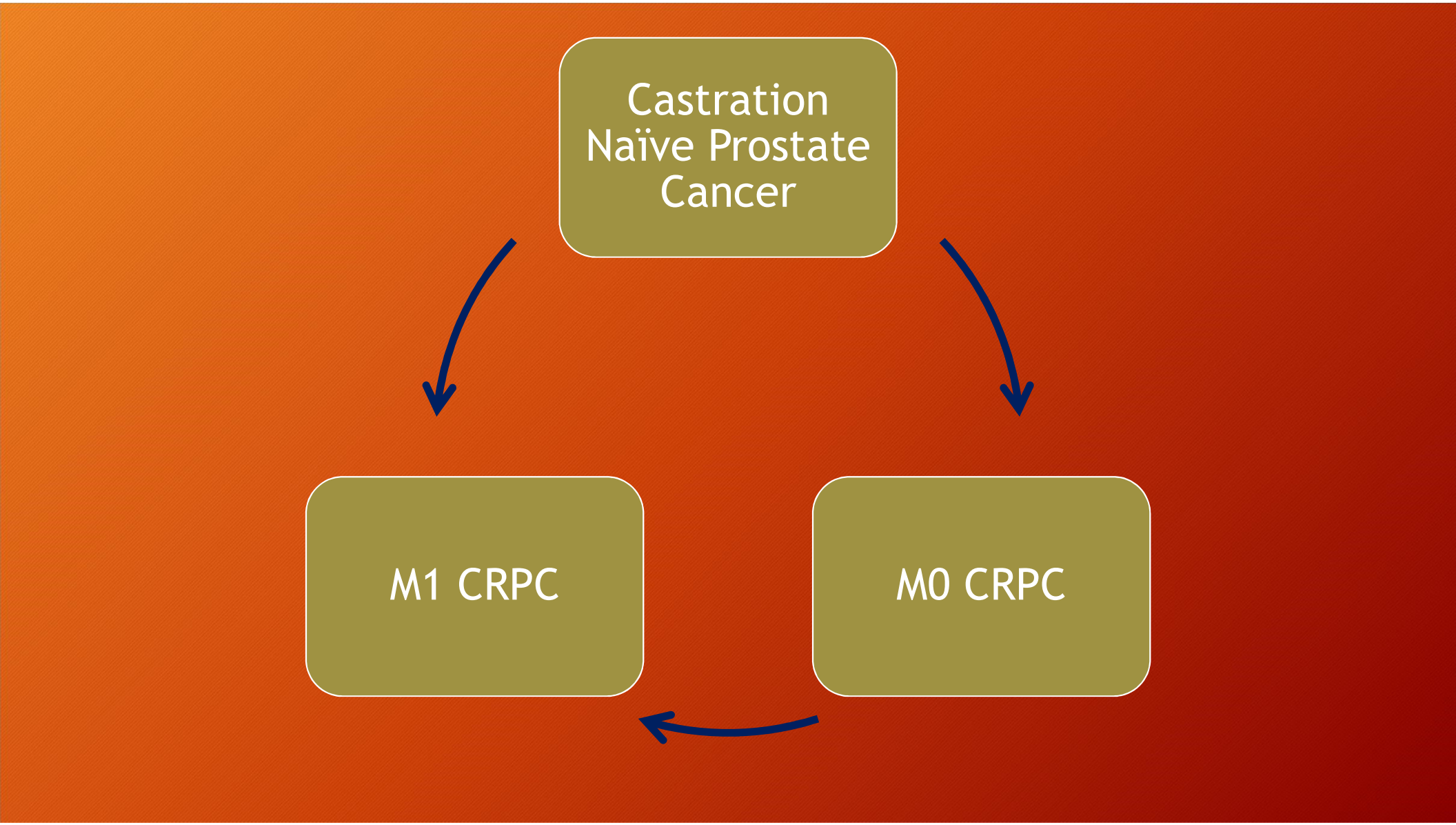
Castration Resistant Prostate Cancer: What is the optimal approach?

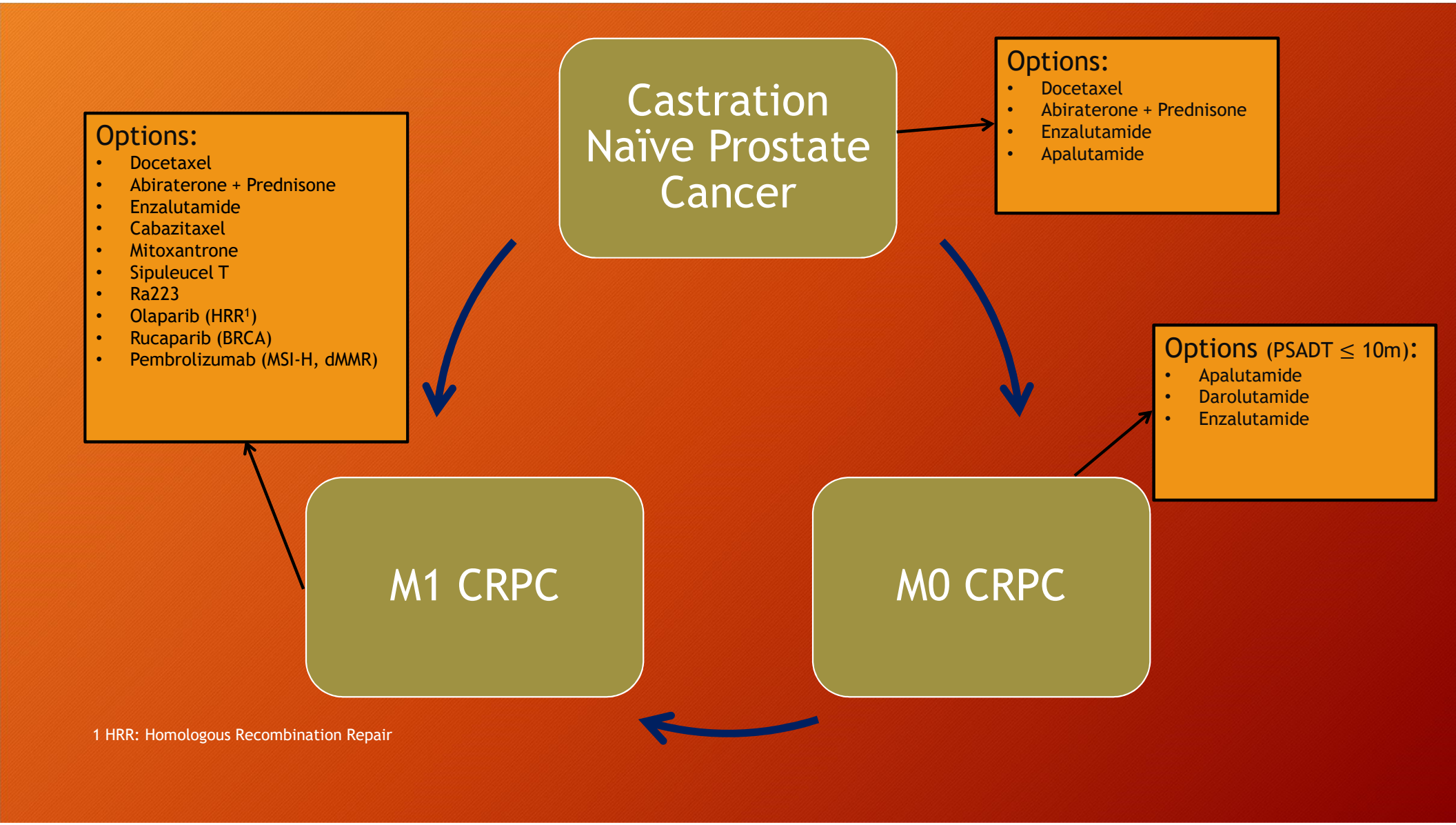
16th California Cancer Consortium Conference

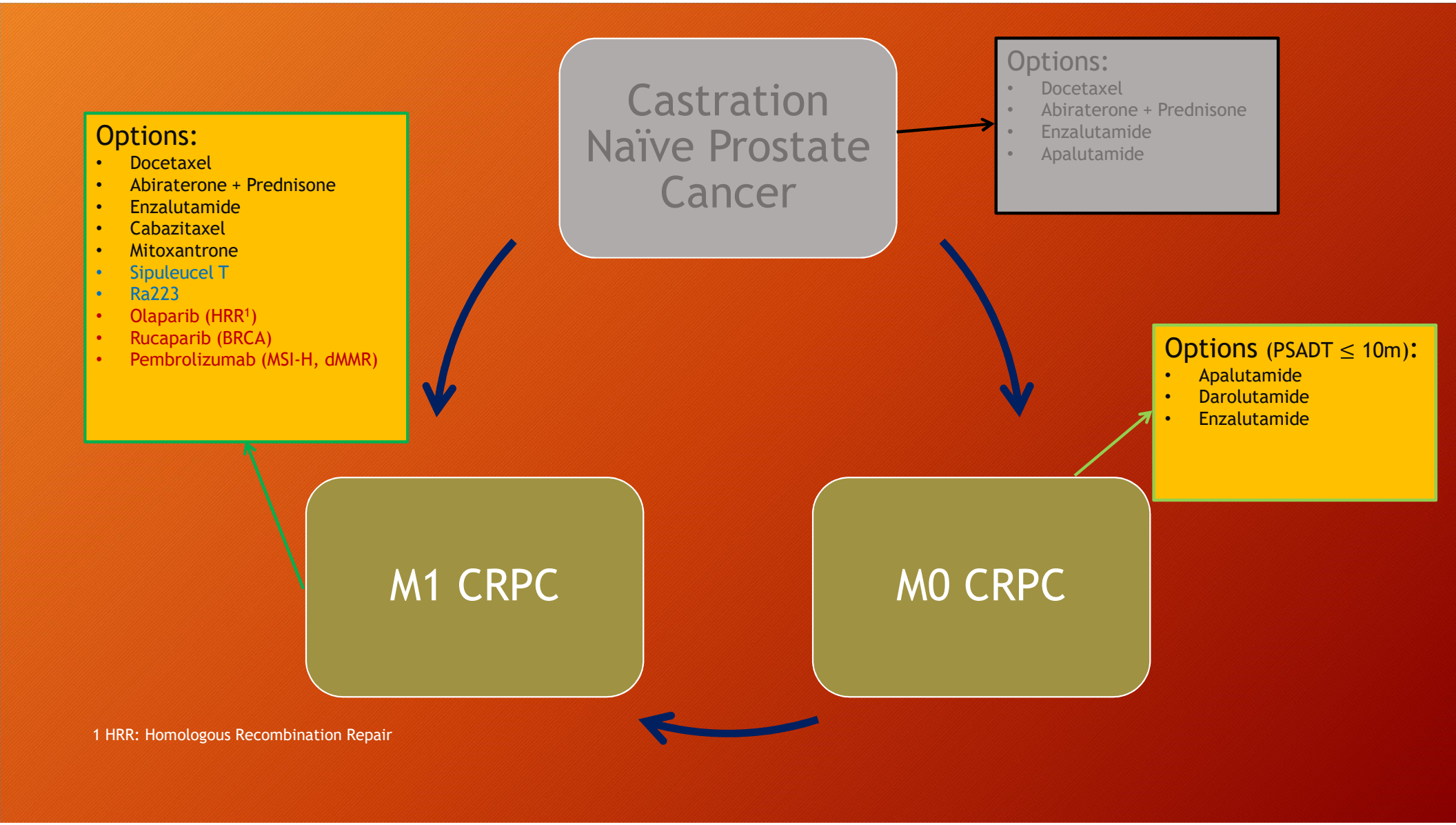
Sarmad Sadeghi, MD, PhD
USC Norris Comprehensive Cancer Center
Oct 31, 2020

