# Castration Resistant Prostate Cancer: What is the optimal approach?

**18th California Cancer Consortium Conference**

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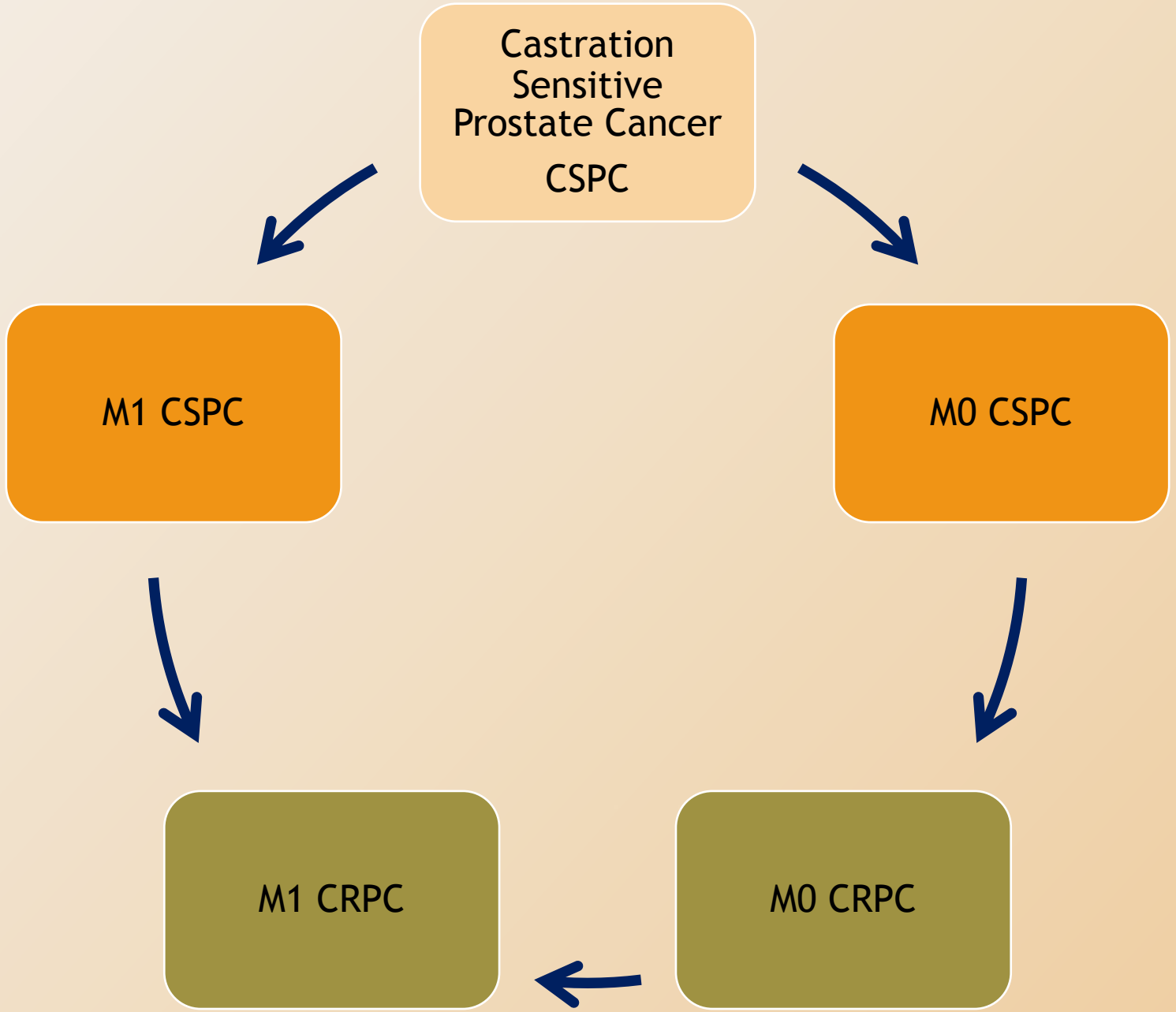
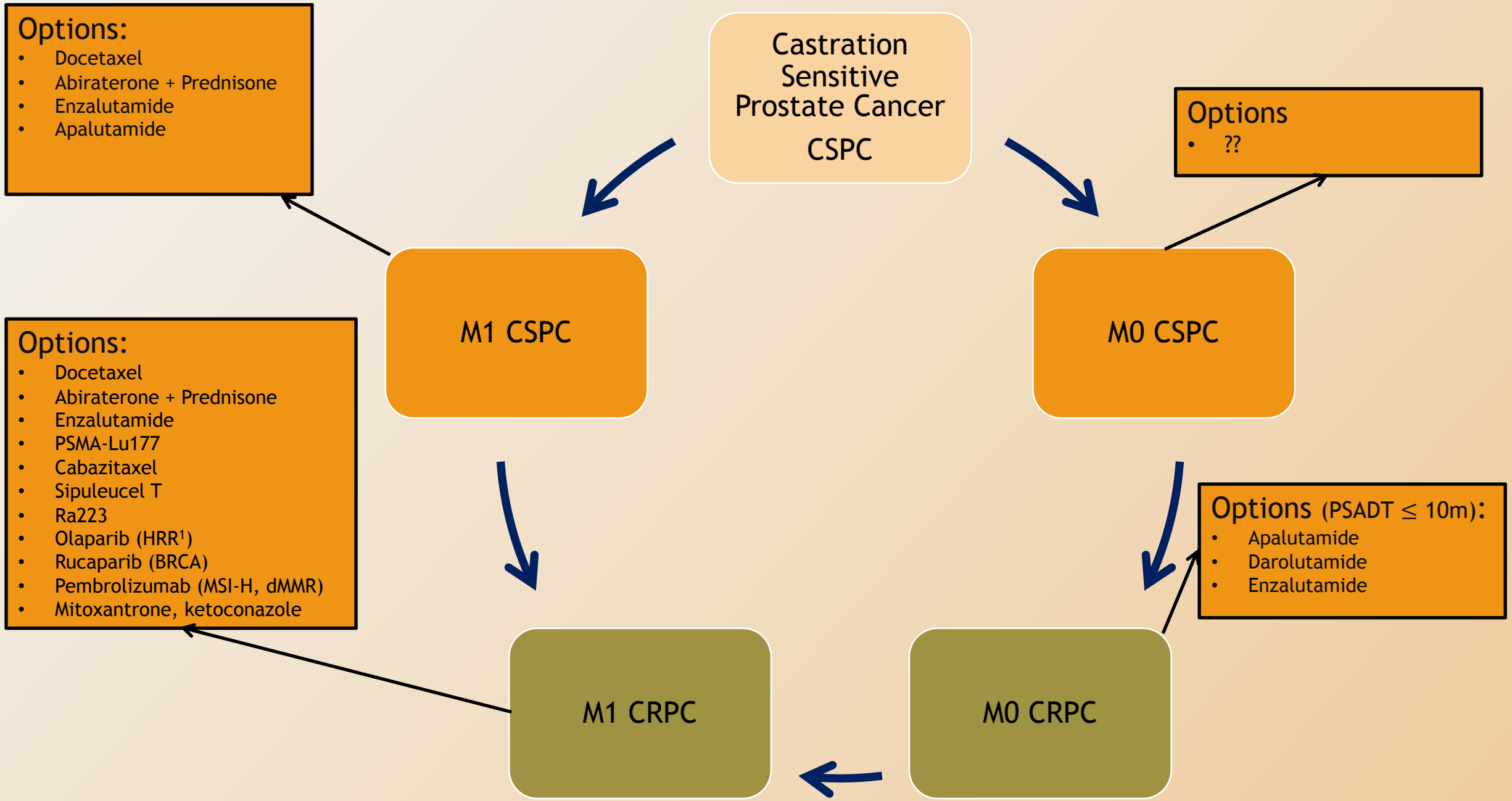
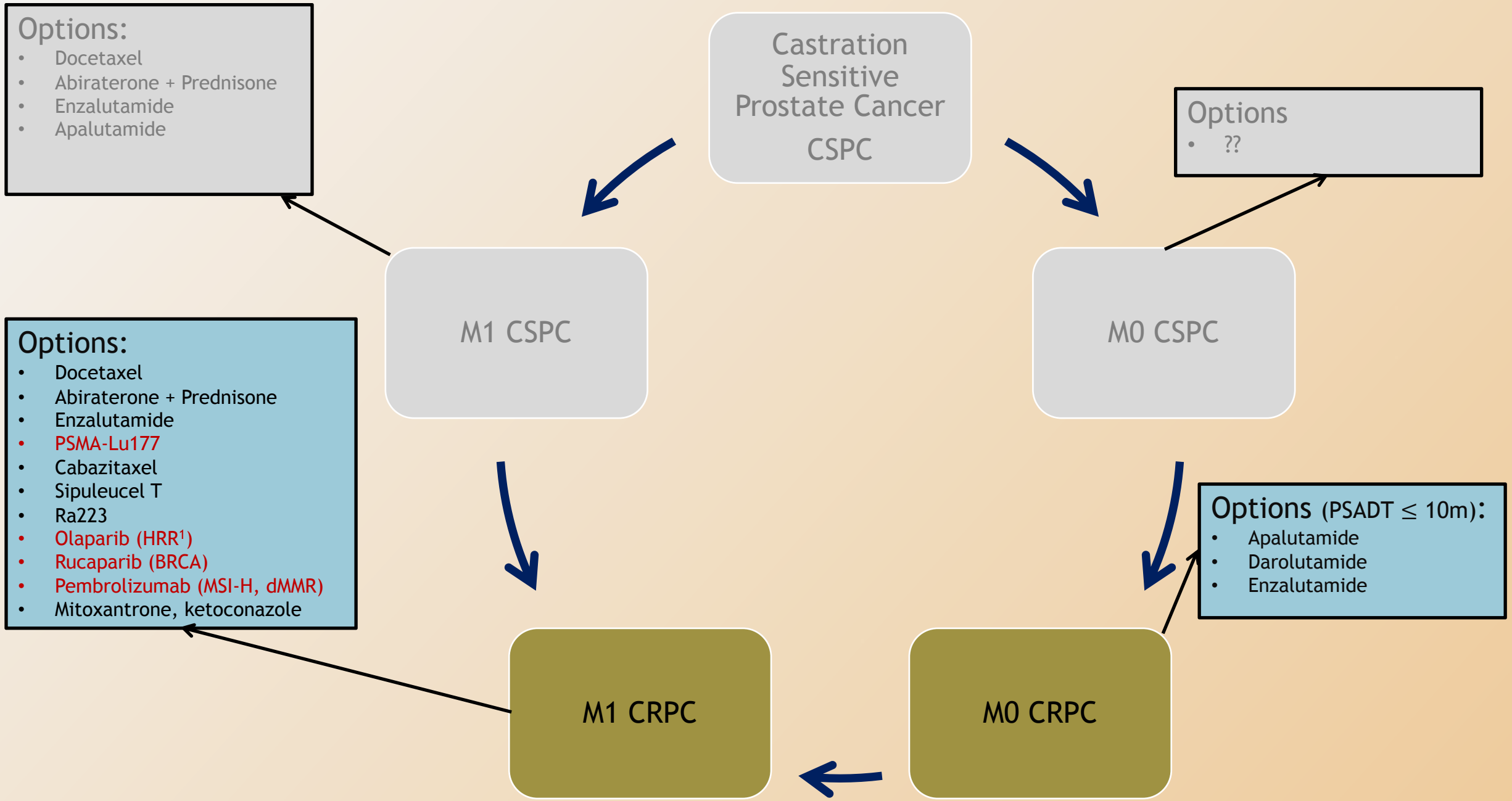
USC Norris Comprehensive Cancer Center
August 20, 2022


Castration Sensitive Prostate Cancer
CSPC
M1 CSPC
M0 CSPC
M1 CRPC
M0 CRPC


Castration Sensitive Prostate Cancer CSPC
Options:
• Docetaxel
• Abiraterone + Prednisone
• Enzalutamide
• Apalutamide
Options
• ??
M1 CSPC
M0 CSPC
Options:
• Docetaxel
• Abiraterone + Prednisone
• Enzalutamide
• PSMA-Lu177
• Cabazitaxel
• Sipuleucel T
• Ra223
• Olaparib (HRR[1])
• Rucaparib (BRCA)
• Pembrolizumab (MSI-H, dMMR)
• Mitoxantrone, ketoconazole
Options (PSADT ≤ 10m):
• Apalutamide
• Darolutamide
• Enzalutamide
M1 CRPC
M0 CRPC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Apalutamide
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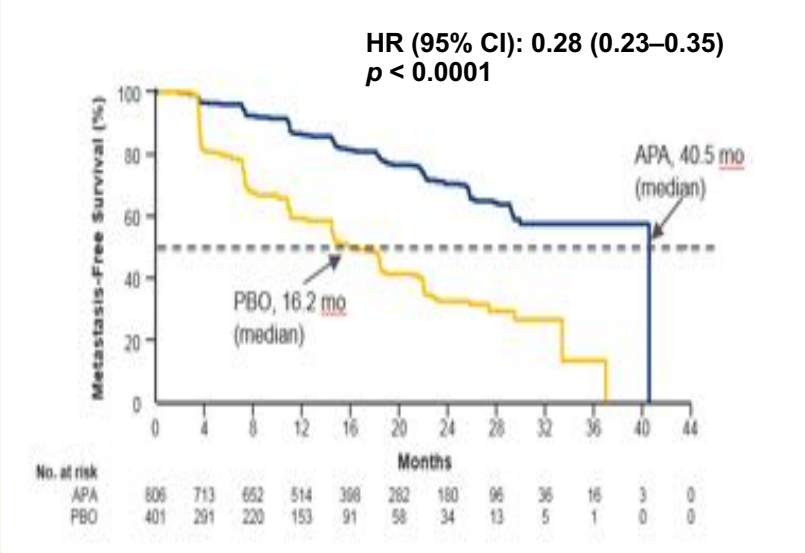
M0 CRPC

# 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

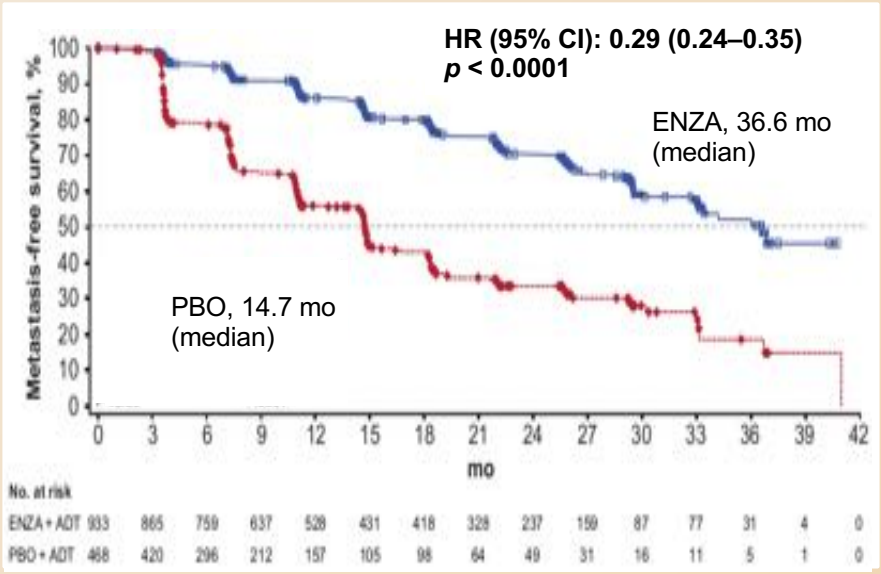
# M0: Metastasis-Free Survival (MFS)

