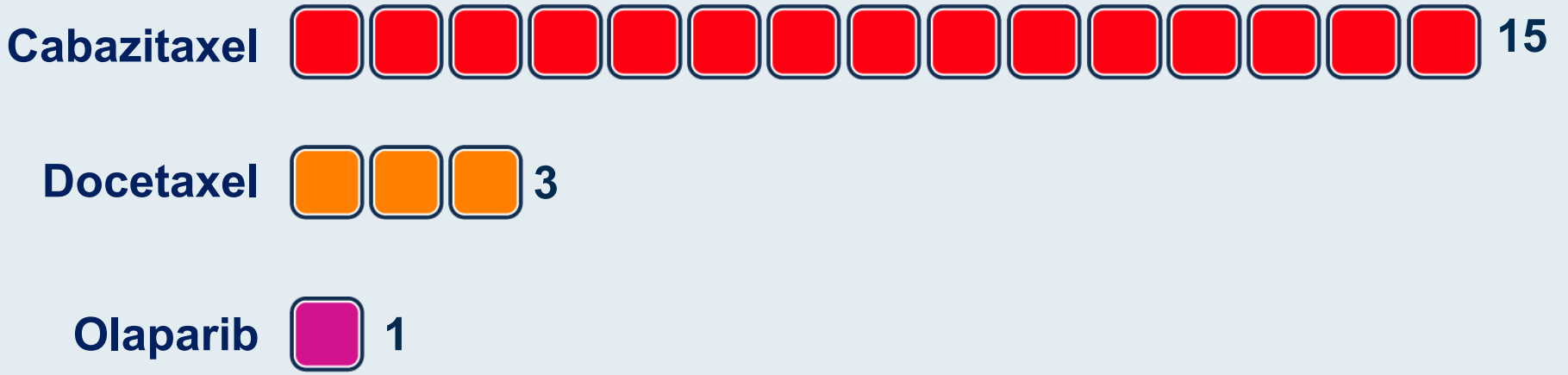


Survey of genitourinary cancer clinical investigators

A 65-year-old man receiving ADT for M0 disease after RP is found to have widespread, moderately symptomatic bone metastases. Genetic testing is negative for HRR mutations. Regulatory and reimbursement issues aside, what systemic treatment would you most likely recommend?

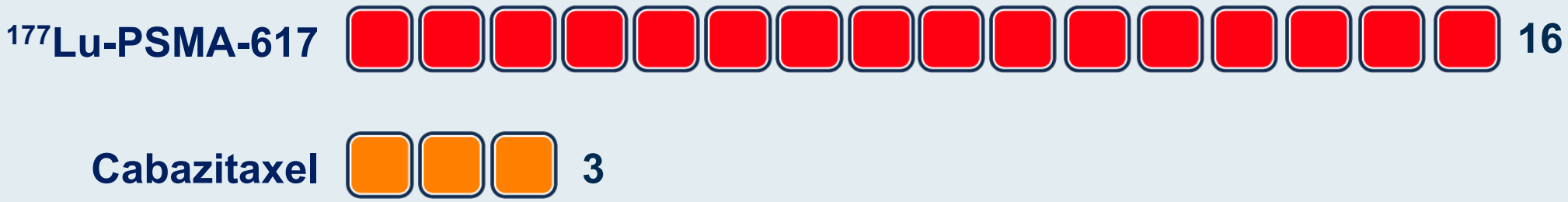
Survey of genitourinary cancer clinical investigators

A 65-year-old man presents with prostate cancer (BRCA wild type) metastatic to the bone and receives ADT + docetaxel with disease progression 1 year later. He responds to enzalutamide for 18 months, then has symptomatic progression in the bone along with new lung lesions. Regulatory and reimbursement issues aside, what is your most likely treatment?



Survey of genitourinary cancer clinical investigators

If ^{177}Lu-PSMA-617 were available, which of the following would you generally recommend first for a patient with PSMA-positive mCRPC?



Survey of genitourinary cancer clinical investigators

If ^{177}Lu-PSMA-617 were available, which of the following would you generally prefer for a patient with PSMA-positive mCRPC and bone-only metastases?

Survey of genitourinary cancer clinical investigators

MODULE 3: Integration of PARP Inhibitors into the Current Management of mCRPC — Dr Beltran

RTP
RESEARCH
TO PRACTICE

Integration of PARP Inhibitors into the Current Management of mCRPC

Misha Beltran, MD
Dana-Farber Cancer Institute
Research To Practice Satellite Symposium (GU ASCO 2022)

Dana-Farber
Cancer Institute

Dr Beltran — Disclosures

Advisory Committee	Astellas, Amgen Inc, Blue Earth Diagnostics, Foundation Medicine, Janssen Biotech Inc, Merck, Oncorus, Pfizer
Consulting Agreement	Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company
Contracted Research	Bristol-Myers Squibb Company, Janssen Biotech Inc
Data and Safety Monitoring Board/Committee	AstraZeneca Pharmaceuticals LP

RTP
RESEARCH
TO PRACTICE

FDA Approved Biomarker-Driven Therapy in mCRPC

- Olaparib: PARP inhibitor approved post-ARPI for germline/somatic homologous recombination repair DNA alterations
- Rucaparib: PARP inhibitor approved post-ARPI + postchemotherapy for patients with germline or somatic *BRCA* alterations
- Pembrolizumab: Immune checkpoint inhibitor approved for microsatellite instability, mismatch repair loss, TMB-high cancer (≥ 10 Mut/Mb)

Precision Medicine is now a Reality for our Patients

NCCN and other guidelines now endorse testing for all patients with advanced prostate cancer

Both Tumor (Somatic) and Germline testing is Recommended for Patients with mCRPC

- **Homologous Recombination DNA repair gene aberrations**
  - Approx 20% of advanced prostate cancer, 8-10% localized prostate cancer
  - Germline alterations- 8- 12% of pts with metastatic prostate cancer, 3.5-6.5% of localized disease
  - mCRPC-- BRCA2 (13.3%), ATM (7.3%), CHEK2 (3%), PALB2 (2%), BRCA1 (0.7%), others

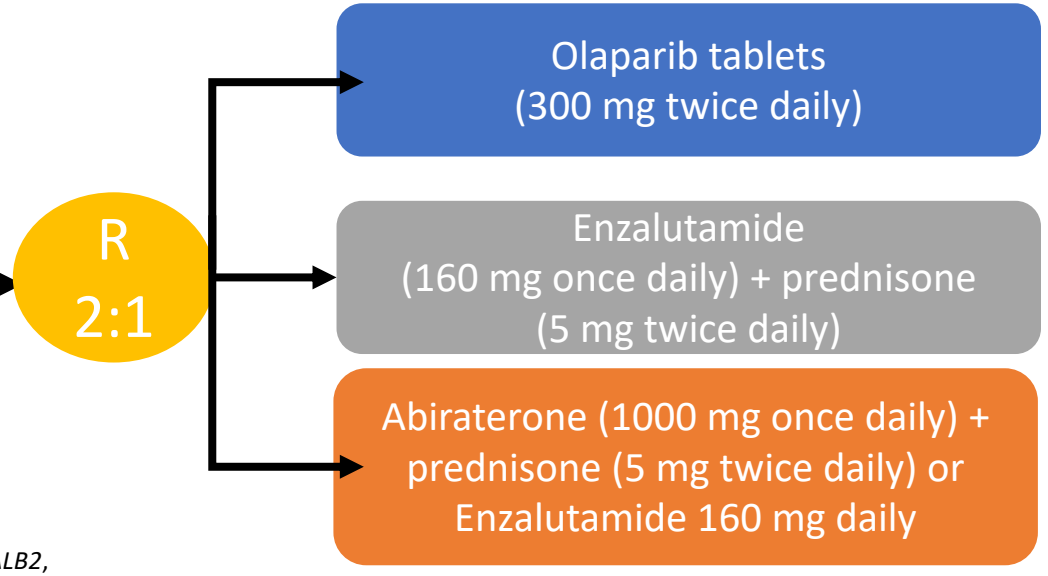
- Paired samples from the primary tumor and metastasis at the time of CRPC have shown no difference in prevalence of somatic homologous recombination gene aberrations, suggesting that these are early events (Mateo et al JCI 2020)

PROfound Trial: Olaparib for mCRPC

- Patients with mCRPC who had disease progression receiving a new hormonal agent (eg, enzalutamide or abiraterone)
- All men had a qualifying alteration in prespecified genes with a direct or indirect role in HRR

- Cohort A (n = 245) had ≥ 1 alteration in *BRCA1, BRCA2,* or *ATM*
- Cohort B (n = 142) had alterations in any of 12 other prespecified genes*, prospectively and centrally determined from tumor tissue

**BARD1, BRIP1, CDK12, CHEK1/2, FANCL, PALB2, PPP2R2A, RAD51B/C/D, RAD54L*



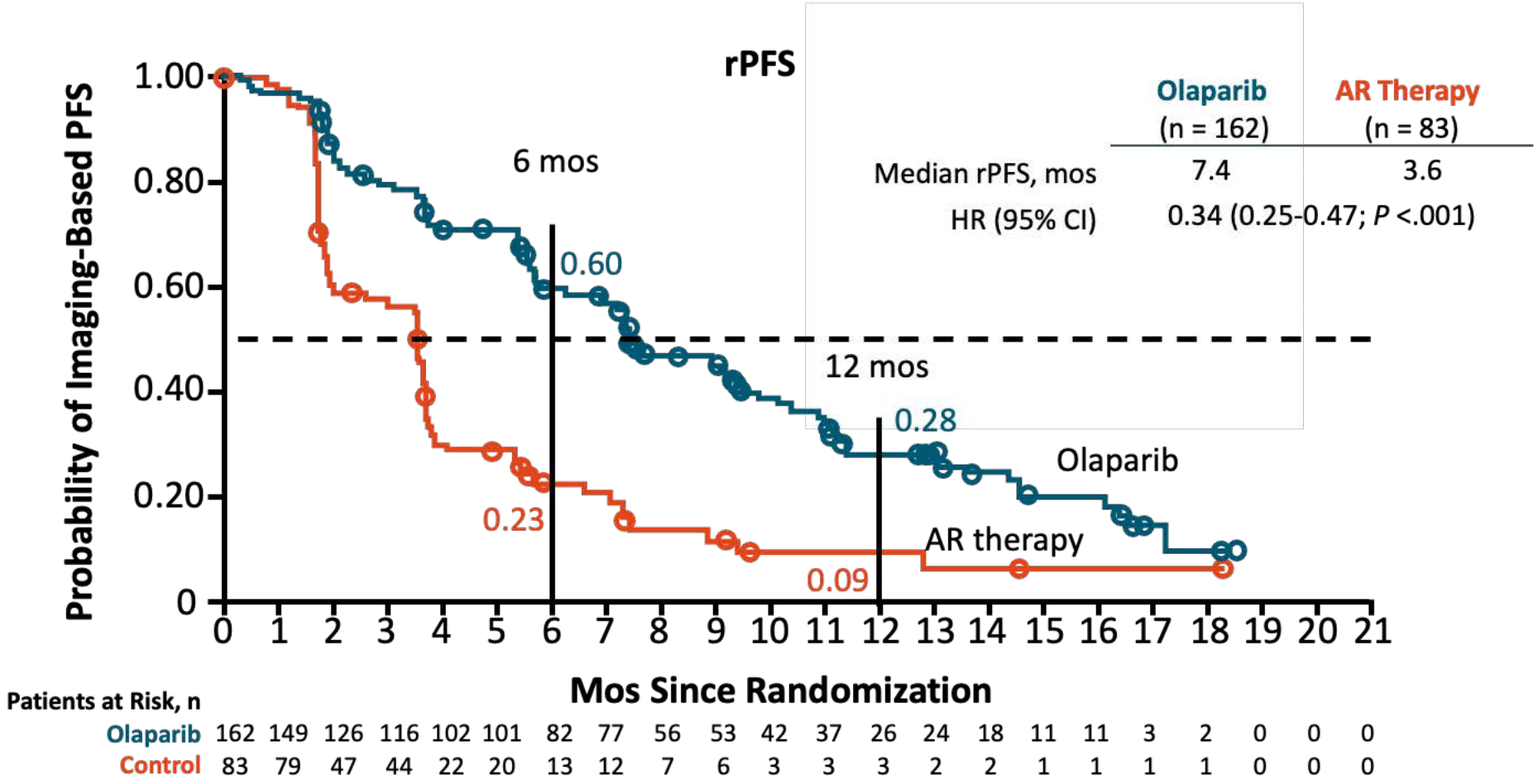
N=387
65% prior taxane

4047 pts submitted tumor samples (approx. 90% archival primary tumors)

31% test failures – path review (6.8%) with estimated tumor fraction <20% or tumor volume <0.2 mm^2), DNA extraction (13.2%), failure after DNA extraction (6.9%)

Hussain M, et al. *N Engl J Med*. 2020;383:2345-2357, Hussain et al, ASCO 2020

Phase III PROfound: rPFS by BICR With Alterations in *BRCA1, BRCA2,* or *ATM* (Cohort A)

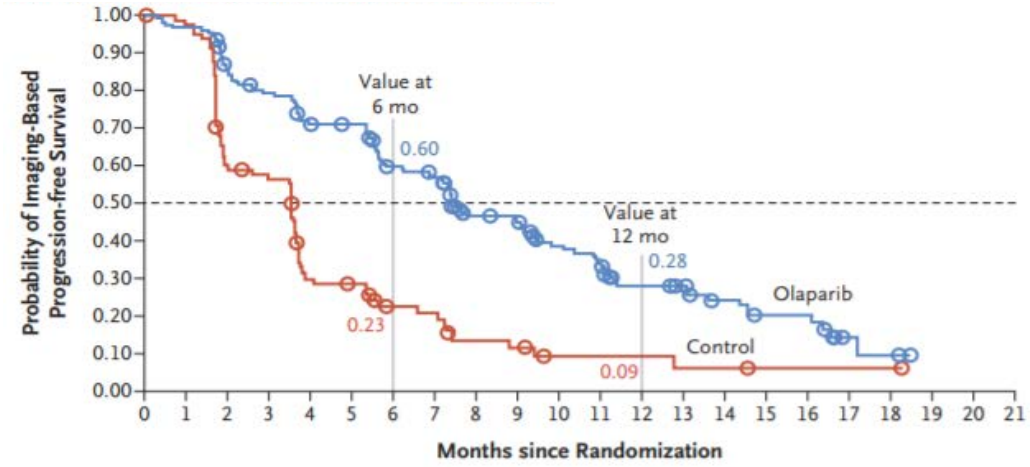


De Bono. NEJM. 2020;382:2091.

BICR = blinded independent central review

PROfound Trial*: PFS*

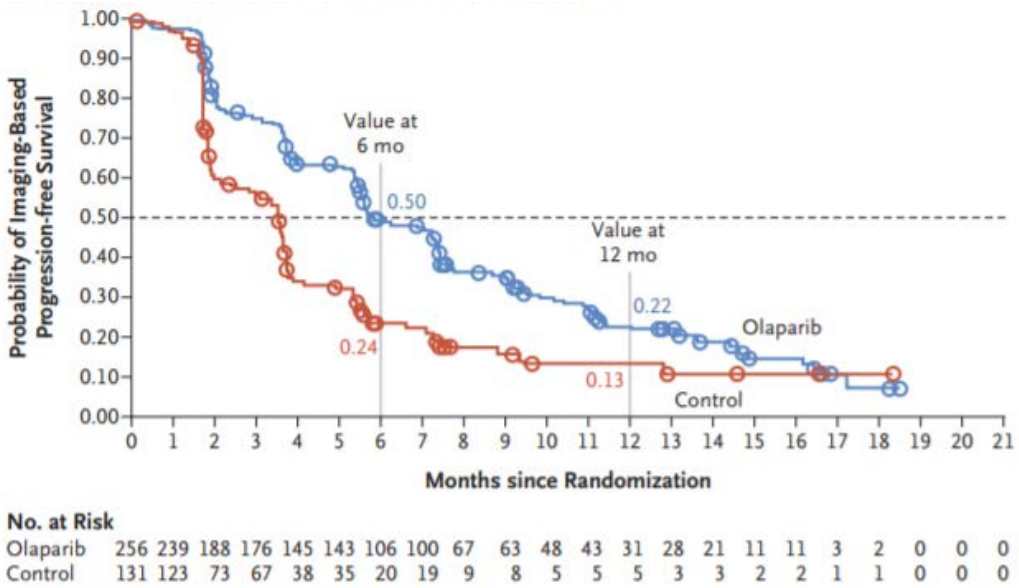
PFS in Cohort A



	Median *mo*
Olaparib	7.4
Control	3.6

Hazard ratio for progression or death, 0.34 (95% CI, 0.25–0.47)
P<0.001

PFS in Both Cohorts



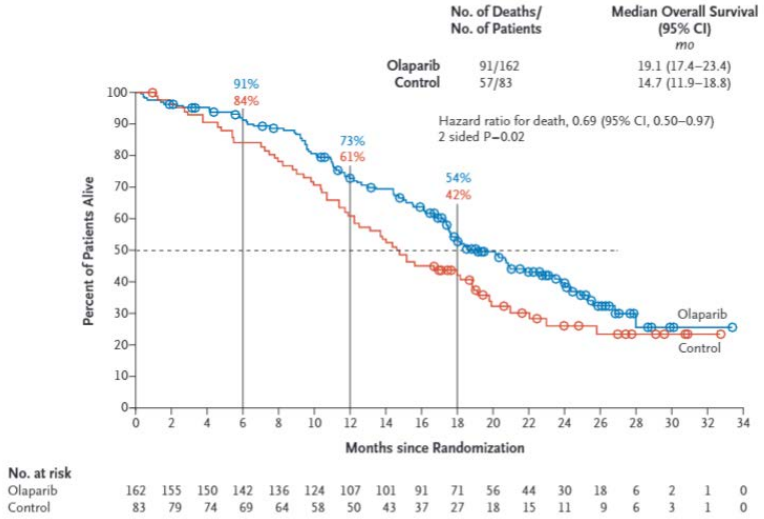
	Median *mo*
Olaparib	5.8
Control	3.5

Hazard ratio for progression or death, 0.49 (95% CI, 0.38–0.63)
P<0.001

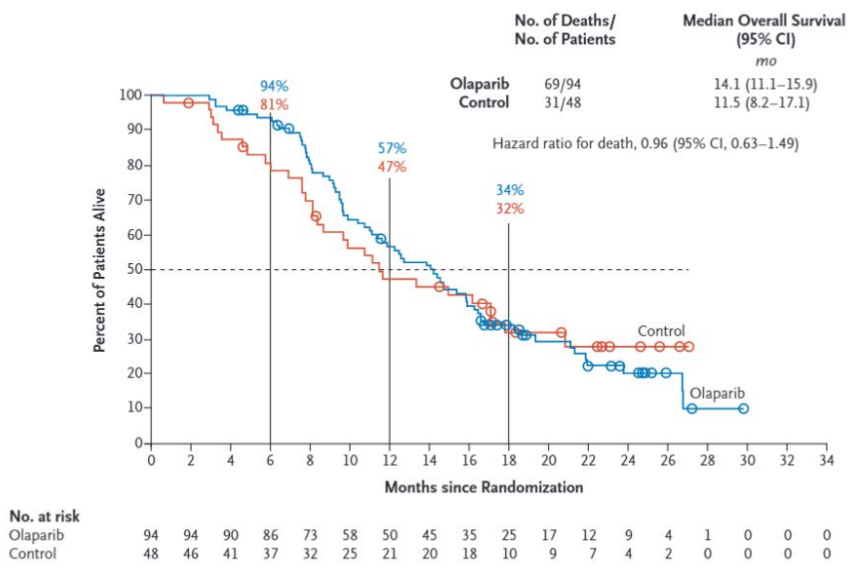
de Bono J, et al. *N Engl J Med*. 2020;382:2091-2102; Hussain M, et al. *N Engl J Med.* 2020;383:2345-2357.