Disclosures

- Research Funding
  - Merck
  - Pfizer
- Consulting
  - Pfizer
  - Janssen
  - Tempus


Castration Naïve Prostate Cancer
M1 CRPC
M0 CRPC


Castration Naïve Prostate Cancer
Options:
Docetaxel
Abiraterone + Prednisone
Enzalutamide
Apalutamide
Options:
Docetaxel
Abiraterone + Prednisone
Enzalutamide
Cabazitaxel
Mitoxantrone
Sipuleucel T
Ra223
Olaparib (HRR1)
Rucaparib (BRCA)
Pembrolizumab (MSI-H, dMMR)
Options (PSADT ≤ 10m):
Apalutamide
Darolutamide
Enzalutamide
M1 CRPC
M0 CRPC
1 HRR: Homologous Recombination Repair

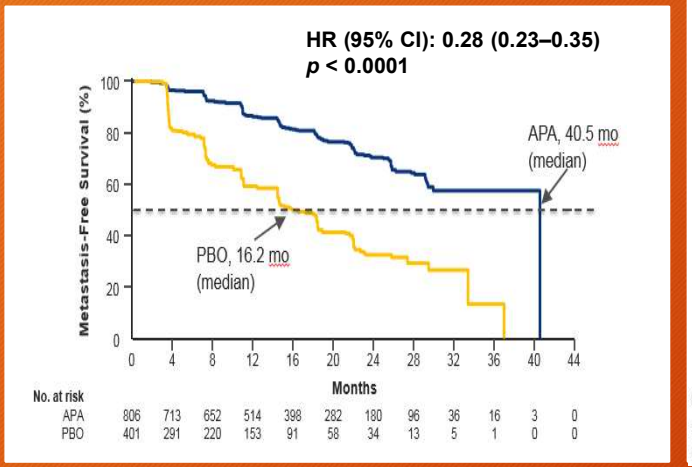

Castration Naïve Prostate Cancer
Options:
Docetaxel
Abiraterone + Prednisone
Enzalutamide
Apalutamide
Options:
Docetaxel
Abiraterone + Prednisone
Enzalutamide
Cabazitaxel
Mitoxantrone
Sipuleucel T
Ra223
Olaparib (HRR1)
Rucaparib (BRCA)
Pembrolizumab (MSI-H, dMMR)
Options (PSADT ≤ 10m):
Apalutamide
Darolutamide
Enzalutamide
M1 CRPC
M0 CRPC
1 HRR: Homologous Recombination Repair

What to Consider to Arrive at the Optimal Approach?

- Treatment history has an impact
- Consider M0 treatment for PSADT $\leq$ 10 months
- Use as many agents with OS benefit as possible

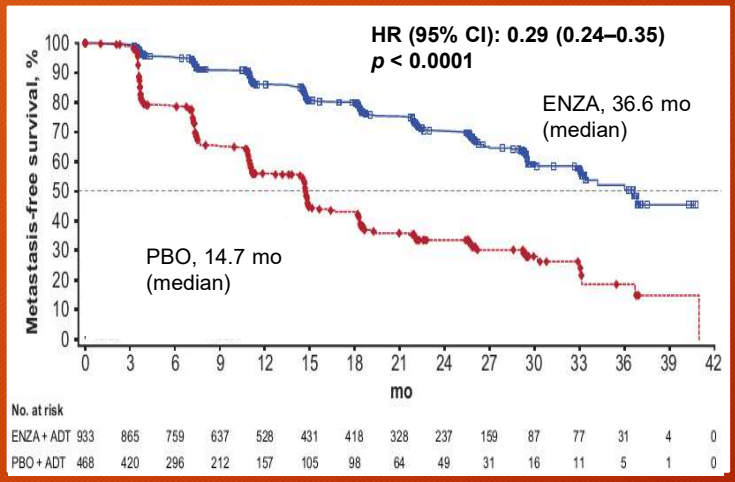
M0: Metastasis-Free Survival (MFS)

Apalutamide: SPARTAN [1]



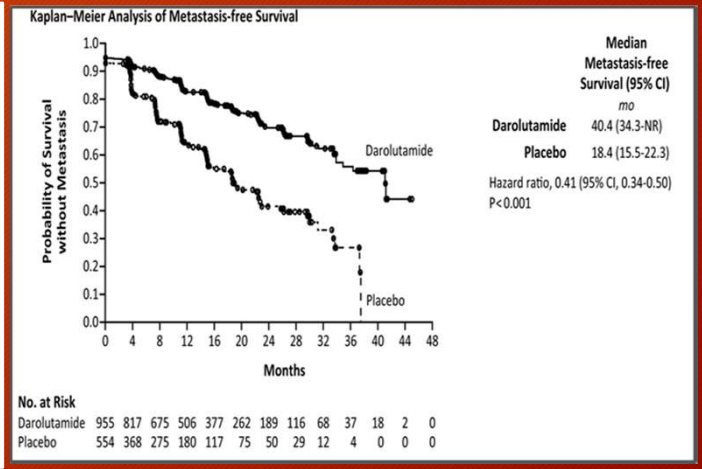
- 72% reduction of distant progression or death
- Median MFS: APA 40.5 months vs PBO 16.2
- 24-month increase in MFS

Enzalutamide: PROSPER [2]



- 71% reduction of distant progression or death
- Median MFS: ENZA 36.6 months vs PBO 14.7
- 22-month increase in MFS

Darolutamide: ARAMIS [3]



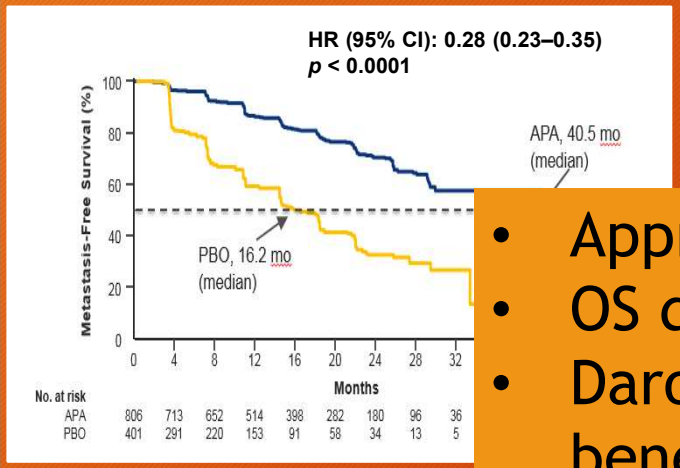
- 59% reduction of distant mets or death
- Median MFS: DARO 40.4 months vs PBO 18.4
- 22-month increase in MFS

1. Smith MR, et al. N Engl J Med 2018.
2. Hussain M, et al. N Engl J Med 2018
3. Fizazi K, et al. N Engl J Med 2019

Courtesy of Dr. Maha Hussain

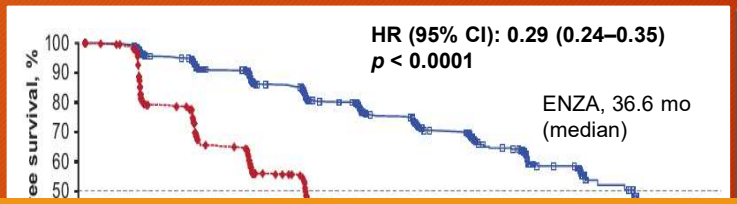
M0: Metastasis-Free Survival (MFS)

Apalutamide: SPARTAN [1]



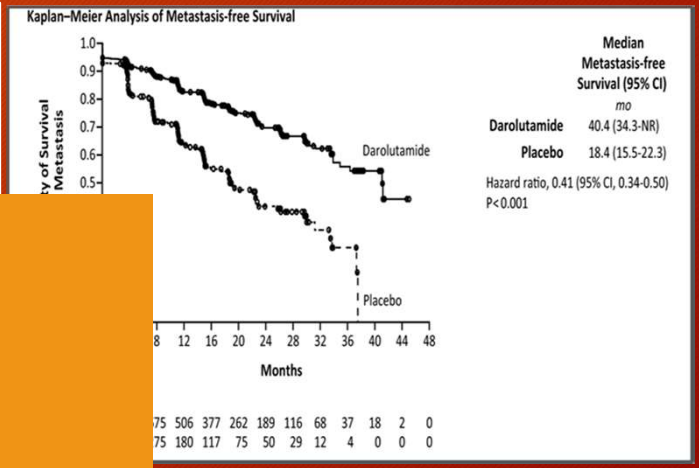
- 72% reduction of distant progression or death
- Median MFS: APA 40.5 months vs PBO 16.2
- 24-month increase in MFS

Enzalutamide: PROSPER [2]



- 71% reduction of distant progression or death
- Median MFS: ENZA 36.6 months vs PBO 14.7
- 22-month increase in MFS

Darolutamide: ARAMIS [3]



- 59% reduction of distant mets or death
- Median MFS: DARO 40.4 months vs PBO 18.4
- 22-month increase in MFS

- Approvals are based on MFS
- OS data are not mature
- Darolutamide has a hint of OS benefit

