Prostate cancer Updates

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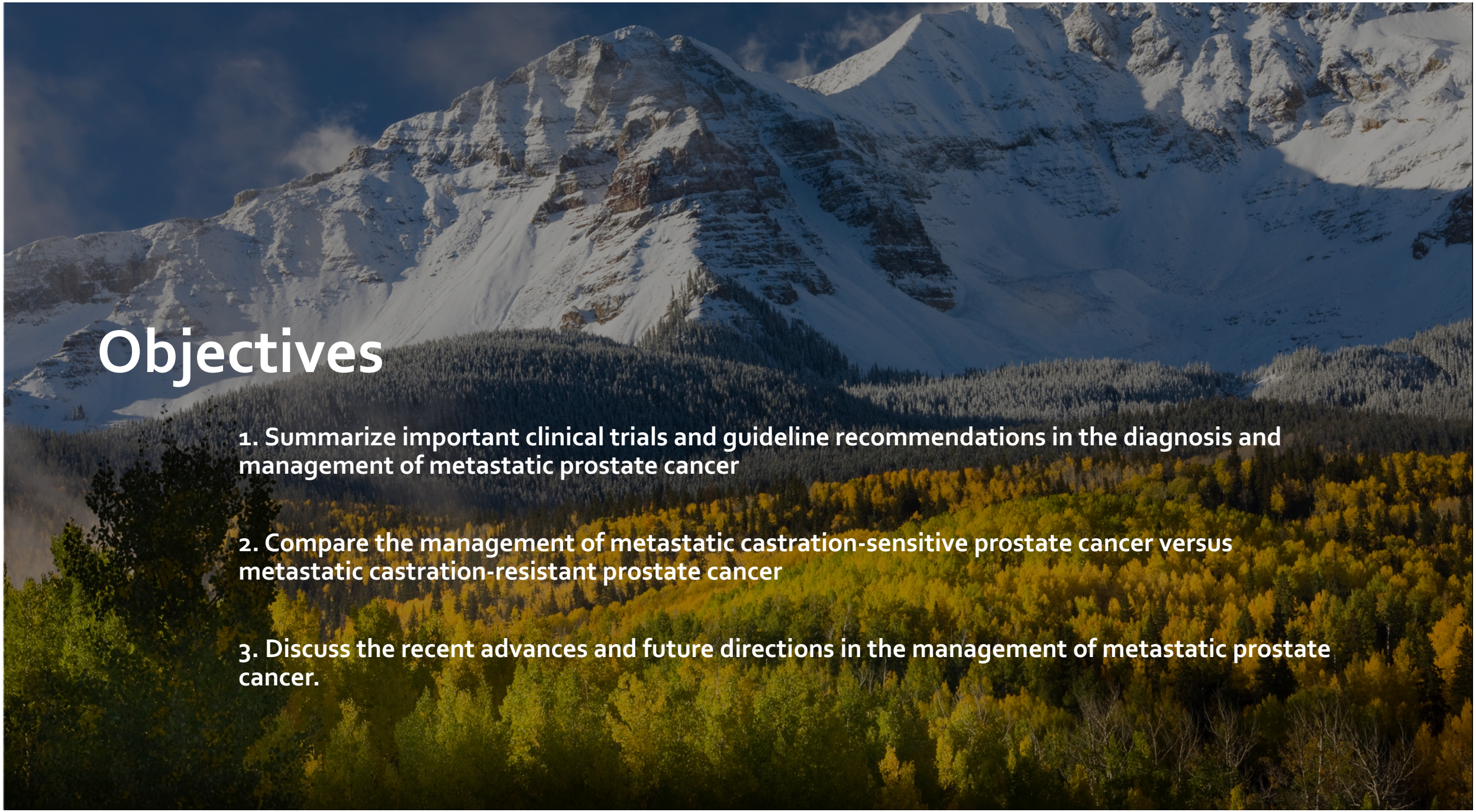


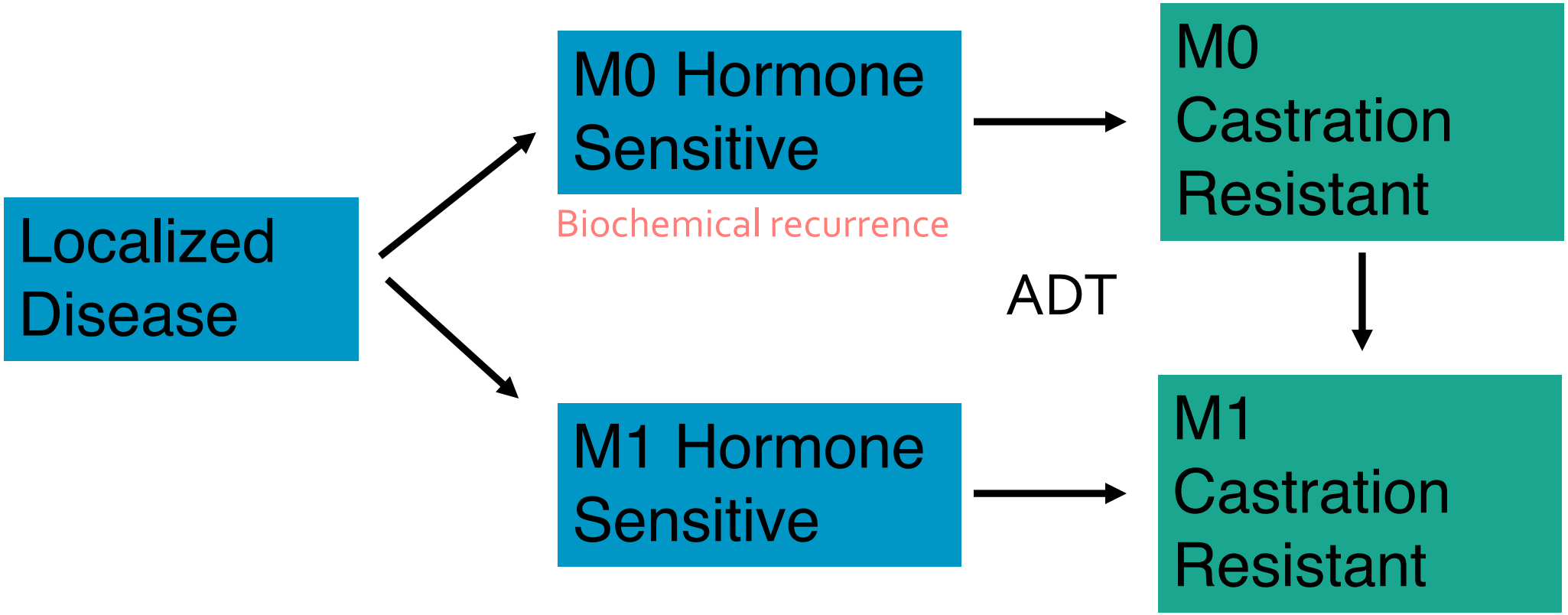
Objectives

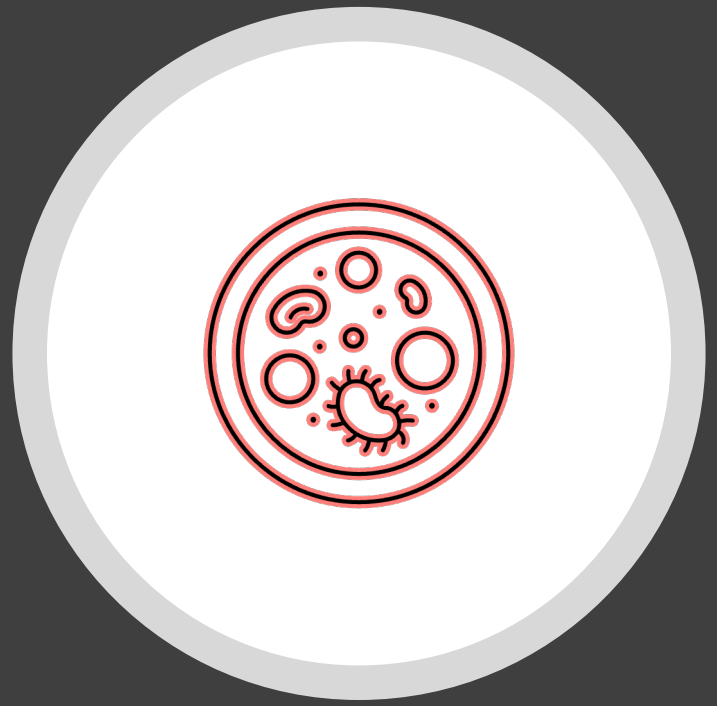
1. Summarize important clinical trials and guideline recommendations in the diagnosis and management of metastatic prostate cancer