PROfound Trial
OS in Cohort A, Cohort B and the Overall Population

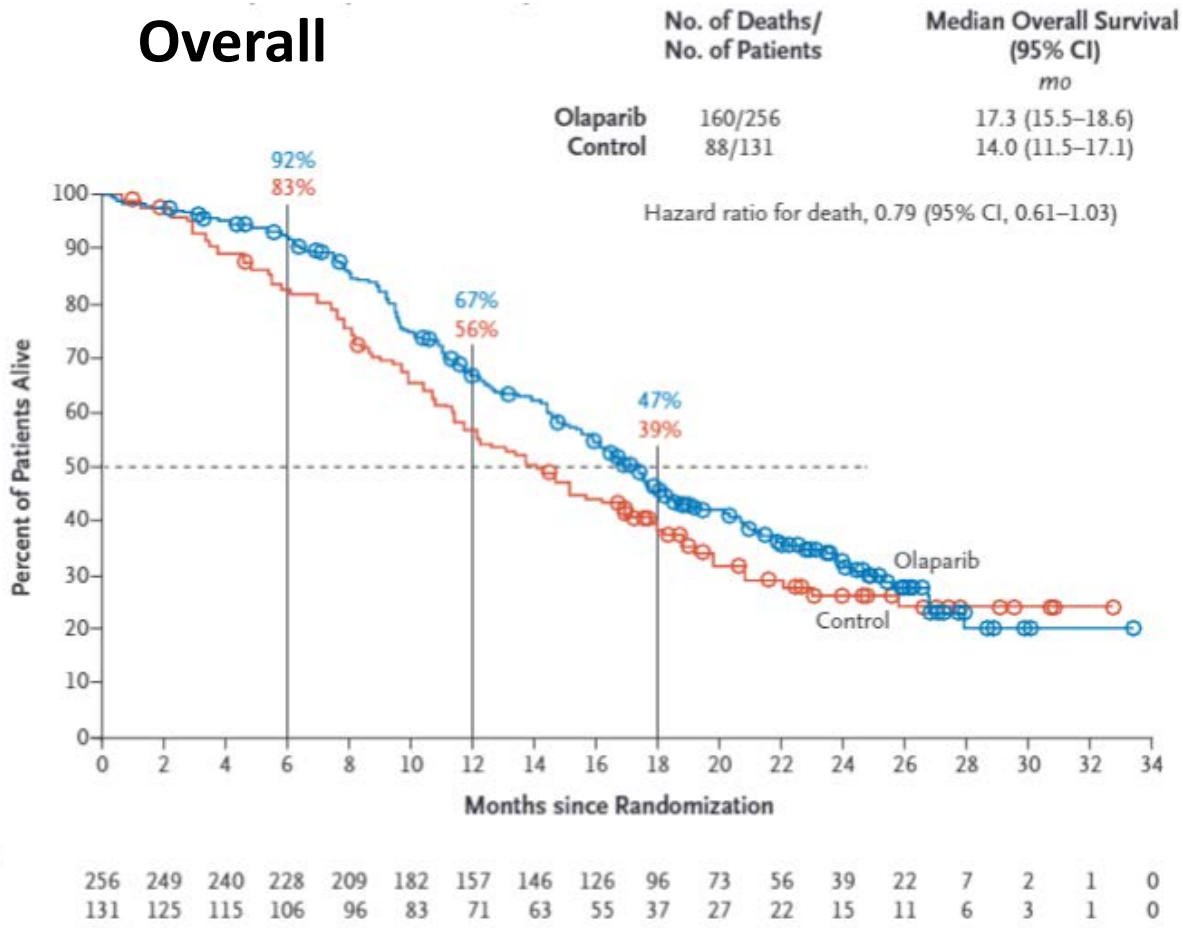
Cohort A



Cohort B



Overall



Benefit could be even greater for cohort A - sensitivity analysis adjusted for the crossover from control Rx to olaparib showed a 58% decrease in the risk of death for these patients

- Hussain M, et al. *N Engl J Med.* 2020;383:2345-2357.

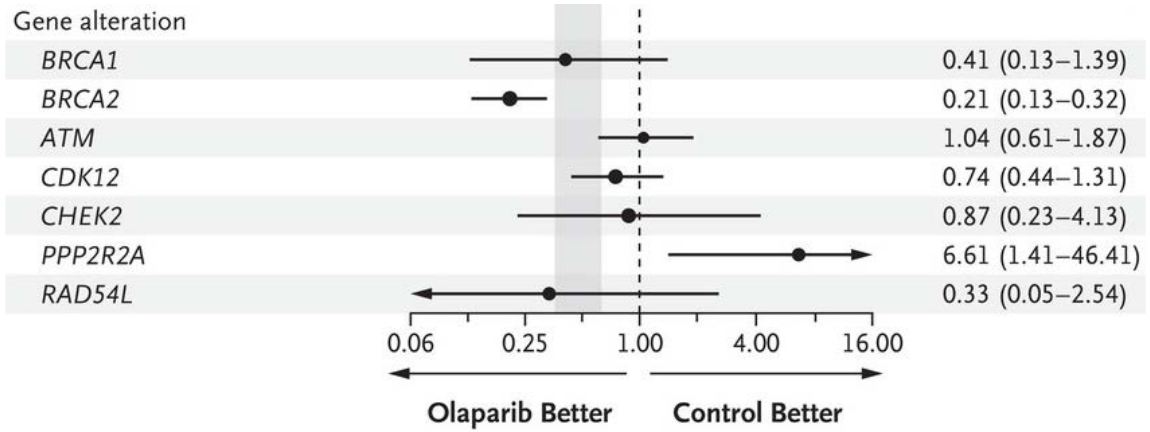
Table 1. Adverse Events in the Overall Population (Cohorts A and B) and in the Subgroup of Patients Who Crossed Over from Control Therapy to Receive Olaparib.*

Event	Olaparib (N=256)		Control (N=130)†		Crossover (N=83)‡	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients with event (percent)					
Any adverse event	246 (96)	133 (52)	115 (88)	52 (40)	77 (93)	49 (59)
Anemia§	127 (50)	58 (23)	20 (15)	7 (5)	43 (52)	24 (29)
Nausea	110 (43)	4 (2)	27 (21)	0	24 (29)	2 (2)
Fatigue or asthenia¶	107 (42)	8 (3)	43 (33)	7 (5)	21 (25)	8 (10)
Decreased appetite	80 (31)	4 (2)	24 (18)	1 (<1)	15 (18)	2 (2)
Diarrhea	55 (21)	2 (<1)	9 (7)	0	12 (14)	0
Vomiting	51 (20)	6 (2)	17 (13)	1 (<1)	16 (19)	1 (1)
Constipation	49 (19)	0	19 (15)	0	12 (14)	0
Back pain	36 (14)	2 (<1)	18 (14)	2 (2)	8 (10)	0
Peripheral edema	34 (13)	0	10 (8)	0	3 (4)	0
Cough	29 (11)	0	3 (2)	0	4 (5)	0
Dyspnea	27 (11)	6 (2)	5 (4)	0	4 (5)	1 (1)
Arthralgia	26 (10)	1 (<1)	14 (11)	0	4 (5)	0
Urinary tract infection	21 (8)	5 (2)	15 (12)	5 (4)	12 (14)	3 (4)
Any serious adverse event‖	94 (37)	NA	39 (30)	NA	27 (33)	NA
Interruption of treatment because of adverse event	119 (46)	NA	25 (19)	NA	44 (53)	NA
Dose reduction because of adverse event	60 (23)	NA	7 (5)	NA	27 (33)	NA
Discontinuation of treatment due to adverse event	51 (20)	NA	11 (8)	NA	11 (13)	NA
Death due to adverse event	10 (4)	NA	6 (5)	NA	3 (4)	NA

Hussain M, et al. *N Engl J Med.* 2020;383:2345-2357.

PROfound: Olaparib was approved for 14 genes:

BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1/2, FANCL, PALB2, RAD51B/C/D, RAD54L



Several genes were not represented in PROfound or were very few

de Bono et al, GU ASCO 2021: An exploratory gene-by-gene analysis in PROfound

Activity of olaparib was observed for patients with alterations in *BRCA1* and/or *BRCA2*, *ATM*, and *CDK12*. Patients with tumors harboring a *BRCA1* and/or *BRCA2* alteration appeared to derive the greatest benefit

		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

CANCER DISCOVERY 10

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Research Article

Biomarkers Associating with PARP Inhibitor Benefit in Prostate Cancer in the TOPARP-B Trial

Suzanne Carreira, Nuria Porta, Sara Arce-Gallego, George Seed, Alba Llop-Guevara, Diletta Bianchini, Pasquale Rescigno, Alec Paschalis, Claudia Bertan, Chloe Baker, Jane Goodall, Susana Miranda, Ruth Riisnaes, Ines Figueiredo, Ana Ferreira, Rita Pereira, Mateus Crespo, Bora Gurel, Daniel Nava Rodrigues, Stephen J Pettitt, Wei Yuan, Violeta Serra, Jan Rekowski, Christopher J Lord, Emma Hall, Joaquin Mateo, and Johann S de Bono

- Phase 2 trial of olaparib for DDRm CRPC (n=96)
- Greatest benefit /exceptional response with homozygous BRCA2 deletion
- Biallelic, but not mono-allelic, PALB2 deleterious alterations associated with benefit
- In the ATM cohort, loss of ATM protein by IHC associated with better outcome
- RAD51 foci loss identified tumors with biallelic BRCA and PALB2 alteration while most ATM- and CDK12-altered tumors had higher RAD51 foci levels.

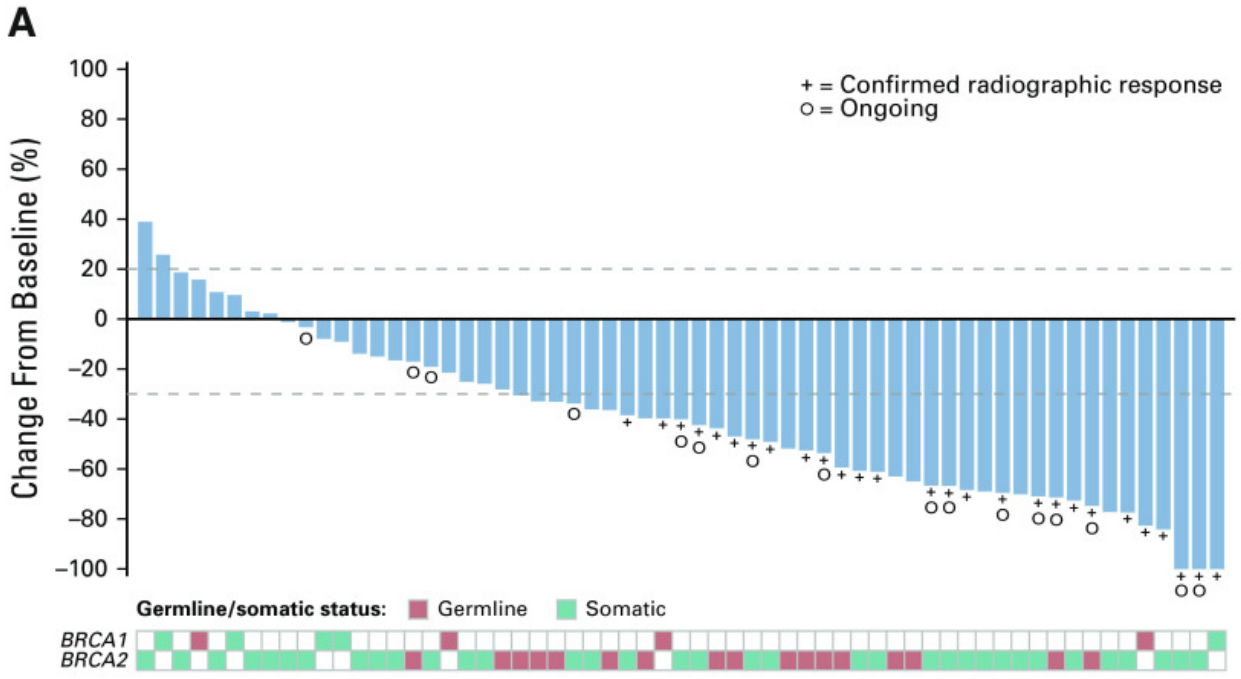
TRITON2: Rucaparib

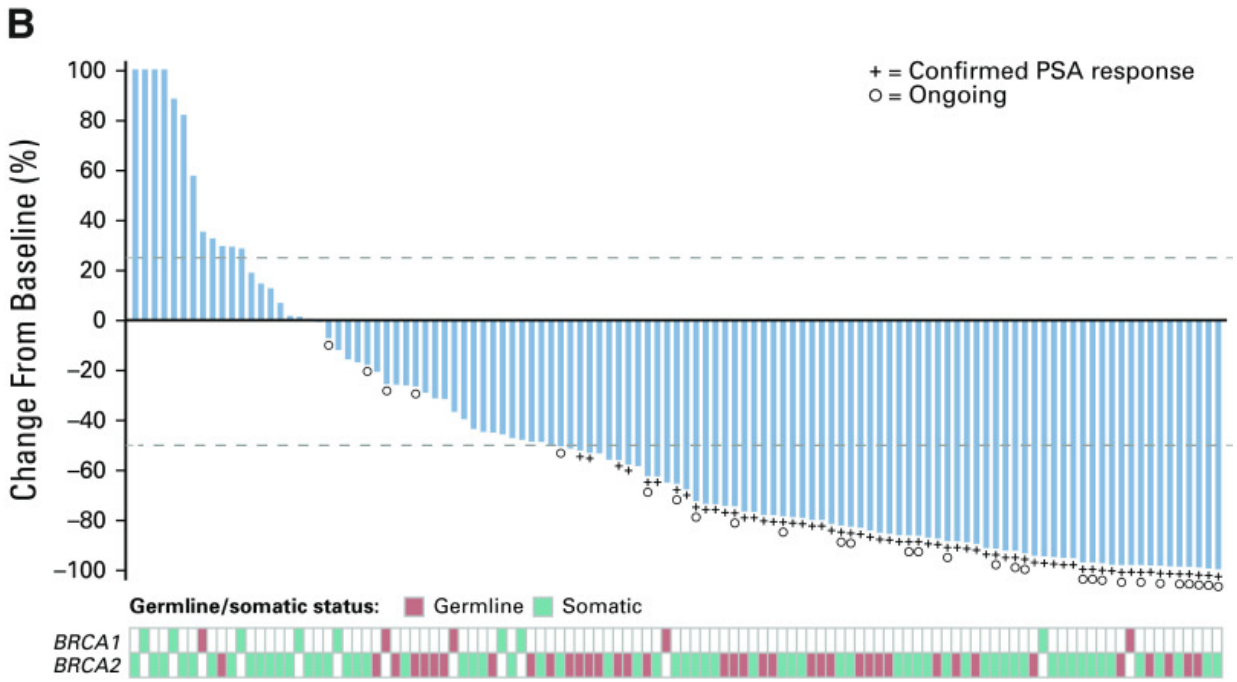
- Open-label, phase 2 study: evaluated safety and efficacy of rucaparib in men with mCRPC associated with DDR deficiency
- Included patients who progressed after one to two lines of next-generation androgen receptor–directed therapy and one taxane-based chemotherapy
- Patients screened for presence of a deleterious somatic or germline alteration in *BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D*, or *RAD54L* via central genomic testing of plasma or tumor tissue or by local testing
- Oral rucaparib 600 mg given twice daily
- Until confirmed radiographic disease progression, assessed by investigator
- Primary endpoint: ORR (radiographic or PSA)

Abida W, et al. *J Clin Oncol.* 2020;38(32):3763–3772.

TRITON2: Rucaparib

Best change from baseline in (A) sum of target lesion(s) in the independent radiology review–evaluable population and in (B) PSA in the overall efficacy population.





ORRs per independent radiology review 43.5% (95% CI, 31.0% to 56.7%; 27 of 62 patients).
PSA response rate 54.8% (95% CI, 45.2% to 64.1%; 63 of 115 patients).

Abida W, et al. *J Clin Oncol.* 2020;38(32):3763–3772.

TRITON2: Other Genes

TRITON2 enrolled 78 patients with a non-*BRCA* DDR gene alteration

ATM (*n* = 49), *CDK12* (*n* = 15), *CHEK2* (*n* = 12), and other DDR genes (*n* = 14)

Radiographic and PSA responses:

ATM [2/19 (10.5%) radiographic and 2/49 (4.1%) PSA],
CDK12 [0/10 (0%) radiographic and 1/15 (6.7%) PSA]
CHEK2 [1/9 (11.1%) radiographic and 2/12 (16.7%) PSA]

No radiographic or PSA responses in 11 patients with *ATM* germline mutations.

Responses were observed in patients with alterations in the DDR genes *PALB2, FANCA, BRIP1*, and *RAD51B*.