1. Smith MR, et al. N Engl J Med 2018. 2. Hussain M, et al. N Engl J Med 2018 3. Fizazi K, et al. N Engl J Med 2019

Courtesy of Dr. Maha Hussain

Ra223

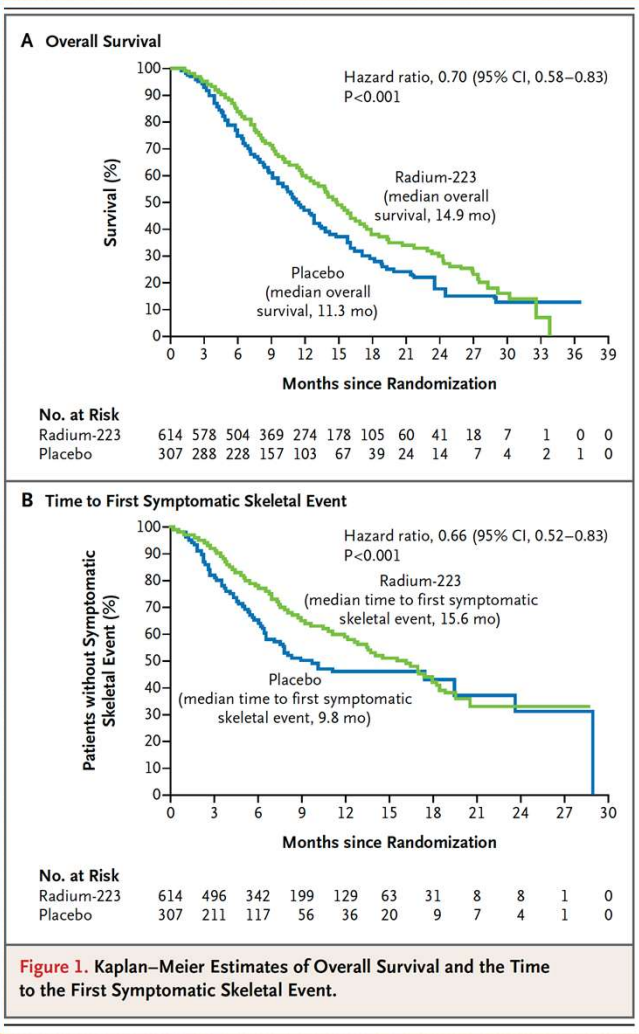


Figure 1. Kaplan–Meier Estimates of Overall Survival and the Time to the First Symptomatic Skeletal Event.

Parker et al, NEJM 2013

Sipuleucel T

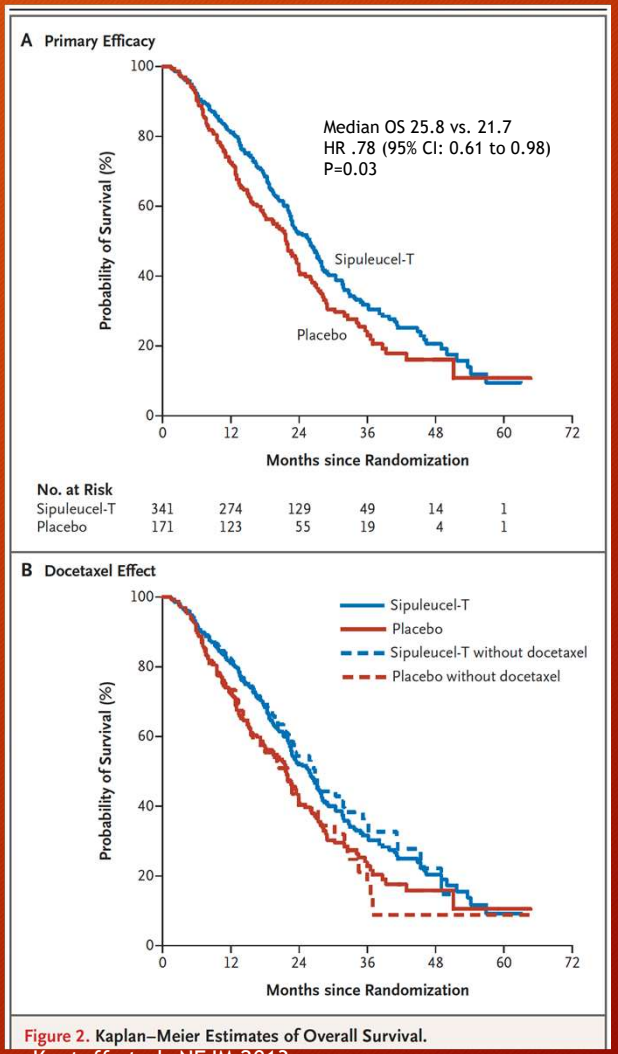


Figure 2. Kaplan–Meier Estimates of Overall Survival.

Kantoff et al, NEJM 2013

Ra223

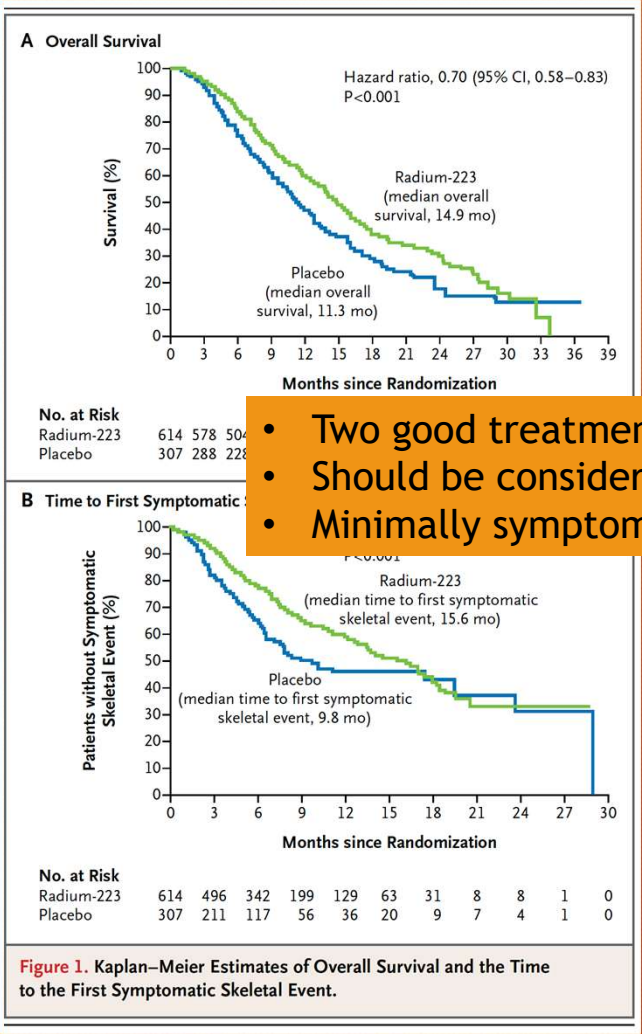


Figure 1. Kaplan–Meier Estimates of Overall Survival and the Time to the First Symptomatic Skeletal Event.

Parker et al, NEJM 2013

Sipuleucel T

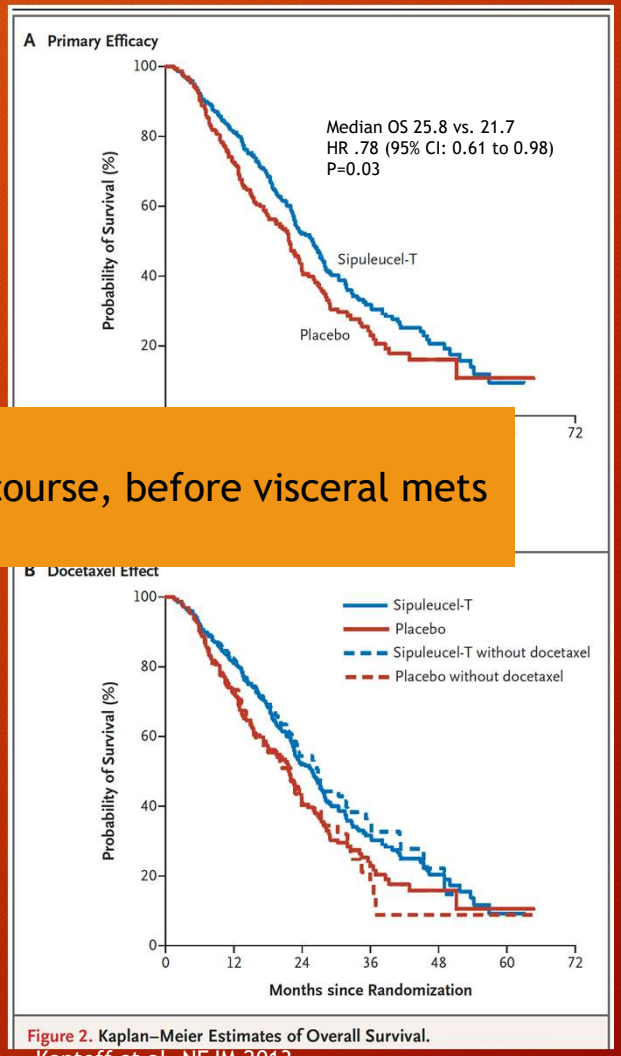


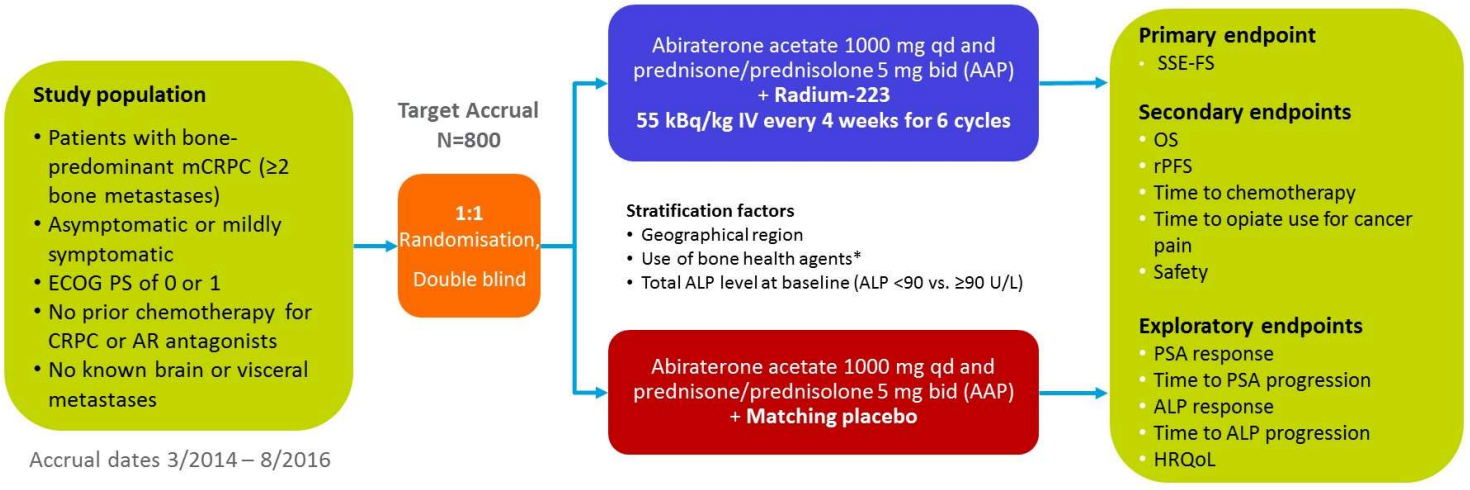
Figure 2. Kaplan–Meier Estimates of Overall Survival.