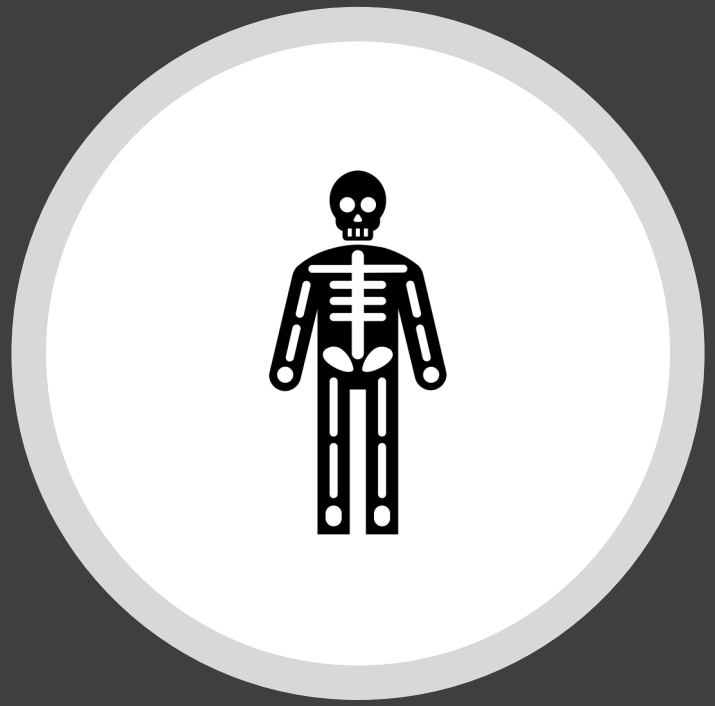
2. Compare the management of metastatic castration-sensitive prostate cancer versus metastatic castration-resistant prostate cancer

3. Discuss the recent advances and future directions in the management of metastatic prostate cancer.

https://morrowcountyhealthdistrict.org/prostate-cancer-infographic1/


Localized Disease
M0 Hormone Sensitive
Biochemical recurrence
M1 Hormone Sensitive
ADT
M0 Castration Resistant
M1 Castration Resistant





Population

population

High Volume

Visceral

4 or more bone lesions - with 1 extra-axial

High Risk

Gleason 8-10

At least 3 bone lesion

Measurable visceral lesions

Newly-diagnosed

Any of:

- Metastatic
- Node-Positive
- ≥2 of: Stage T3/4
  PSA≥40ng/ml
  Gleason 8-10

All patients

- Fit for all protocol treatment
- Fit for follow-up
- WHO performance status 0-2
- Written informed consent

Relapsing after previous RP or RT with ≥1 of:

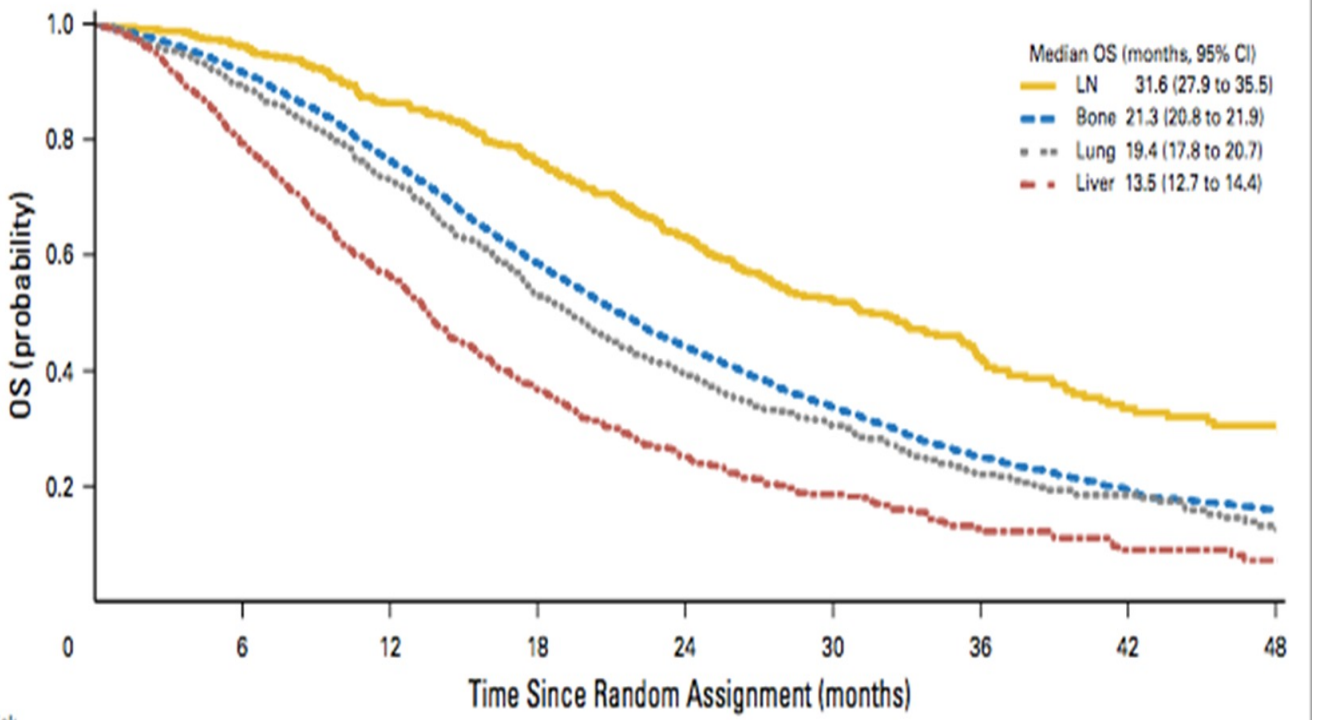
- PSA ≥4ng/ml and rising with doubling time <6m
- PSA ≥20ng/ml
- Node-positive
- Metastatic

Full criteria

www.stampedetrial.org

Stratification

Staging in prognostication



ADT Alone (using CHAARTED and GETUG)	Median OS
Relapsed Low Volume	~8 y
Relapsed High Volume	4.5
De Novo Low Volume	4.5
De Novo High Volume	3