Abida W, et al. *CCR, 2020*

Talazoparib monotherapy in mCRPC with DNA repair alterations (TALAPRO-1): an open-label, phase 2 trial

- Talazoparib inhibits PARP catalytic activity and most efficient PARP1/2 trapping on DNA single-strand break sites
- DDR-HRR gene alterations

  ATM, *ATR*, *BRCA1*, *BRCA2*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, *RAD51C*
- Post ARPI and taxane chemotherapy
- 128 pts ORR 29.8% (31 of 104 patients; 95% CI 21·2–39·6)
- ORR 46% in BRCA1/2, ORR 25% in PALB2, ORR 12% in ATM pts
  - 2 pts with ATM mutation responded – both pts had homozygous loss
- PSA ≥50% decline: 46% in all pts, PSA ≥50% decline: 66% in BRCA1/2 pts

De bono et al, Lancet Oncol 2021

GALAHAD: A phase II study of niraparib in patients with mCRPC and biallelic DNA-repair gene defects

- DDR-HRR gene alterations
- *Required biallelic* alterations in *BRCA1/2 (BRCA cohort) or ATM, FANCA, PALB2, CHEK2, BRIP1, HDAC2 (non-BRCA cohort)*
- *Monoallelic allowed if germline*
- Post ARPI and taxane chemotherapy
- 223 patients included in the overall efficacy analysis population, which included *BRCA* (n=142) and non-*BRCA* (n=81) cohorts
  - BRCA alterations- ORR was 34%, median duration of response 6.2 mo, rPFS 8.08 mo, OS as 13 mo
  - non-BRCA - ORR 10.6%, rPFS 3.7 mo, OS 9.63 mo
- On October 3, 2019, the FDA granted breakthrough therapy designation to niraparib for the treatment of men with BRCA1/2-mutant mCRPC who have previously received taxane-based chemotherapy and an androgen receptor (AR) inhibitor

Smith et al, Lancet Oncol 2022

Sequencing Implications of PARP Inhibitors

- PARP inhibitors: SOC for select group of patients with DNA-repair defects
  - Especially for *BRCA2*, and likely *BRCA1*, *PALB2*, *FANCA*
  - Less pronounced for *ATM*, *CDK12* , data still emerging for other variants
  - Could functional readouts or mutational signatures complement genomics?
- Platinum also may be an option- exceptional responses may be seen (particularly for *BRCA2*)
- *Do PARP inhibitors work in earlier stages of the disease (mHSPC)?*
- *Do PARP inhibitors potentiate benefits of AR inhibition in patients without DNA repair defects?*

Abida et al *PNAS*. 2020; Mateo et al. *Eur Urol.* 2018; Thoma C. *Nat Rev Urol.* 2020;17:432; Jang A, et al. *Cancers.* 2020;12:3467; Schmidt et al, *JAMA Netw Open.* 2020.

Tumor Testing Considerations for Homologous Recombination Genes

Primary tumor
- Advantages: non-invasive, HRD alterations tend to be early events
- Disadvantages: tissue quality (in PROfound, quality control failures in 31%), heterogeneity

Metastatic tumor
- Advantages: captures acquired alterations and tissue phenotype (eg., neuroendocrine)
- Disadvantages: invasive, bone metastatic biopsies for NGS are challenging

Liquid biopsy (ctDNA)
- Advantages: non-invasive, reflects matched tumor biopsy
- Disadvantages: dependent on tumor content, deletions (eg, *BRCA2*) not as robust as mutations, can be confounded by clonal hematopoiesis (particularly for *ATM*)

Germline testing (blood/saliva)
- Noninvasive, family implications, somatic testing should not replace germline

Concordance of DNA Repair Gene Mutations in Paired Primary Prostate Cancer Samples and Metastatic Tissue or Cell-Free DNA

Overall concordance between prostate cancer metastatic biopsy and ctDNA > 80%

- Wyatt et al JNCI 2014, Adalsteinsson et al, Nat Comm 2017

Schweizer et al, JAMA Oncol 2021- 72 men with known DDR alterations

- Concordance of DDR status across primary/met/ctDNA samples was 84%

Tukachinsky et al, CCR 2021- Foundation Medicine ctDNA from 3,334 pts with mCRPC

- Including 1,674 screening samples from rucaparib trials (TRITON 2 and TRITON 3)
- 94% detectable ctDNA (median ctDNA fraction 7.5%)
- 72/837 had *BRCA1/2* mutations in tissue, 67 (93%) also identified by ctDNA
- Did not report copy number alterations (eg., BRCA2 deletions)
- Did detect clonal hematopoiesis (CH) mutations

Clonal Hematopoesis

- Clonal hematopoiesis of indeterminate potential (CHIP) = somatic mutations and clonal expansion of hematopoietic cells (non-tumor derived), occurs in 10-20% of individuals > 70 yrs

- Jensen et al.. Pritchard, JAMA Oncol 2021 – cfDNA of 69 pts with mCRPC
  - CHIP variants at >2% variant fraction in cfDNA from 13/ 69 men (19%; 95% CI, 10%-30%).
  - **7 men (10%; 95% CI, 4%-20%) had CHIP variants in DNA repair genes, including ATM (n = 5), BRCA2 (n = 1), and CHEK2 (n = 1).**
  - Overall, CHIP variants accounted for almost half of the somatic DNA repair gene variants detected.
  - CHIP interference variants could be distinguished from prostate cancer variants using a paired whole-blood control

Case Presentation

59 yo with mCRPC s/p abiraterone, docetaxel, Lu-PSMA-617, Act-PSMA-225. Sequencing of ctDNA BRCA2 mutation, primary tumor c/w biallelic BRCA2 loss (mutation+ deletion)

4/2/21 started on olaparib 200 mg BID (dose reduced due to low counts)
4/2/21: PSA 653.70 ng/ml,

4/7/21: PSA 703 ng/ml

4/21/21: PSA 783 ng/ml

4/28/21: PSA 655.70 ng/ml

5/26/21: PSA 361.90 ng/ml

7/2021: PSA 147 ng/ml

8/18/21: PSA 110.90 ng/ml counts improved on therapy, feels better (energy, pain)

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7/2021: PSA 147 ng/ml

8/18/21: PSA 110.90 ng/ml counts improved on therapy, feels better (energy, pain)

Now- PSA 285.40– new cord compression

Circulating tumor DNA

Biomarker Findings

Blood Tumor Mutational Burden - 20 Muts/Mb
Microsatellite status - MSI-High Not Detected
Tumor Fraction - 37%

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

BRCA2 N1718_E1912del, D1476_D1868>ERTK, D1807_E1811del, V1681_S2152del, E1812Q, S1733_L1904del, K1783_D2005>H, L1768_K1823del, E1812Y, D1807_K1872del, E1812K, V1804_I1831del, E1812*, splice site 4674_6841+206>ATACA, rearrangement exon 11, deletion exon 11

PTEN loss

EGFR E1079*

TMPRSS2 TMRSS2-ERG fusion

BCORL1 W1468*

DNMT3A F414fs*237

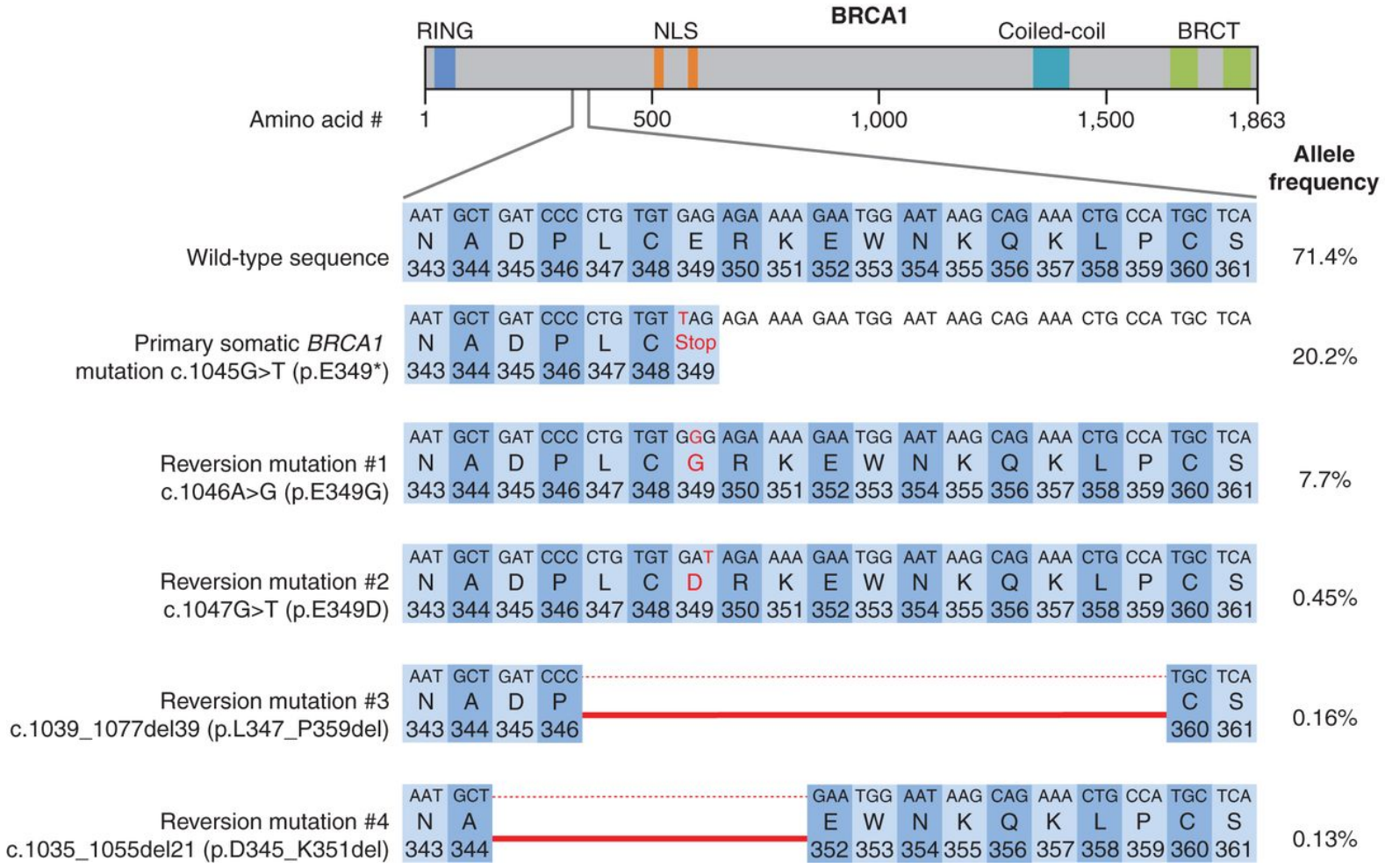
RAD51 deletion exon 4

SPEN rearrangement exon 11

GENOMIC FINDINGS		VAF %
BRCA2 -	N1718_E1912del	0.12%
	D1476_D1868>ERTK	0.32%
	D1807_E1811del	0.35%
	V1681_S2152del	0.18%
	E1812Q	0.98%
	S1733_L1904del	0.63%
	K1783_D2005>H	1.4%
	L1768_K1823del	0.45%
	E1812Y	5.3%
	D1807_K1872del	0.16%
	E1812K	4.4%
	V1804_I1831del	1.7%
	E1812*	22.3%
	splice site 4674_6841+206>ATACA	0.15%
	rearrangement exon 11	0.12%
	deletion exon 11	1.3%

16 NEW BRCA2 mutations!

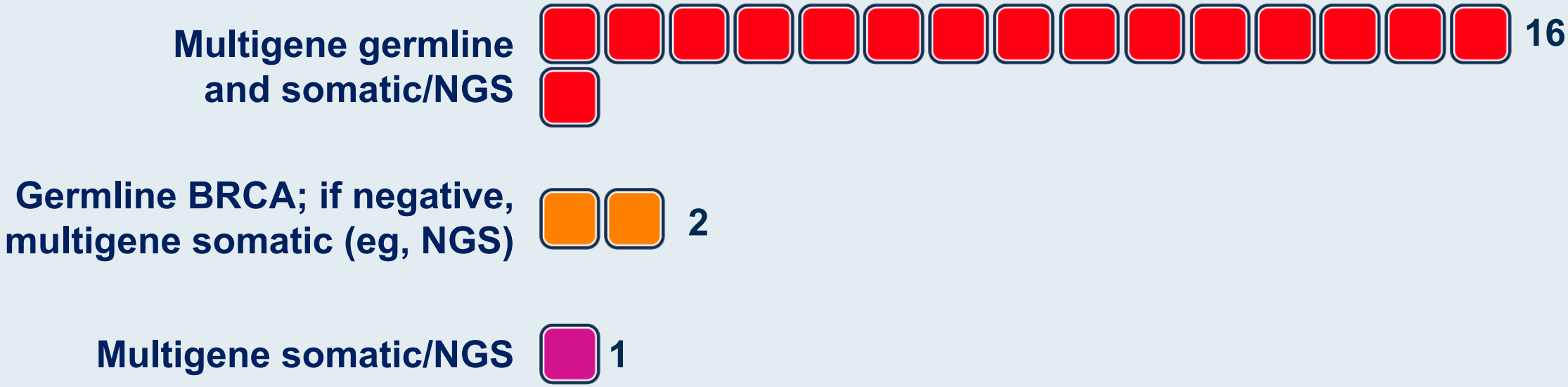
Reversion mutations are **secondary mutations**, often small deletions, in a mutant BRCA1/2 allele that convert the initial frameshift mutation into an in-frame internal deletion that produces a partly functional protein product.



Lin et al. Cancer Discov 2019;9:210-219

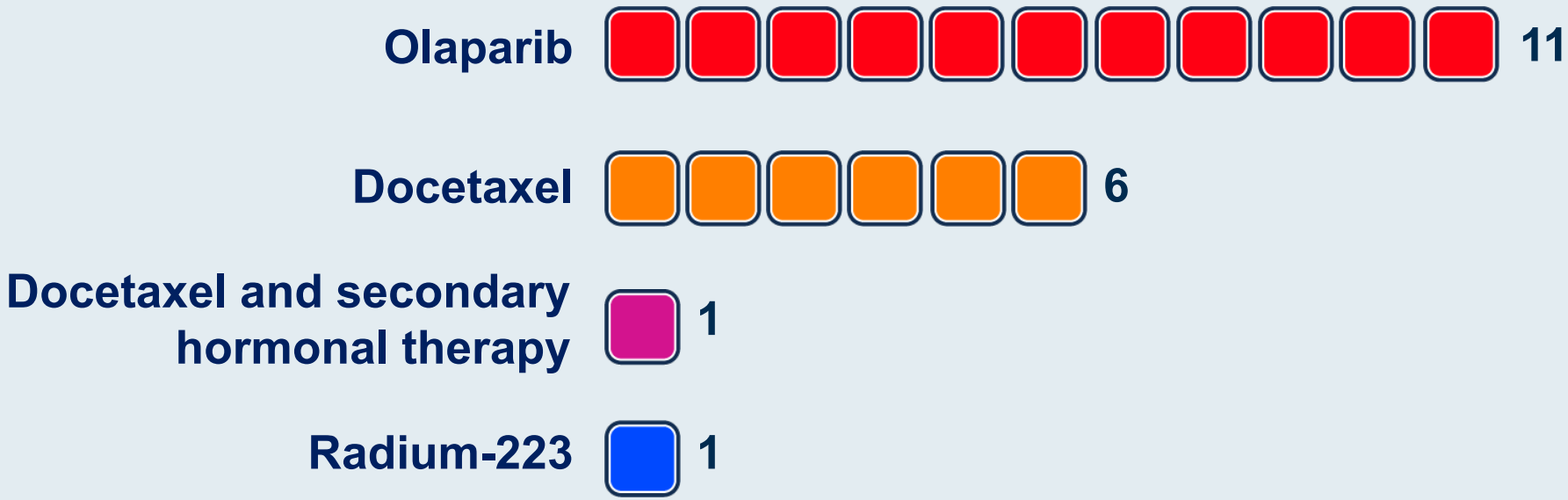
Clinical Investigator Survey Results

In general, what is the optimal approach to mutation testing for possible use of a PARP inhibitor for a patient with mCRPC?



Survey of genitourinary cancer clinical investigators

A 65-year-old man with a germline BRCA2 mutation who is receiving ADT and enzalutamide for HSPC metastatic to the bone develops new high-volume symptomatic bone metastases. Regulatory and reimbursement issues aside, what systemic treatment would you most likely recommend?