Kantoff et al, NEJM 2013

- Two good treatment options
- Should be considered earlier in the course, before visceral mets
- Minimally symptomatic patients

EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

ERA 223 (NCT02043678)



Accrual dates 3/2014 – 8/2016

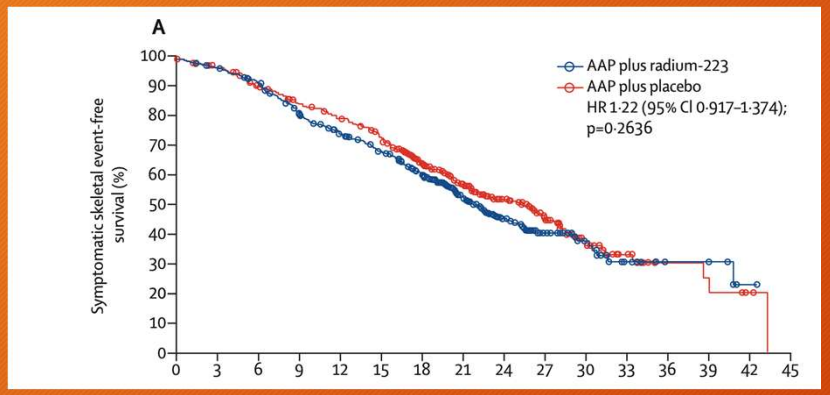
Bone health agents (denosumab or bisphosphonates) only permitted in patients receiving them at baseline; Initiation during study was prohibited to prevent confounding effects.

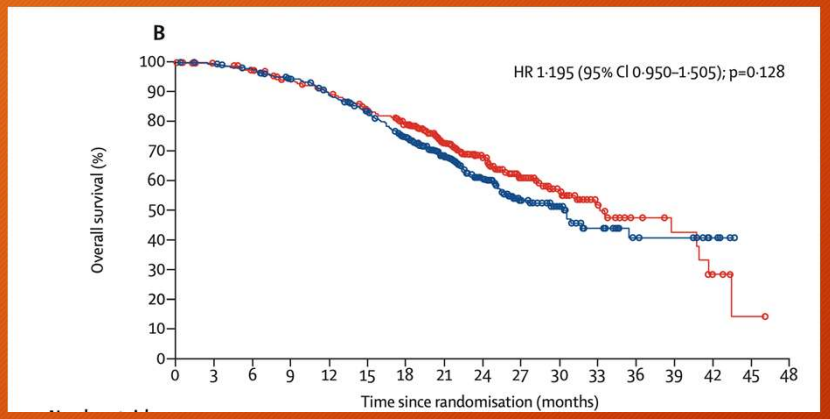
389 events were required to detect a 39% increase in SSE-FS using a test with a 2-sided alpha of 0.05, 90% power and 1:1 randomisation

ALP, alkaline phosphatase; CRPC, castration-resistant prostate cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; IV, intravenous; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PSA, prostate-specific antigen; rPFS, radiological progression-free survival; SSE-FS, symptomatic skeletal event-free survival.

Smith M *et al.* Presented at European Society for Medical Oncology; Munich, Germany; October 19–23, 2018.

ERA 223 study

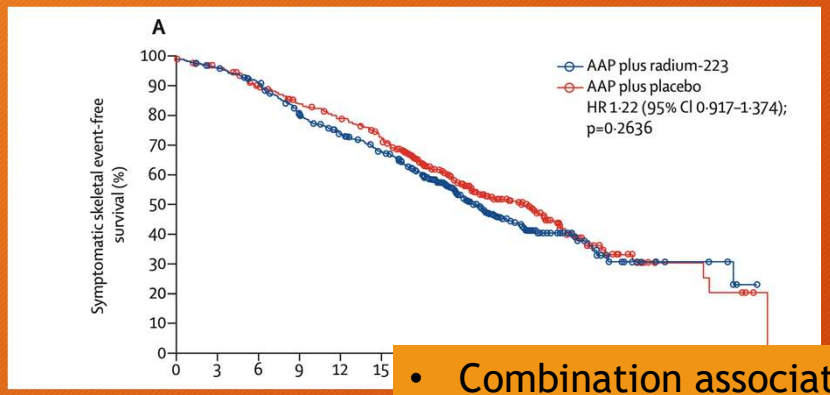




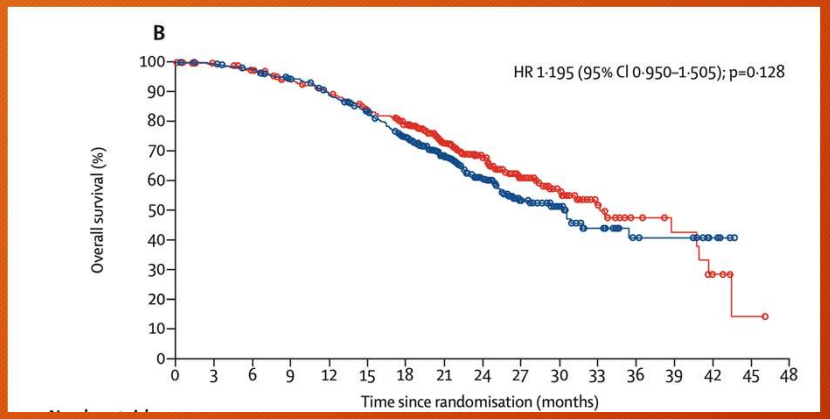
	AAP plus radium-223 group (n=392)	AAP plus placebo group (n=394)
Fractures		
Patients with at least one fracture by investigator assessment	112 (29%)	45 (11%)
Time to first fracture		
<6 months	45 (11%)	11 (3%)
6 to <12 months	46 (12%)	15 (4%)
12 to <24 months	19 (5%)	16 (4%)
≥24 months	2 (1%)	3 (1%)
Deaths		
n	151 (39%)	140 (36%)
Cause of death		
Progressive disease	109 (28%)	102 (26%)
Adverse event associated with clinical progression	13 (3%)	12 (3%)
Adverse event not associated with clinical progression	13 (3%)	12 (3%)
Unknown	8 (2%)	5 (1%)
Other	8 (2%)*	9 (2%)†
Relationship between fracture and death		
Death with no previous fracture	109 (28%)	121 (31%)
Death with previous symptomatic skeletal event fracture	23 (6%)	9 (2%)
Death with previous non-symptomatic skeletal event fracture	25 (6%)	12 (3%)

Smith et al, Lancet Oncol 2019

ERA 223 study



- Combination associated with more fractures and more deaths
- It should be avoided



	AAP plus radium-223 group (n=392)	AAP plus placebo group (n=394)
Fractures		
Patients with at least one fracture by investigator assessment	112 (29%)	45 (11%)
Time to first fracture		
<6 months	45 (11%)	11 (3%)
6 to <12 months	46 (12%)	15 (4%)
12 to <24 months	19 (5%)	16 (4%)
		3 (1%)
		140 (36%)
Cause of death		
Progressive disease	109 (28%)	102 (26%)
Adverse event associated with clinical progression	13 (3%)	12 (3%)
Adverse event not associated with clinical progression	13 (3%)	12 (3%)
Unknown	8 (2%)	5 (1%)
Other	8 (2%)*	9 (2%)†
Relationship between fracture and death		
Death with no previous fracture	109 (28%)	121 (31%)
Death with previous symptomatic skeletal event fracture	23 (6%)	9 (2%)
Death with previous non-symptomatic skeletal event fracture	25 (6%)	12 (3%)

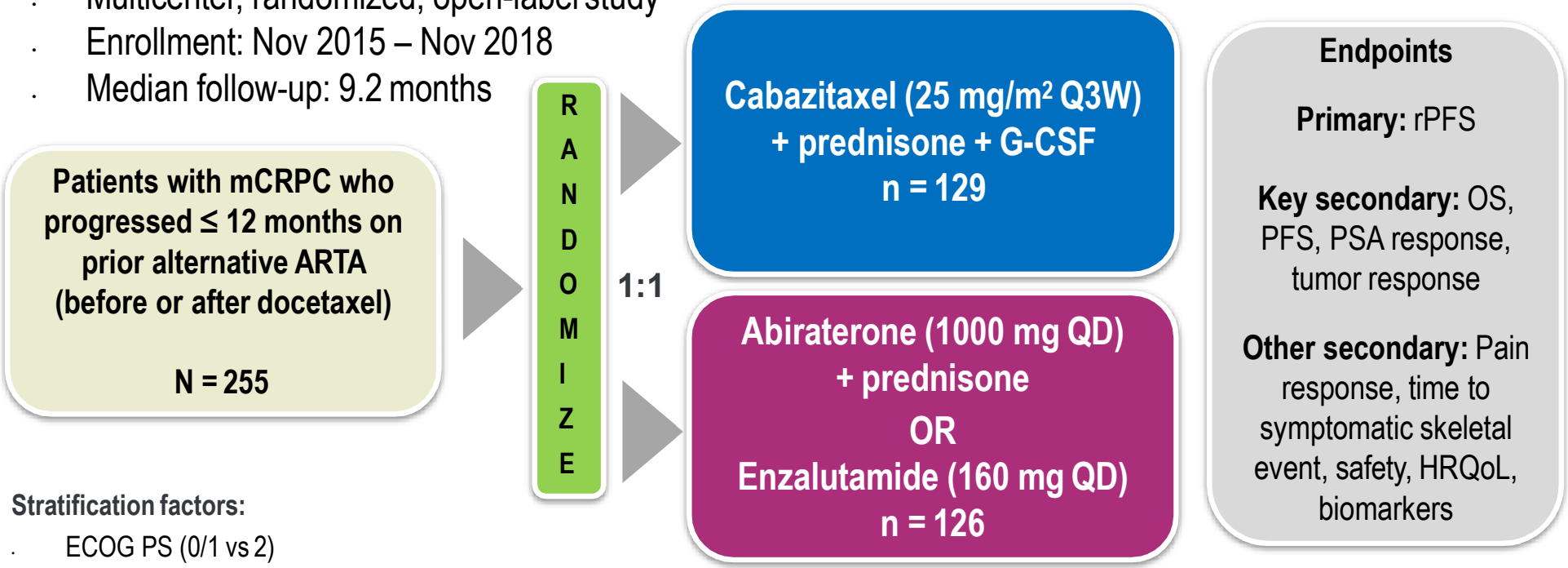
Smith et al, Lancet Oncol 2019

What to Consider to Arrive at the Optimal Approach?