Halabi, JCO, 2016; Gravis Eur Urol 2018; Kyriakopoulos JCO 2018

Treatment Intensification

Prostate Cancer is *Androgen* Dependent

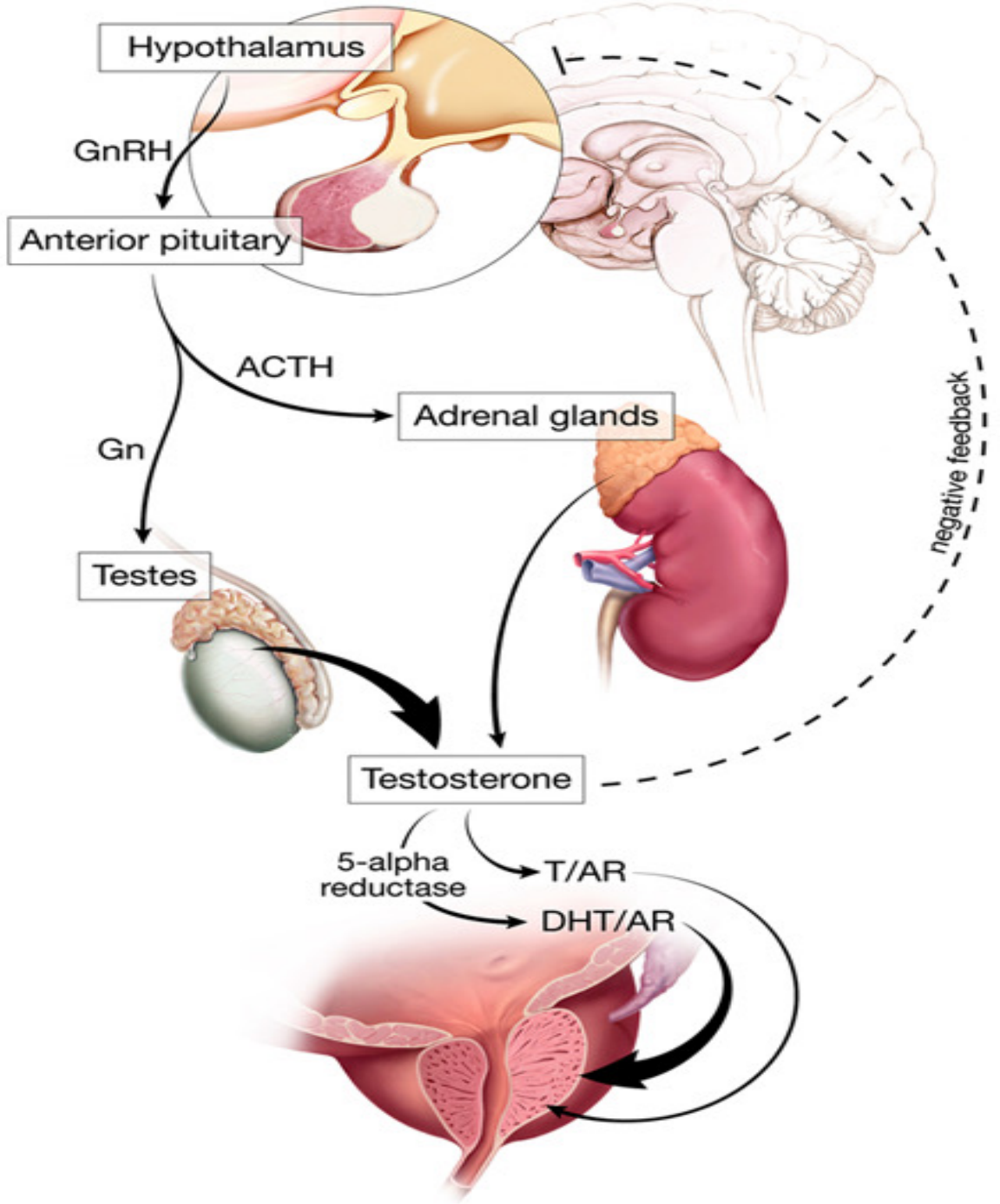
4 sources of androgen

Testicles (95%)

Adrenals

Periphery

Intratumoral



Androgen Deprivation Therapy (ADT) is the Mainstay of Treatment

There is an **Overall Survival** Benefit to Treatment Intensification With:

Abiraterone/Prednisone

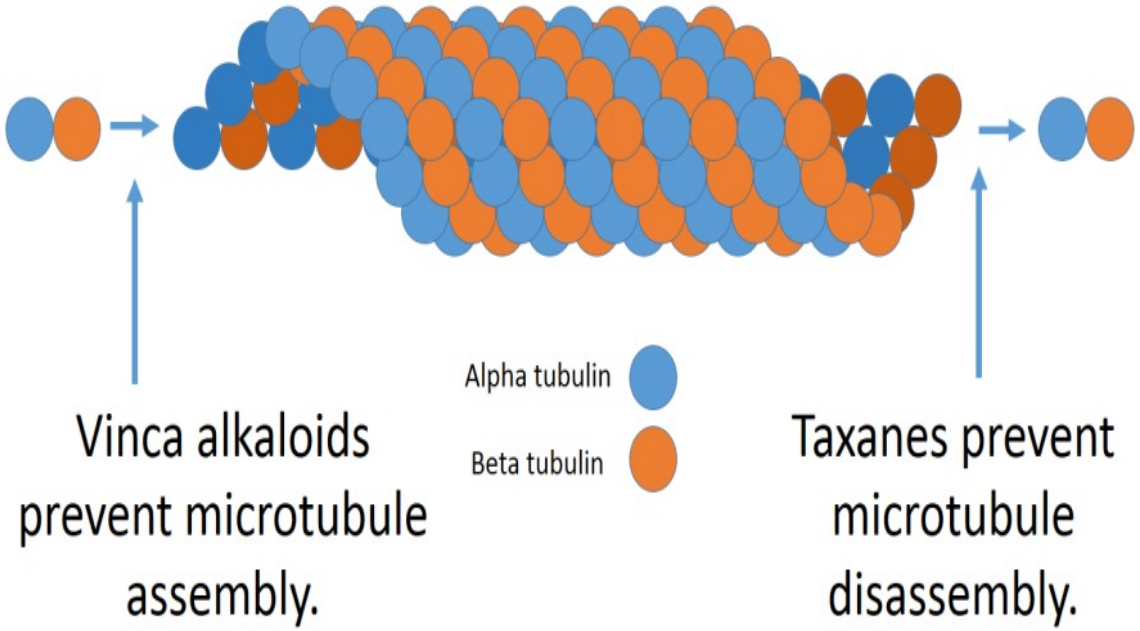
Enzalutamide or Apalutamide

Docetaxel

Radiation to the prostate in low volume disease

	Chemo		Abi			Apa	Daro	Enza	
Study	**Chaarted**	**Stampede**	**Latitude**	**Stampede**	**Peace1**	**Titan**	**ARASENS**	**Arches**	**Enzamet**
Pop	M1 High (66%) Low (33%)	M1 (61%) N+ (15% N0M0 (24%)	M1	M1 (52%) N+ (20%) N0M0 (28%)	M1 High (57%) All de novo	Metastatic (at least 1 bone lesion) High (62.7%) Low (37.3%)	M1a (3%) M1b 79% M1c (18%)	Metastatic High (64%) Low (38%)	Metastatic High (52%) Low (48%)
mOS	48	40	50	56	61	*	**		
Age	63	65	67	67	66	68	67 (16-17% >75)	70	69
Chemo	100%	100%	0	0	50%	10%	100%	18%	45%

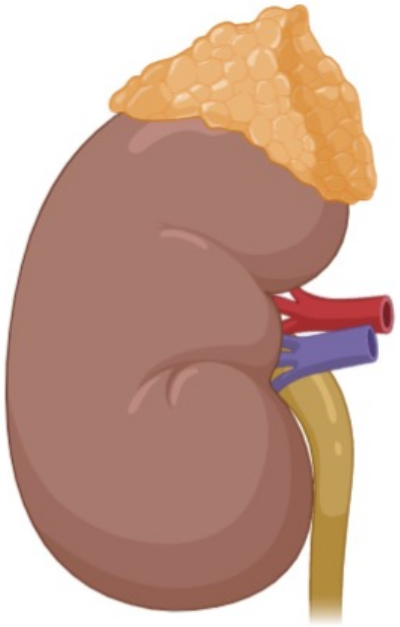
Docetaxel


Alpha tubulin
Beta tubulin
Vinca alkaloids prevent microtubule assembly.
Taxanes prevent microtubule disassembly.