Survey of genitourinary cancer clinical investigators

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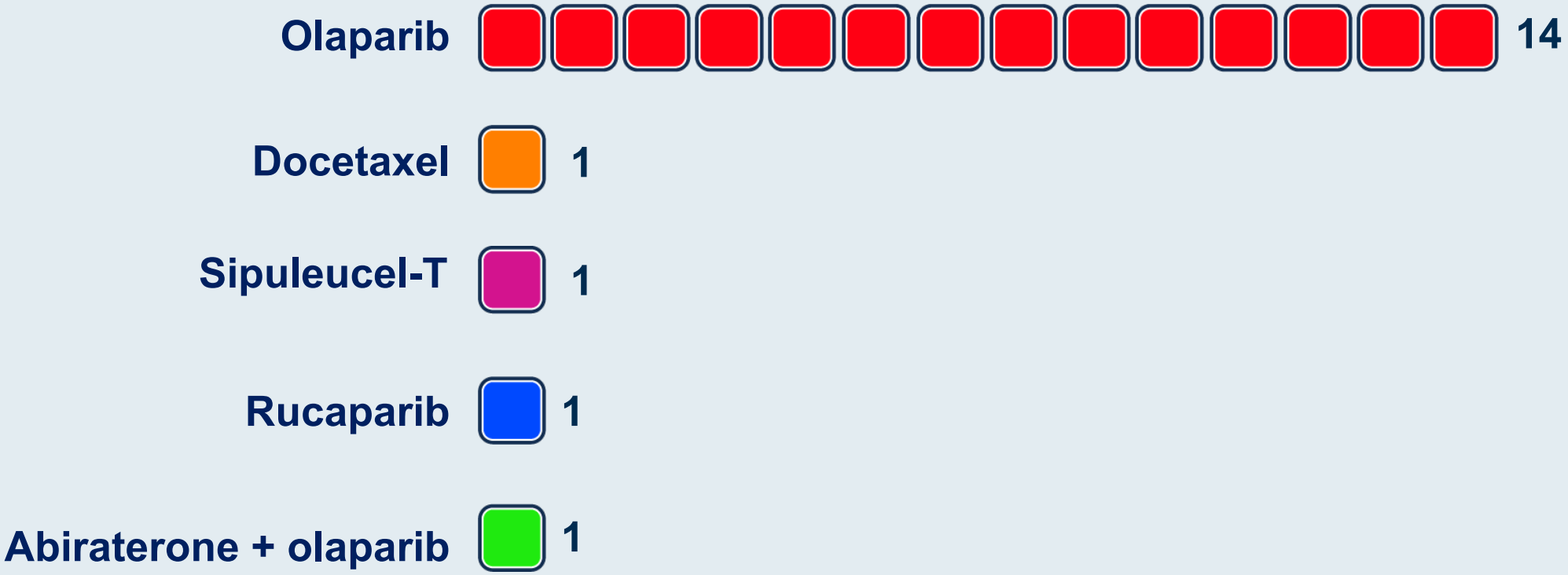
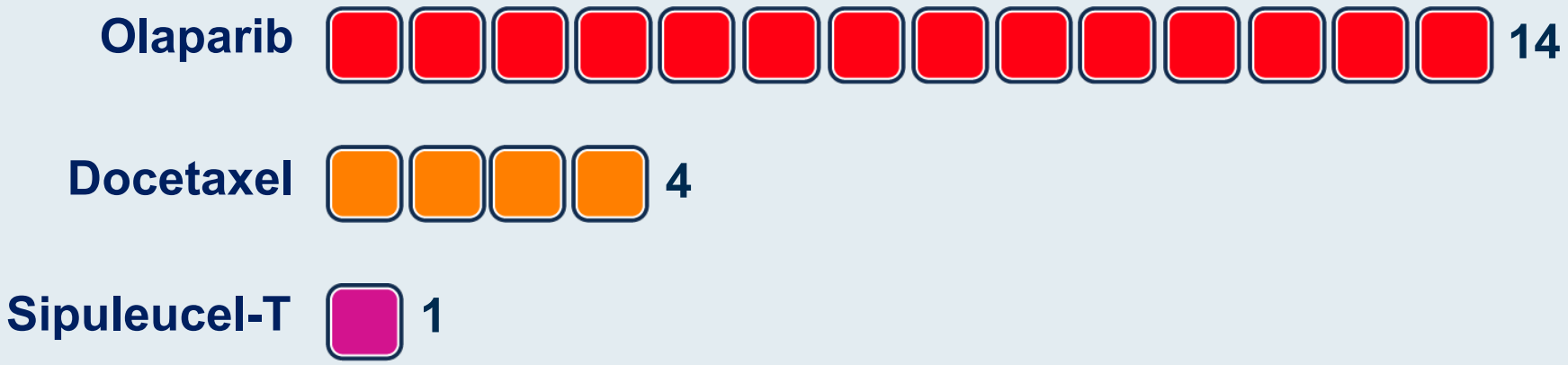


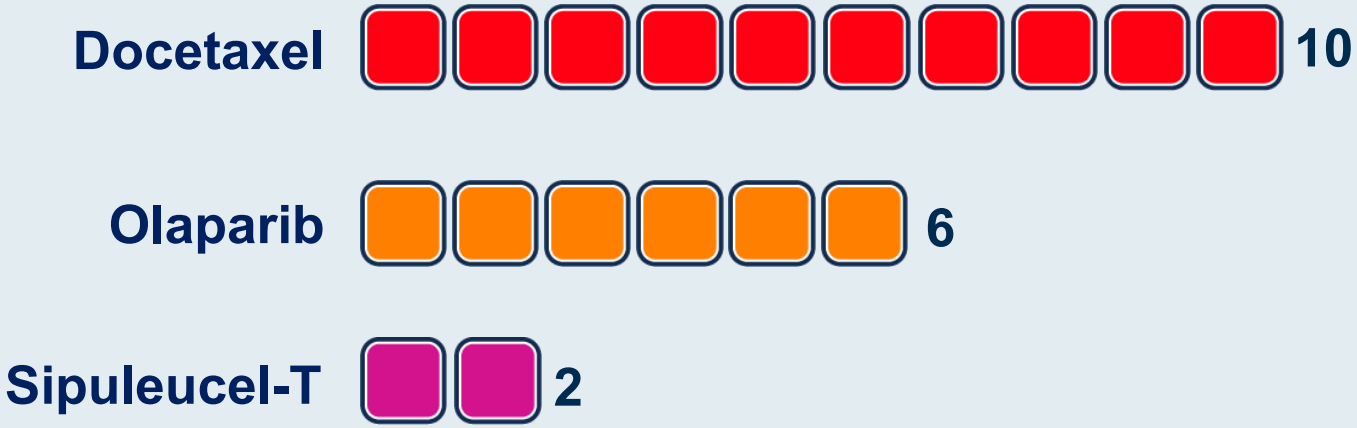
Survey of genitourinary cancer clinical investigators

A 65-year-old man with a germline PALB2 mutation presents with minimally symptomatic prostate cancer metastatic to the bone and receives enzalutamide and ADT with response followed by progression. Regulatory and reimbursement issues aside, what would you recommend?



Survey of genitourinary cancer clinical investigators

A 65-year-old man with a germline ATM mutation presents with minimally symptomatic prostate cancer metastatic to the bone and receives enzalutamide and ADT with response followed by progression. Regulatory and reimbursement issues aside, what would you recommend?



Survey of genitourinary cancer clinical investigators

MODULE 4: Available Data with, Ongoing Investigation of and Potential Future Role of PARP Inhibitor-Based Combinations — Dr Bryce

MAYO CLINIC

PARP+ IN PROSTATE CANCER:
TOWARDS COMBINATION THERAPIES

Alan H. Bryce, MD
Chair, Division of Hematology and Medical Oncology
Chair, Genitourinary Disease Group
Mayo Clinic

Dr Bryce — Disclosures

Advisory Committee	Merck
Contracted Research	Janssen Biotech Inc

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EARLY DATA ON PARP + 2ND GEN ANDROGEN PATHWAY INHIBITORS

Rationale: 1) PARP inhibition and AR pathway inhibition are distinct approaches to prostate cancer therapy with largely non overlapping toxicity
2) AR signaling regulates DNA repair in prostate cancer cells[1], with potential for synergy[2]

Clinical trials	Phase	Clinical disease setting	Treatment arm	Control arm	Patients	Primary takeaways (if any)
Clarke N, et al.[3] NCT0197221	2	mCRPC patients who had prior chemotherapy (not more than 2) and were candidates for novel hormonal therapy No genetic selection	Olaparib + Abiraterone	Placebo+ Abiraterone	171	**rPFS** - 13.8 mo vs. 8.2 mo (HR: 0.65; 95% CI: 0.44-0.97) **OS** - 22.7 mo vs. 20.9 mo (HR: 0.91; 95% CI: 0.60-1.38)
Saad F, et al.[4] NCT02924766	1b	mCRPC patients who had 1-line of prior taxane-based chemotherapy and at least 1-line prior NHT (apalutamide or abiraterone) No genetic selection	Niraparib + Abiraterone or Niraparib + Apalutamide	Not applicable	33	Niraparib + Abiraterone was tolerable with no new safety signals. RP2D: Niraparib 200mg/d

1. POLKINGHORN W, ET AL. CANCER DISCOVERY 2013 NOV;3 (11):1245-53. DOI: 10.1158/2159-8290.CD-13-0172
2. ASIM M, ET AL. NATURE COMMUNICATIONS 2017 AUG; 8:374. https://doi.org/10.1038/s41467-017-00393-y
3. CLARKE N, ET AL. . LANCET ONCOL. 2018 JUL;19(7):975-986. DOI: 10.1016/S1470-2045(18)30365-6
4. SAAD F, CET AL. CANCER CHEMOTHER PHARMACOL. 2021 JUL;88(1):25-37. DOI: 10.1007/S00280-021-04249-7.

PROPEL

- Abiraterone with olaparib or placebo in a genetically unselected population
  - Serum Collected for cfDNA on all patients
  - **No tissue genetic testing**
- All patients submitted tissue for NGS
- Primary outcome: rPFS- data presented today
- Secondary outcome: OS- not yet mature

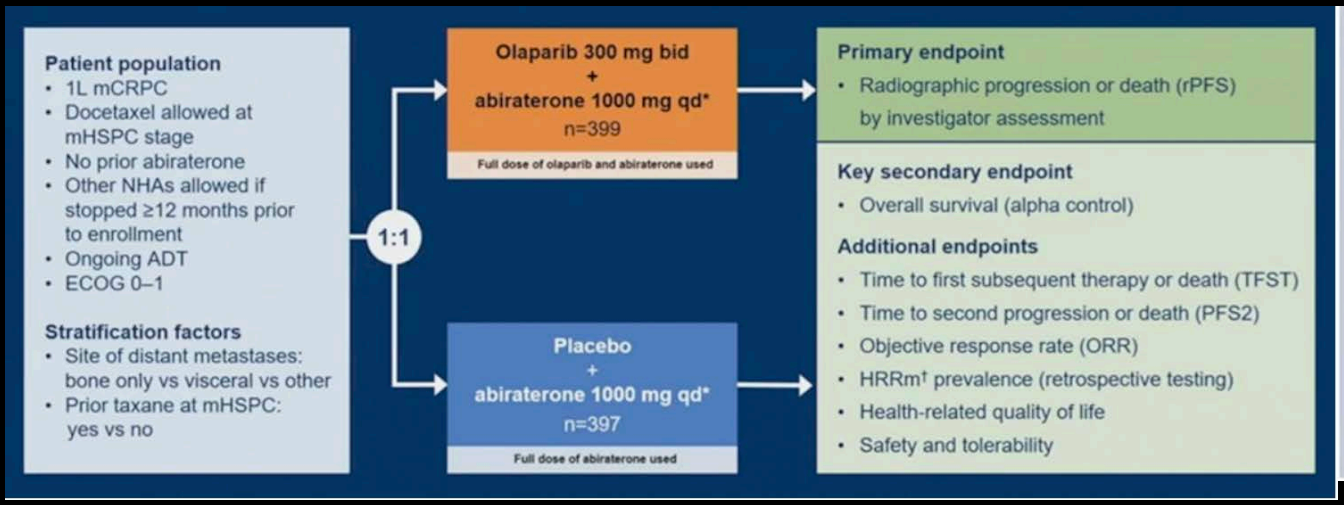
	Olaparib + abiraterone (n=399)	**Placebo + Abiraterone (n=397)**
Events, n (%)	157 (39.3%)	218 (54.9)
Median rPFS (mos)	27.6	16.4
HR (95% CI)	0.61 (0.49-0.74) P<0.0001	
HRR mut (n=226) HR (95% CI)	0.50 (0.34-0.73)	
Non-HRR mut (n=552) HR (95% CI)	0.76 (0.60-0.97)	

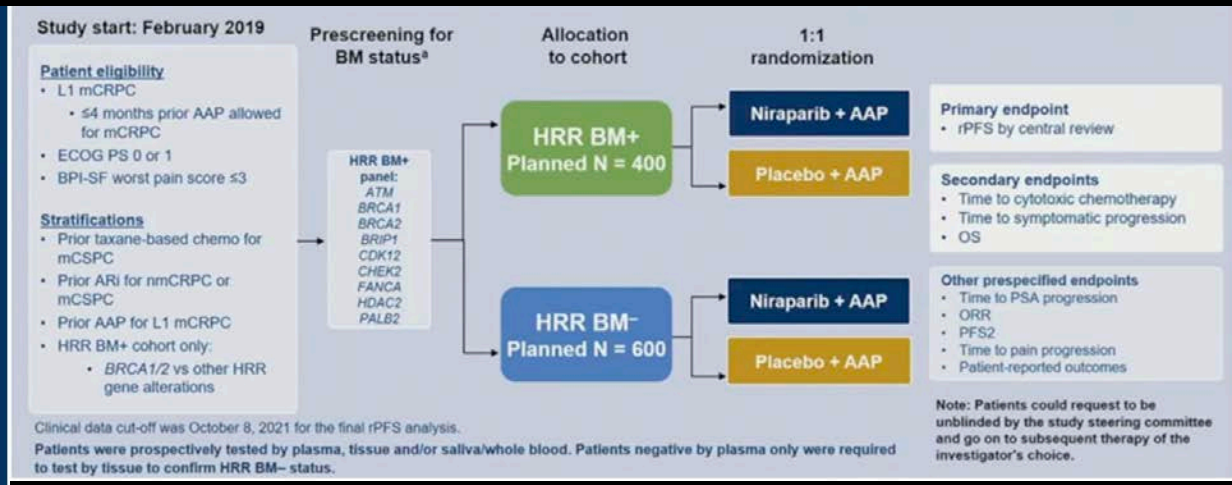
MAGNITUDE

- Abiraterone with or without niraparib in the pre chemotherapy setting
- 765 patients
- **Tissue and Serum for genetic testing required for entry to study**
- HRR gene alteration as follows:
  - **Cohort 1: positive for HRR gene alteration**
    - **population for presented data**
  - Cohort 2: not positive for DRD
    - Halted for futility
- Primary outcome: rPFS
- Secondary outcome: **OS not yet mature**

Cohort 1: HRR mutated

	Niraparib + abiraterone (n=399)	Placebo + Abiraterone (n=397)
Number	212	211
Median rPFS (mos)	16.5	13.7
HR (95% CI)	0.73 (0.56-0.96) P=0.0217	





PROpel		
Eligiblity criteria	Taxane -based chemotherapy allowed in mCSPC	
	No prior AAP allowed	
	Other NHT allowed in mCSPC if stopped more than year prior to enrollment	
HRR testing	ctDNA	
Arms	OLA+AAP	PBO+AAP
Events	168 (42.1%)	226 (56.9%)
Median rPFS	24.8	16.6
HRR+	111 (28%)	115 (29%)
BRCA mutations	Not reported	Not reported

MAGNITUDE		
Eligiblity criteria	Taxane -based chemotherapy allowed in mCSPC	
	Up to 4 months of AAP for mCRPC allowed	
	Prior NHT allowed for nmCRPC or mCSPC	
HRR testing	Tumor-based (negative cfDNA confirmed by tissue)	
Arms	NIRA+AAP	PBO+AAP
Events	NR	NR
Median rPFS	16.6	10.9
HRR+	212 (100%)	211 (100%)
BRCA mutations	98 (46.2%)	92 (43.6%)

Ongoing Phase 3 trials of PARP inhibitors with secondary hormonal agents in mCRPC and mHSPC

Clinical trials		Phase	Comparison	Population	Enrollment	Primary endpoint
AMPLITUDE	**NCT04497844**	3	Niraparib + Abiraterone vs. Placebo + Abiraterone	**mHSPC**	788	rPFS
TALAPRO-3	**NCT04497844**	3	Talazoparib + Enzalutamide vs Placebo + Enzalutamide	**mHSPC**	550	rPFS
TALAPRO-2	**NCT03395197**	3	Talazoparib + Enzalutamide vs. Placebo + Enzalutamide	mCRPC (1st line)	1038	rPFS
CASPAR	**NCT04455750**	3	Rucaparib + Enzalutamide vs. Placebo + Enzalutamide	mCRPC (1st line)	1002	rPFS + OS

PARP INHIBITORS IN COMBINATION WITH IMMUNE CHECKPOINT INHIBITORS

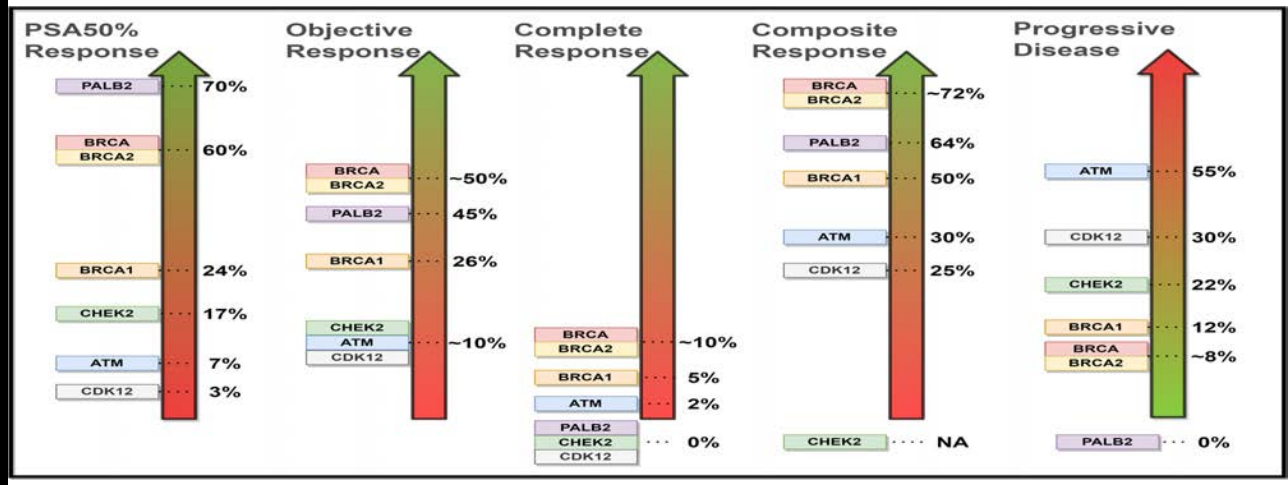
- Rationale: 1) In preclinical models of various solid tumors, PARP inhibitors were found to activate cytotoxic T cells, upregulate immune checkpoint expression, sensitize tumor cells to natural killer cell–killing, and increase proinflammatory signaling.[1-3]
- 2) PARP inhibitors have been shown to upregulate PDL1 expression in breast cancer models[4]

Clinical trials	Phase	Clinical disease setting	Treatment arm	Genotype	Patients	Primary takeaways (if any)
KEYNOTE-365 (cohort A)[5] NCT02861573	2	Docetaxel-pretreated mCRPC (≤2 2nd gen API)	Pembrolizumab + Olaparib	unselected	85	ORR: 8%
NCT02484404[6]	2	Post-2nd gen API mCRPC	Durvalumab + Olaparib	unselected	17	Radiographic and/or PSA ORR: 53%
Checkmate 9kd (Cohort A1)[7] NCT03338790	2	mCRPC treated with 1-2 prior taxanes (≤2 2nd gen API)	Nivolumab + Rucaparib	HRD(+) and HRD(-)	88	ORR: Total = 10.3% HRD+ = 17.2% (n=45)
Checkmate 9kd (Cohort A2)[8] NCT03338790	2	mCRPC treated with ≤2 2nd gen API, no prior chemo	Nivolumab + Rucaparib	HRD(+) and HRD(-)	71	ORR: Total = 15.4% HRD+ = 25% (n=20)