- Treatment history has an impact
- Consider M0 treatment for PSADT $\leq$ 10 months
- Use as many agents with OS benefit as possible
- Consider Sipuleucel T and Ra223 earlier in the course
- Avoid combining Ra223 and abiraterone

CARD: STUDY DESIGN

- Multicenter, randomized, open-label study
- Enrollment: Nov 2015 – Nov 2018
- Median follow-up: 9.2 months



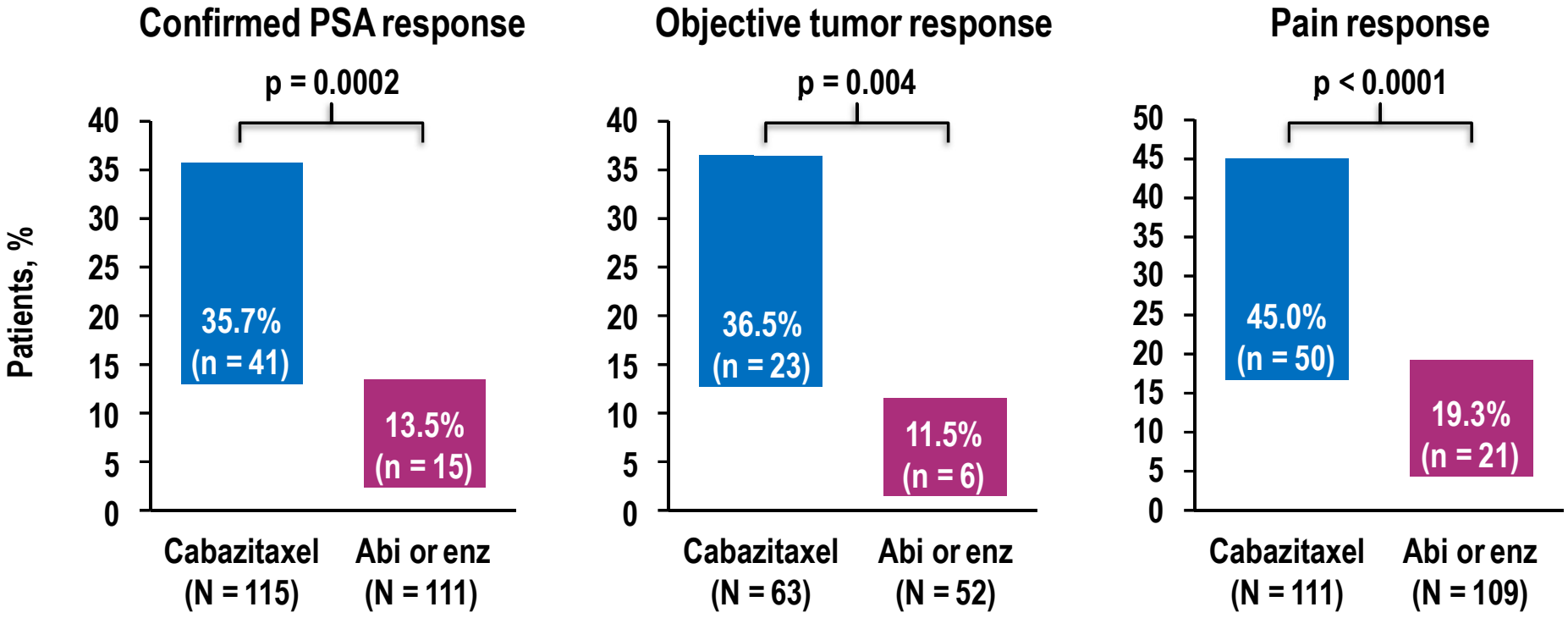
Stratification factors:

- ECOG PS (0/1 vs 2)
- Time to progression on prior alternative ARTA (0–6 vs > 6–12 months)
- Timing of ARTA (before vs after docetaxel)

ECOG PS, Eastern Cooperative Oncology Group performance status; G-CSF, granulocyte-colony stimulating factor; HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; QD, once daily; Q3W, every 3 weeks; rPFS, radiographic progression-free survival.

De Wit et al, ESMO 2019

PSA, TUMOR AND PAIN RESPONSES



Response definitions

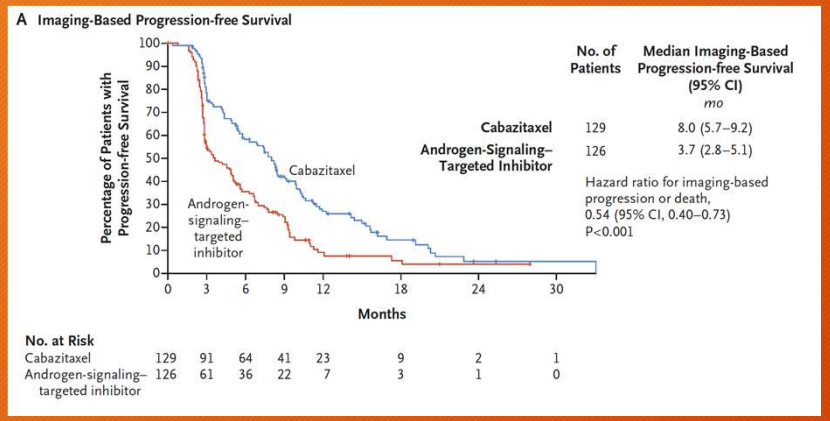
PSA: PSA reduction ≥ 50% from baseline, confirmed by a second value at least 3 weeks later. Tumor: complete or partial responses according to RECIST 1.1 criteria. Pain: decrease ≥ 30% from baseline in average BPI-SF pain intensity score at 2 consecutive evaluations ≥ 3 weeks apart without increase in analgesic usage score.

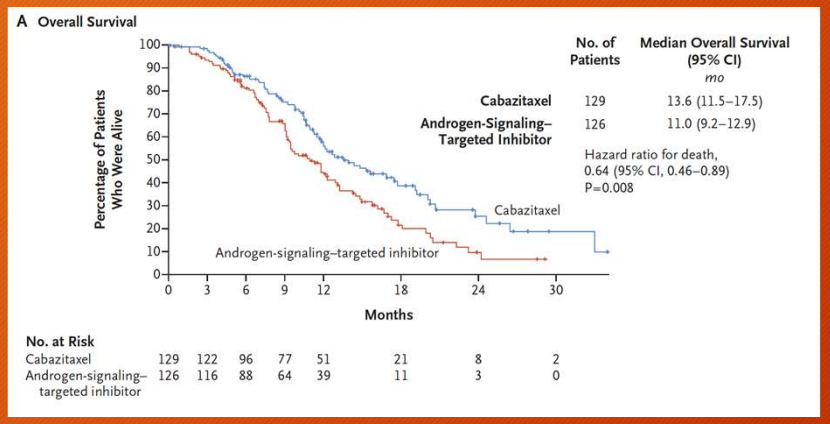
N, patients evaluable for PSA, tumor or pain response.

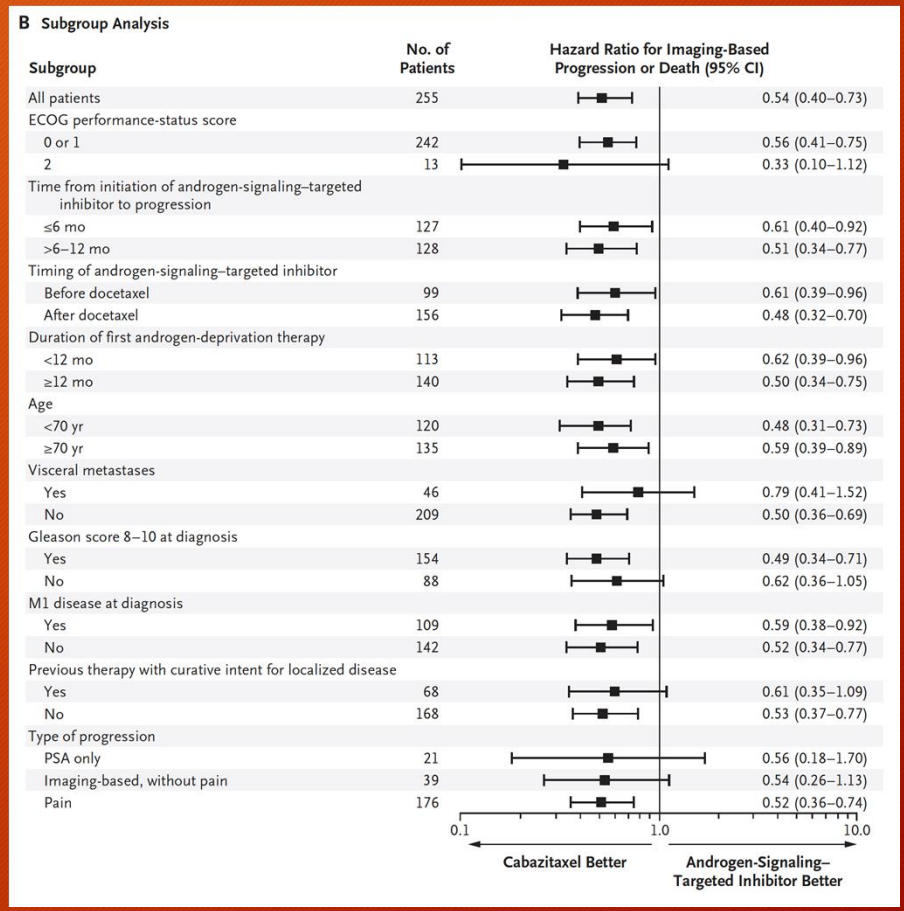
BPI-SF, Brief Pain Inventory - Short Form.