Cholesterol

Abiraterone

17α-h oxylase



17-Hydroxypregenolone

3β-hydroxysteroid dehydrogenase

DHEA

3β-hydroxysteroid dehydrogenase

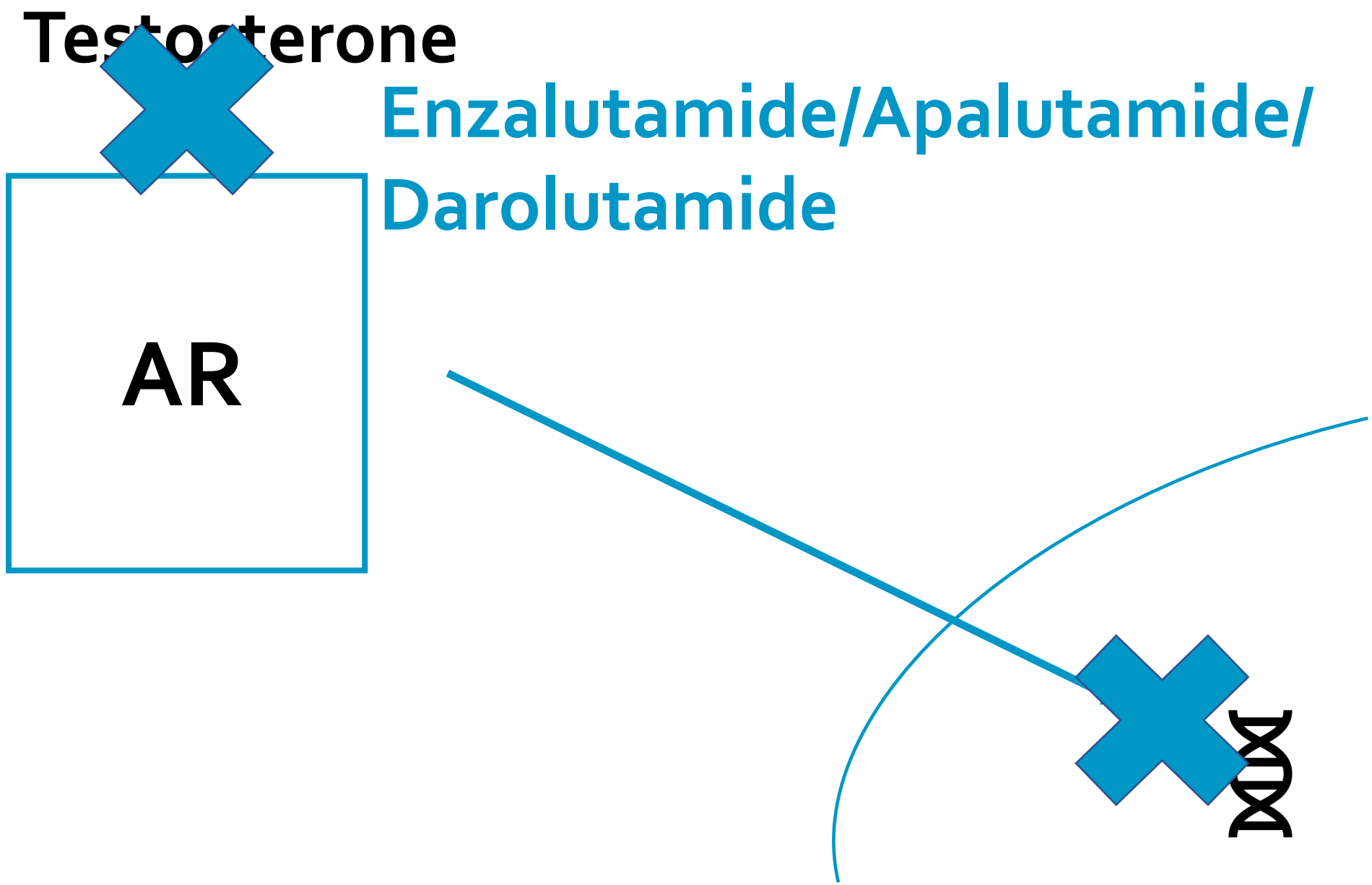
Androstenedione

Aldo-keto reductase 1C3 (AKR1C3)

Testosterone

5α-reductase

DHT

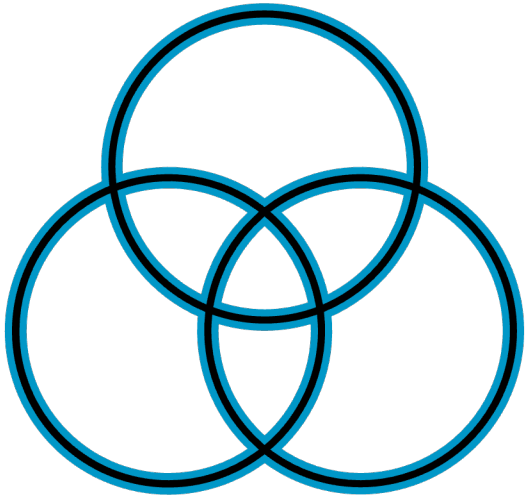

Testosterone
Enzalutamide/Apalutamide/
Darolutamide
AR
DNA

So many options… How to choose?!

Side effects, disease burden, cost, schedule, patient preference, subsequent therapy

Is More, More?

PEACE-1: Docetaxel + Abi + ADT



ARASENS: Docetaxel + Darolutamide + ADT

TRIPLET?

Perhaps best suited for poorest prognosis disease

- De Novo
- "fit" for chemo (geriatric assessment)
- Have only combined NHT+ chemo v chemo. No comparison of NHT+ chemo v NHT
- No benefit in low volume (PEACE1) and not reported for ARASENS


How do we treat castration resistant disease?

FDA Approved Therapies for M1 CRPC

Abiraterone

Enzalutamide

Docetaxel

Cabazitaxel

Sipuleucel-T

Radium-223

Lu177-PSMA

For MMRd/TMB-H:

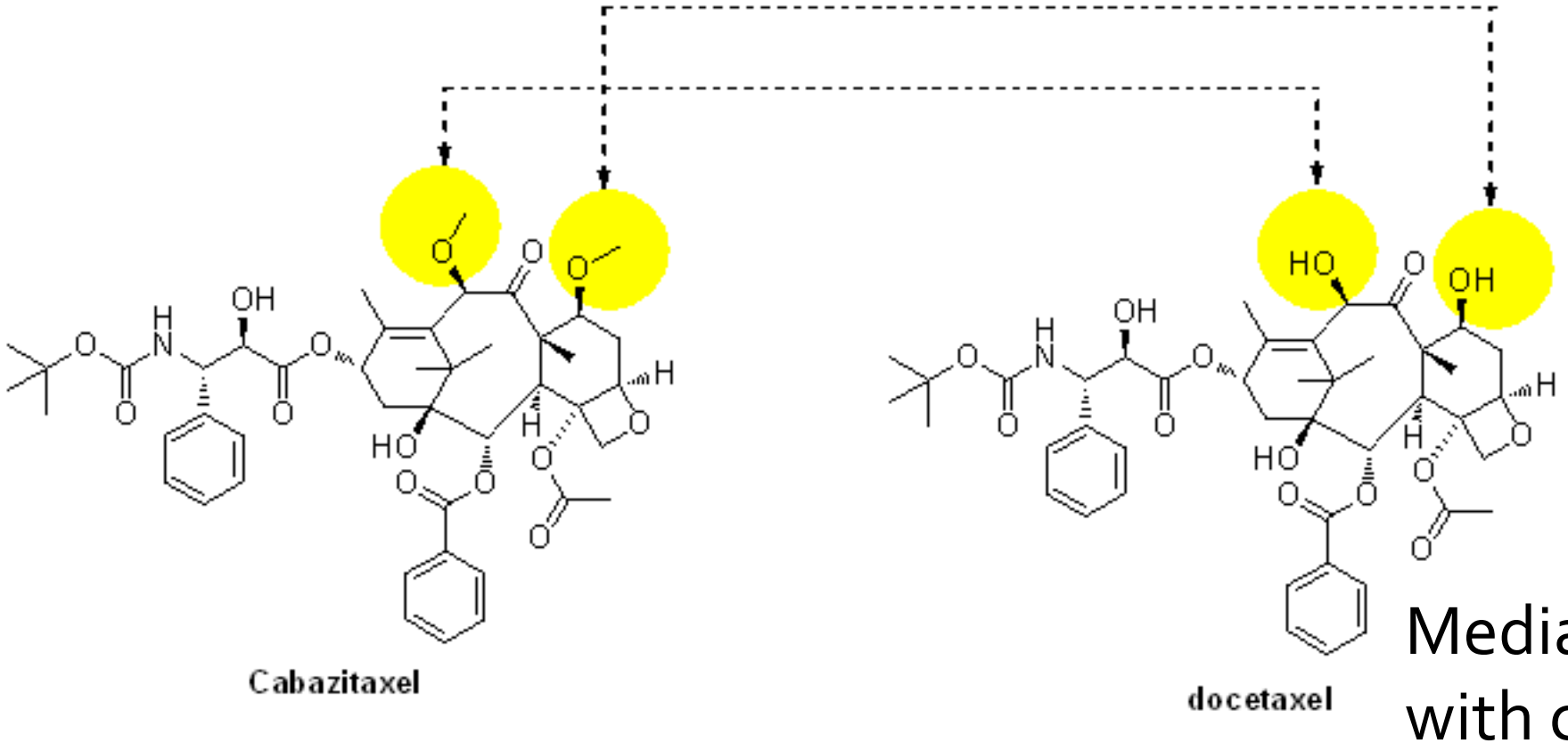
Pembrolizumab

For HRD:

Olaparib

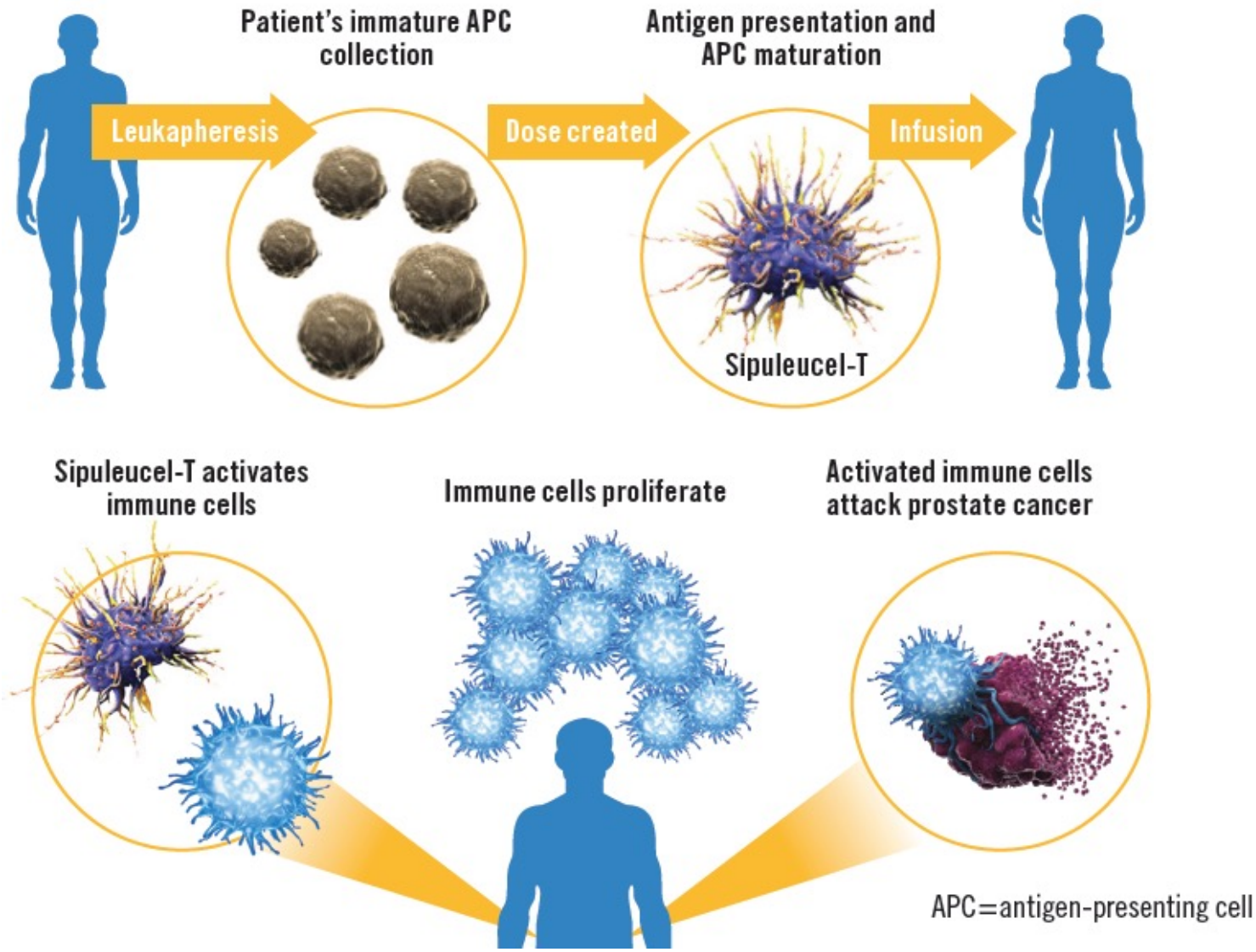
Rucaparib

Cabazitaxel (2010)



Median OS **15.1 months** with cabazitaxel vs. **12.7 months** with mitoxantrone

Sipuleucel-T (2010)



Median OS **25.8 months** with sipuleucel-T vs. **21.7 months** in placebo

Uclahealth.org

Abiraterone (2011)

COU301

De Bono et al. NEJM 2011

Scher et al. Lancet Oncology 2012

COU302

Ryan et al. NEJM 2012

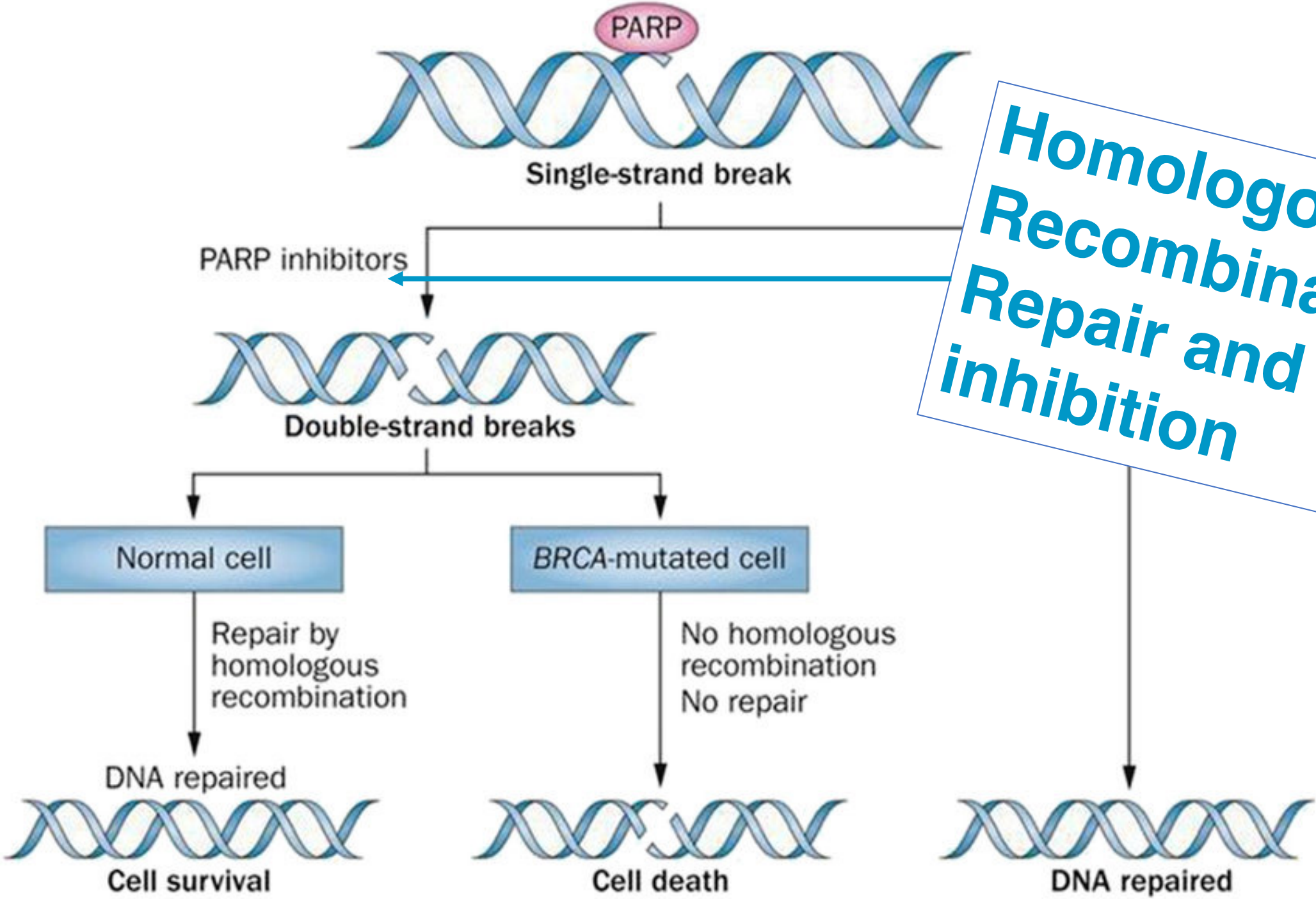
Enzalutamide (2012)

AFFIRM

Scher et al. NEJM 2012

PREVAIL

Beer et al. NEJM 2014



Homologous Recombination Repair and PARP inhibition

Homologous Recombination Repair and PARP inhibition (2021)

Rucaparib approved for men with mCRPC and *BRCA1/2* mutations. Post NHT, chemotherapy

Olaparib approved for men with mCRPC and mutations in one of 14 HRR genes. Post NHT

Triton 2

Abida et al JCO 2020

Profound

deBono NEJM 2020

Is More More?