## Apalutamide: SPARTAN [1]



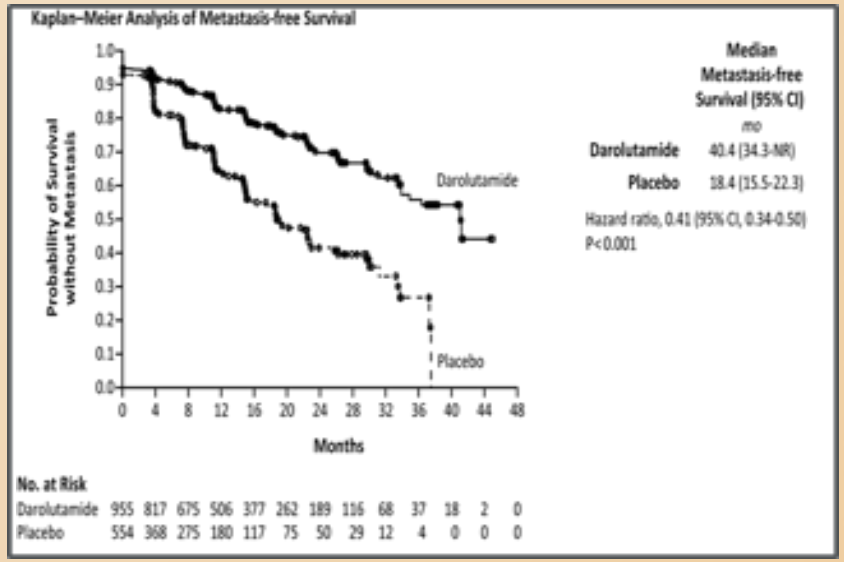

- **72% reduction of distant progression or death**
- **Median MFS: APA 40.5 months vs PBO 16.2**
- **24-month increase in MFS**

## 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]



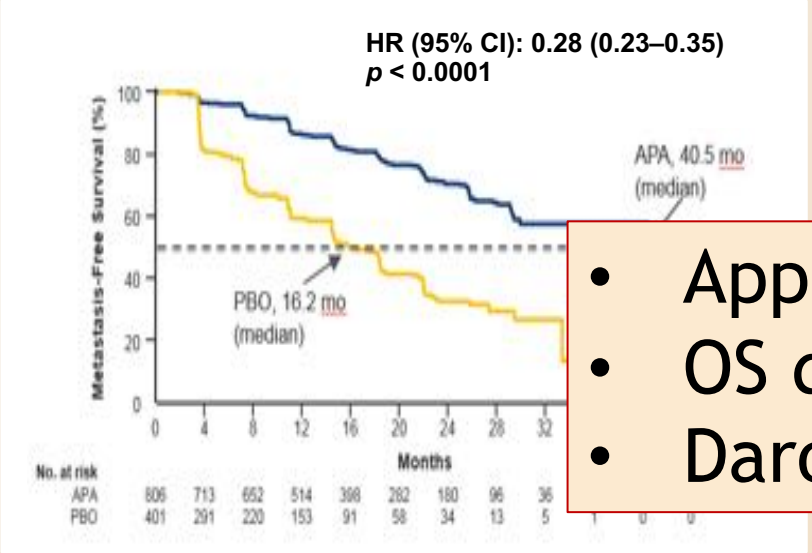

- **59% reduction of distant mets or death**
- **Median MFS: DARO 40.4 months vs PBO 18.4**
- **22-month increase in MFS**


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]

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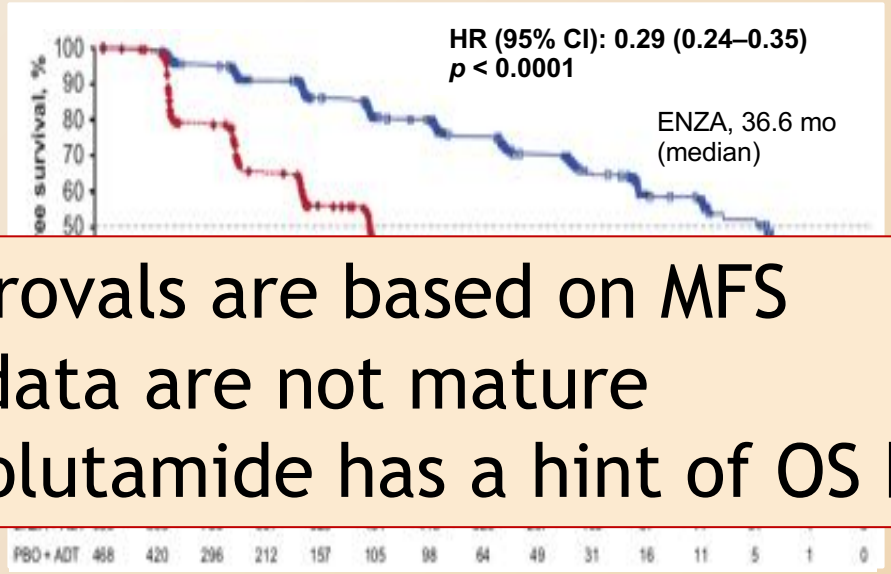


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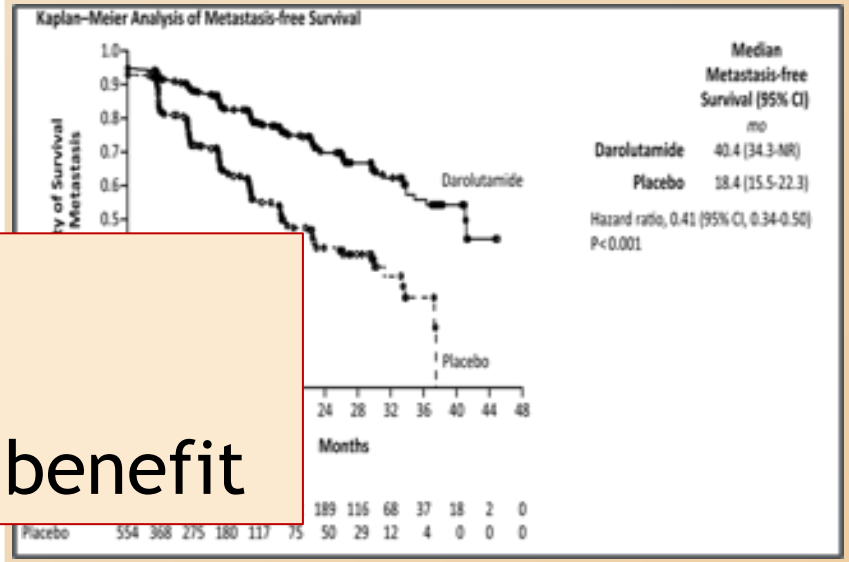



- **59%** reduction of distant mets or death
- Median MFS: DARO 40.4 months vs PBO 18.4
- 22-month increase in MFS

- 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

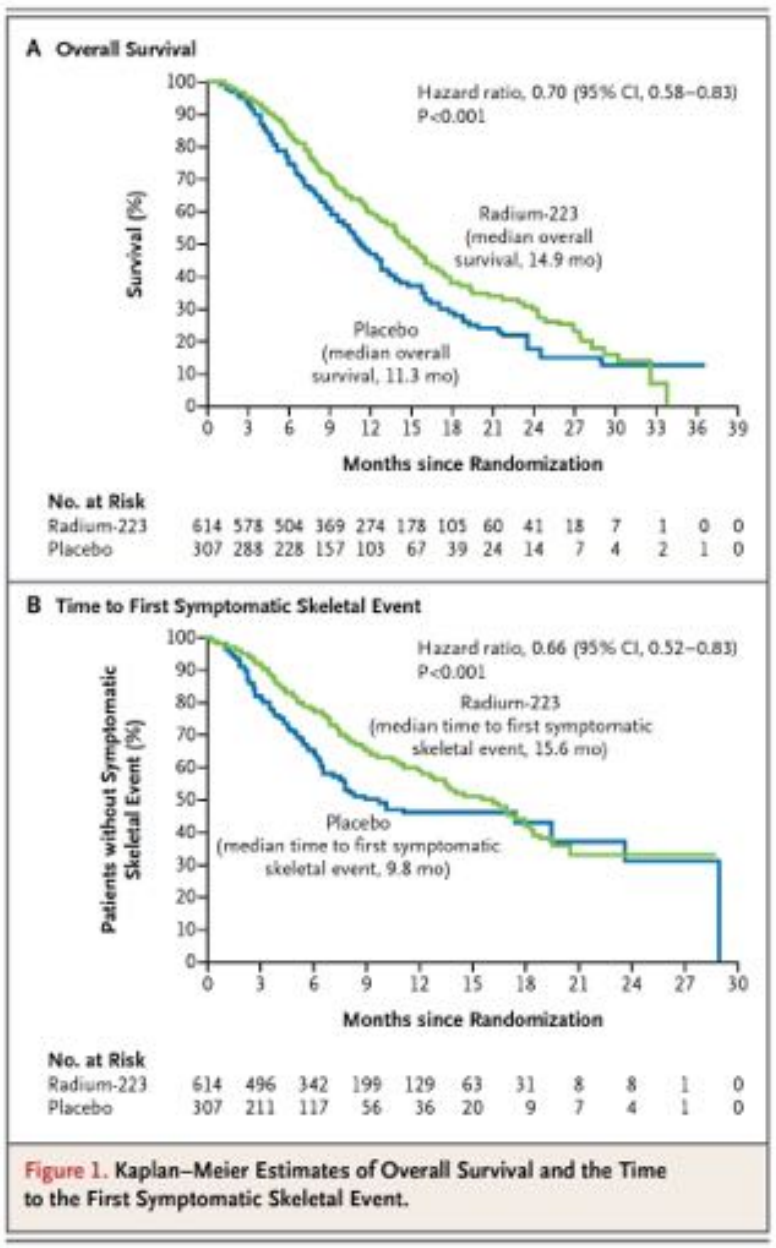



Figure 1. Kaplan–Meier Estimates of Overall Survival and the Time to the First Symptomatic Skeletal Event.

Parker et al, NEJM 2013

## Sipuleucel T

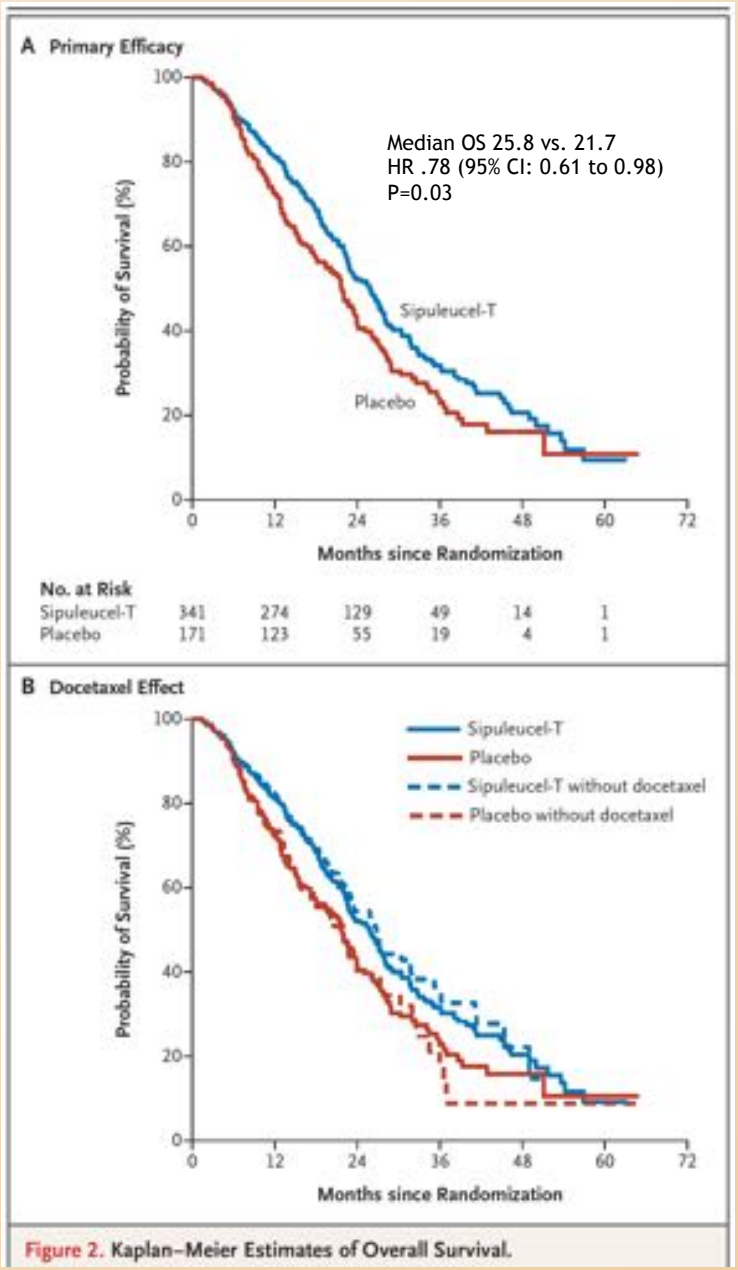
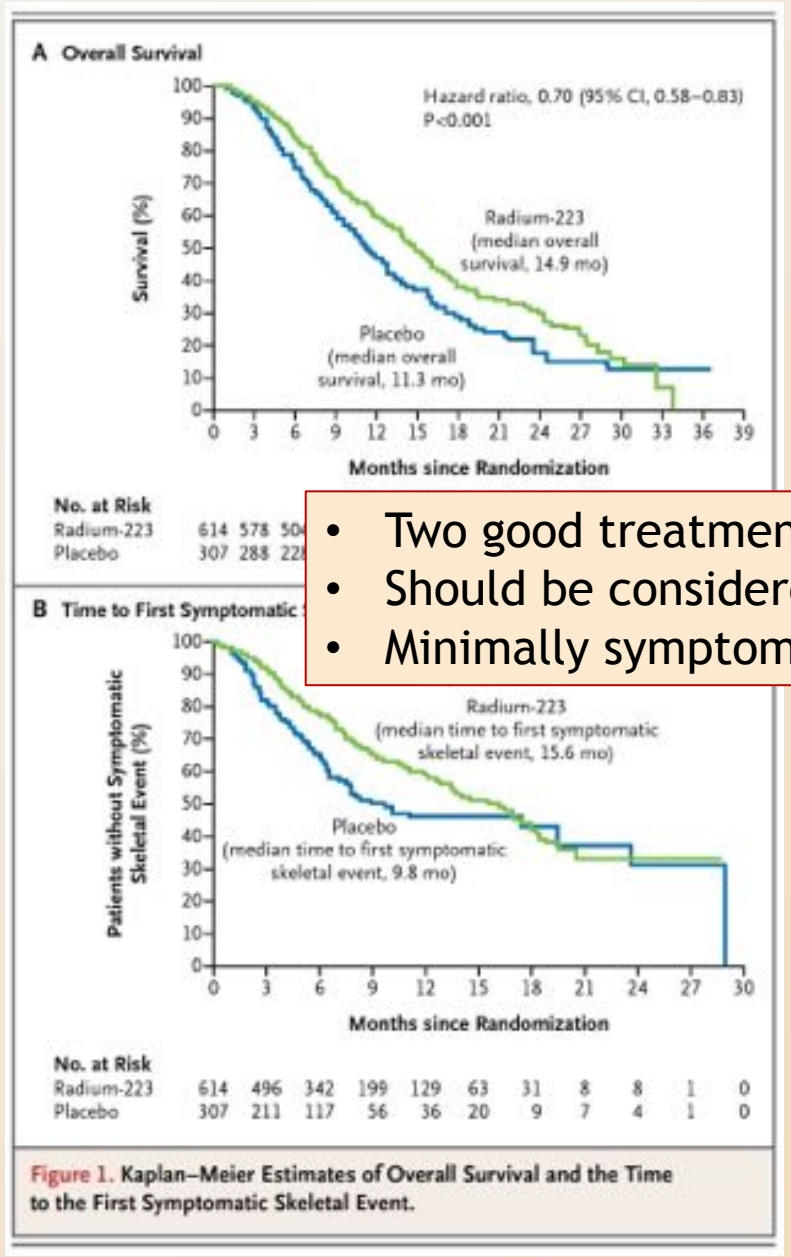



Figure 2. Kaplan–Meier Estimates of Overall Survival.