1. Fenerty KE, et al.. *J Immunother Cancer*. 2018;6(1):133. doi:10.1186/s40425-018-0445-4
2. Huang J, et al. *Biochem Biophys Res Commun*. 2015;463(4):551-556. doi:10.1016/j.bbrc.2015.05.083
3. Sen T et al. *Cancer Discov*. 2019;9(5):646-661. doi:10.1158/2159-8290.CD-18-1020
4. Jiao S, Xia W,, et al. *Clin Cancer Res*. 2017;23(14):3711-3720. DOI: 10.1158/1078-0432.CCR-16-3215
5. Yu EY, et al. *J Clin Oncol*. 2020;38(6_suppl):100-100. doi:10.1200/JCO.2020.38.6_suppl.100
6. Karzai F, et al. *J Immunother Cancer*. 2018;6(1):141. doi:10.1186/s40425-018-0463-2
7. Pachynski R, et al. *Journal of Clinical Oncology* 2021;39(15)S1:5044. DOI:10.1200/JCO.2021.39.15_suppl.5044
8. Petrylak D, et al. Annals of Oncology (2021) 32 (suppl_5): S626-S677. DOI:10.1016/annonc/annonc702

SUMMARY

- PARP inhibitors can be safely combined with many other agents for the treatment of Prostate Cancer
- Rationale exists for synergy with APIs and Checkpoint inhibitors
- The role of PARP in non HRD(+) patients is being studied in many settings (Propel)
  - To Target or not to Target, is that the question

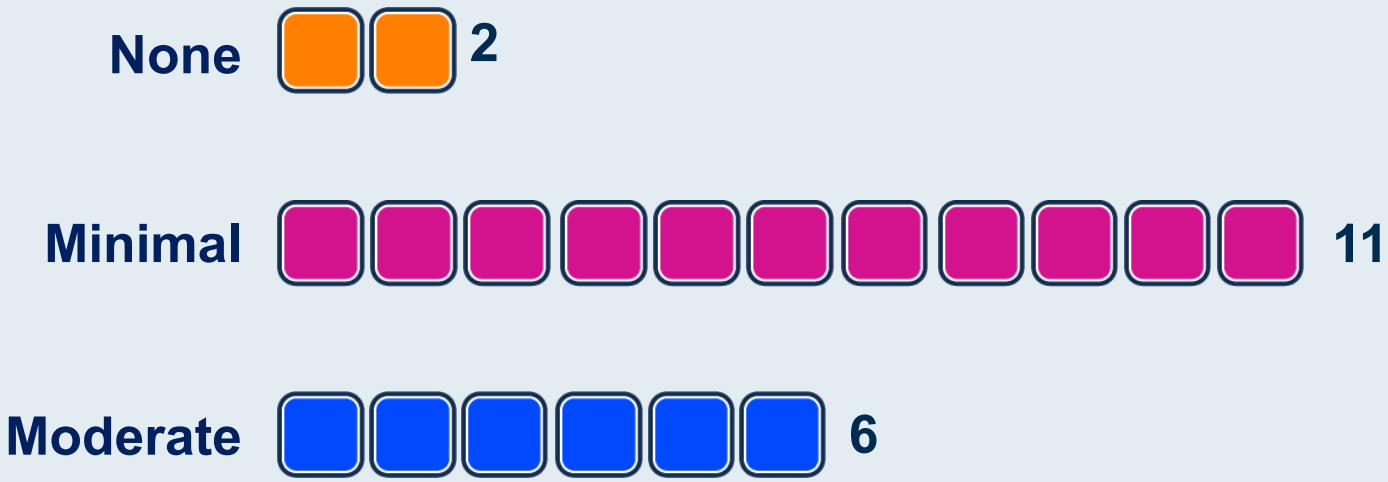


SUMMARY
PROPEL AND MAGNITUDE

- Very Different studies- meaningful cross study comparisons are not possible
- Overall survival data will be critical
  - The studies have not established that concurrent will be better than sequential
  - Prolonged treatment with a myelosuppressive drug can impact later lines of therapy
- Study populations are very different on the basis of prior treatment with 1st generation API in the first line
  - Reflected in the striking difference in rPFS on the control arms
- Method of assessing HRR status is likely to make a difference
- Review of more detailed data in the respective publications will be crucial- what treatments did patients receive for mHSPC?

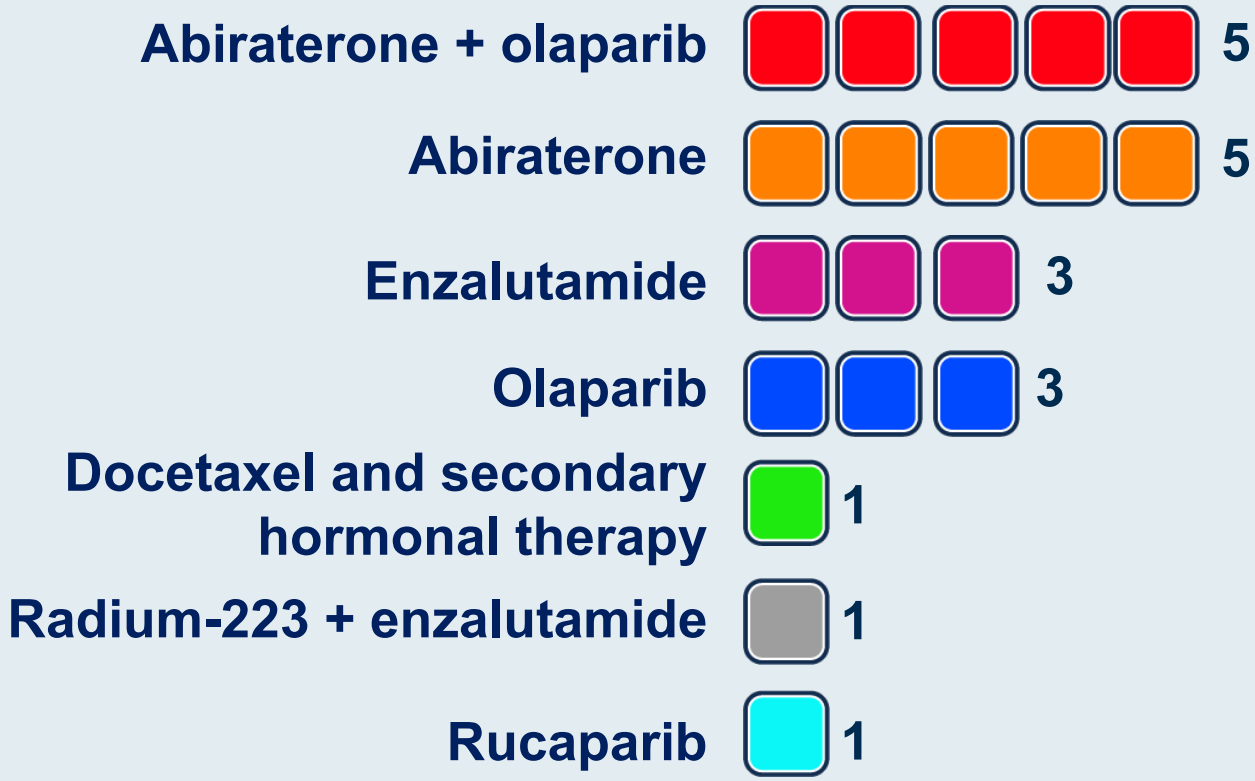
Clinical Investigator Survey Results

How much benefit do you anticipate will be seen in the PROpel and MAGNITUDE studies in patients with BRCA wild-type disease without documented HRR gene mutations?



Survey of genitourinary cancer clinical investigators

A 65-year-old man with a germline BRCA2 mutation who is receiving ADT and docetaxel for HSPC metastatic to the bone develops new high-volume symptomatic bone metastases 1 year after completing chemotherapy. Regulatory and reimbursement issues aside, what systemic treatment would you most likely recommend?

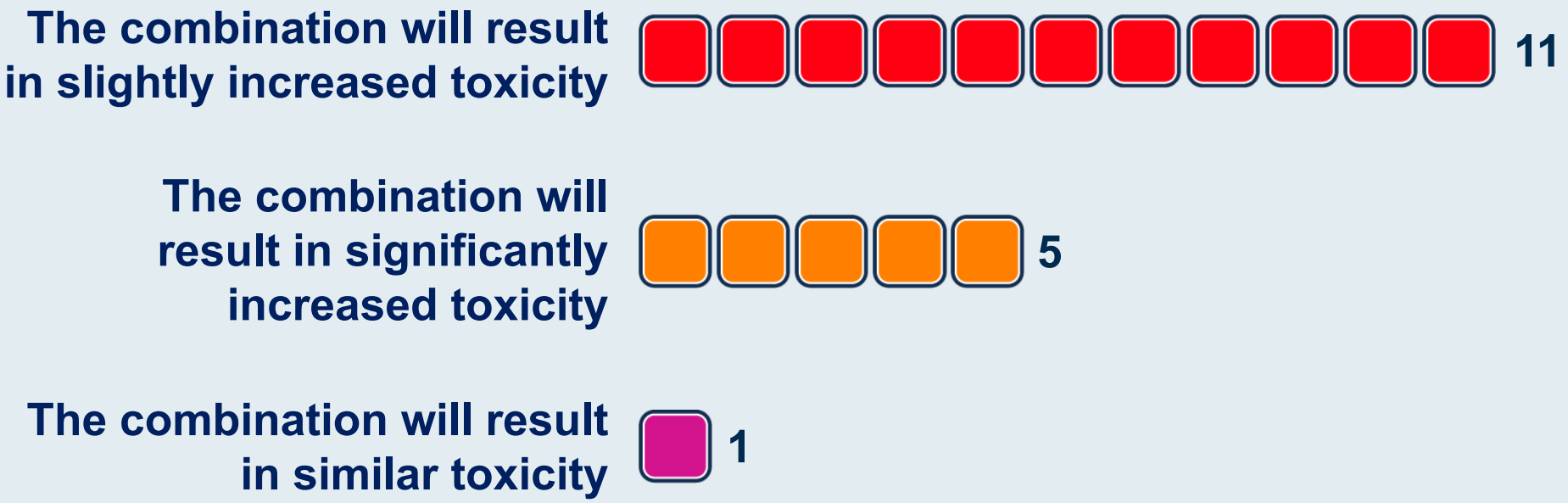


Survey of genitourinary cancer clinical investigators

A 65-year-old man with a germline BRCA2 mutation who is receiving ADT and docetaxel for hormone-sensitive prostate cancer (HSPC) metastatic to the bone develops new low-volume asymptomatic bone metastases 1 year after completing chemotherapy. Regulatory and reimbursement issues aside, what systemic treatment would you most likely recommend?

Survey of genitourinary cancer clinical investigators

Which of the following do you predict regarding the global tolerability/toxicities of a PARP inhibitor combined with a secondary hormonal agent versus what might be expected from either of these approaches alone?



Survey of genitourinary cancer clinical investigators

MODULE 5: Novel Investigational Strategies for Patients with PC — Dr Agarwal

RTP
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Novel Treatment Strategies for Metastatic Prostate Cancer : Immune Checkpoint Inhibitors and AKT inhibitors

Neeraj Agarwal, MD

Professor of Medicine
Senior Director for Clinical Research Innovation, Huntsman Cancer Institute (HCI)
HCI Presidential Endowed Chair of Cancer Research
Director, Center of Investigational Therapeutics
Director, Genitourinary Oncology Program
Huntsman Cancer Institute, University of Utah (NCI-CCC)

Dr Agarwal — Disclosures

Consulting Agreements	Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Calithera Biosciences, Clovis Oncology, Eisai Inc, EMD Serono Inc, Exelixis Inc, Foundation Medicine, Genentech, a member of the Roche Group, Janssen Biotech Inc, Lilly, MEI Pharma Inc, Merck, Nektar, Novartis, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Seagen Inc.

RTP
RESEARCH
TO PRACTICE

Agenda

- Immune checkpoint inhibitors (ICIs)
  - Cabozantinib + atezolizumab combination (Phase 1 Cosmic-021 and ongoing phase 3 Contact-2)
  - Other combinatorial regimens with ICIs
  - Novel Redirected T-Cells-Based Therapies (CART, BITES)

- AKT Inhibitors

Immune Checkpoint Inhibitors Based Combinations

Abstract # LBA24

2021 ESMO congress

Cabozantinib in combination with atezolizumab in patients with metastatic castration-resistant prostate cancer (mCRPC): results of expanded cohort 6 of the COSMIC-021 Study

Neeraj Agarwal,[1] Bradley McGregor,[2] Benjamin L. Maughan,[1] Tanya B. Dorff,[3] William Kelly,[4] Bruno Fang,[5] Rana R. McKay,[6] Parminder Singh,[7] Lance Pagliaro,[8] Robert Dreicer,[9] Sandy Srinivas,[10] Yohann Loriot,[11] Ulka Vaishampayan,[12] Sanjay Goel,[13] Dominic Curran,[14] Ashok Panneerselvam,[14] Li-Fen Liu,[14] Toni K. Choueiri,[2*] Sumanta Pal[3*]

[1]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [2]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [3]City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [4]Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA, USA; [5]Regional Cancer Care Associates, East Brunswick, NJ, USA; [6]University of California San Diego, San Diego, CA, USA; [7]Department of Oncology, Mayo Clinic, Scottsdale, AZ, USA; [8]Department of Oncology, Mayo Clinic, Rochester, MN, USA; [9]University of Virginia Cancer Center, Charlottesville, VA, USA; [10]Division of Medical Oncology, Stanford University Medical Center, Stanford, CA, USA; [11]Department of Cancer Medicine, Gustave Roussy Institute, INSERM 981, University Paris-Saclay, Villejuif, France; [12]Karmanos Cancer Center, Wayne State University, Detroit, MI, USA (Current affiliation: Division of Hematology/Oncology, University of Michigan, Ann Arbor, MI, USA); [13]Department of Medical Oncology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA; [14]Exelixis, Inc., Alameda, CA, USA

*Co-senior authors

Background

- Cabozantinib inhibits tyrosine kinases including MET, VEGF receptors, and TAM family of kinases (TYRO3, MER, and AXL)[1]
- Cabozantinib promotes an immune-permissive environment that may enhance response to immune checkpoint inhibitors[2-4]
- This phase 1b study evaluates cabozantinib in combination with the anti-PD-L1 antibody atezolizumab in various solid tumors including CRPC, RCC, UC, and NSCLC
- Encouraging activity and a tolerable safety profile were observed for the first 44 patients enrolled in mCRPC cohort 6, including in patients with visceral metastases and/or extrapelvic lymphadenopathy,[5] a group with poor prognosis
- Results are reported for extended enrollment in cohort 6 in mCRPC previously treated with enzalutamide and/or abiraterone

[1]Yakes M, Mol Cancer Ther, 2011; [2]Kwilas AR, J Transl Med, 2014; [3]Apolo AB, J Clin Oncol, 2014; [4]Tolaney SM, Oncologist, 2017; [5]Agarwal, J Clin Oncol, 2020;38 (Suppl 15).

Study Design of the Expansion for CRPC Cohort 6

mCRPC
- **Radiographic progression in soft tissue after enzalutamide and/or abiraterone**
- **Measurable disease per RECIST v1.1**
- **ECOG PS 0 or 1**
- **Prior chemotherapy not permitted except docetaxel for mCSPC**

Confirmation of initial results

Cabozantinib 40 mg QD PO + Atezolizumab 1200 mg Q3W IV (N=30) → **First extended enrollment** (N=50) → **Second extended enrollment** (N=50)

Tumor assessments per RECIST v1.1 by the investigator every 6 weeks for the first year and every 12 weeks thereafter; treatment until loss of clinical benefit or intolerable toxicity.