Magnitude: Abiraterone + Niraparib + ADT

PROpel: Abiraterone + Olaparib + ADT

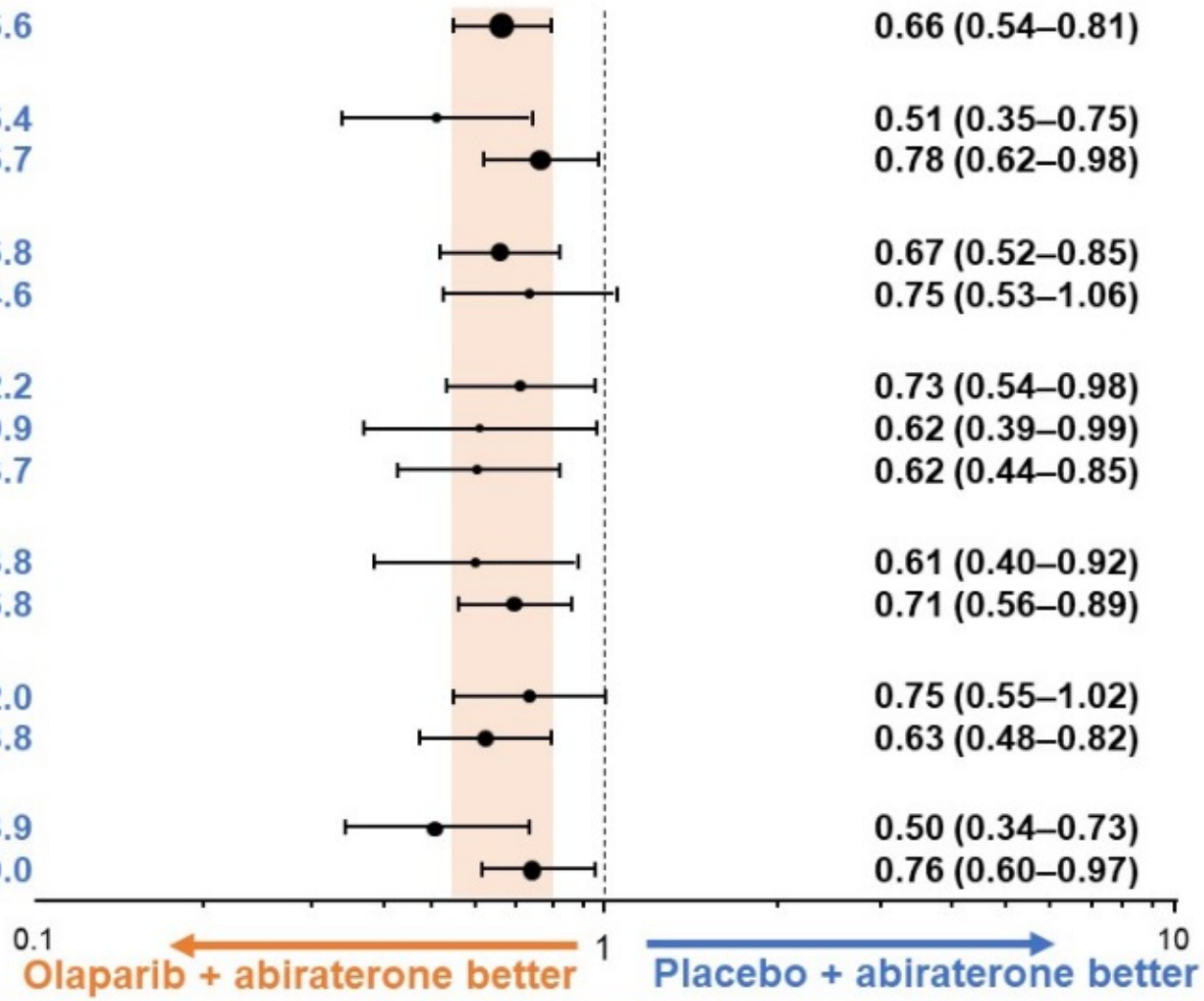
Magnitude: secondary endpoints

	ALL HRR GENE MUTATIONS			*BRCA1/2*-MUTATED		
	NIRAPARIB + ABIRATERONE/	PLACEBO + ABIRATERONE/	HR/RR (95% CI); *P* VALUE	NIRAPARIB + ABIRATERONE/ PREDNISONE	PLACEBO + ABIRATERONE/ PREDNISONE	HR/RR (95% CI); *P* VALUE
Radiographic progression-free survival	16.5 months	13.7 months	0.73 (0.56-0.96); .0217	16.6 months	10.9 months	0.53 (0.36-0.79); .0014
Time to cytotoxic chemotherapy	NE	26.0 months	0.59 (0.39-0.89); .0108	NE	26.0 months	0.58 (0.33-1.01); .0495
Time to symptomatic progression	NE	NE	0.69 (0.47-0.99); .0444	NE	19.8 months	0.68 (0.42-1.11); .1224
Time to PSA progression	18.5 months	9.3 months	0.57 (0.43-0.76); .0001	NE	9.2 months	0.46 (0.30-0.69); .0002
Overall response rate	60%	28%	2.13; < .001	52%	31%	1.66; .035

HRR, homologous recombination repair; NE, not evaluable; PSA, prostate-specific antigen; RR, relative risk.

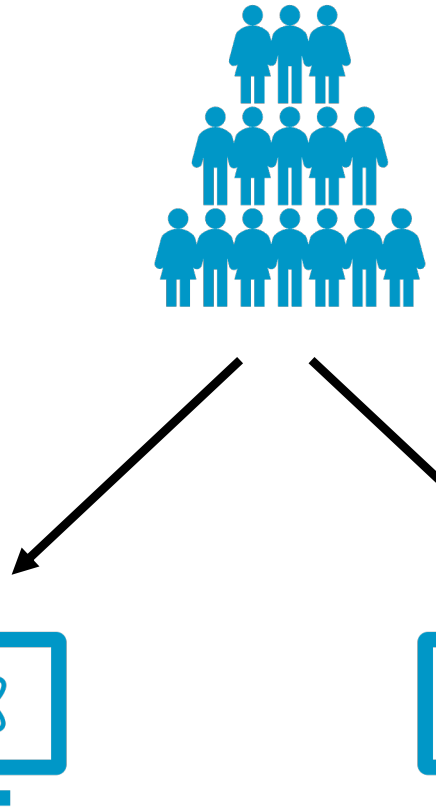
PROpel: subgroup of rPFS

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



ALSYMPCA

Parker et al. NEJM 2013



921 patients with mCRPC

Symptomatic Osseous metastases
PSA of 5 or more
Post-chemotherapy
NO Visceral metastases

Placebo

Radium-223 x 6

Radium-223 (2013)

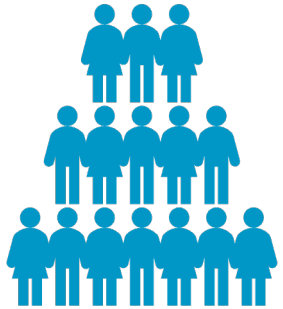
Lu-177 PSMA (2022)

Prostate-Specific Membrane Antigen (PSMA): transmembrane protein highly expressed in mCRPC