Kantoff et al, NEJM 2013

## Ra223




Parker et al, NEJM 2013

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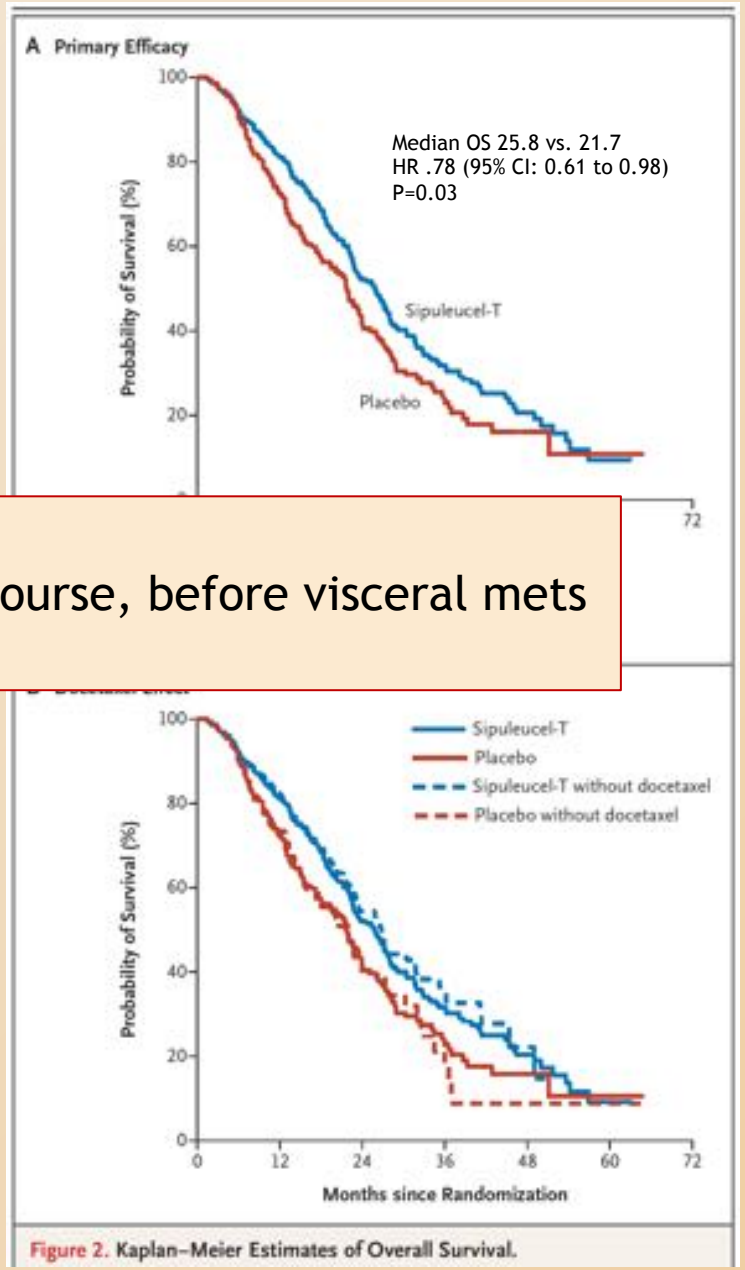
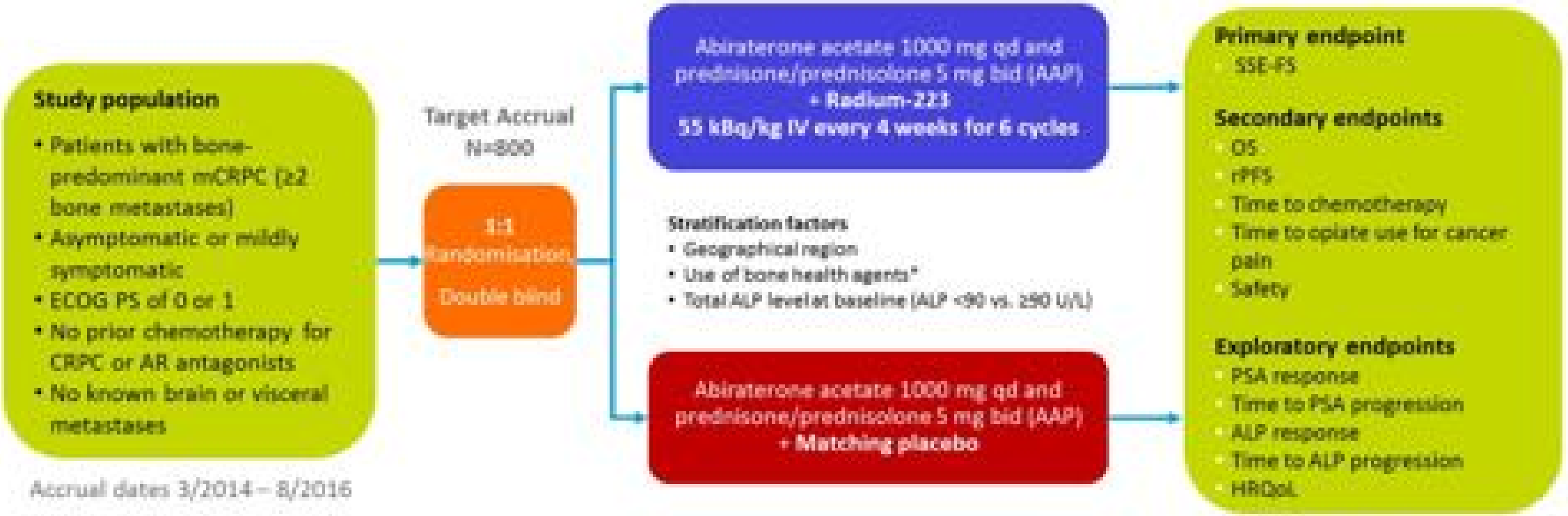



Kantoff et al, NEJM 2013

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

# ERA 223 (NCT02043678)



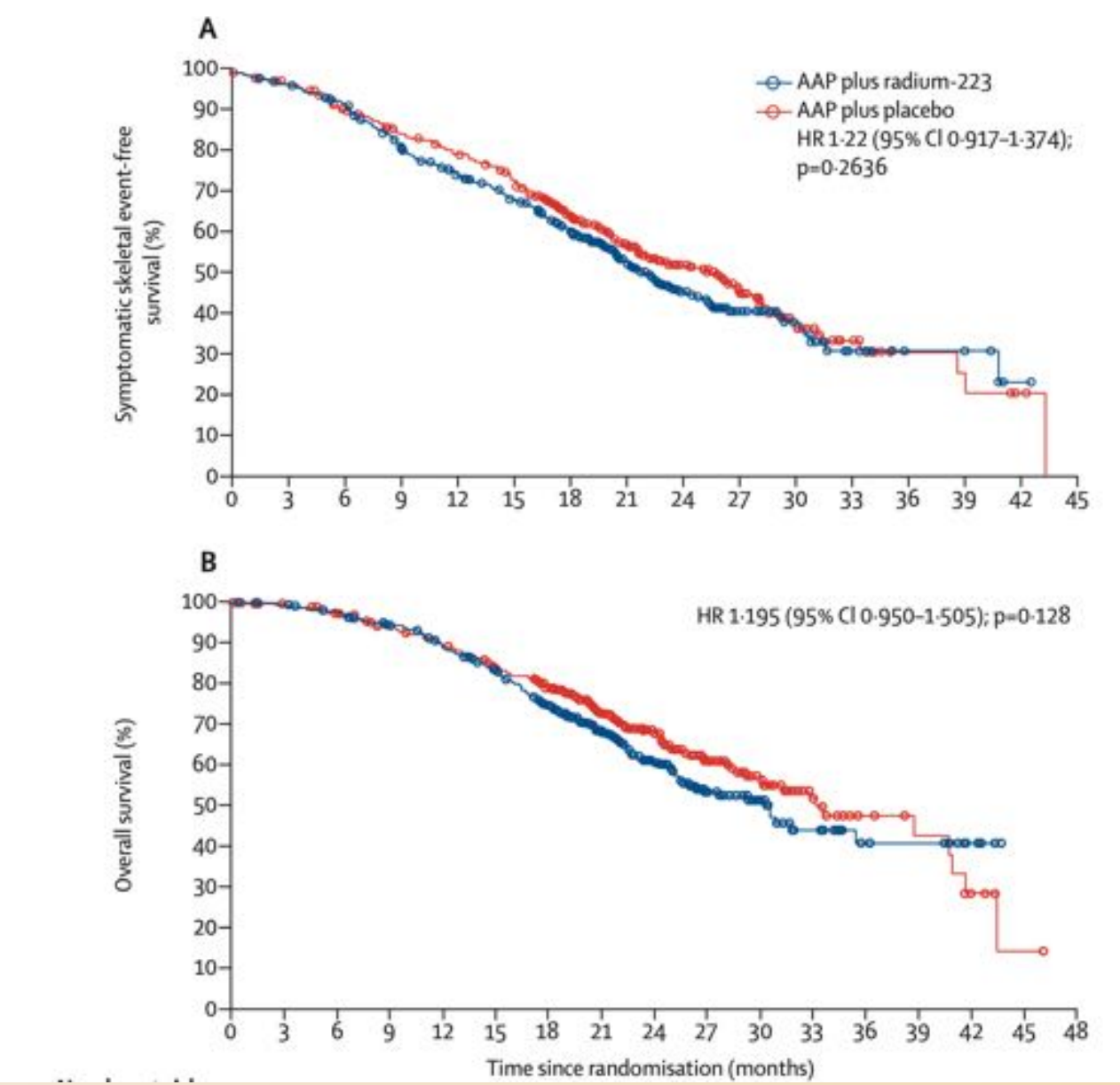

Bone health agents (denosumab or bisphosphonates) only permitted in patients receiving them at baseline; initiation during study was prohibited to prevent confounding effects.

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.

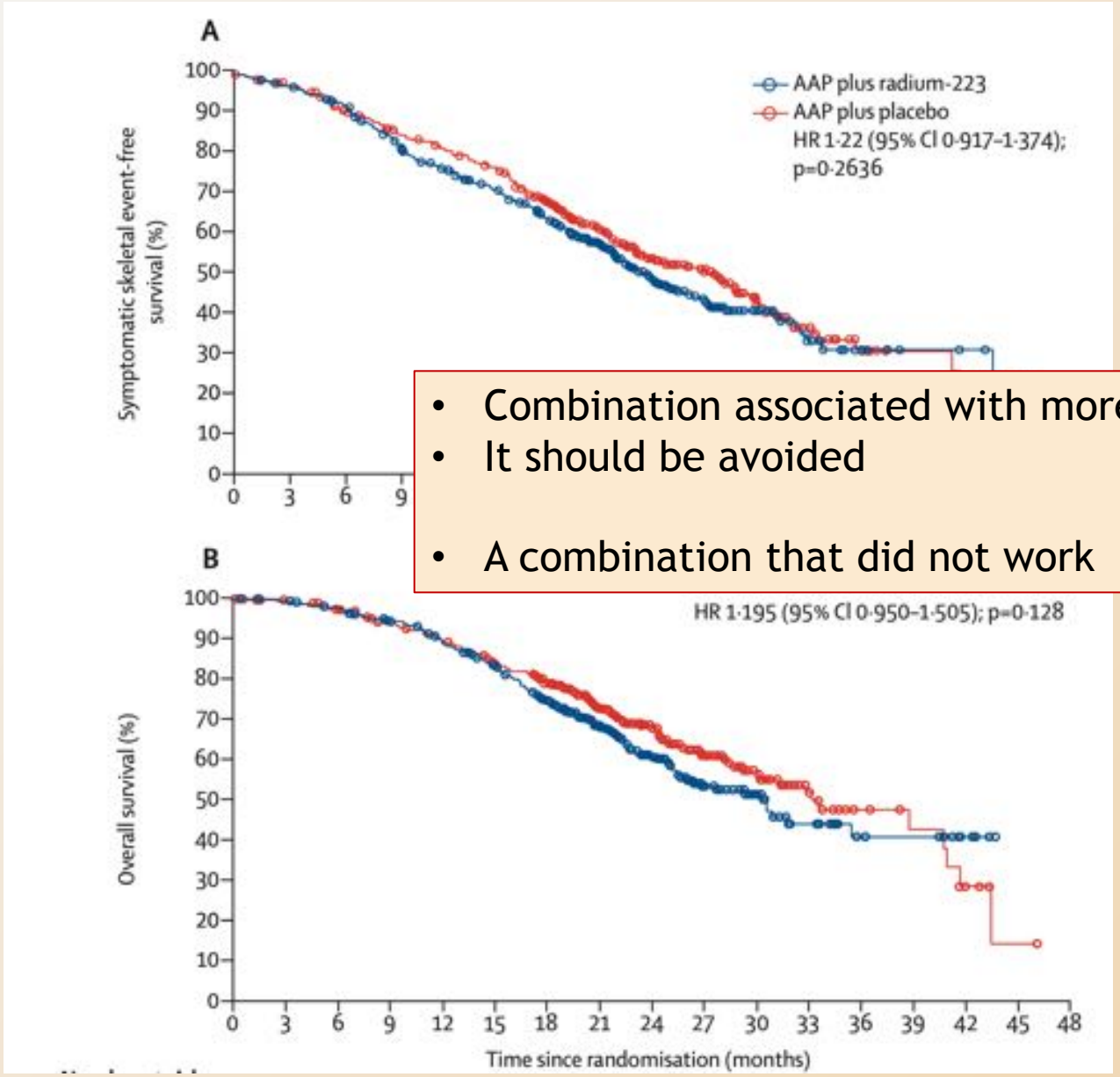
# ERA 223 study




| | 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

- A combination that did not work

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- Recognize combinations that don’t work