- Primary endpoint: investigator-assessed ORR per RECIST v1.1
- Secondary endpoint: safety including adverse events (AEs) and AEs of special interest (AESIs)
- Exploratory endpoints: PFS, OS, and biomarkers analyses
- Visceral metastases and/or extrapelvic lymphadenopathy (Visc/EPLN) was a key subgroup
- ORR and PFS were also analysed by blinded independent review committee (BIRC)
- Data as of Feb 19, 2021; 132 patients enrolled with a median follow-up of 15.2 mo (range, 5.7–33.9)

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Tumor Response by RECIST v1.1

	ORR per Investigator		ORR per BIRC	
	mCRPC (n=132)	Visc/EPLN mCRPC (n=101)	mCRPC (n=132)	Visc/EPLN mCRPC (n=101)
Objective response rate, % (95% CI)	23 (17, 32)	27 (18, 37)	15 (10, 22)	18 (11, 27)
Best overall response, %				
Complete response	2	2	0	0
Partial response	21	25	15	18
Stable disease	61	61	66	66
Progressive disease	14	11	17	15
Missing	2	1	2	1
Disease control rate,* %	84	88	81	84
Stable disease for ≥24 weeks, %	17	21	27	32
Median duration of response (95% CI), mo	6.9 (4.2, 11.0)	6.9 (4.2, 9.8)	6.9 (4.1, 8.4)	6.9 (4.1, 9.5)
Median time to objective response, mo	1.7	1.7	2.8	2.8

- PD-L1 status (known for 75 patients) did not associate with response

All responses were confirmed; 99% and 93% of patients had measurable disease per investigator and per BIRC, respectively; percentages are calculated from all patients; three patients had complete responses per investigator for mCRPC and two for Visc/EPLN mCRPC; *disease control rate = complete response + partial response + stable disease

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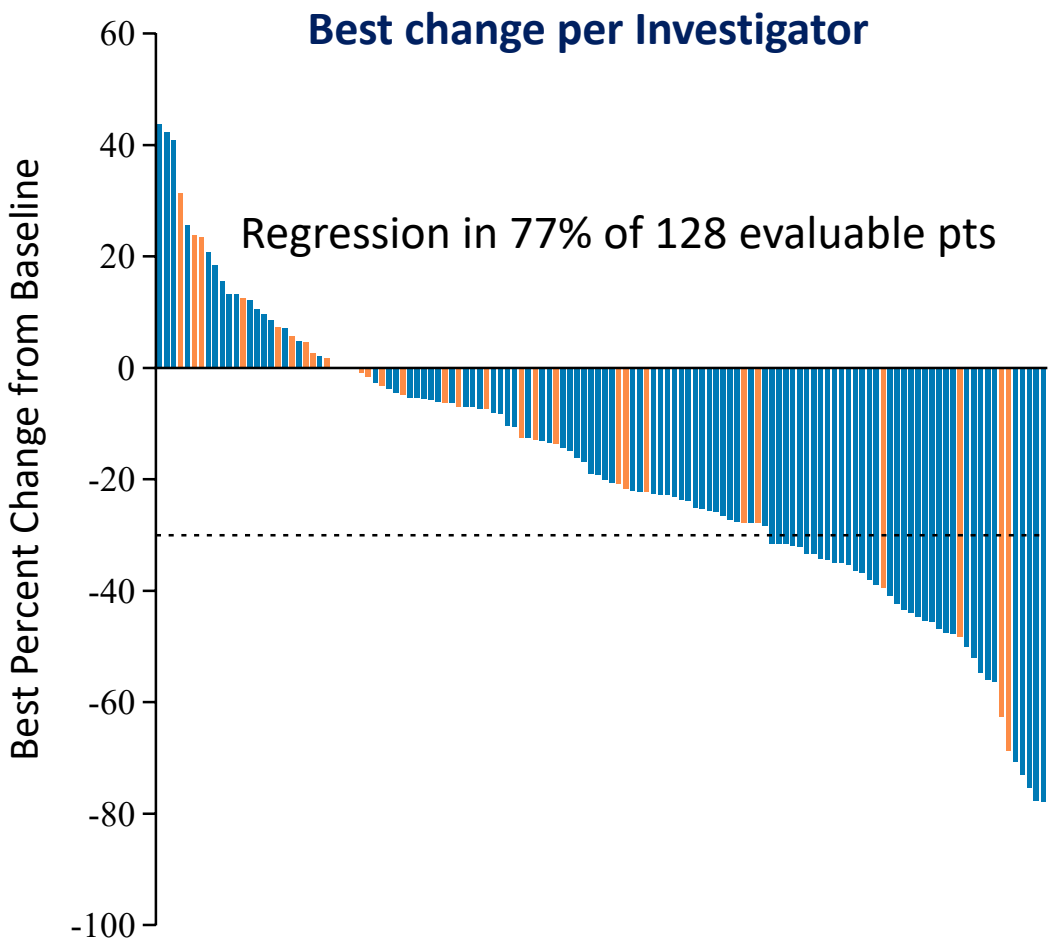
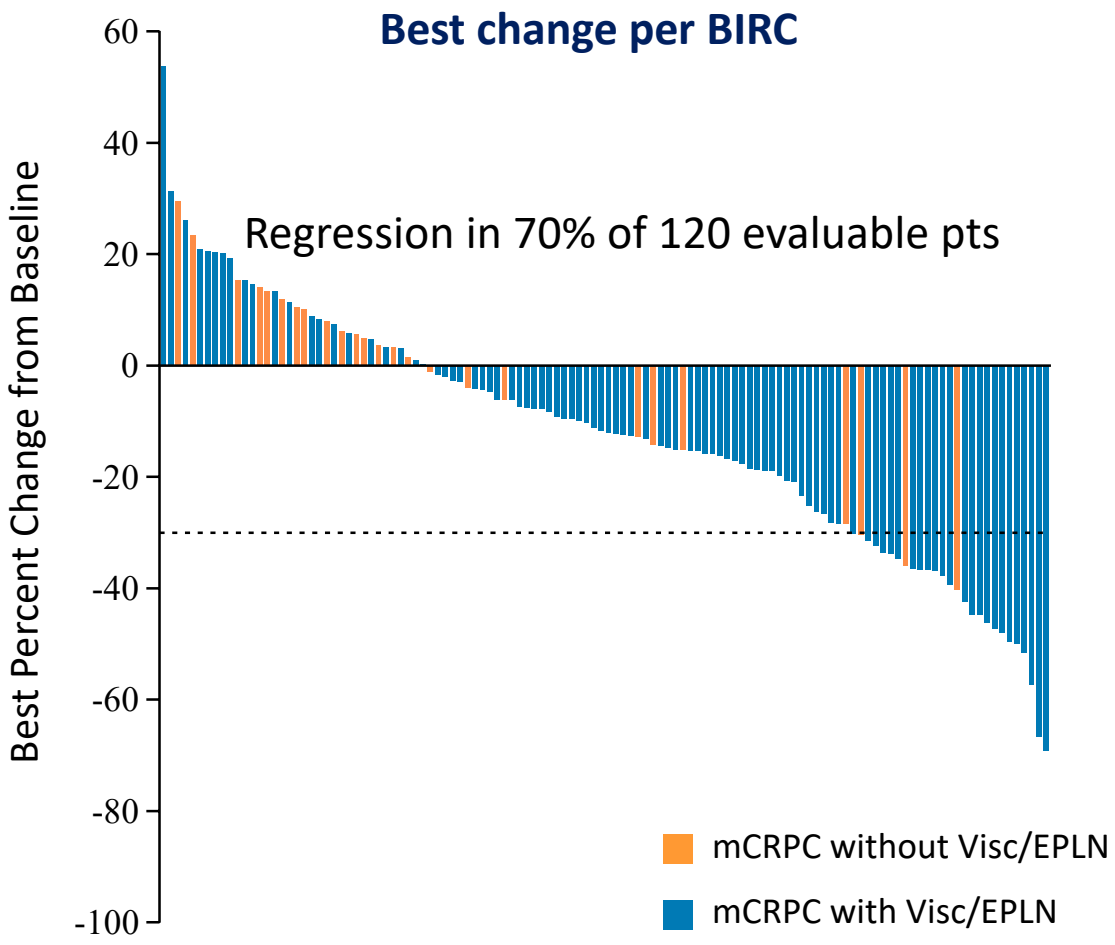
Best Change From Baseline in Sum of Target Lesions





Evaluable patients (pts) had measurable disease and at least one post-baseline scan; the three patients with complete responses per investigator had lymph node metastases as target lesions.

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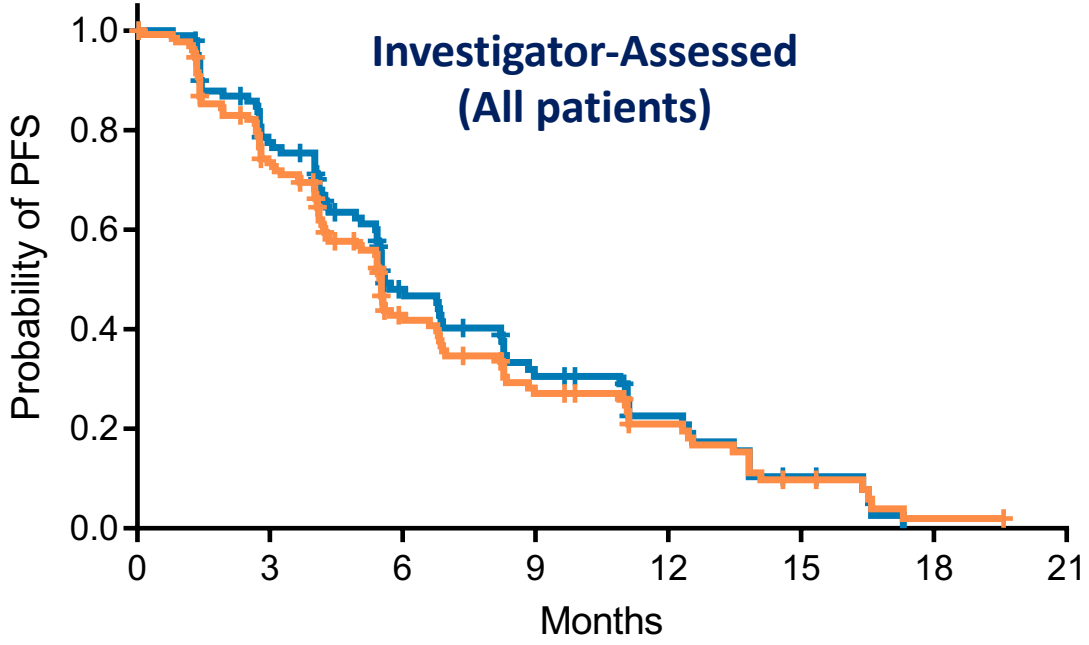
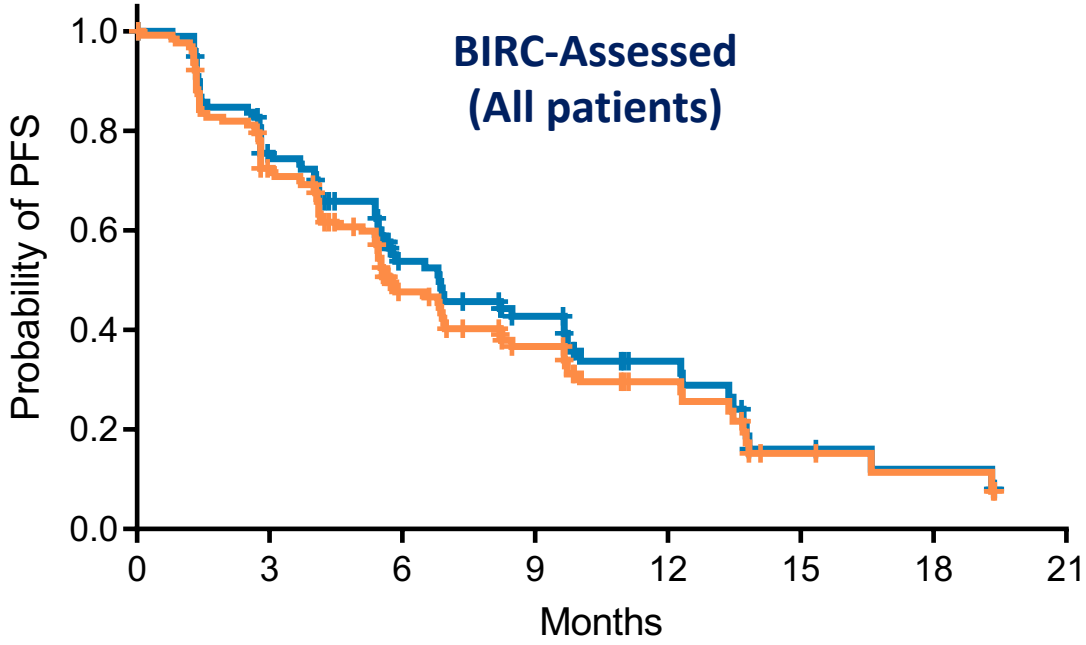
Progression-Free Survival per RECIST v1.1



	N	No. of Events	Median (95% CI), months
All patients	132	101	5.5 (4.3, 6.6)
Visc/EPLN	101	77	5.6 (5.4, 8.2)



	N	No. of Events	Median (95% CI), months
All patients	132	87	5.7 (5.4, 7.0)
Visc/EPLN	101	65	6.8 (5.5, 9.7)

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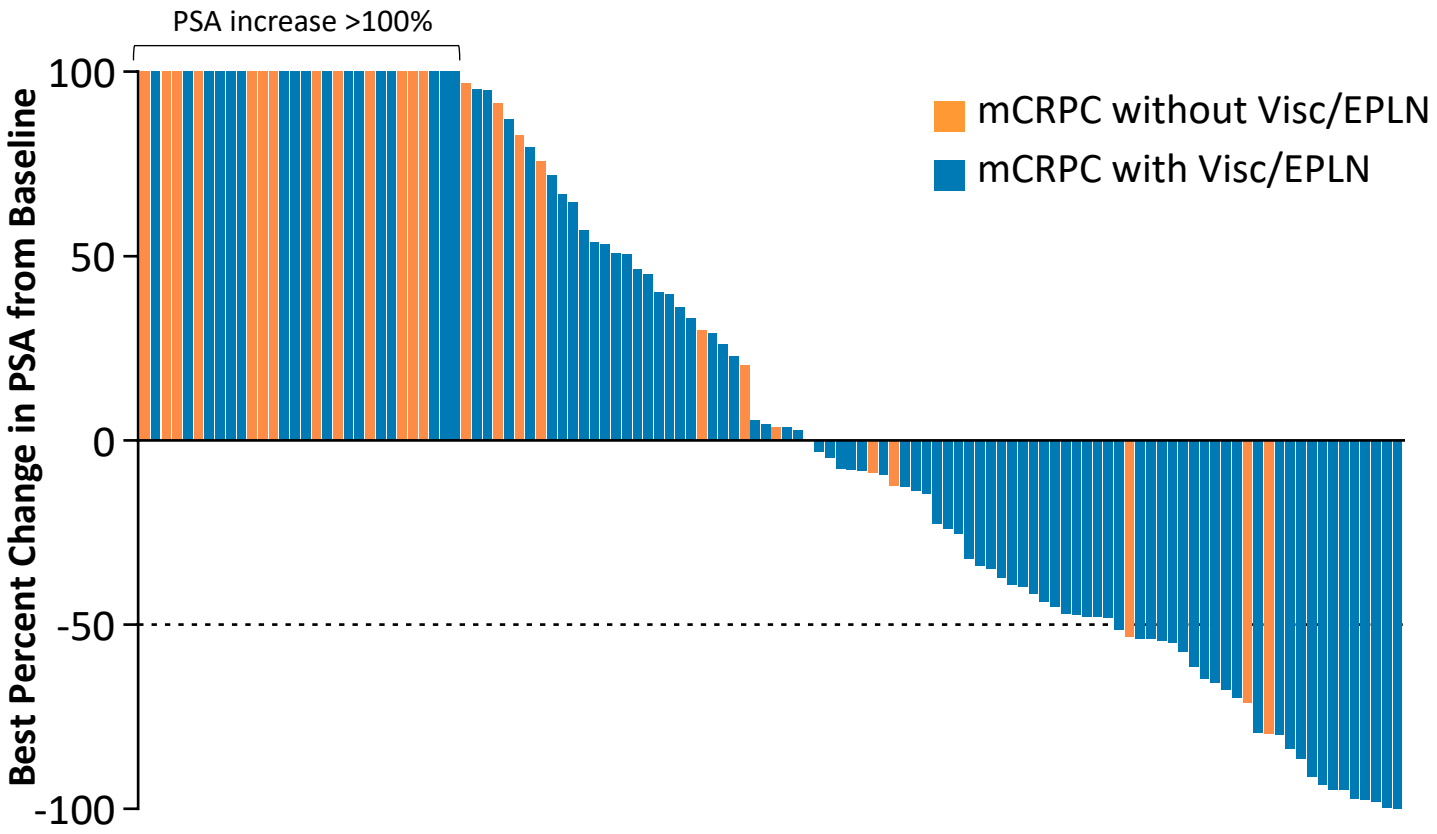
Best Change in Prostate-Specific Antigen From Baseline



- In 118 patients with post-baseline assessments, 55 (47%) had a decrease in PSA, and 27 (23%) had a decrease ≥50%
- In 92 patients with Visc/EPLN, 50 (54%) had a decrease in PSA, and 24 (26%) had a decrease ≥50%

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Treatment-Related Adverse Events in ≥10% of Patients

	mCRPC (N=132)	
	Any Grade	Grade 3/4
Any AE, %	95	55
Diarrhea	55	6.8
Fatigue	43	6.8
Nausea	42	0.8
Decreased appetite	34	1.5
Dysgeusia	27	0
Palmar-plantar erythrodysesthesia	25	2.3
Vomiting	23	1.5
Weight decreased	23	1.5
Aspartate aminotransferase increased	20	3.0
Stomatitis	16	0.8
Hypertension	14	6.8
Alanine aminotransferase increased	14	3
Dysphonia	13	0
Hypothyroidism	12	0
Pulmonary embolism	11	8.3

- Grade 4 treatment-related AEs were experienced by 3%
- There was one treatment-related grade 5 event of dehydration in a 90 year-old patient

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Adverse Events of Special Interest

	mCRPC (N=132)	
	Any Grade	Grade 3/4
Any AESI,* %	66	20
Rash	41	3.0
Hepatitis (diagnosis and lab abnormalities)	29	5.3
Hypothyroidism	15	0
Pancreatitis	14	6.1
Adrenal insufficiency	4.5	2.3
Colitis	3.8	3.0
Hyperthyroidism	3.8	0
Infusion-related reactions	2.3	0.8
Hepatitis (diagnosis)	1.5	0.8
Pneumonitis	1.5	0
Encephalitis	0.8	0.8
Myocarditis	0.8	0.8

- 23 (17%) of patients required high-dose steroids for AEs (defined as ≥ 40 mg of prednisone or equivalent)

*AESIs are potential immune-related events provided by the sponsor and summarized as grouped MedDRA terms irrespective of causality; No grade 5 events were reported.