De Wit et al, ESMO 2019

CARD study

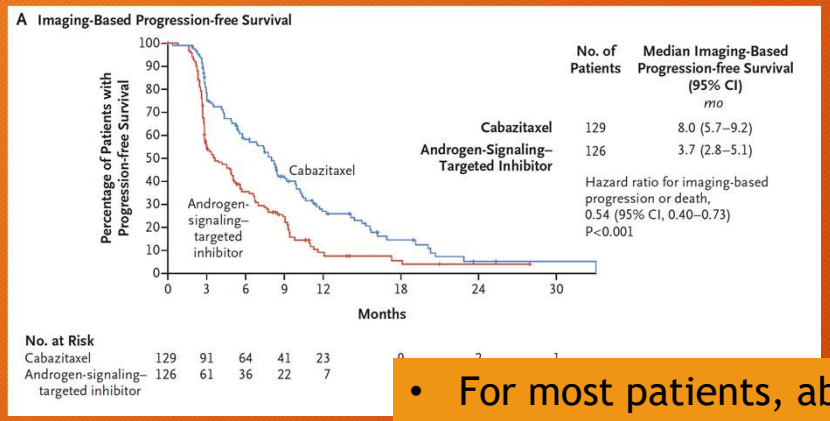


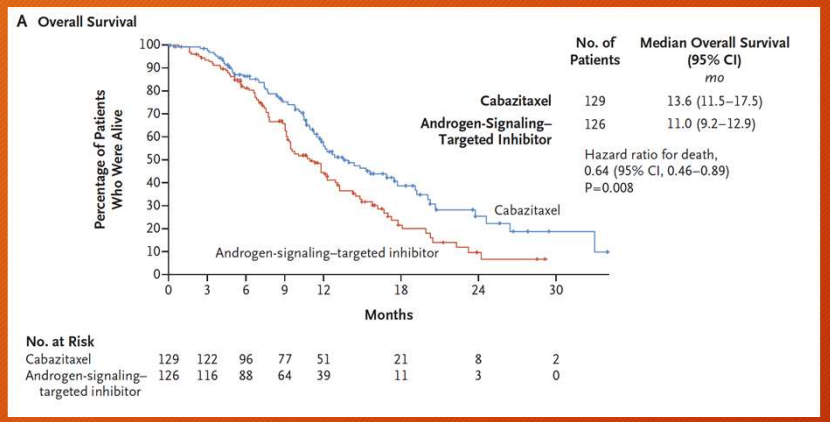




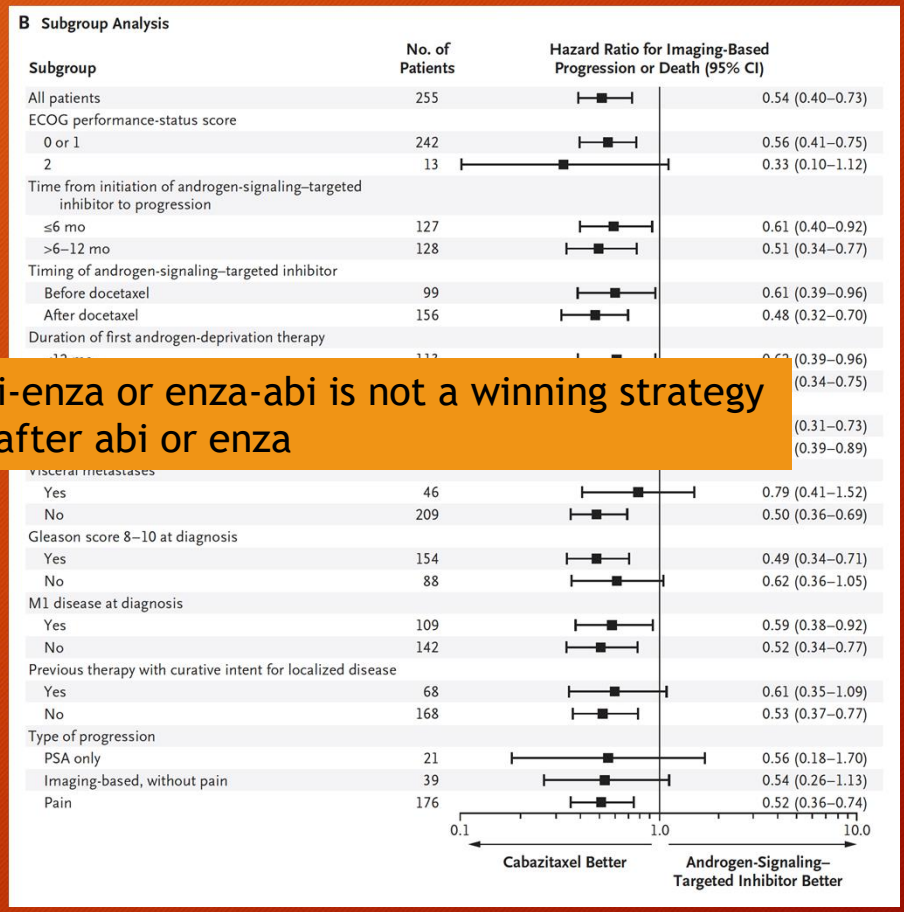
De Wit et al, NEJM 2019

CARD study





- For most patients, abi-enza or enza-abi is not a winning strategy
- Consider cabazitaxel after abi or enza

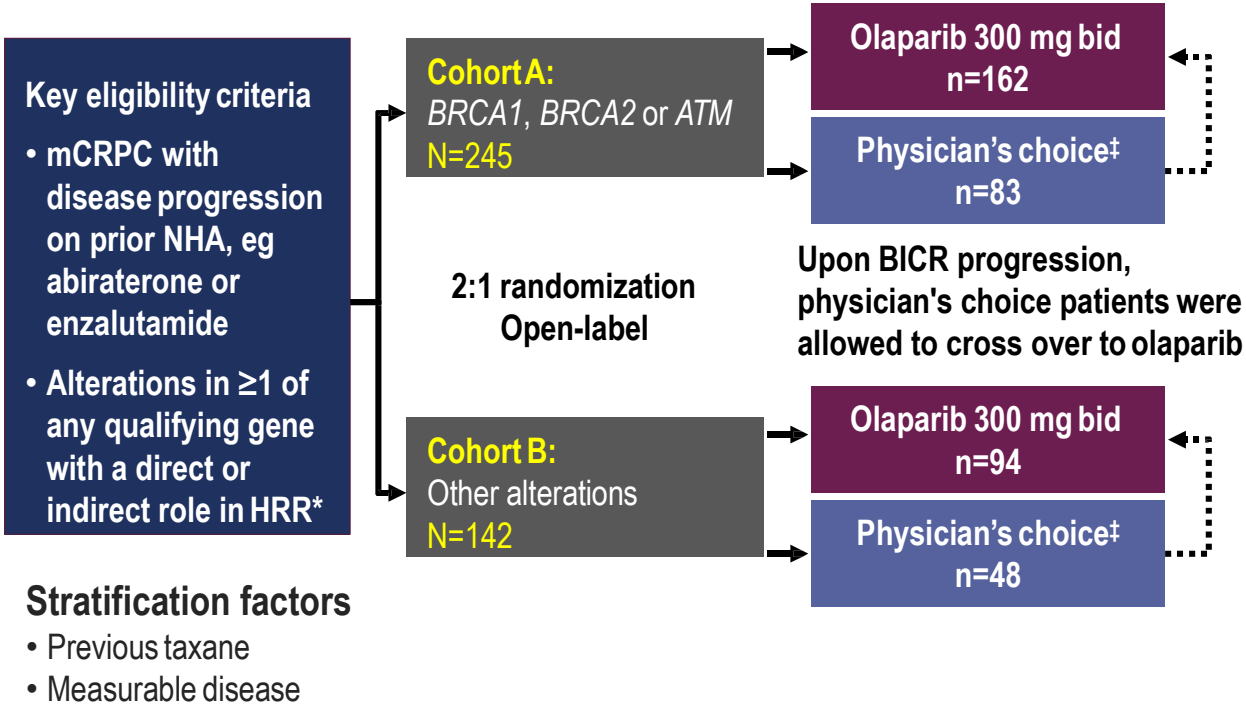


De Wit et al, NEJM 2019

What to Consider to Arrive at the Optimal Approach?

- Treatment history has an impact
- Consider M0 treatment for PSADT $\leq$ 10 months
- Use as many agents with OS benefit as possible
- Consider Sipuleucel T and Ra223 earlier in the course
- Avoid combining Ra223 and abiraterone
- Avoid using abiraterone after enzalutamide or vice versa

PROfound STUDY DESIGN



Stratification factors
- Previous taxane
- Measurable disease

Primary Endpoint

Radiographic progression-free survival (rPFS) in Cohort A (RECIST 1.1 & PCWG3 by BICR)

Key Secondary Endpoints

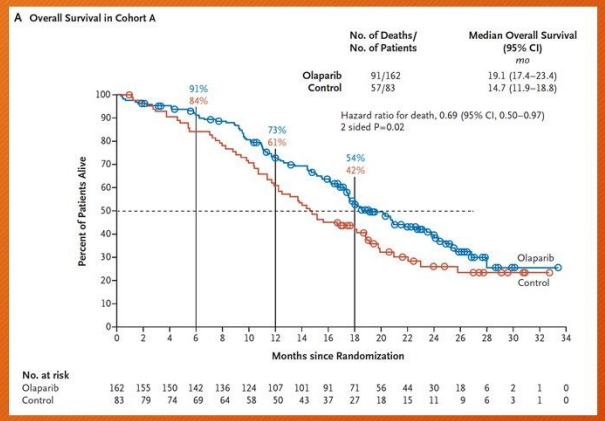
- rPFS in Cohorts A+B
- Confirmed radiographic objective response rate (ORR) in Cohort A
- Time to pain progression (TTPP) in Cohort A
- Overall survival (OS) in Cohort A

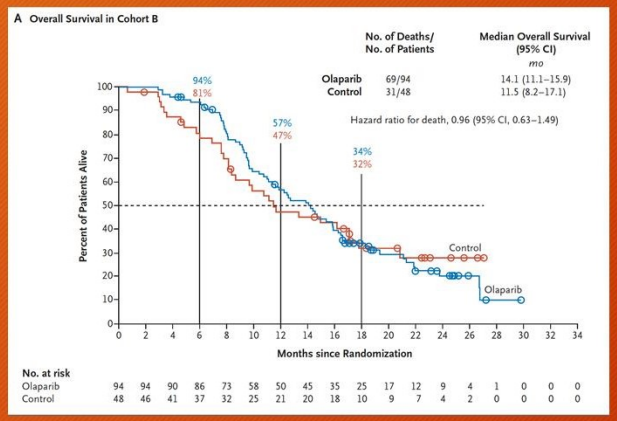
***An investigational Clinical Trial Assay, based on the FoundationOne® CDx next-generation sequencing test**
Developed in partnership with Foundation Medicine Inc, and used to prospectively select patients harboring alterations in *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* and/ or *RAD54L* in their tumor tissue

‡Physician's choice of either enzalutamide (160 mg qd) or abiraterone (1000 mg qd + prednisone [5 mg bid])
BICR, blinded independent central review