# CARD: STUDY DESIGN

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

**Patients with mCRPC who progressed ≤ 12 months on prior alternative ARTA (before or after docetaxel)**

**N = 255**

RANDOMIZE

1:1

**Cabazitaxel (25 mg/m² Q3W) + prednisone + G-CSF**
**n = 129**

**Abiraterone (1000 mg QD) + prednisone**
**OR**
**Enzalutamide (160 mg QD)**
**n = 126**

**Endpoints**

**Primary:** rPFS

**Key secondary:** OS, PFS, PSA response, tumor response

**Other secondary:** Pain response, time to symptomatic skeletal event, safety, HRQoL, biomarkers

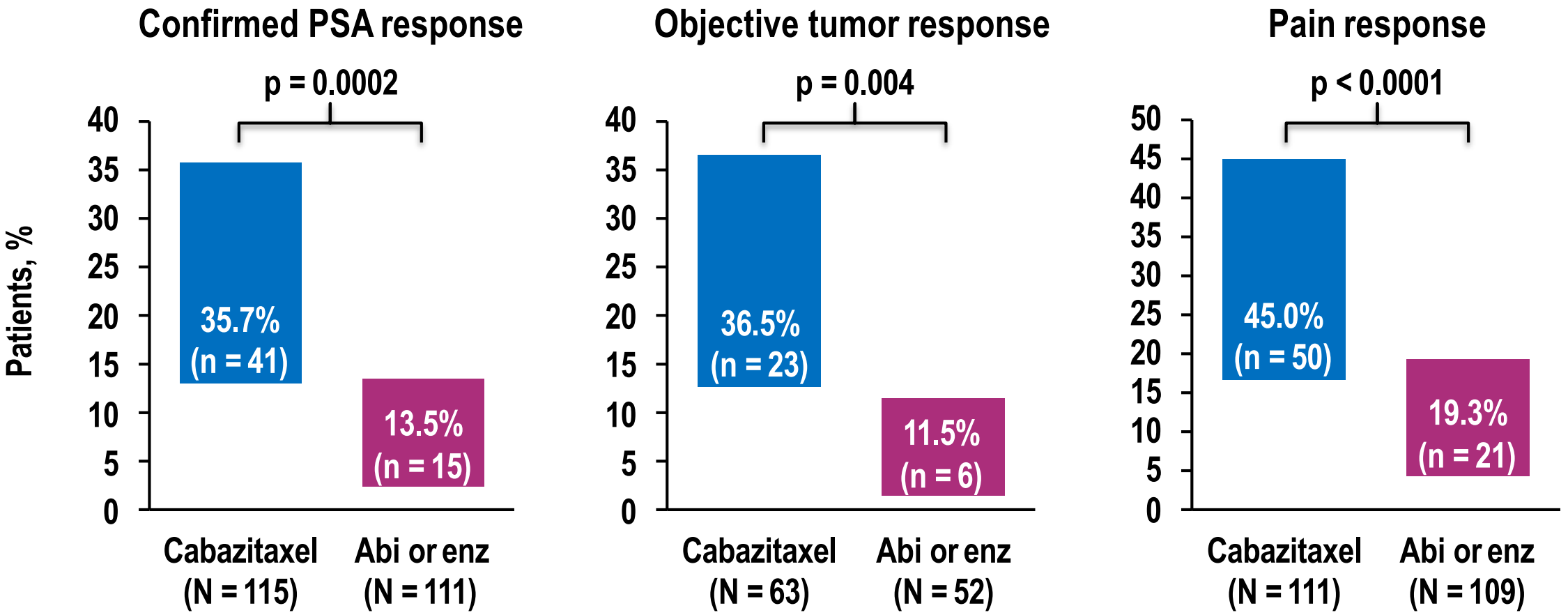
**Stratification factors:**

- 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**

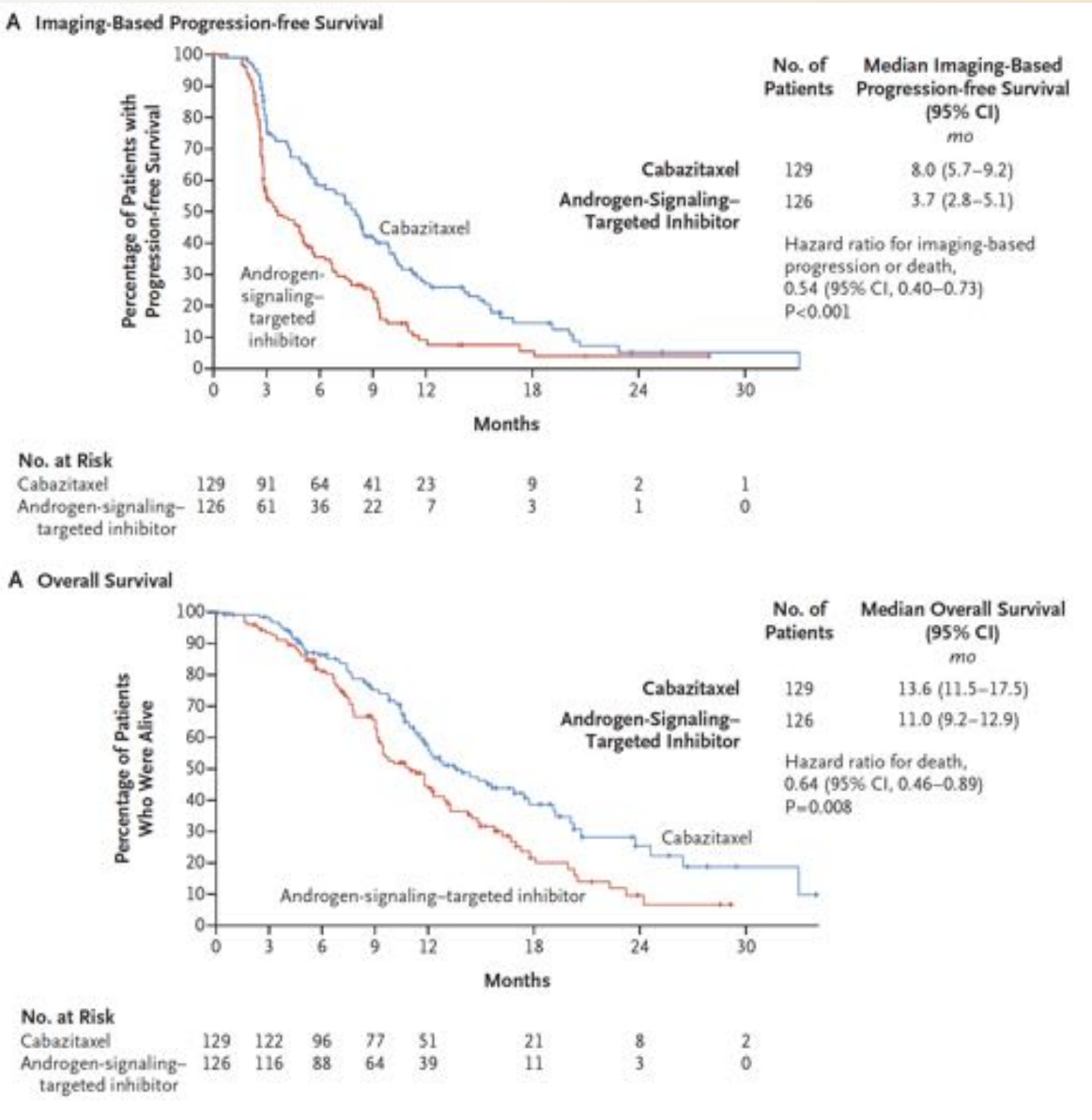
**PSA: PSA reduction ≥ 50% from baseline, confirmed by a second value at least 3 weeks later. Tumor: complete or partial responses according to RECIST 1.1 criteria. Pain: decrease ≥ 30% from baseline in average BPI-SF pain intensity score at 2 consecutive evaluations ≥ 3 weeks apart without increase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

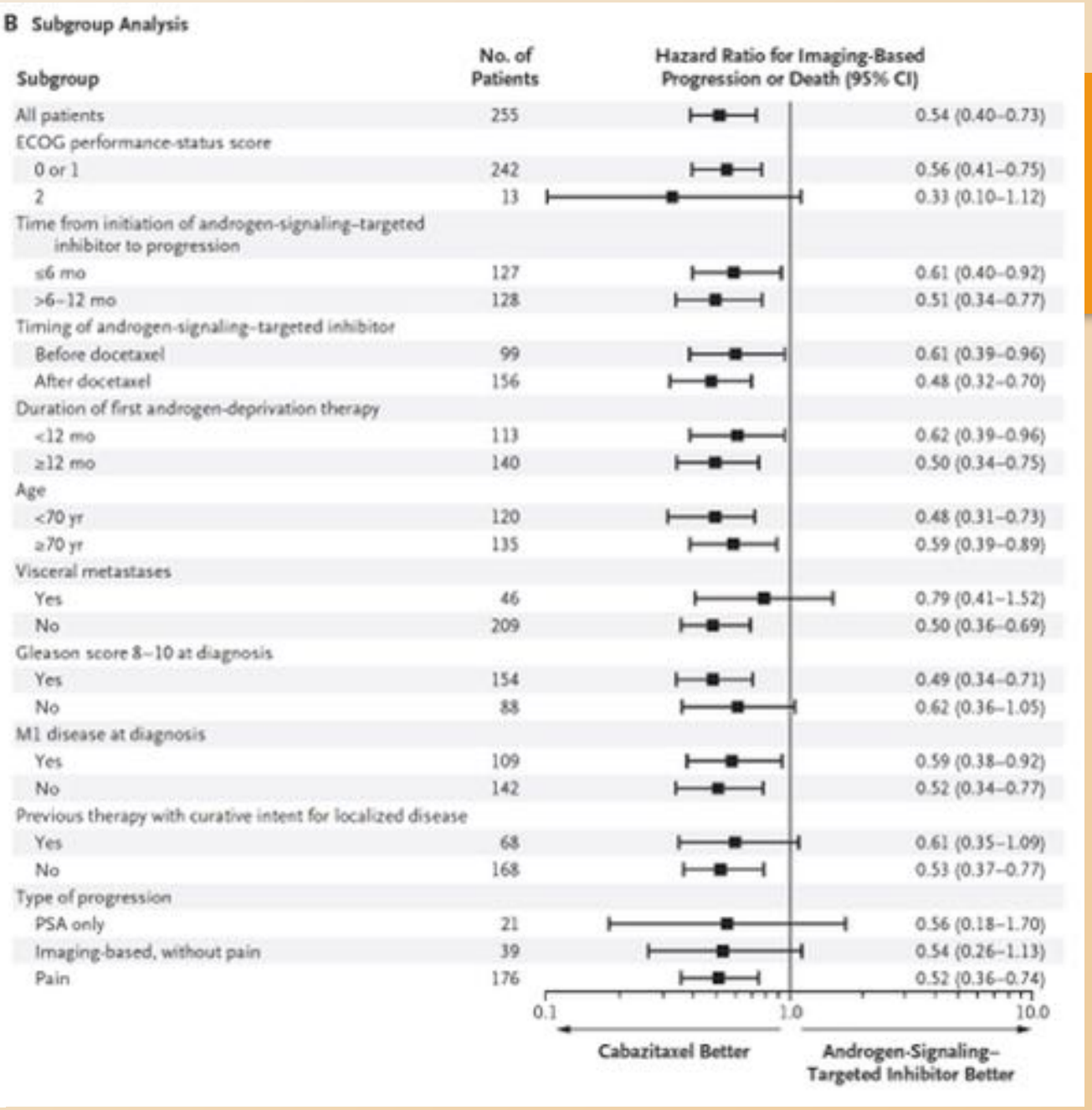
N, patients evaluable for PSA, tumor or pain response.

*BPI-SF, Brief Pain Inventory - Short Form.*

De Wit et al, ESMO 2019

# CARD study




De Wit et al, NEJM 2019

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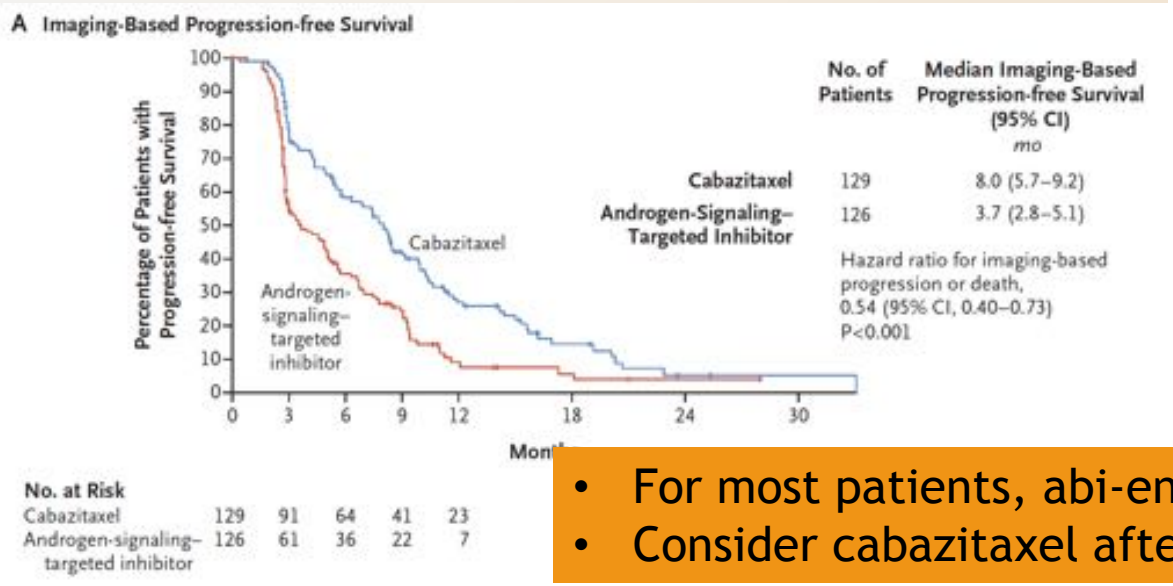
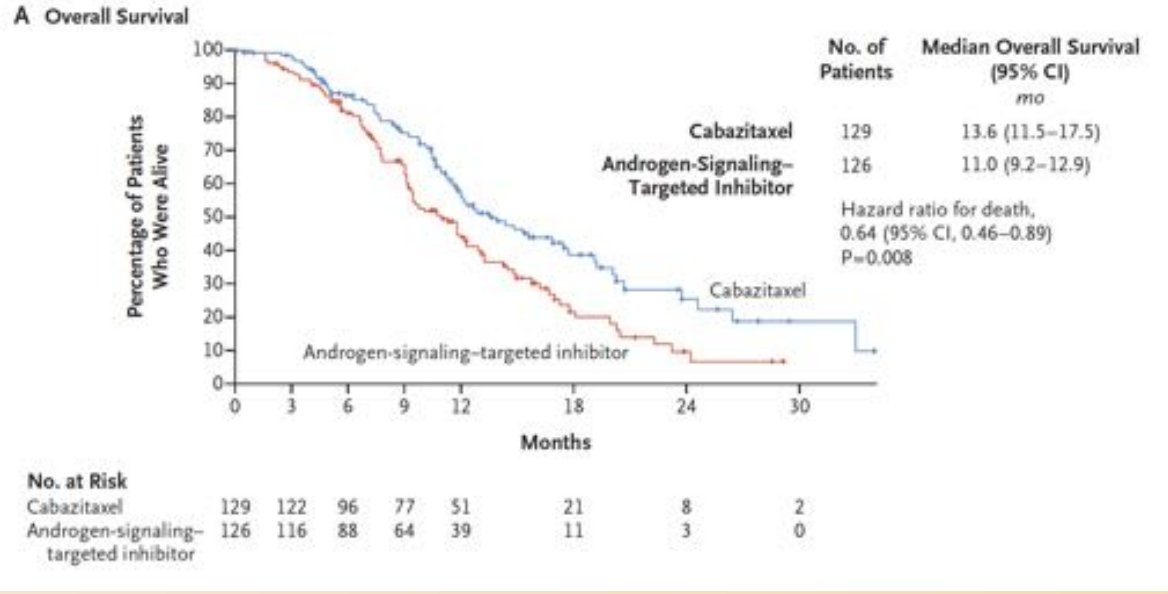
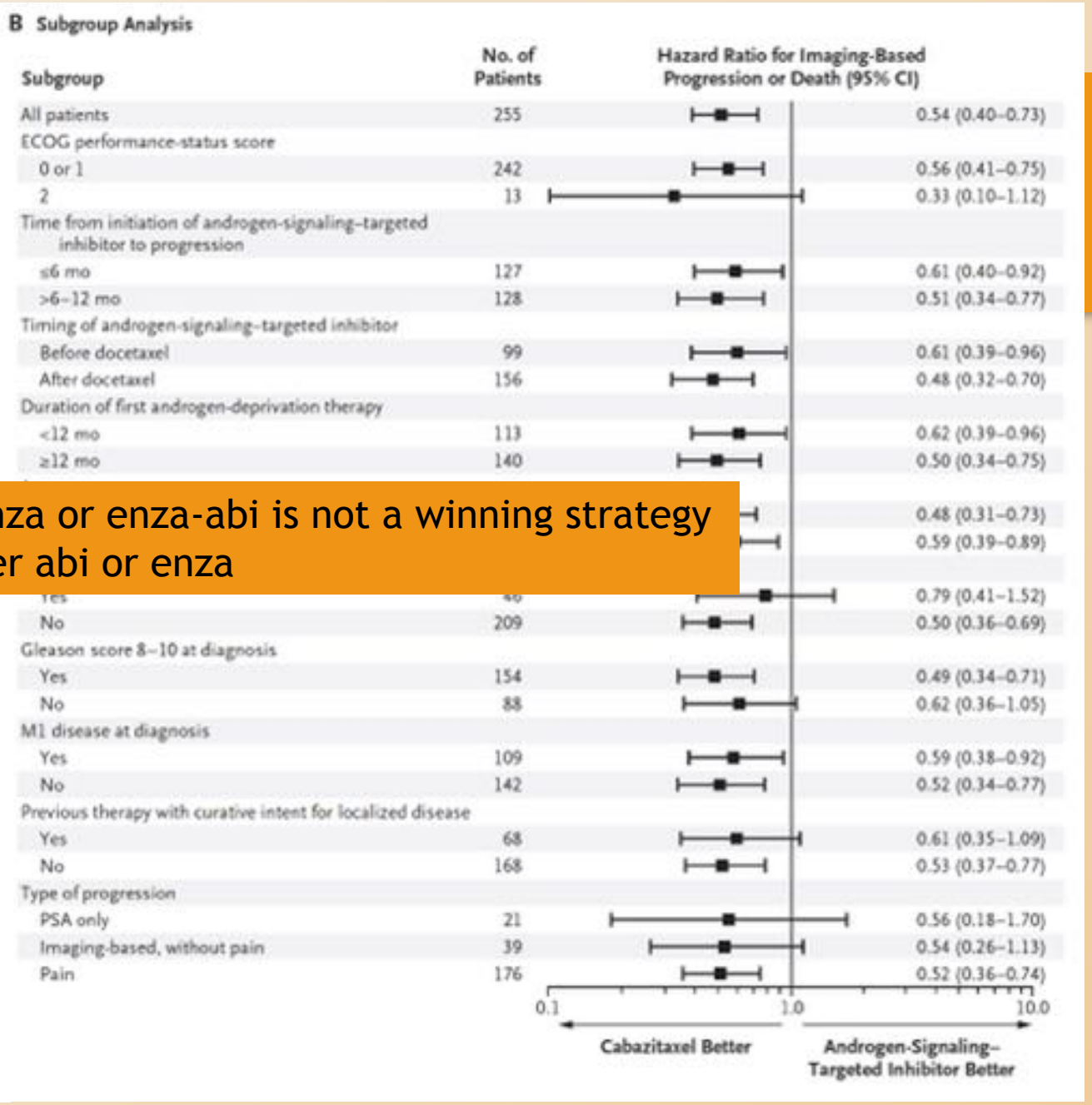