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Conclusions

- The combination of cabozantinib and atezolizumab demonstrated encouraging clinical activity in patients with mCRPC, confirmed by blinded independent review
- Antitumor activity was maintained in the subgroup of patients with features associated with poor prognosis: visceral disease or distant lymph node metastasis
- The safety profile was manageable, consistent with the previously reported data
- A phase 3 study (CONTACT-02) of cabozantinib plus atezolizumab in mCRPC patients with visceral or extrapelvic lymph node metastasis after one prior NHT is enrolling

NHT; novel hormonal therapy

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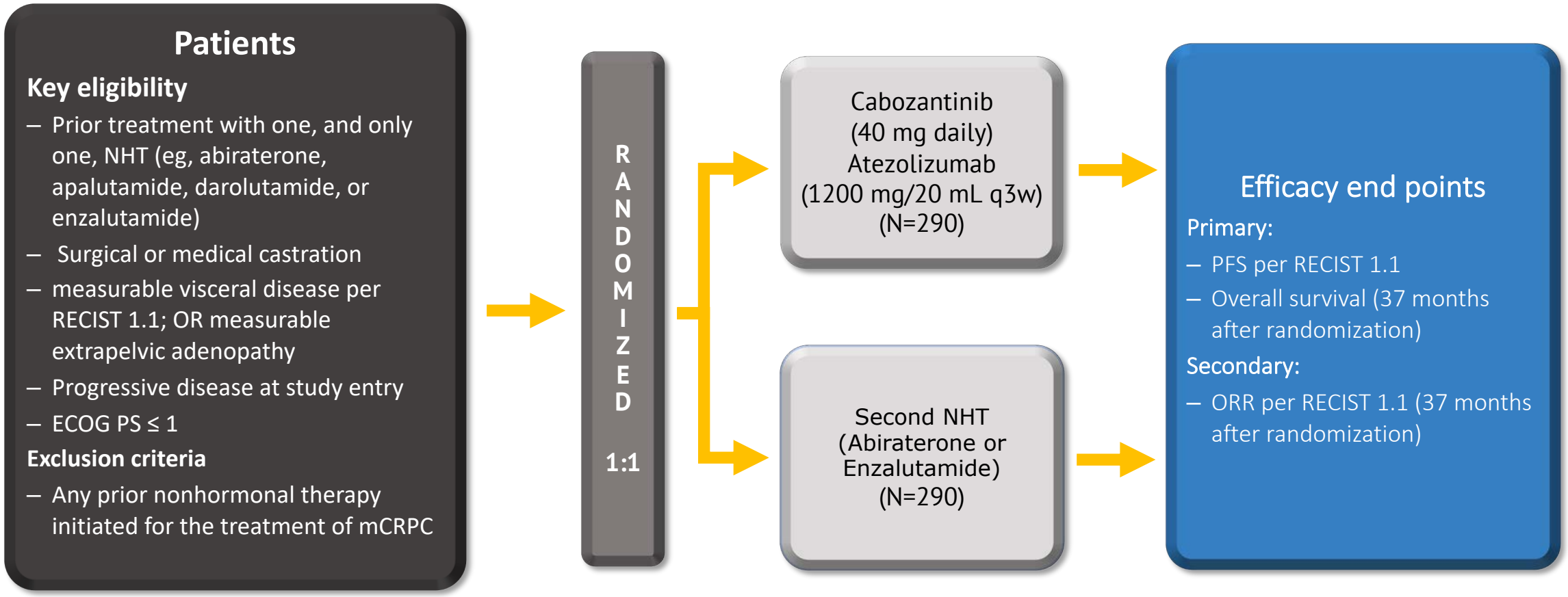
CONTACT-02 Trial Design



ClinicalTrials.gov : NCT04446117

Agarwal N et al. Future Oncology 2022

Combinatorial Regimens of Immune Checkpoint inhibitors in mCRPC

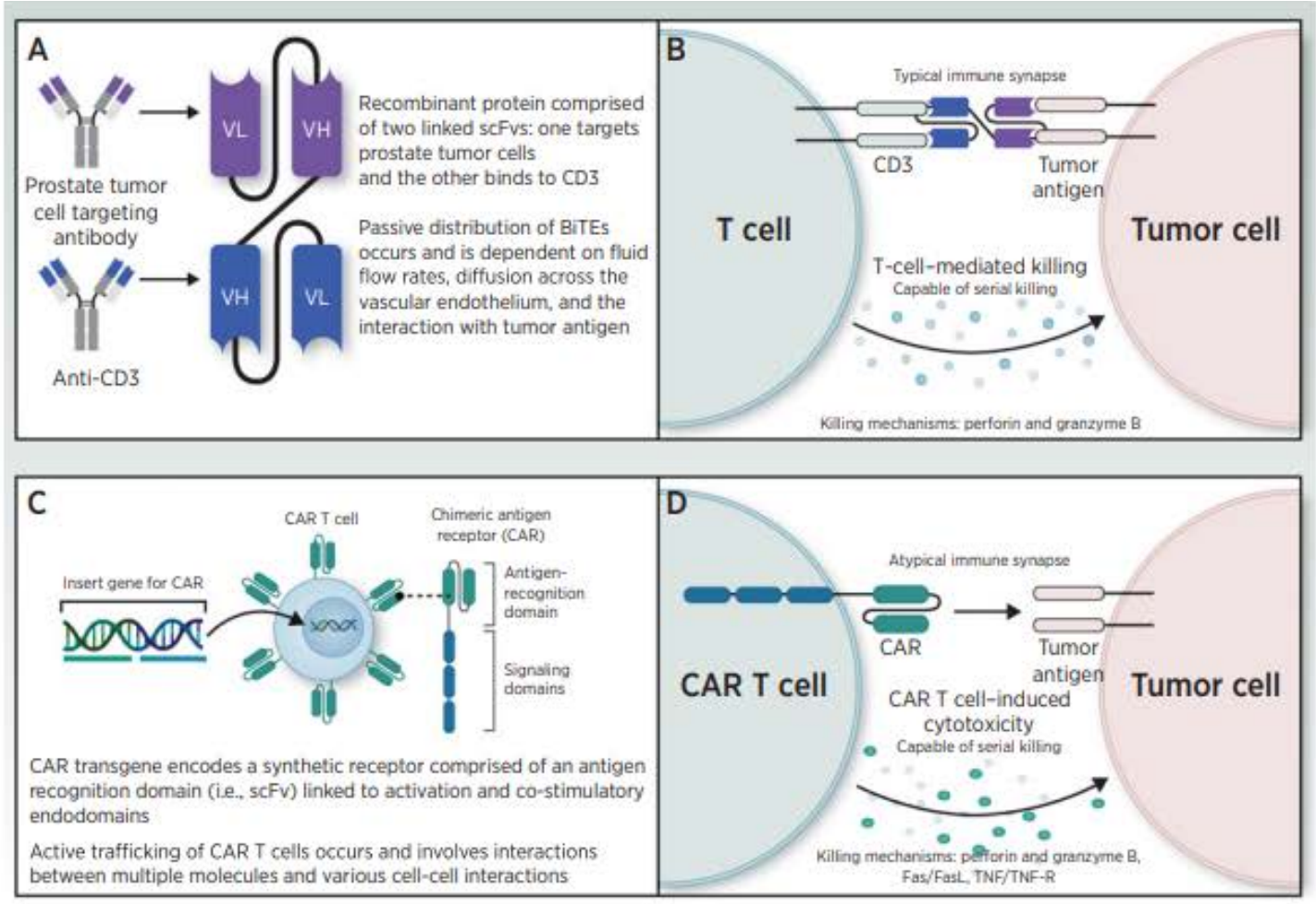
	Cabozantinib + Atezolizumab			Nivolumab + Ipilimumab	Pembrolizumab + Enzalutamide	Atezolizumab + Enzalutamide	Enzalutamide
	COSMIC-021 (C6)			CM-650 (1)[1]	KN-365 (C)[2]	IMbassador250[3]	IMbassador250
N	132			45	102	379	380
Population	**Must have rPD in soft tissue** Enzalutamide and/or abiraterone Docetaxel for mCSPC allowed			PSA, bone, or soft tissue PD **Liver metastases excluded** **TMB high 49%**	PSA, bone, or soft tissue PD No prior enzalutamide	PSA, bone, or soft tissue PD No prior enzalutamide	
Prior Therapy	**2+ NHTs: 45%** Prior doce: 25%			Post-NHT Prior doce: 11%	Post-Abiraterone (including intolerant)	Post-Abiraterone Prior doce: 50%	
Measurable Disease	**99%**			71%	39%	35%	
Visceral Disease Liver Lung	32% **13%** 19%			24% - 22%	17% 5% -	37% 11% -	
		All	**Visc/EPLN***				
ORR	**INV**	23%	**27%**	25% (INV)	12% (BIRC)	14% (BIRC)	7% (BIRC)
	BIRC	15%	18%				
DCR	**INV**	84%	**88%**	66% (INV)	56% (BIRC)	56% (BIRC)	49% (BIRC)
mDOR (mo)	**INV**	6.9		NR	NR	12.4 (BIRC)	NE
mPFS (mo)	**INV**	5.5	5.6	5.5 (INV)	6.1 (BIRC, PCWG)	4.2 (BIRC)	4.1 (BIRC)
	BIRC	5.7	**6.8**				
G3-4 TRAEs **G5 TRAEs**	55% 0.8%			42.2% 4%	39.2% 1%	28% 2%	10% <1%
Duration of Treatment	**5.7 mo**			2.1 mo	-	**Courtesy: Dr. Cora Sternberg. ESMO, 2021.**	

*Visc/EPLN = Patients with measurable visceral or extra pelvic lymph node metastases [1]Sharma et al, 2020. Cancer Cell, [2]Berry et al, 2020. ASCO GU, [3]Sweeney et al, 2020. AACR.

Beyond ICIs: BiTE antibody and CAR-T Cell Therapies

BiTE Antibody Therapies

CAR-T Cell Therapies



Dorff et al. *Clin Cancer Res.* 2021. (online ahead of print)

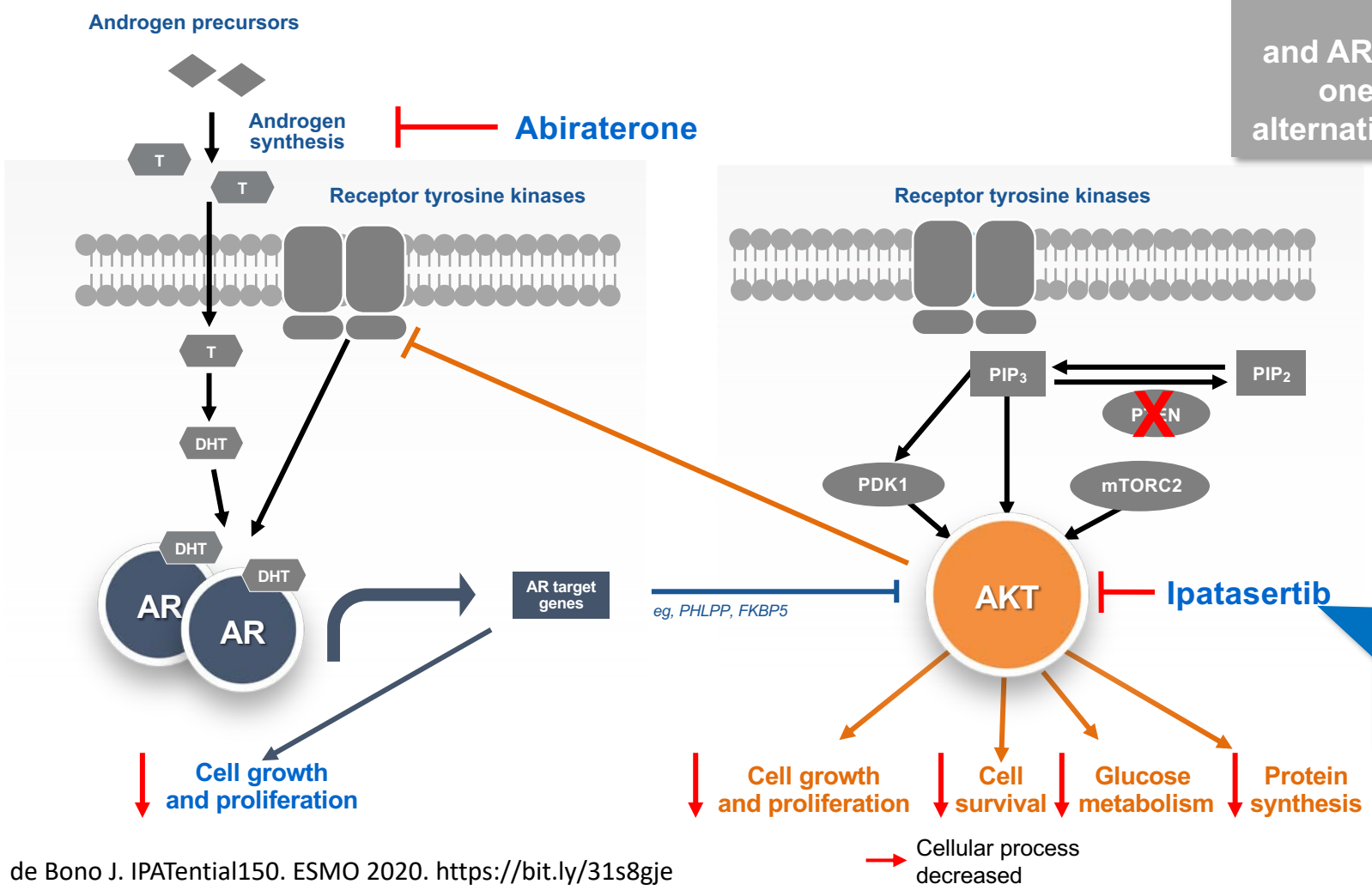
AKT Inhibitors

Ipatasertib plus abiraterone and prednisolone in metastatic castration-resistant prostate cancer (IPATential150): a multicentre, randomised, double-blind, phase 3 trial

Christopher Sweeney, Sergio Bracarda, Cora N Sternberg, Kim N Chi, David Olmos, Shahneen Sandhu, Christophe Massard, Nobuaki Matsubara, Boris Alekseev, Francis Parnis, Vagif Atduev, Gary L Buchschacher Jr, Rustem Gafanov, Luis Corrales, Michael Borre, Daniil Stroyakovskiy, Gustavo Vasconcelos Alves, Evangelos Bournakis, Javier Puente, Marie-Laurence Harle-Yge, Jorge Gallo, Geng Chen, Justin Hanover, Matthew J Wongchenko, Josep Garcia, Johann S de Bono

Sweeney. De bono, Lancet, 2021.

Rationale for dual pathway inhibition



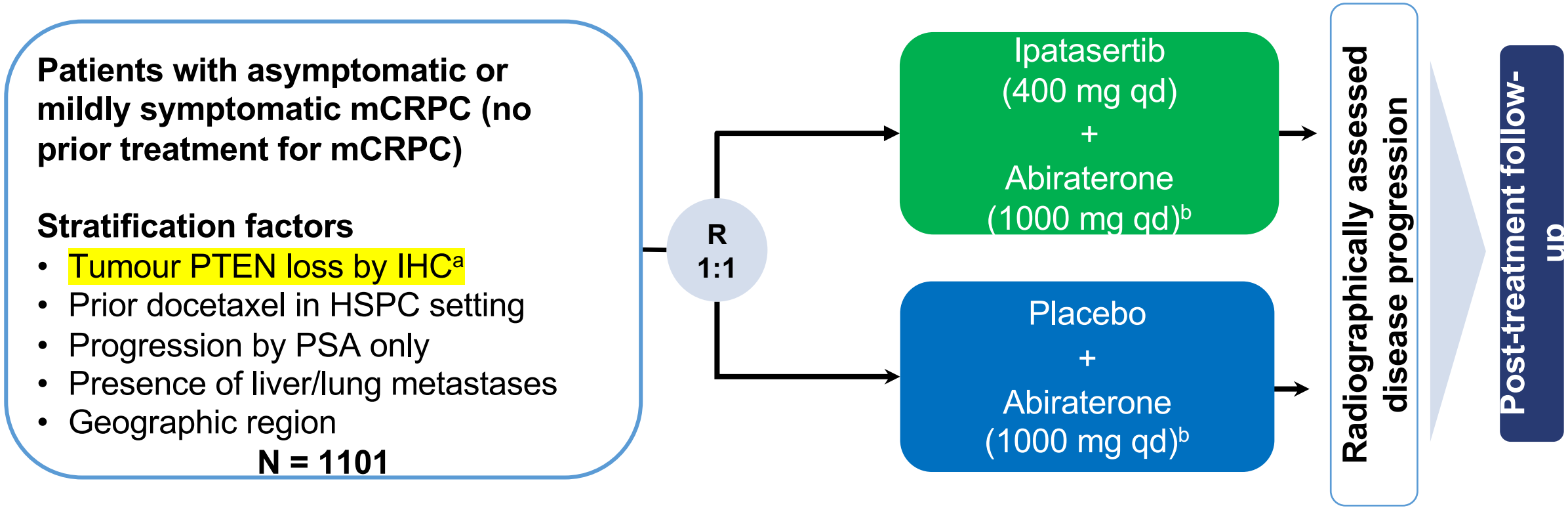
Cross talk between the PI3K/AKT and AR pathways leads to reciprocal activation when one of the pathways is inhibited, providing an alternative mechanism for tumour growth and survival

Dual targeting of both pathways may increase anti-tumour activity

Ipatasertib is a potent, novel, selective, ATP-competitive inhibitor of all 3 isoforms of AKT

de Bono J. IPATential150. ESMO 2020. https://bit.ly/31s8gje

IPATential150 study design

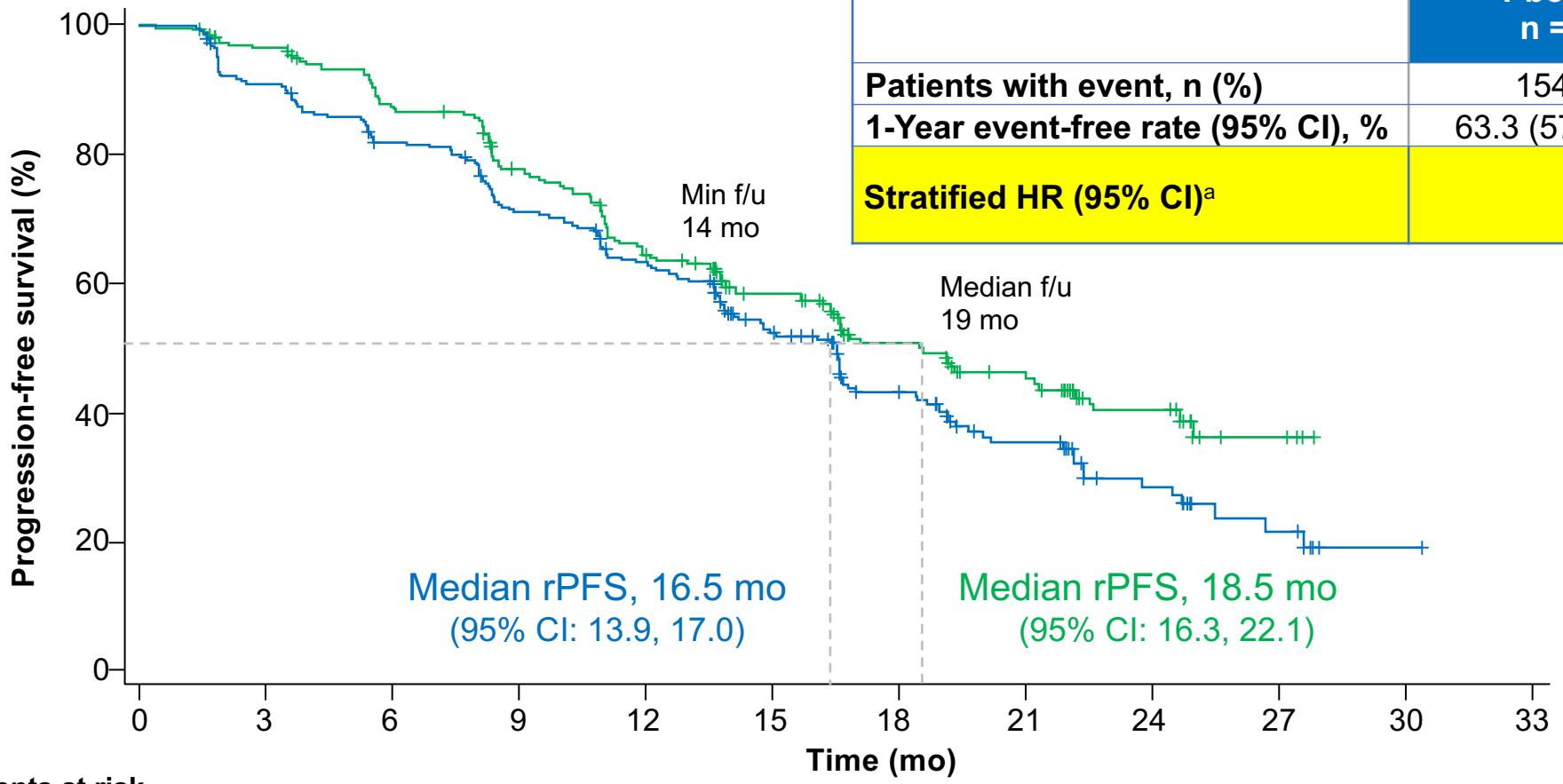


- Co-primary endpoints: investigator-assessed rPFS (PCWG3 criteria) in ITT and PTEN-loss (by IHC) populations
- Secondary endpoints included: OS, time to pain progression, time to initiation of chemotherapy, ORR, investigator-assessed rPFS in PTEN-loss (by NGS) population

de Bono J. IPATential150. ESMO 2020. https://bit.ly/31s8gje

rPFS in the PTEN-loss by IHC Population

	Pbo + abi n = 261	Ipat + abi n = 260
Patients with event, n (%)	154 (59)	124 (48)
1-Year event-free rate (95% CI), %	63.3 (57.3, 69.3)	64.4 (58.3, 70.5)
Stratified HR (95% CI)[a]	**0.77 (0.61, 0.98)** *P* = 0.0335[b]	