Hussain et al, ESMO 2019

PROfound study





Subgroup	Olaparib	Control	Hazard Ratio for Death (95% CI)
	no. of deaths/no. of patients		
All patients	91/162	57/83	0.69 (0.50–0.97)
Previous use of taxane			
Yes	60/106	41/52	0.56 (0.38–0.84)
No	31/56	16/31	1.03 (0.57–1.92)
Measurable disease at baseline			
Yes	55/95	33/46	0.73 (0.47–1.13)
No	36/67	24/37	0.67 (0.40–1.15)
Metastases at baseline			
Bone only	30/57	15/23	0.64 (0.35–1.22)
Visceral	29/46	22/32	0.99 (0.57–1.74)
Other	27/49	16/23	0.62 (0.34–1.18)
ECOG performance-status score at baseline			
0	46/84	18/34	0.94 (0.55–1.66)
1	35/67	36/46	0.55 (0.35–0.88)
2	10/11	3/3	0.98 (0.30–4.37)
Age at randomization			
<65 yr	29/54	16/23	0.62 (0.34–1.17)
≥65 yr	62/108	41/60	0.74 (0.50–1.10)
Region			
Asia	32/57	18/28	0.86 (0.49–1.55)
Europe	36/68	29/38	0.52 (0.32–0.85)
North America or South America	23/37	10/17	0.99 (0.48–2.18)
Race			
White	61/109	38/55	0.69 (0.46–1.04)
Black	1/2	1/1	NC
Asian	23/43	12/19	0.76 (0.39–1.59)
Other	1/1	1/1	NC
PSA level at baseline			
≥Median	43/68	37/48	0.65 (0.42–1.01)
<Median	46/92	19/33	0.88 (0.52–1.53)

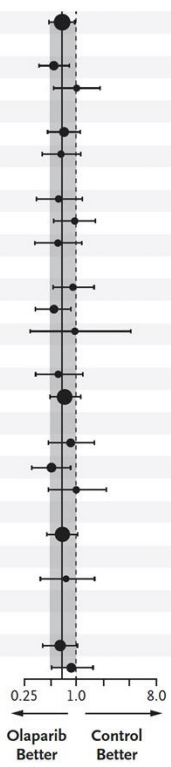
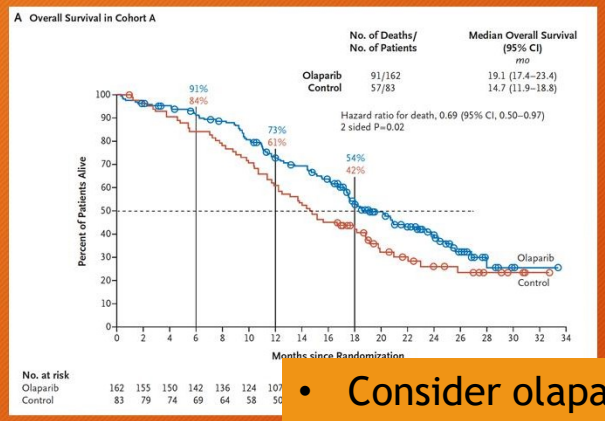
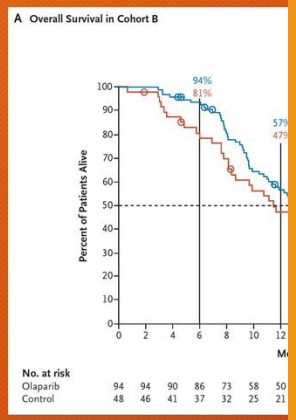


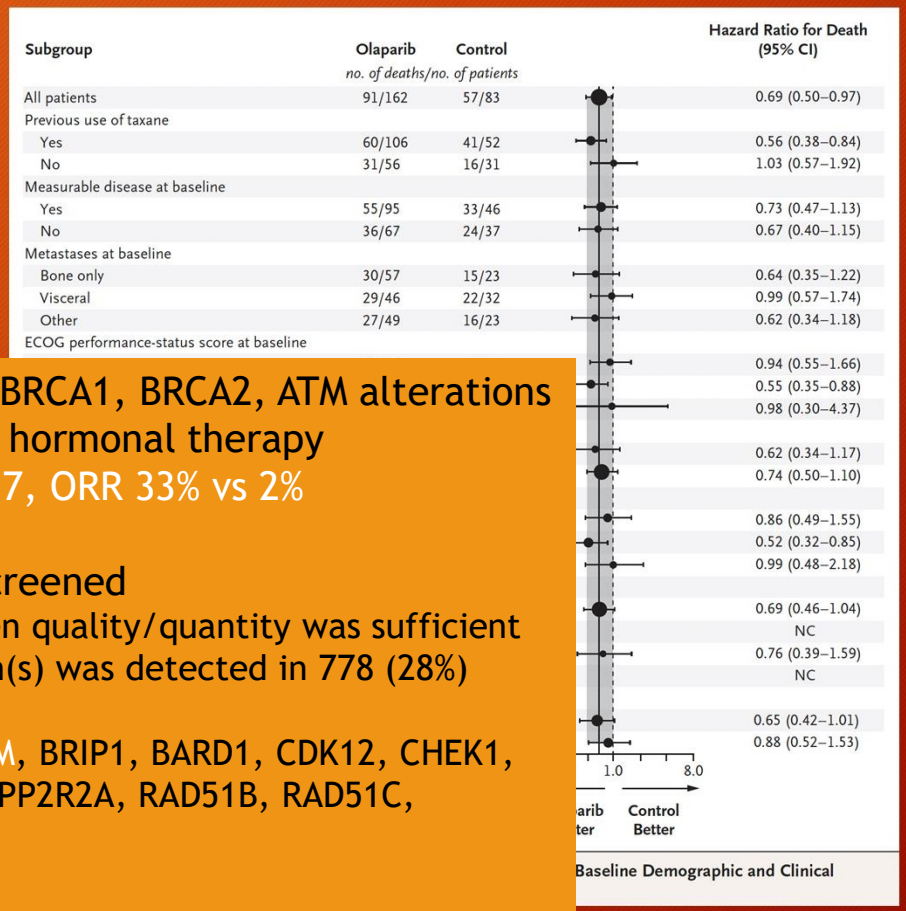
Figure 4. Subgroup Analyses of Overall Survival in Cohort A, According to Baseline Demographic and Clinical Characteristics of the Patients.

De Wit et al, NEJM 2019

PROfound study







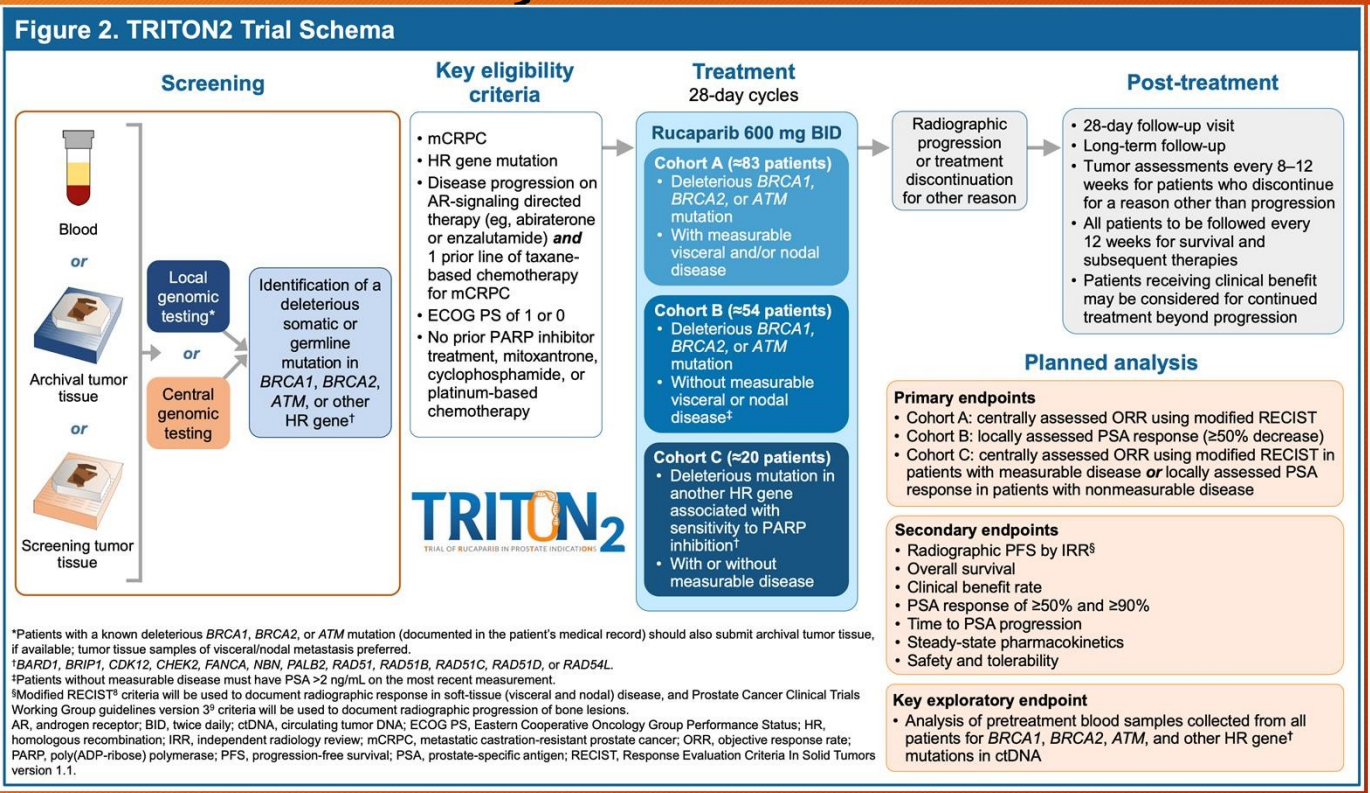
- Consider olaparib for BRCA1, BRCA2, ATM alterations after next generation hormonal therapy
- Median OS 19.1 vs 14.7, ORR 33% vs 2%

- 4425 patients were screened
  - 2792 (69%) specimen quality/quantity was sufficient
    - HRR alteration(s) was detected in 778 (28%)