Lu-177 PSMA delivers beta-particle radiation to PSMA expressing cells

VISION

Sartor et al. NEJM 2021



831 patients with mCRPC

PSMA positive on PET

Post abi/enza

Post-chemotherapy

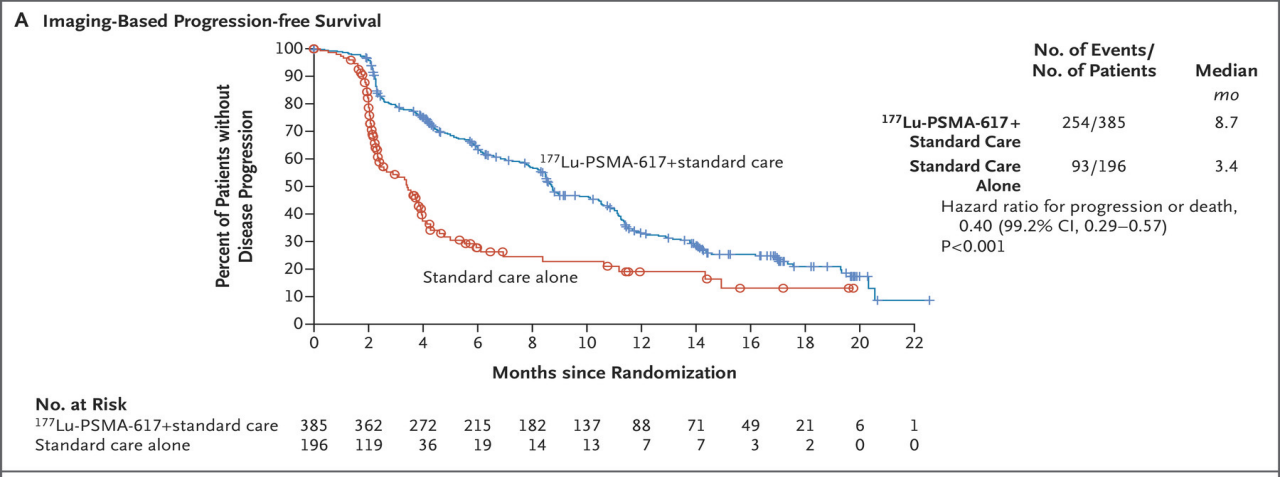
Standard of Care

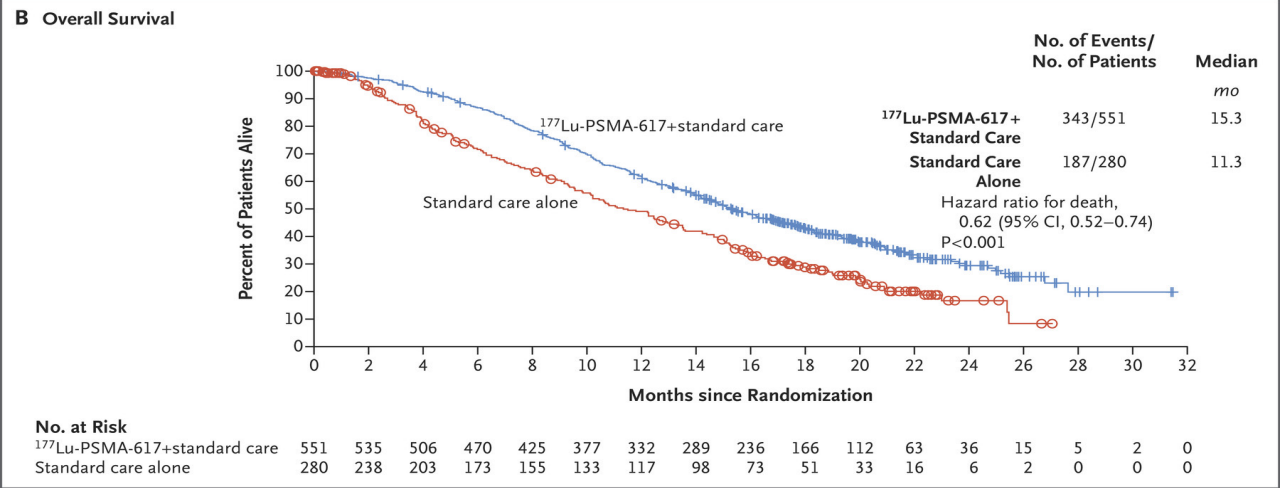
*Excluding chemotherapy, radioligands, immunotherapy, experimental agents

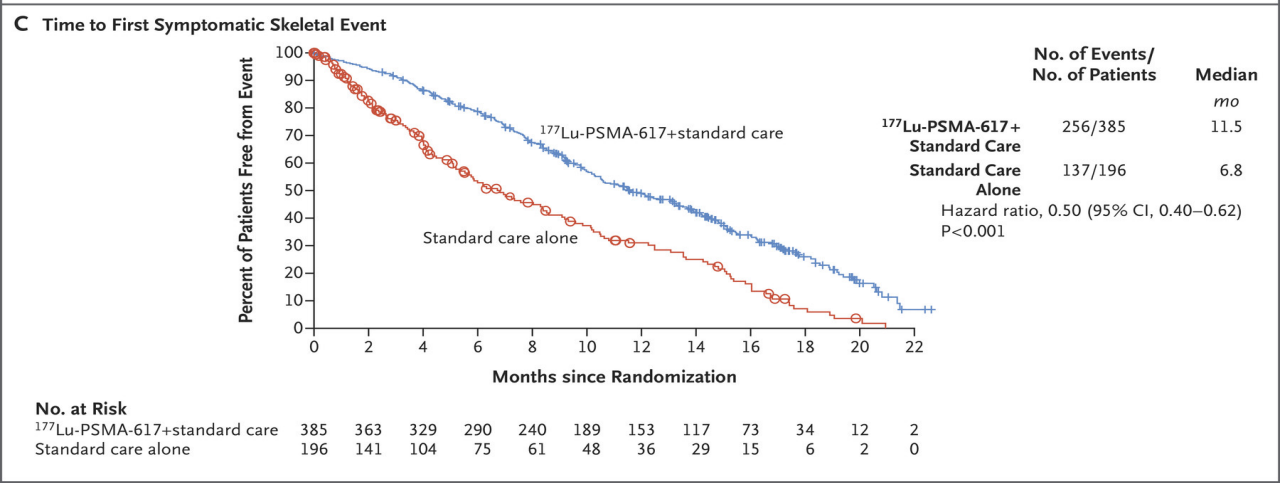
Lu-177 PSMA x 4-6 cycles

Table 1. Characteristics of the Patients at Baseline, According to Analysis Set.*

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)
Median age (range) — yr	71.0 (52–94)	72.0 (51–89)	70.0 (48–94)	71.5 (40–89)
ECOG performance-status score of 0 or 1 — no. (%)†	352 (91.4)	179 (91.3)	510 (92.6)	258 (92.1)
Site of disease — no. (%)				
Lung	35 (9.1)	20 (10.2)	49 (8.9)	28 (10.0)
Liver	47 (12.2)	26 (13.3)	63 (11.4)	38 (13.6)
Lymph node	193 (50.1)	99 (50.5)	274 (49.7)	141 (50.4)
Bone	351 (91.2)	179 (91.3)	504 (91.5)	256 (91.4)
Median PSA level (range) — ng/ml	93.2 (0–6988)	90.7 (0–6600)	77.5 (0–6988)	74.6 (0–8995)
Median alkaline phosphatase level (range) — IU/liter‡	108.0 (26–2524)	96.0 (34–1355)	105.0 (17–2524)	94.5 (28–1355)
Median LDH (range) — IU/liter‡	230.5 (119–5387)	232.0 (105–2693)	221.0 (88–5387)	224.0 (105–2693)
Median time since diagnosis (range) — yr	7.3 (0.9–28.9)	7.0 (0.7–26.2)	7.4 (0.9–28.9)	7.4 (0.7–26.2)
Gleason score at diagnosis — no. (%)§				
8–10	226 (58.7)	118 (60.2)	324 (58.8)	170 (60.7)
Unknown	28 (7.3)	19 (9.7)	42 (7.6)	24 (8.6)
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)