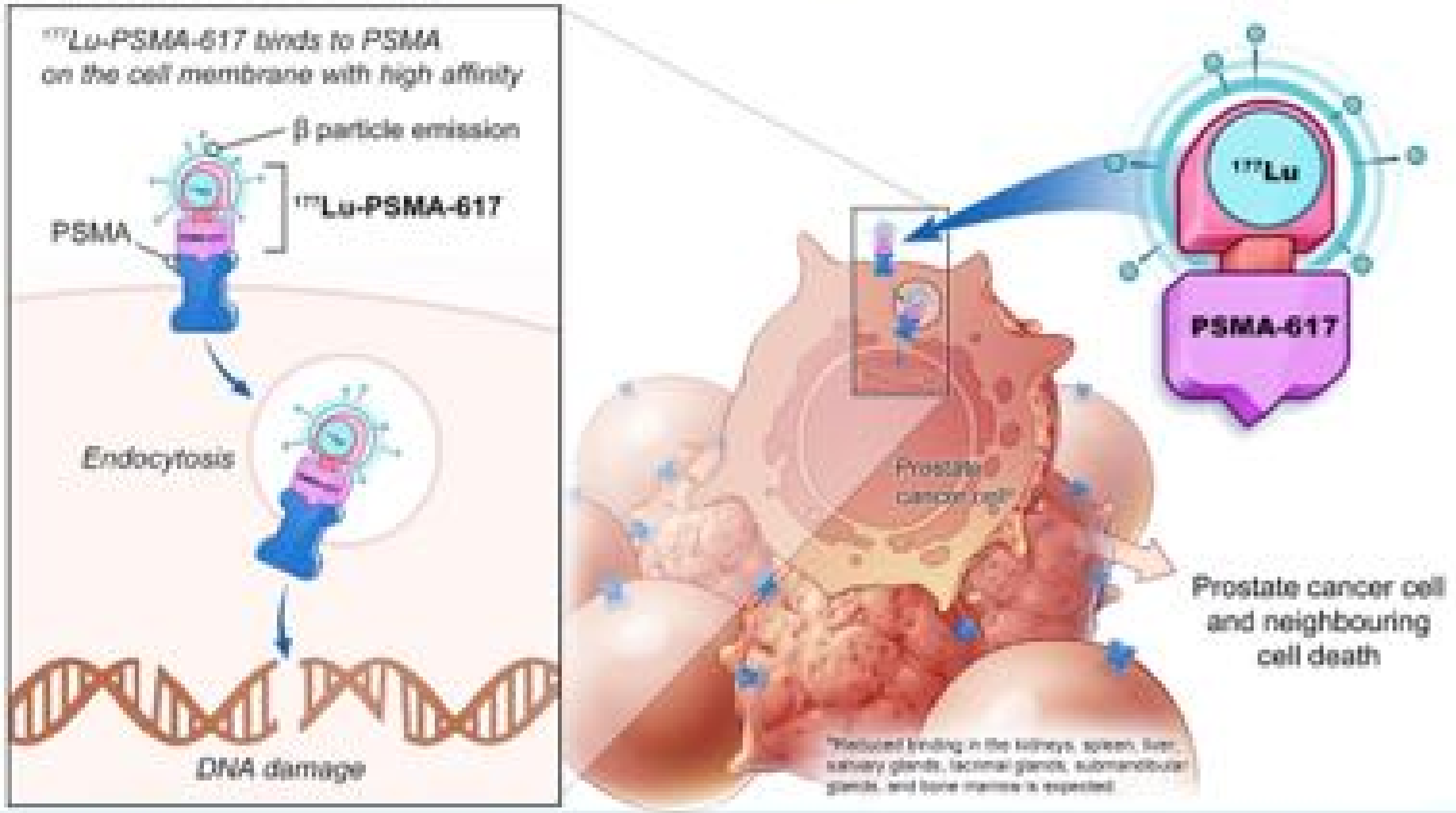

- For most patients, abi-enza or enza-abi is not a winning strategy
- Consider cabazitaxel after abi or enza

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
- Recognize combinations that don’t work
- Avoid using abiraterone after enzalutamide or vice versa

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



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

**Eligible patients**

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


- Randomization stratified by
  - ECOG status (0–1 or 2)
  - LDH (high or low)
  - Liver metastases (yes or no)
  - Androgen receptor pathway inhibitors in SOC (yes or no)
- CT/MRI/bone scans
  - Every 8 weeks (treatment)
  - Every 12 weeks (follow-up)
  - Blinded independent central review


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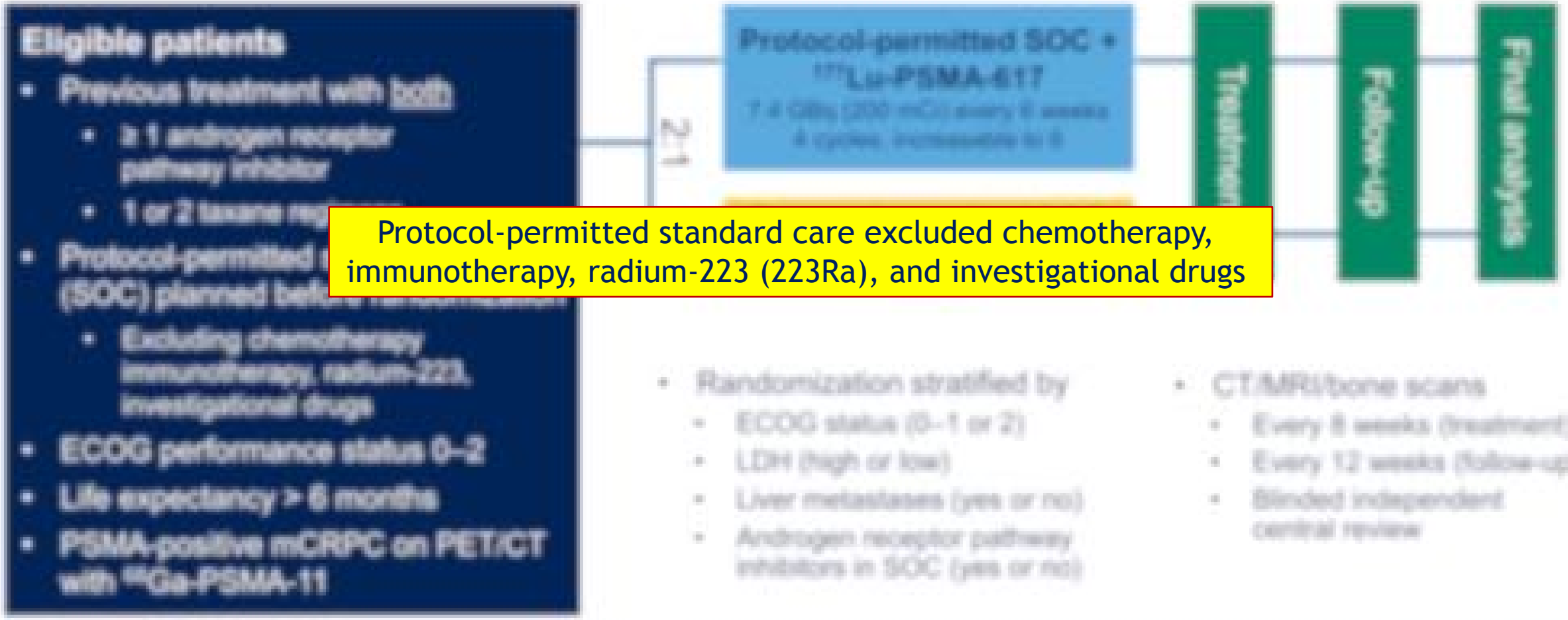


Protocol-permitted standard care excluded chemotherapy, immunotherapy, radium-223 (223Ra), and investigational drugs


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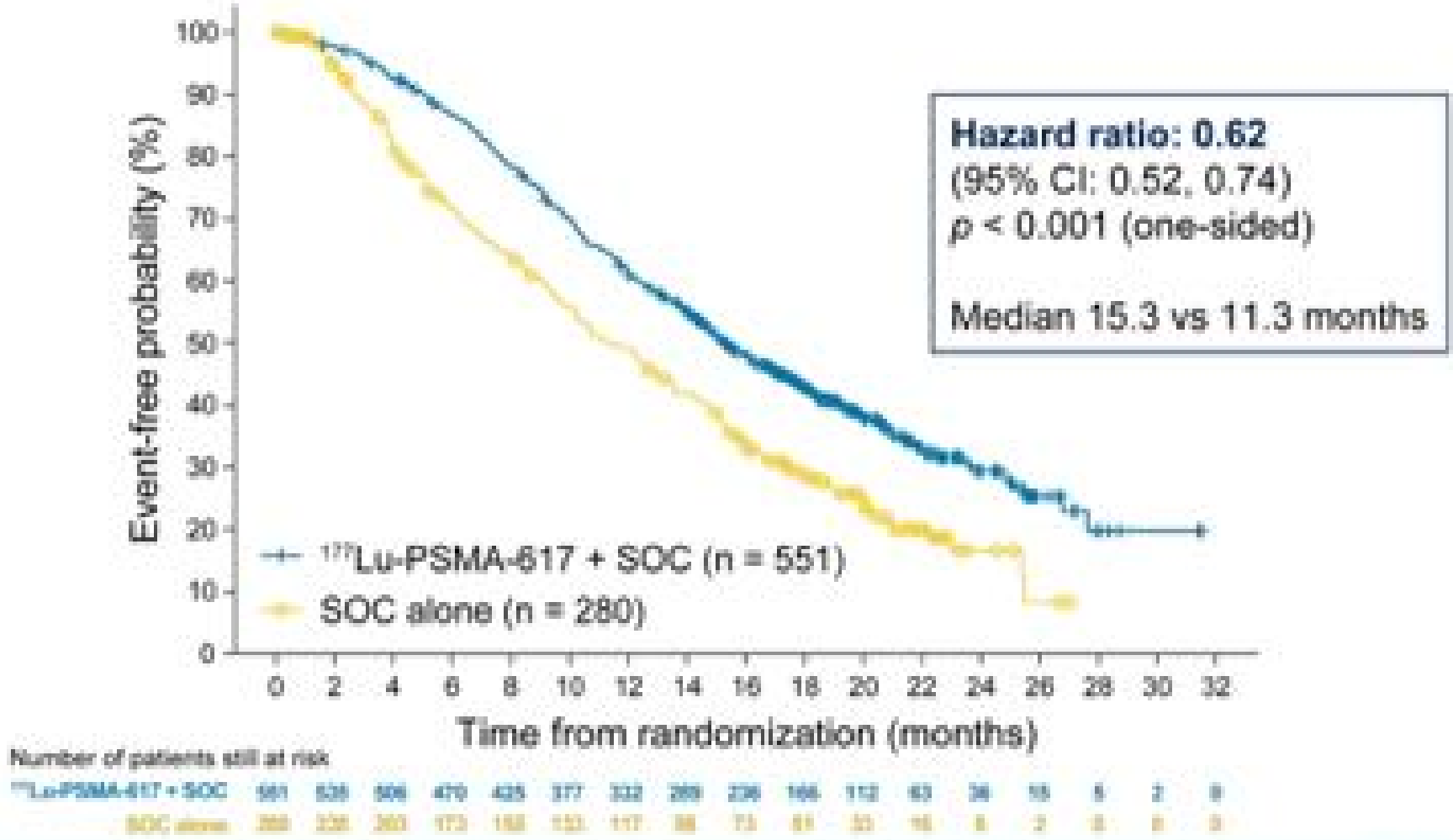
# Primary endpoints: $^{177}$Lu-PSMA-617 prolonged OS

## Primary analysis

All randomized patients (N = 831)

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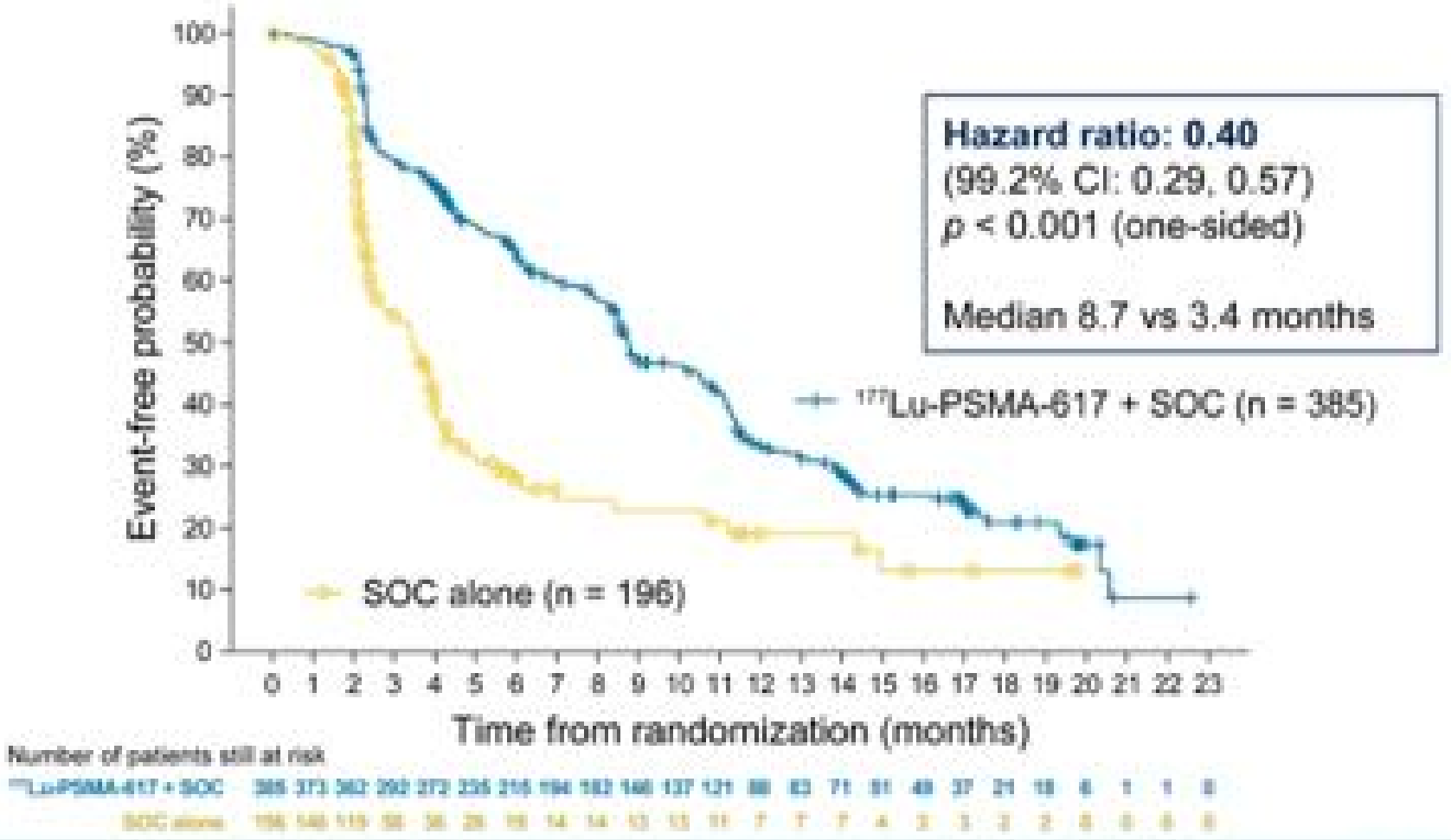
# Primary endpoints: $^{177}$Lu-PSMA-617 improved rPFS