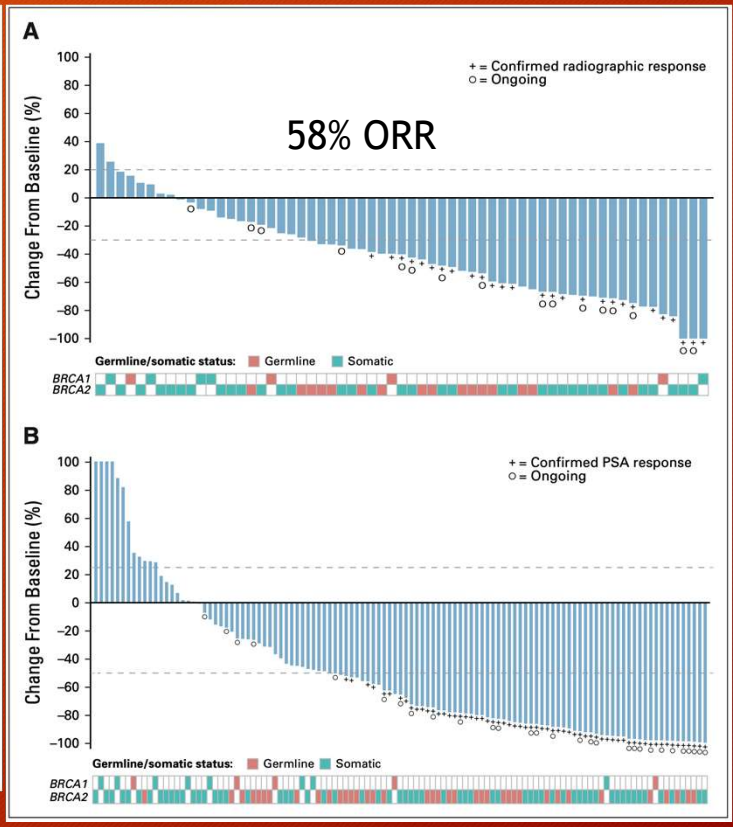
- HHR: BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L

De Wit et al, NEJM 2019

Triton2 study



Abida et al, ASCO GU 2018



Abida et al, JCO 2020

What to Consider to Arrive at the Optimal Approach?

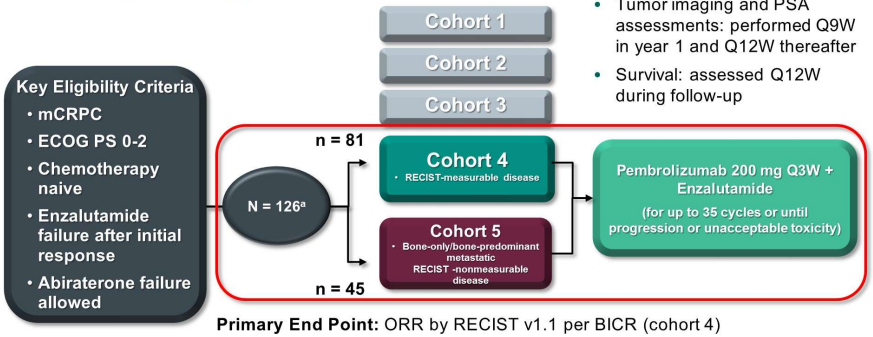
- Treatment history has an impact
- Consider M0 treatment for PSADT $\leq$ 10 months
- Use as many agents with OS benefit as possible
- Consider Sipuleucel T and Ra223 earlier in the course
- Avoid combining Ra223 and abiraterone
- Avoid using abiraterone after enzalutamide or vice versa
- Look for BRCA1, BRCA2, ATM alterations
- Consider olaparib and rucaparib

KEYNOTE-199 Cohorts 4 and 5: Pembrolizumab Plus Enzalutamide for Enzalutamide-Resistant Metastatic Castration-Resistant Prostate Cancer

KEYNOTE-199 Cohorts 4 and 5: Pembrolizumab Plus Enzalutamide for Enzalutamide-Resistant Metastatic Castration-Resistant Prostate Cancer

J. N. Graff[1]; E. S. Antonarakis[2]; C. J. Hoimes[3]; S. T. Tagawa[4]; C. Hwang[5]; D. Kilari[6]; A. J. Ten Tije[7]; A. Omlin[8]; R. McDermott[9]; U. N. Vaishampayan[10]; A. Elliott[11]; H. Wu[12]; J. Kim[12]; C. Schloss[12]; J. S. de Bono[13]

Study Design



- Tumor imaging and PSA assessments: performed Q9W in year 1 and Q12W thereafter
- Survival: assessed Q12W during follow-up

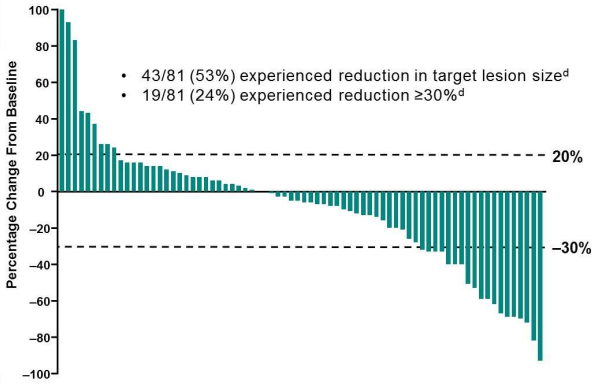
Primary End Point: ORR by RECIST v1.1 per BICR (cohort 4)
Secondary End Points: DCR (RECIST v1.1), rPFS (PCWG3-modified RECIST v1.1), PSA response rate, OS, and safety (cohorts 4 and 5); DOR (RECIST v1.1, cohort 4)

[a]Enrollment regions include North America, EU region, and Rest of World.

Best Confirmed Response by BICR per RECIST v1.1

n (%)	Cohort 4 n = 81	Cohort 5 n = 45
ORR	**10 (12)**	**NA**
CR	2 (2)	NA
PR	8 (10)	NA
SD of any duration	31 (38)	0 (0)
Non-CR/non-PD of any duration	0 (0)	23 (51)
DCR (CR + PR + SD or non-CR/non-PD)	**41 (51)**	**23 (51)**
PD	31 (38)	20 (44)
Nonevaluable[a]	2 (2)	1 (2)
No assessment[b]	7 (9)	1 (2)

Target Lesion Change From Baseline: RECIST-Measurable Disease (cohort 4)[c]



[a]Patients who had poor image quality or insufficient follow-up (<6 months) with best overall response (unconfirmed) of SD, CR, or PR. [b]Had a baseline assessment but no postbaseline assessment on the data cutoff date, including missing, discontinuing or death before first postbaseline imaging. [c]Plot is based on patients who had RECIST-evaluable disease at baseline and ≥1 evaluable postbaseline imaging assessment (n = 74). [d]Calculation is based on patients who had non-missing target lesions at baseline.
Data cutoff: June 24, 2019.

- Combination had a manageable safety profile
  - Incidence of all-grade rash and grade 3 rash resolved with standard-of-care treatment
- Combination is being evaluated in a phase 3 trial (KEYNOTE-641, NCT03834493)

What to Consider to Arrive at the Optimal Approach?

- Treatment history has an impact
- Consider M0 treatment for PSADT $\leq$ 10 months
- Use as many agents with OS benefit as possible
- Consider Sipuleucel T and Ra223 earlier in the course
- Avoid combining Ra223 and abiraterone
- Avoid using abiraterone after enzalutamide or vice versa
- Look for BRCA1, BRCA2, ATM alterations
- Consider olaparib and rucaparib
- Consider pembrolizumab for DNA MMR deficiency based on 2017 FDA approval (not specific to prostate cancer)

What's next?

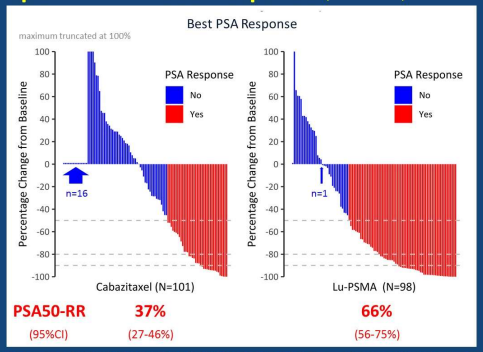
A randomised phase II trial of ^{177}Lu-PSMA-617 (Lu-PSMA) theranostic versus cabazitaxel in metastatic castration resistant prostate cancer (mCRPC) progressing after docetaxel: Initial results

TheraP (ANZUP 1603)

Michael Hofman, Louise Emmett, Shahneen Sandhu, Amir Iravani, Anthony Joshua, Jeffrey Goh, David Pattison, Hsiang Tan, Ian Kirkwood, Siobhan Ng, Roslyn Francis, Craig Gedye, Natalie Rutherford, Alison Zhang, Margaret McJannett, Martin Stockler, John Violet, Scott Williams, Andrew Martin, Ian Davis

ANZUP

Primary endpoint: PSA ≥ 50% response (PSA50-RR)



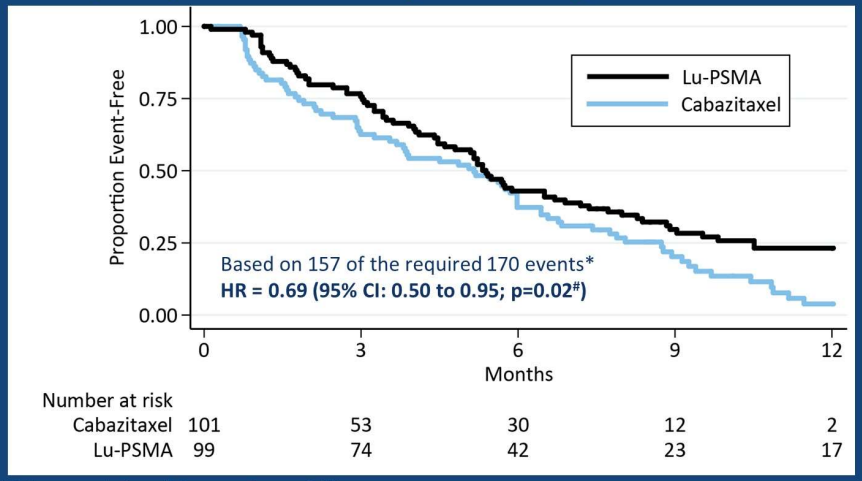
PSA50-RR	37%	66%
(95%CI)	(27-46%)	(56-75%)

Lu-PSMA: 29% absolute (95% CI 16%-42%; p<0.0001) greater PSA50-RR compared to cabazitaxel

For sensitivity analysis per-protocol, the difference was 23% (95% CI 9%-37%; p=0.0016)

Secondary endpoint: PSA PFS (preliminary)

ANZUP



Number at risk					
Cabazitaxel	101	53	30	12	2
Lu-PSMA	99	74	42	23	17

* Primary analysis at 170 events (as per SAP)
# p<0.0027 is required to trigger rejection of null hypothesis prior to planned primary analysis at 170 events (as per SAP)
There have been 71 deaths in total.

11/30/13
Canon 6D, Sigma 35mm, ISO 640, f/1.6, 1/30s