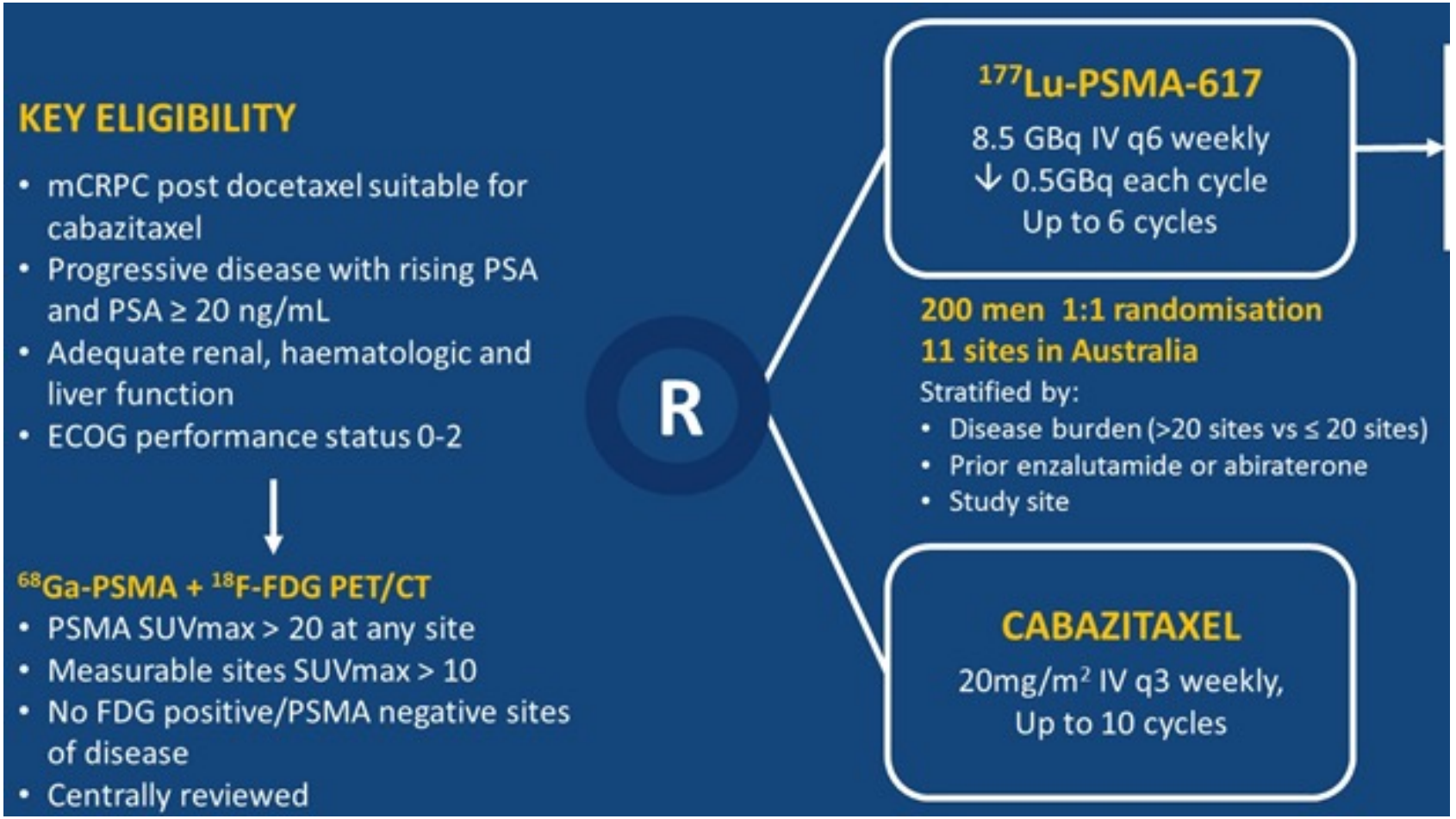
Median rPFS **8.7 months** with Lu177-PSMA vs. **3.4 months** in control

Median OS **15.3 months** with Lu177-PSMA vs. **11.3 months** in control

Median time to first skeletal event **11.5 months** with Lu177-PSMA vs. **6.8 months** in control

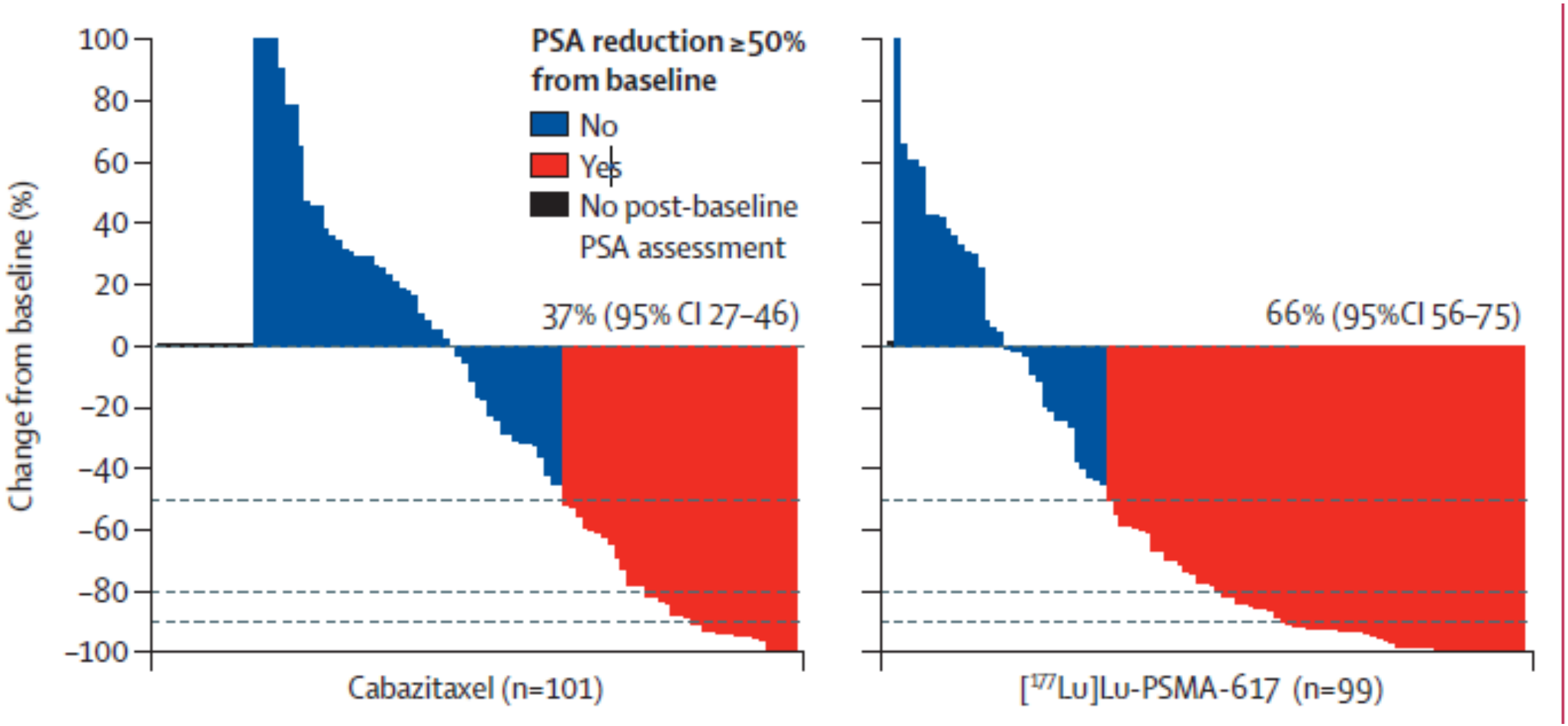
TheraP trial

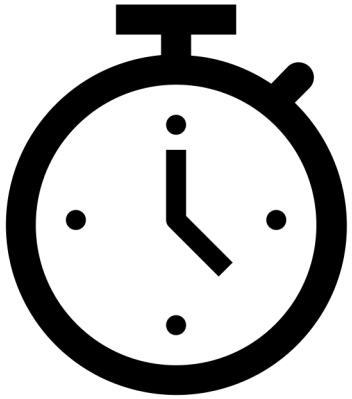
Lu-PSMA-617 versus Cabazitaxel



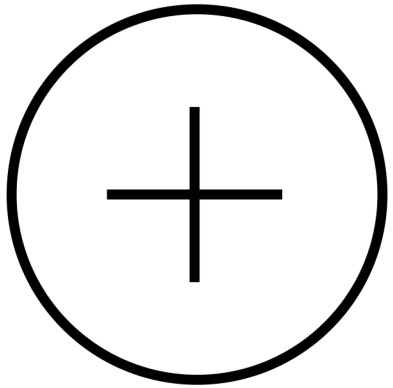
- Prior NHT 91%
- >20 sites of disease – 80%
- mPSA 110/ 94

Hofman, Lancet 2021


PSA reduction ≥50% from baseline
No
Yes
No post-baseline PSA assessment
Change from baseline (%)
100
80
60
40
20
0
-20
-40
-60
-80
-100
37% (95% CI 27–46)
66% (95%CI 56–75)
Cabazitaxel (n=101)
[177Lu]Lu-PSMA-617 (n=99)



Earlier use of effective therapy



Combination treatment to avoid resistance


Cancer Center
NCI-DESIGNATED COMPREHENSIVE CANCER CENTER
Prevent and conquer cancer. **Together**.

Thank you!