## Primary analysis

rPFS analysis set (n = 581)



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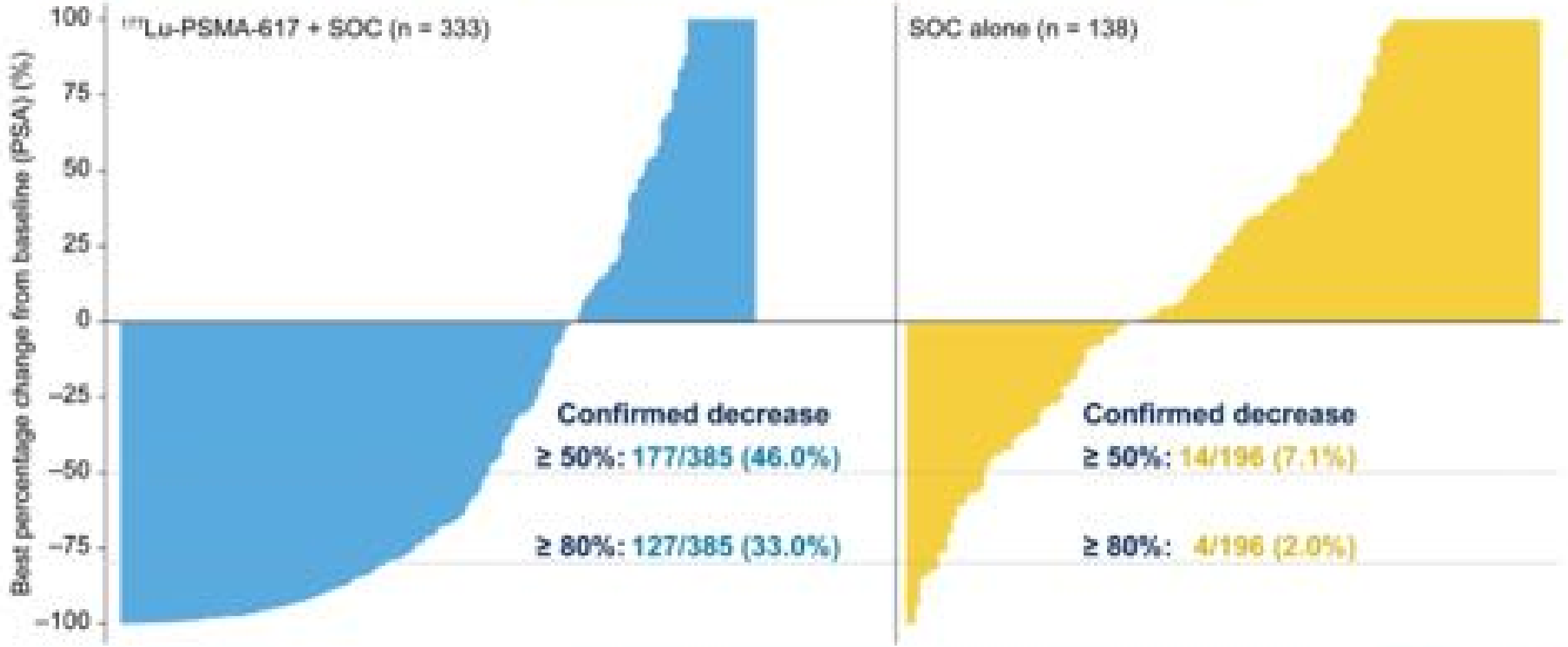
# Secondary endpoint: PSA responses favored the $^{177}$Lu-PSMA-617 arm among evaluable patients



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# Treatment-emergent adverse events grouped as topics of interest: no unexpected or concerning safety signals

| Patients, n (%) | All grades | | Grade 3–5 | |
|---|---|---|---|---|
| | $^{177}$Lu-PSMA-617 + SOC (n = 529) | SOC alone (n = 205) | $^{177}$Lu-PSMA-617 + SOC (n = 529) | SOC alone (n = 205) |
| Fatigue | 260 (49.1) | 60 (29.3) | 37 (7.0) | 5 (2.4) |
| Bone marrow suppression | 251 (47.4) | 36 (17.6) | 124 (23.4) | 14 (6.8) |
| Leukopenia | 66 (12.5) | 4 (2.0) | 13 (2.5) | 1 (0.5) |
| Lymphopenia | 75 (14.2) | 8 (3.9) | 41 (7.8) | 1 (0.5) |
| Anemia | 168 (31.8) | 27 (13.2) | 68 (12.9) | 10 (4.9) |
| Thrombocytopenia | 91 (17.2) | 9 (4.4) | 42 (7.9) | 2 (1.0) |
| Dry mouth | 208 (39.3) | 2 (1.0) | 0 (0.0) | 0 (0.0) |
| Nausea and vomiting | 208 (39.3) | 35 (17.1) | 8 (1.5) | 1 (0.5) |
| Renal effects | 46 (8.7) | 12 (5.9) | 18 (3.4) | 6 (2.9) |
| Second primary malignancies | 11 (2.1) | 2 (1.0) | 4 (0.8) | 1 (0.5) |
| Intracranial hemorrhage | 7 (1.3) | 3 (1.5) | 5 (0.9) | 2 (1.0) |



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# Key findings of the phase 3 VISION trial

- Targeted radioligand therapy with $^{177}$**Lu-PSMA-617** plus protocol-permitted SoC **significantly prolonged rPFS and OS** compared with protocol-permitted SoC alone in patients with advanced PSMA PET-positive metastatic castration-resistant prostate cancer[1]

**rPFS**[a]
HR 0.40 (99.2% CI: 0.29–0.57)
$p < 0.001$

**OS**[b]
HR 0.62 (95% CI: 0.52–0.74)
$p < 0.001$

- Benefits were consistent across pre-specified subgroups[1]

**Objective of this *post hoc* exploratory analysis:**
to assess the consistency of treatment effect in subgroups, based on prior and concomitant cancer-directed therapies

[a]In the PFS analysis set; [b]In the full analysis set
CI: confidence interval; HR: hazard ratio; OS: overall survival; PET: positive emission tomography; PSMA: prostate-specific membrane antigen; rPFS: radiographic progression-free survival; SoC: standard of care
1. Sartor O et al. N Engl J Med 2021;385:1091–103.


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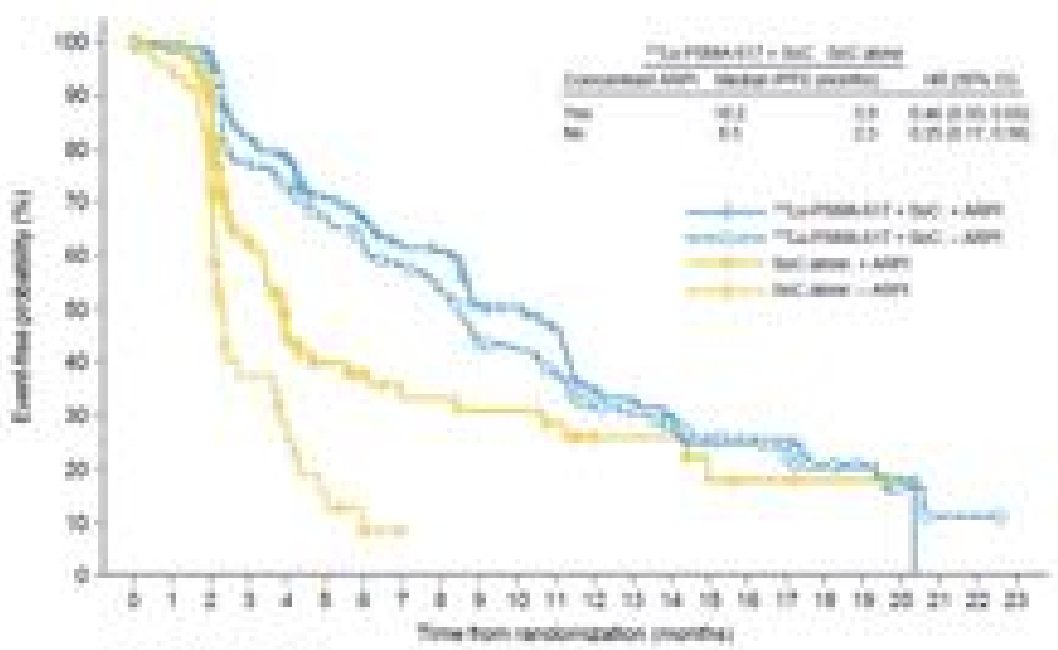
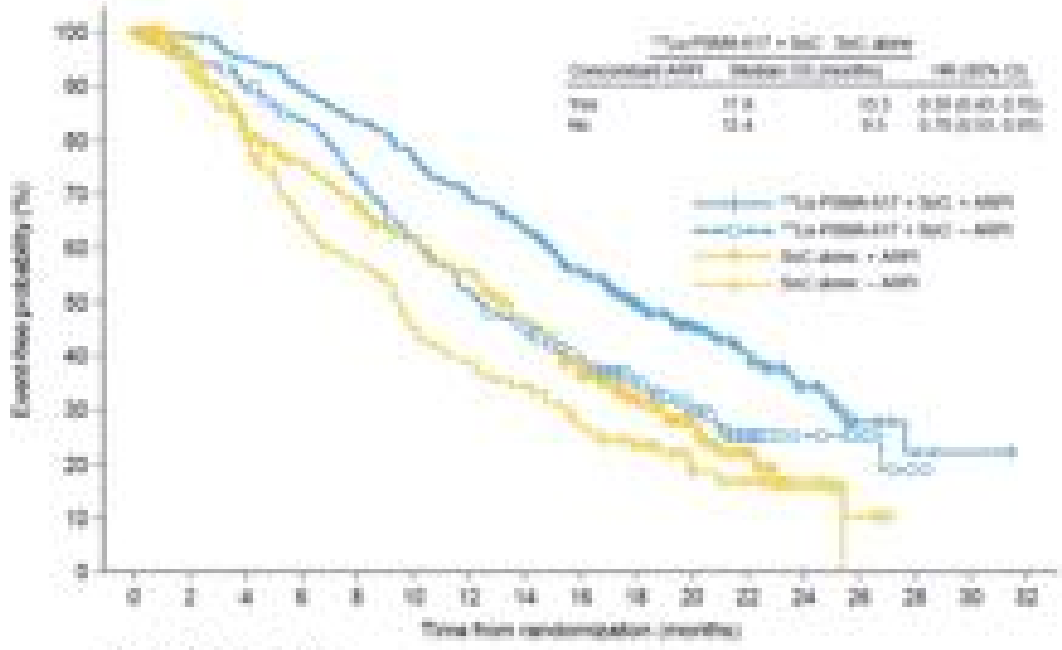
# rPFS and OS by concomitant ARPI treatment




**Consistent effect of $^{177}$Lu-PSMA-617 treatment with and without concomitant ARPIs**

ARPI, androgen receptor pathway inhibitor; CI, confidence interval; HR, hazard ratio; OS, overall survival; PSMA, prostate-specific membrane antigen; rPFS, radiographic progression-free survival; SoC, standard of care



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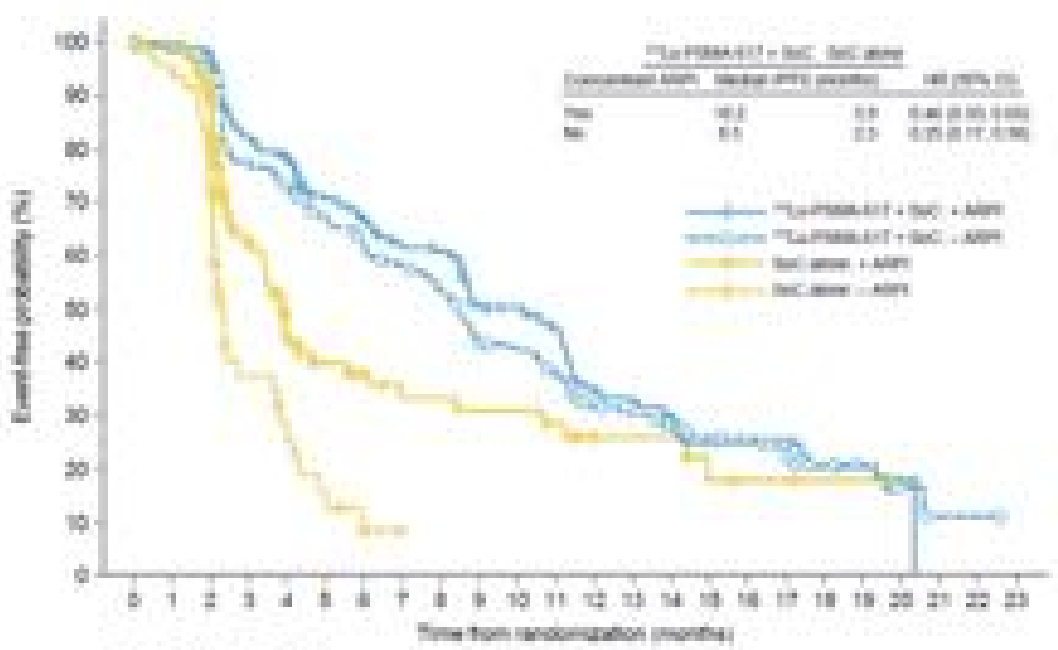
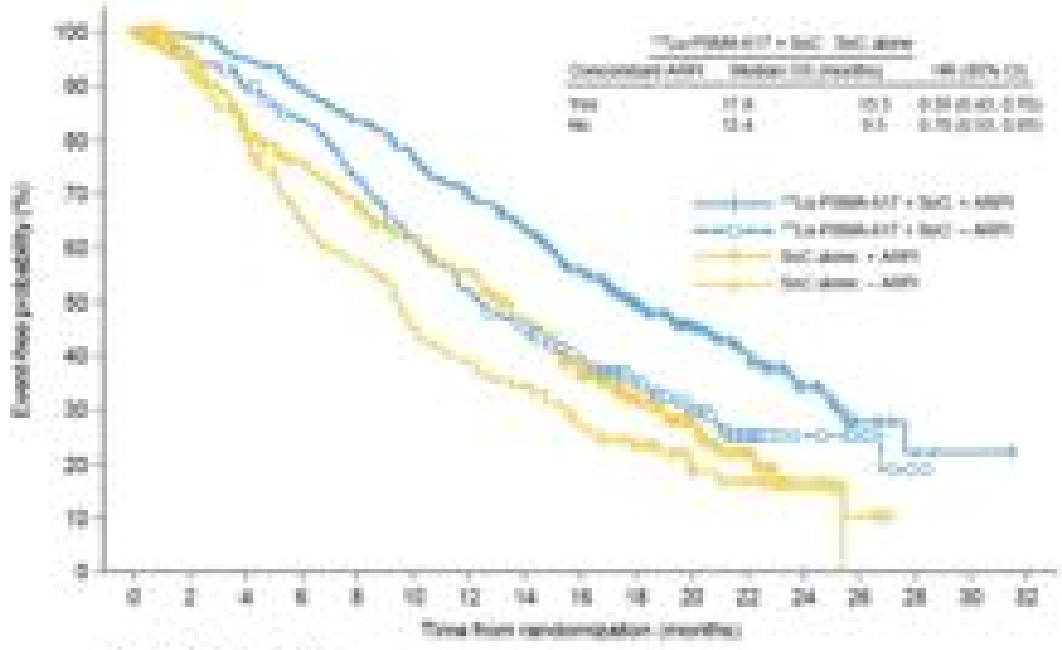
# rPFS and OS by concomitant ARPI treatment

A combination that seems to work!