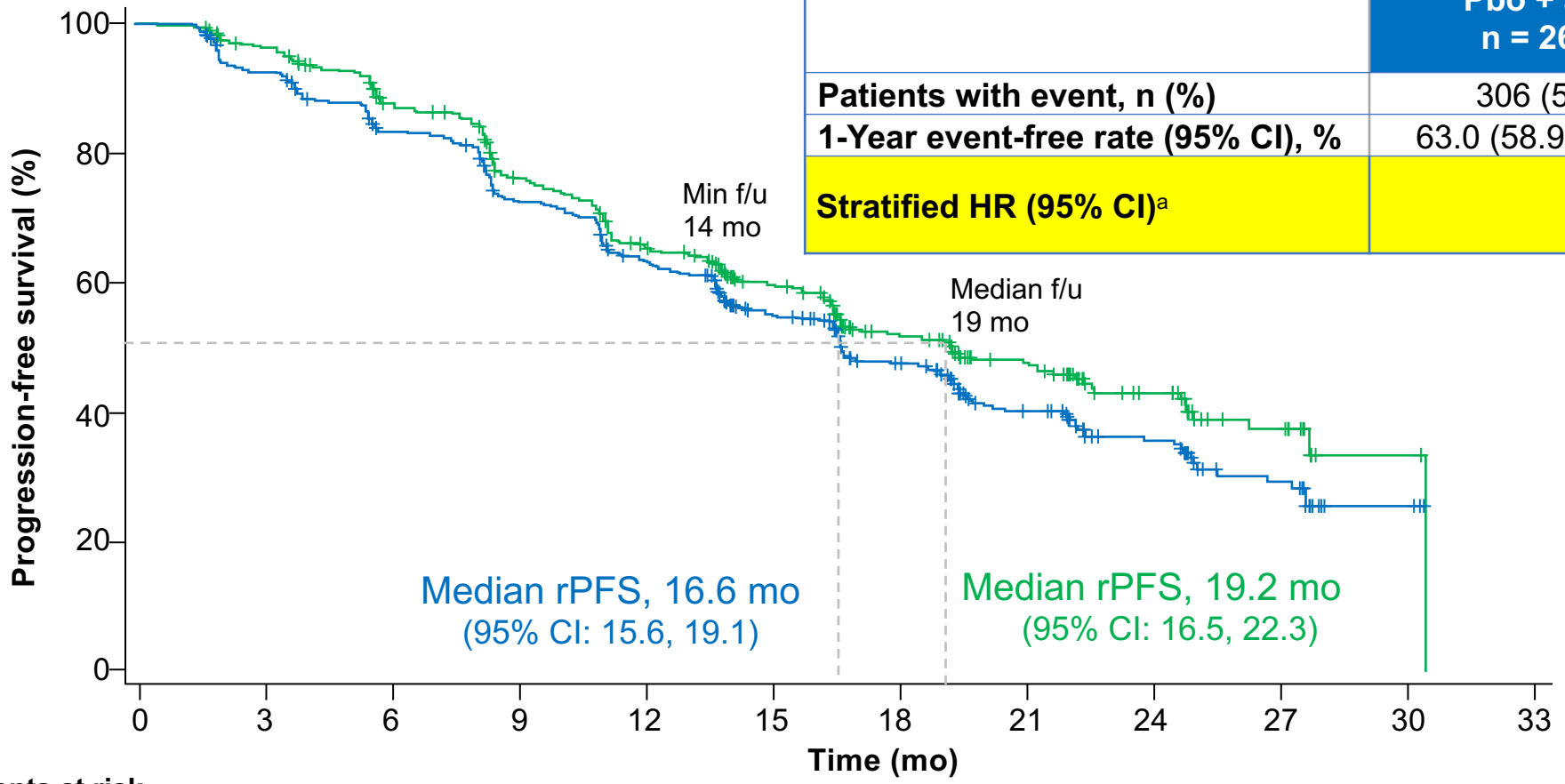
Patients at risk

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 J. IPATential150. ESMO 2020. https://bit.ly/31s8gje

rPFS in the ITT population

	Pbo + abi n = 261	Ipat + abi n = 260
Patients with event, n (%)	306 (55)	252 (46)
1-Year event-free rate (95% CI), %	63.0 (58.9, 67.1)	65.3 (61.1, 69.5)
Stratified HR (95% CI)[a]	**0.84 (0.71, 0.99)** *P* = 0.0431[b]	

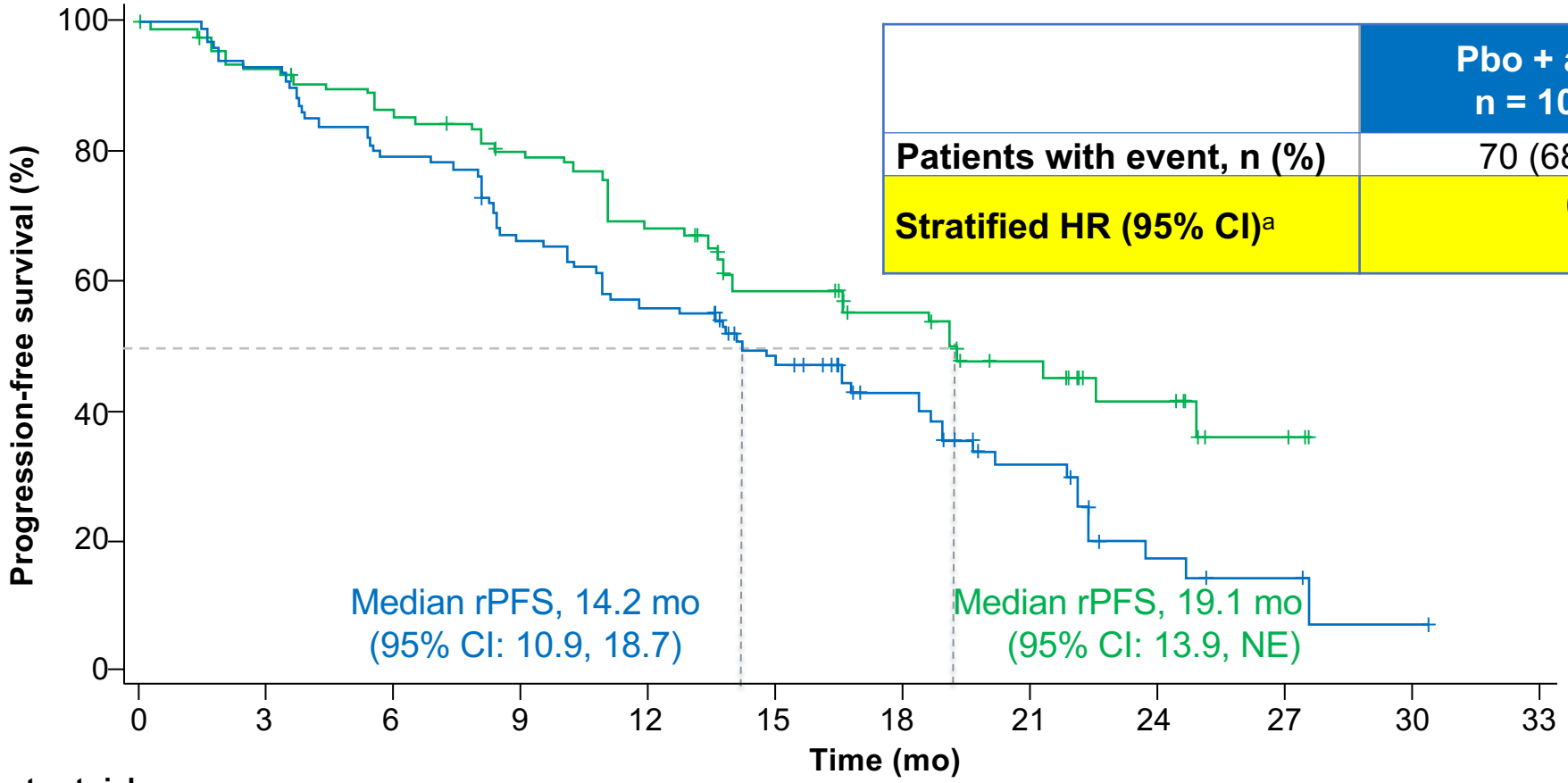


Patients at risk

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

de Bono J. IPATential150. ESMO 2020. https://bit.ly/31s8gje

rPFS in the NGS-defined PTEN-loss Population



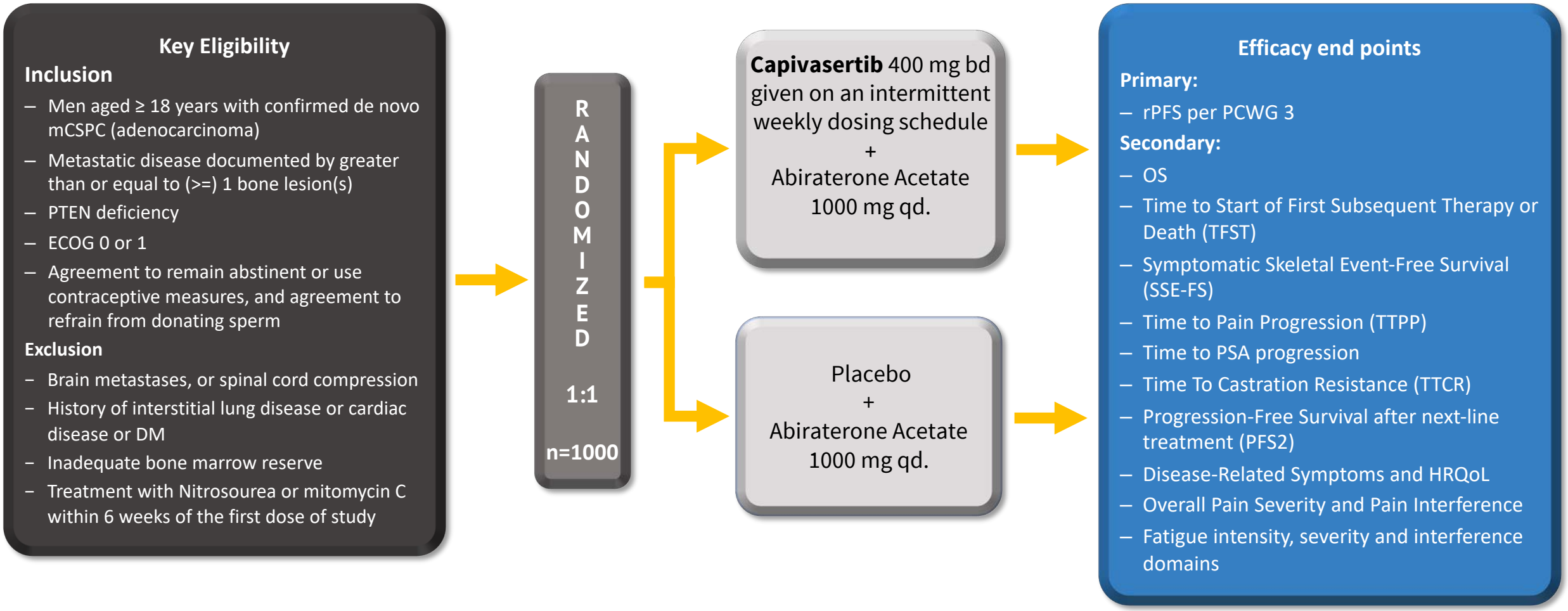
	Pbo + abi n = 103	Ipat + abi n = 105
Patients with event, n (%)	70 (68)	47 (45)
Stratified HR (95% CI)[a]	0.65 (0.45, 0.95) *P* = 0.0206[b]	

Patients at risk

Pbo + abi	103	94	80	66	56	40	29	17	6	4	1
Ipat + abi	105	92	83	74	63	45	30	21	12	4	

de Bono J. IPATential150. ESMO 2020. https://bit.ly/31s8gje

Capivasertib in mCSPC: Phase 3 CAPItello-281 Trial



www.clinicaltrials.gov: NCT04493853

Final Conclusions

- *Treatment of metastatic prostate cancer has undergone a revolution in the last decade leading to approval of multiple novel agents, and more coming soon*
- *However, disease eventually progresses and remains lethal*
- *Identification of new molecular targets and biomarkers of response remain critical to improve our patients' lives*

Thank you!

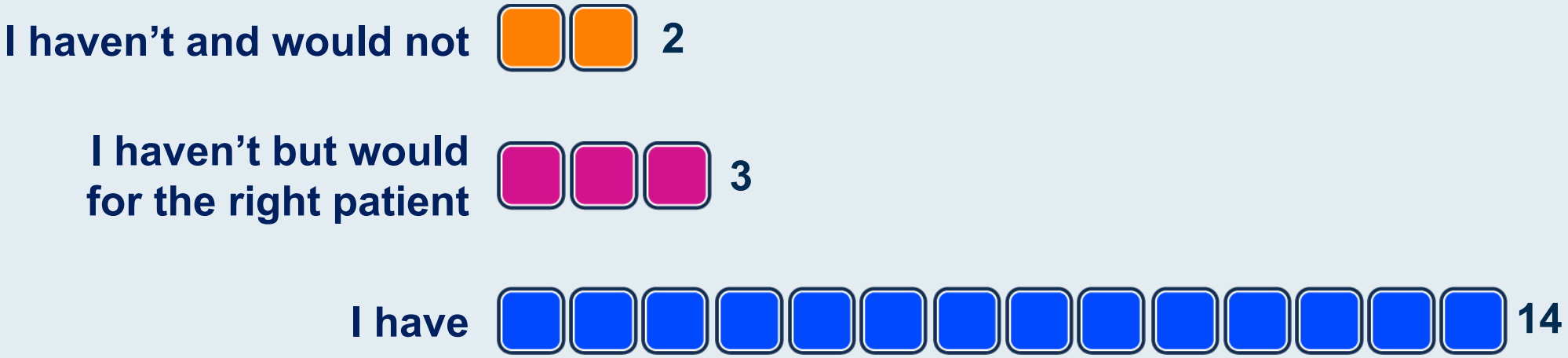
Acknowledgements:

- Umang Swami, MD
- Roberto Nussenzveig, PhD
- Benjamin Louis Maughan, MD
- Nicolas Sayegh, MD

@neerajaiims

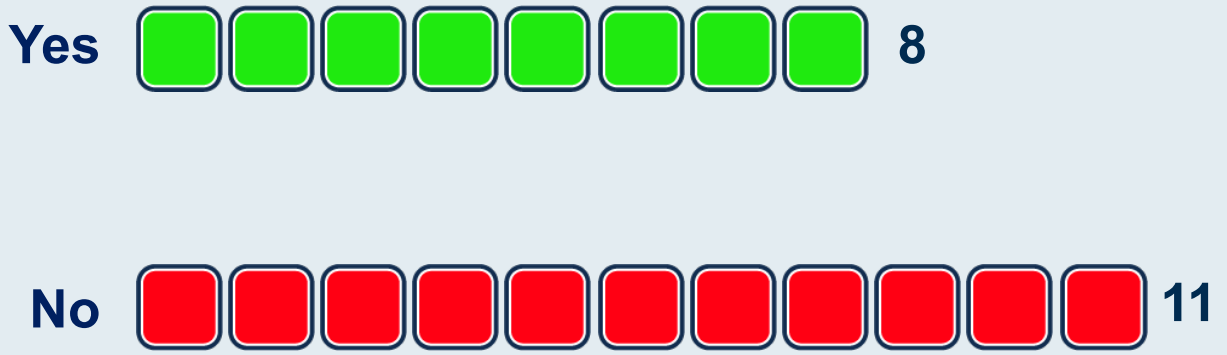
Clinical Investigator Survey Results

Have you offered or would you offer an anti-PD-1/anti-PD-L1 antibody-based treatment to a patient with microsatellite-stable mCRPC outside of a protocol setting?



Survey of genitourinary cancer clinical investigators

Based on the current clinical trial database, if the combination of atezolizumab and cabozantinib were available today for patients with mCRPC, would you recommend it?



Survey of genitourinary cancer clinical investigators

Thank you for attending!

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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.

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