**Consistent effect of $^{177}$Lu-PSMA-617 treatment with and without concomitant ARPIs**



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# TheraP Trial Schema

ANZUP

**KEY ELIGIBILITY**
- mCRPC post docetaxel
- Rising PSA and PSA ≥ 20 ng/mL
- ECOG 0-2

**$^{68}$Ga-PSMA-11 + FDG PET/CT**
- PSMA SUVmax > 20 at any site
- No FDG positive/PSMA negative sites of disease
- Centrally reviewed

R

**$^{177}$Lu-PSMA-617**
8.5 GBq IV q6 weekly
↓ 0.5GBq each cycle
Up to 6 cycles

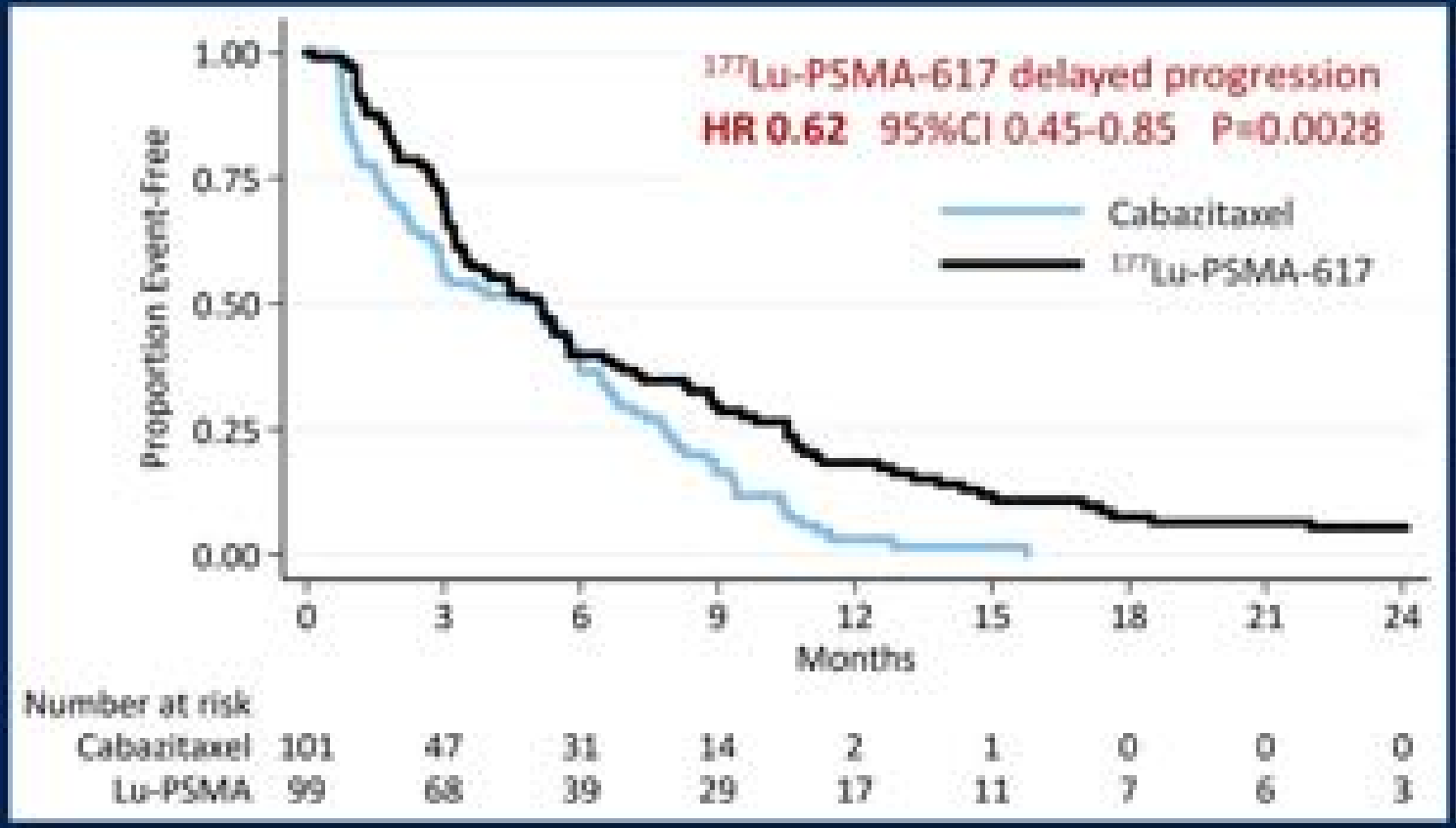
**SPECT/CT @ 24 hours**
suspend Rx if no or minimal uptake (centrally reviewed)

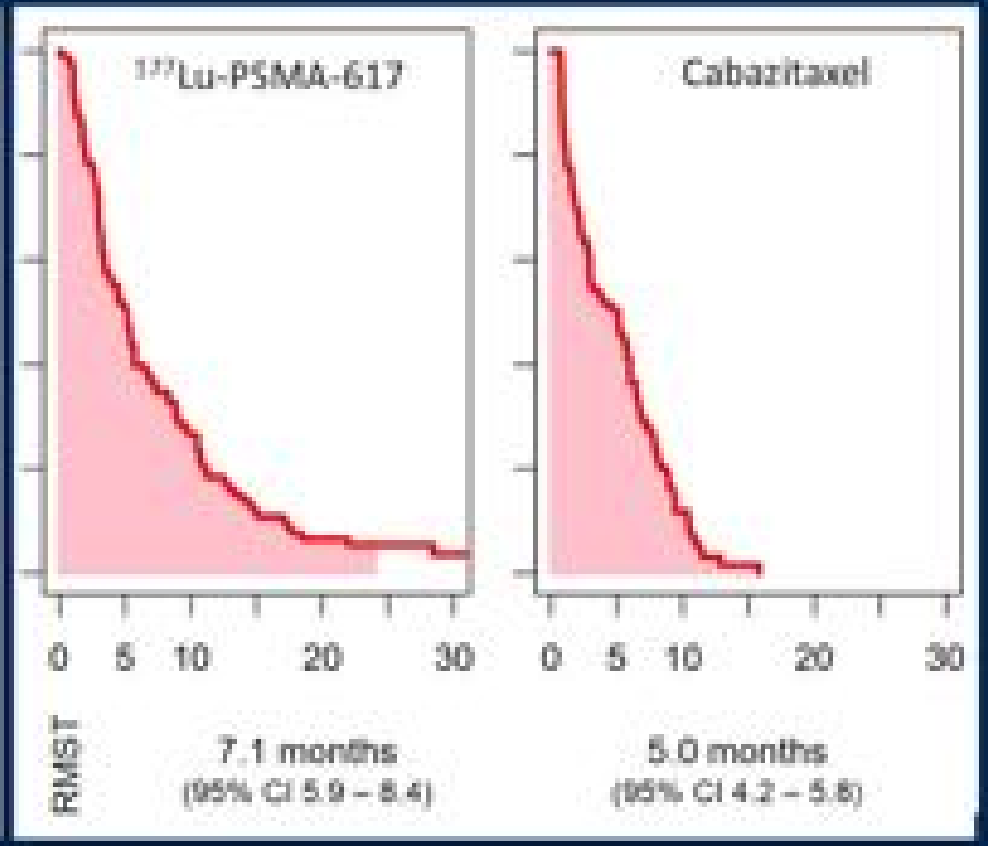
**200 men 1:1 randomisation**
**11 sites in Australia**
Stratified by:
- Disease burden (>20 sites vs ≤ 20 sites)
- Prior enzalutamide or abiraterone
- Study site

**CABAZITAXEL**
20mg/m$^2$ IV q3 weekly,
Up to 10 cycles

# Progression Free Survival (PSA and radiographic)

ANZUP

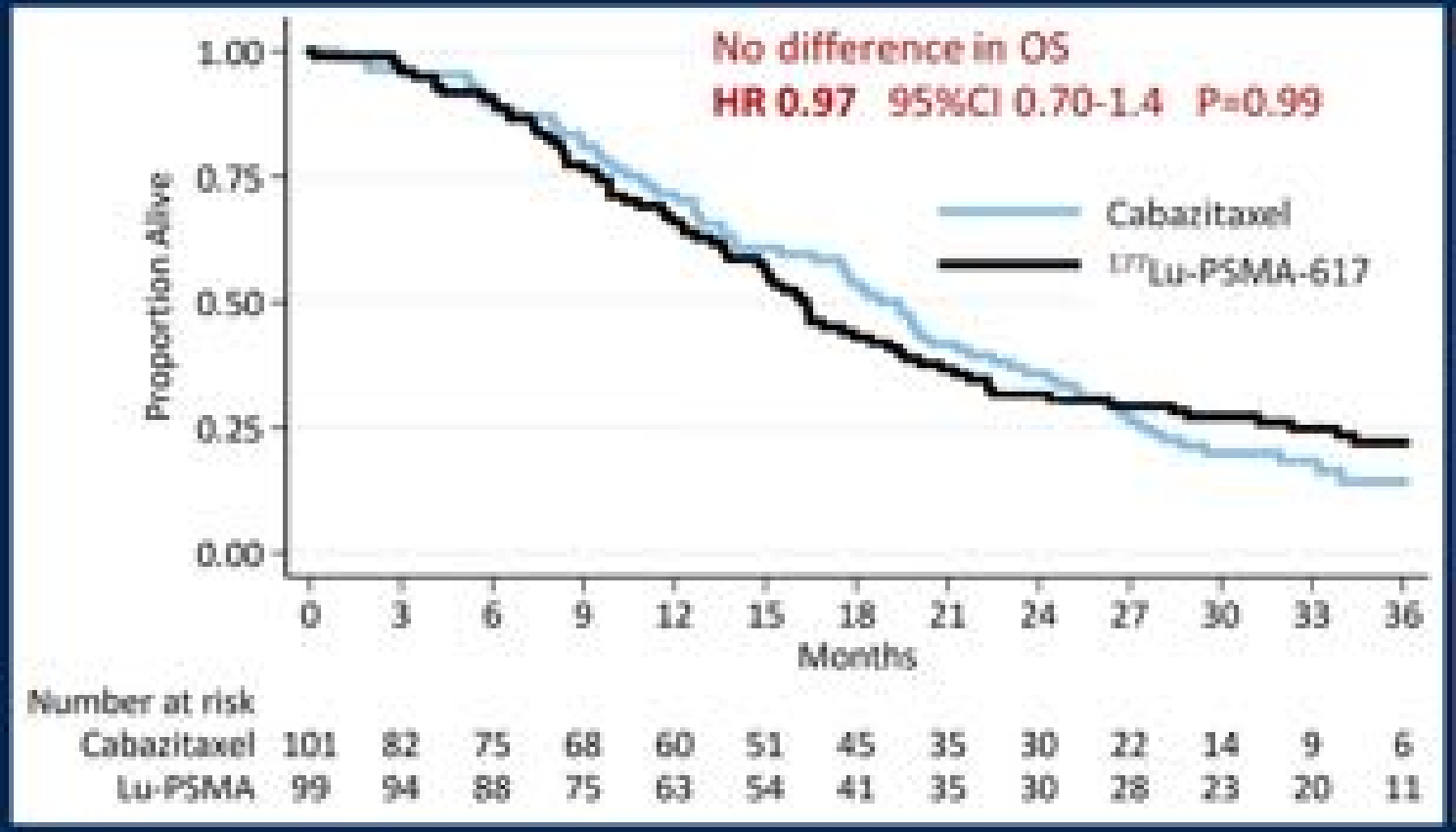


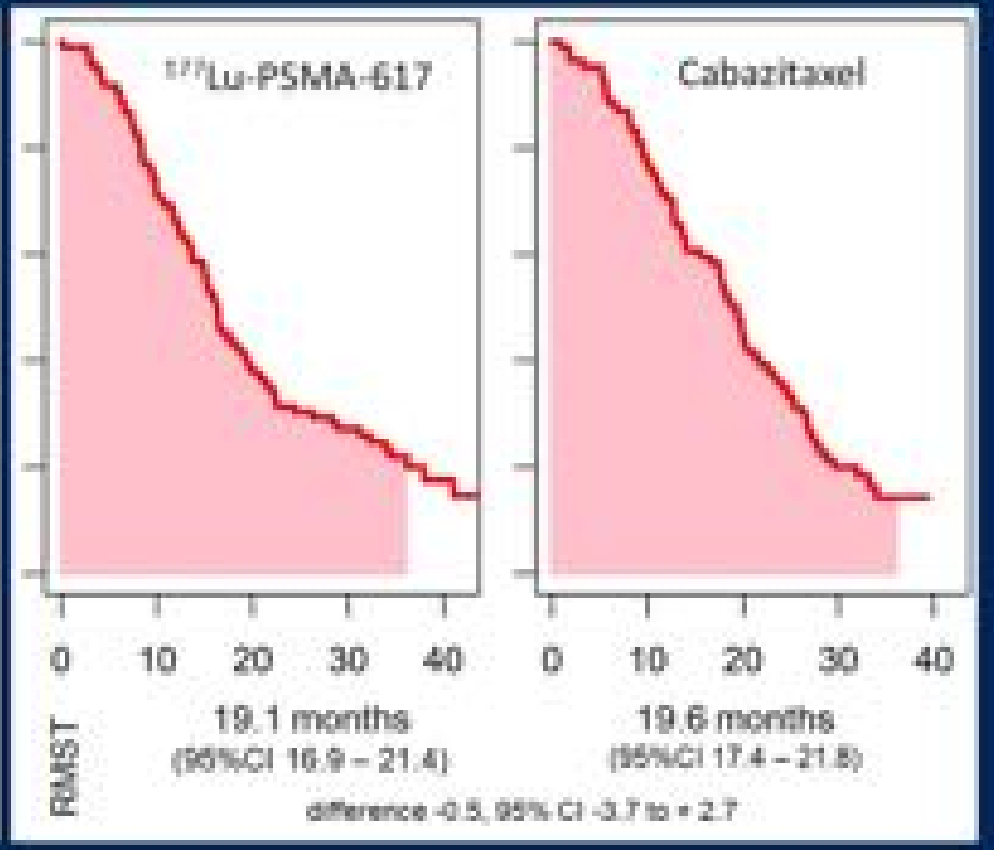




- Treatment effect not constant with respect to time → restricted mean survival time (RMST)
- 177 progression events. Cut-off 31 DEC 2020 for non-OS endpoints.
- Similar HR for rPFS (0.65) and PSA-PFS (0.60), and in per-protocol sensitivity analyses

# Overall survival (ITT)

ANZUP




- Cut-off 31 DEC 2021 for OS
- At 36 months follow-up, death reported in 147/200; 70/101 assigned cabazitaxel vs. 77/99 assigned LuPSMA
- Per-protocol analysis: no difference in OS
- No additional safety signals with longer follow-up.

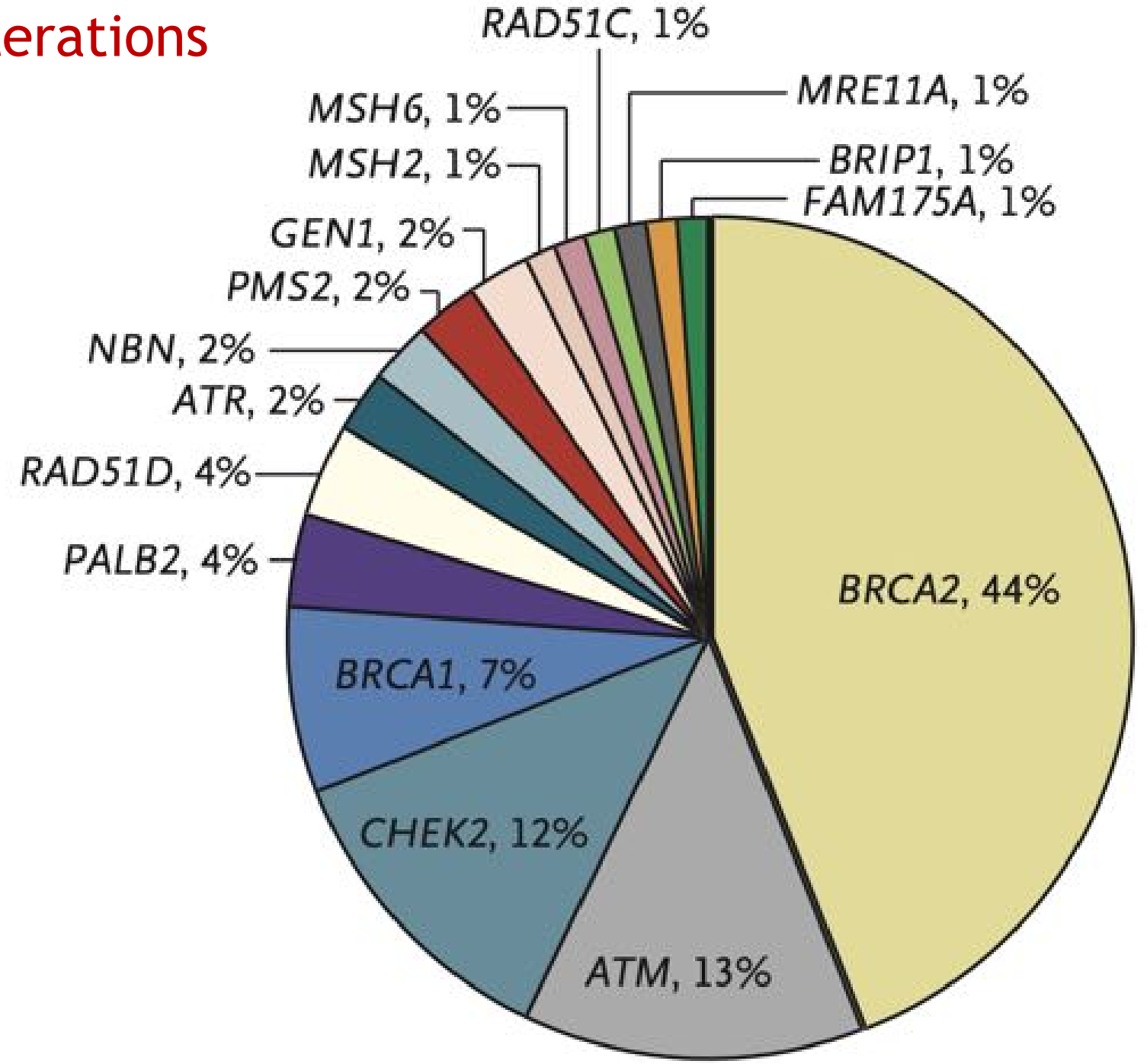
# What to Consider to Arrive at the Optimal Approach?

- 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
- Recognize combinations that don’t work
- Avoid using abiraterone after enzalutamide or vice versa
- PSMA-Lu177 is approved for CRPC in addition to SOC
- Combination of PSMA-Lu177 with ARPI may work

# Germline DNA Repair Gene Alterations

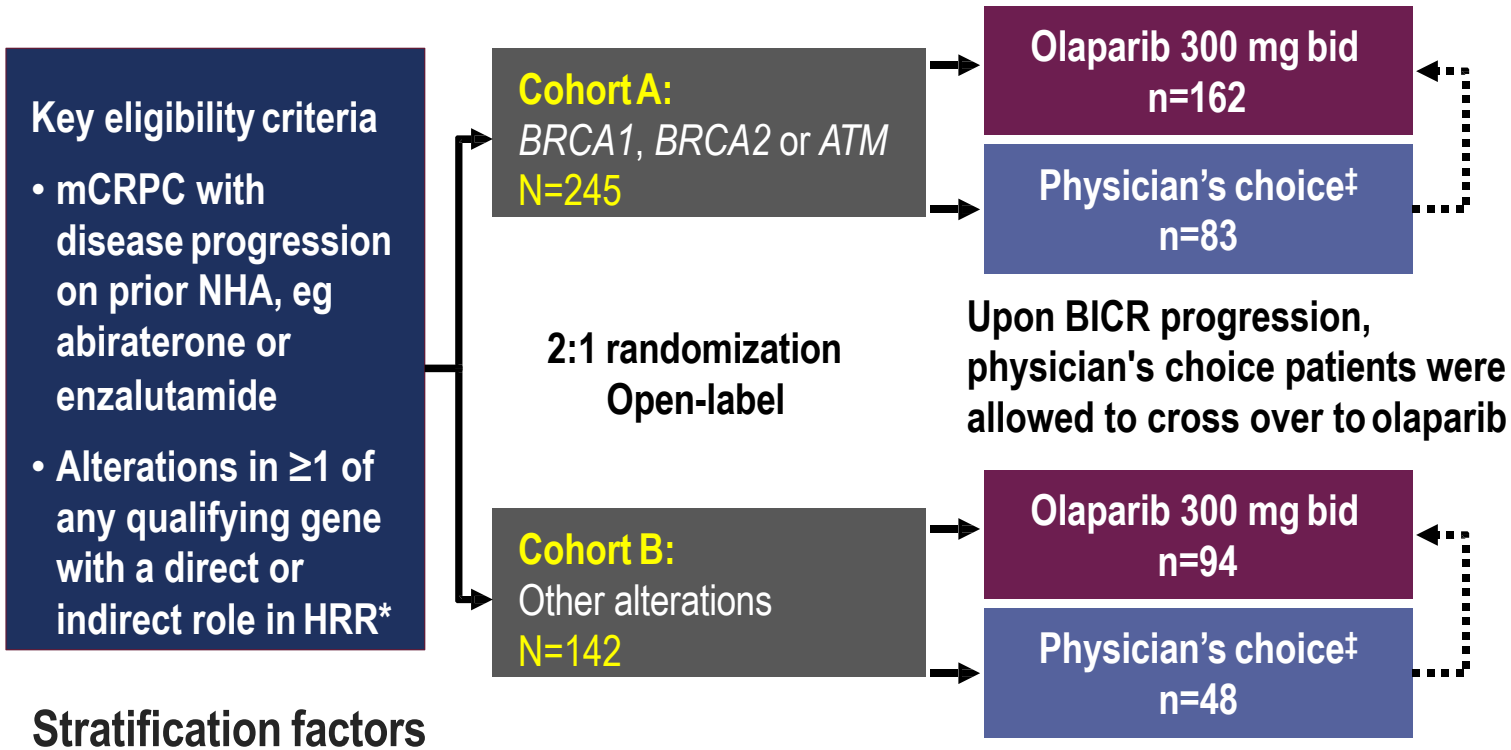
**Table 3. Germline DNA-Repair Gene Mutations in Seven Metastatic Prostate Cancer Case Series.**

| Case Series | Description | Patients | Patients with Mutations |
|---|---|---|---|
| | | *no.* | *no. (%)* |
| 1 | Stand Up To Cancer–Prostate Cancer Foundation discovery series | 150 | 15 (10.0) |
| 2 | Stand Up To Cancer–Prostate Cancer Foundation validation series | 84 | 9 (10.7) |
| 3 | Royal Marsden Hospital | 131 | 16 (12.2) |
| 4 | University of Washington | 91 | 8 (8.8) |
| 5 | Weill Cornell Medical College | 69 | 7 (10.1) |
| 6 | University of Michigan | 43 | 4 (9.3) |
| 7 | Memorial Sloan Kettering Cancer Center | 124 | 23 (18.5) |
| Total | | 692 | 82 (11.8) |




Pritchard et al NEJM 2016, PMID 27433846

# 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

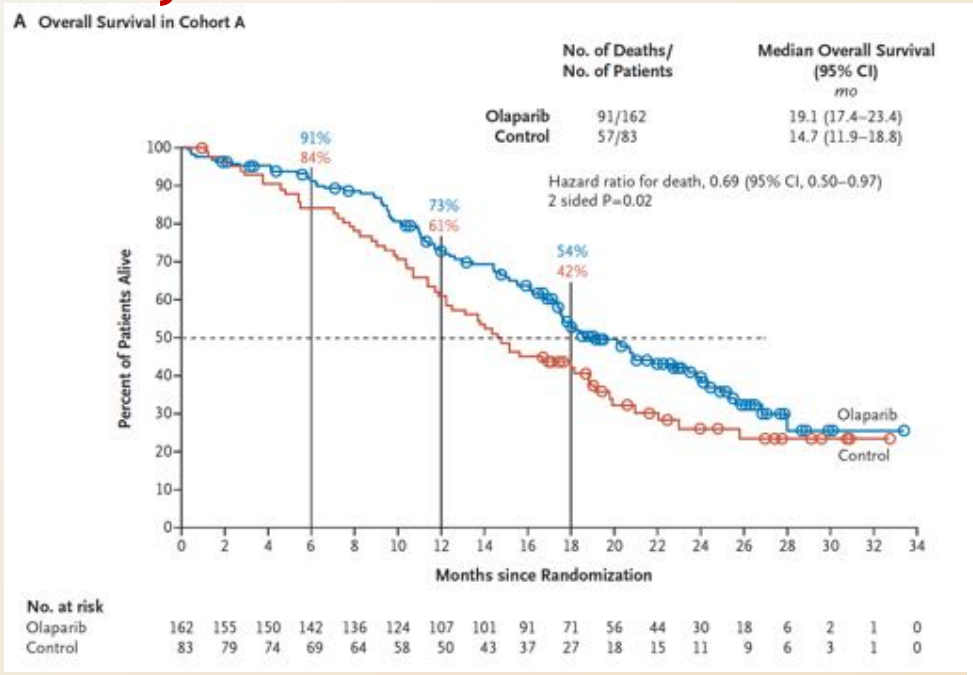
- rPFS in Cohorts A+B
- Confirmed radiographic objective response rate (ORR) in Cohort A
- Time to pain progression (TTPP) in Cohort A
- Overall survival (OS) in Cohort A

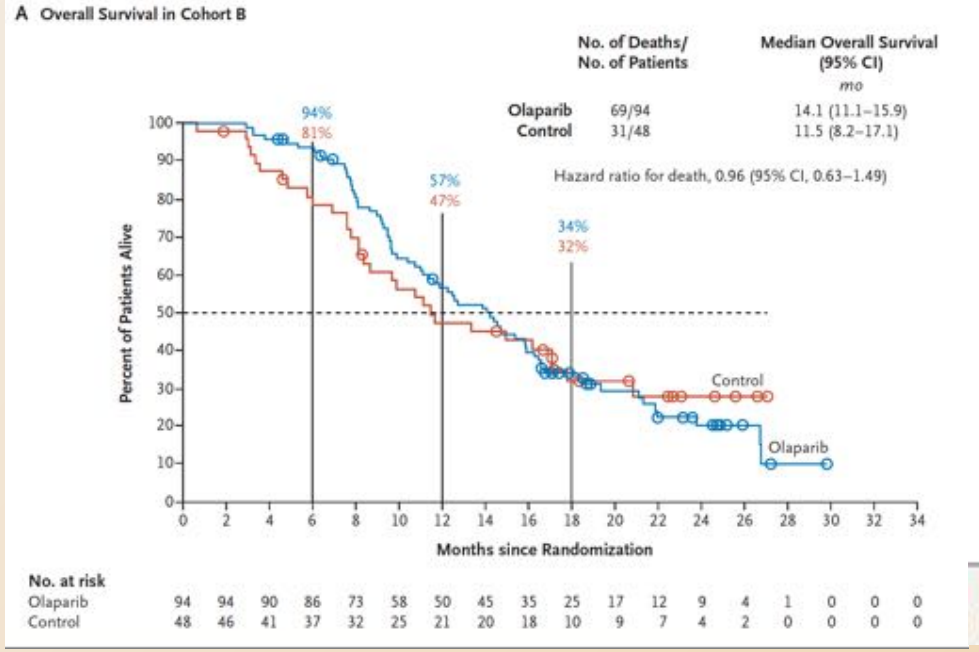
***An investigational Clinical Trial Assay, based on -- next-generation sequencing test** Developed in partnership with Foundation Medicine Inc, and used to prospectively select patients harboring alterations in *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *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) |

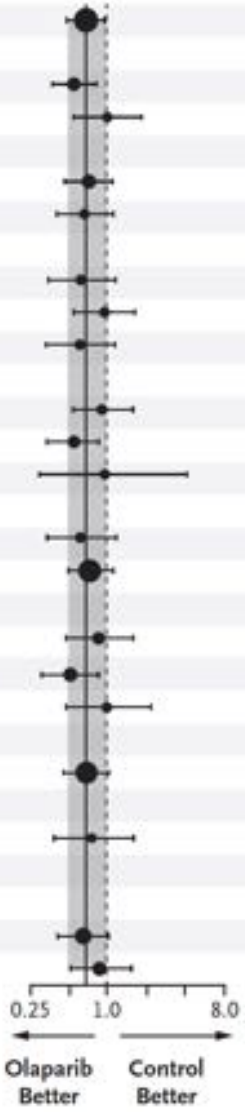
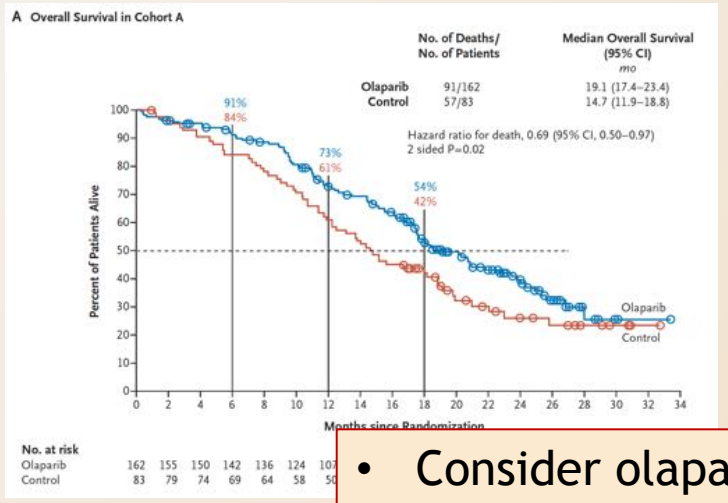
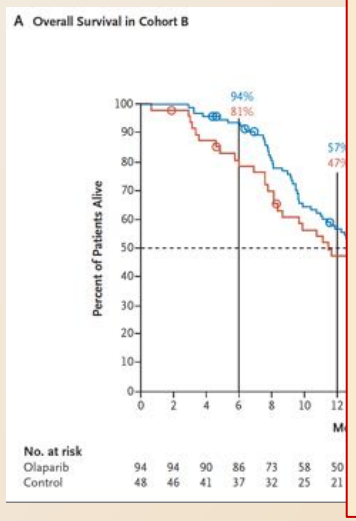



**Figure 4. Subgroup Analyses of Overall Survival in Cohort A, According to Baseline Demographic and Clinical Characteristics of the Patients.**

De Wit et al, NEJM 2019

# PROfound study

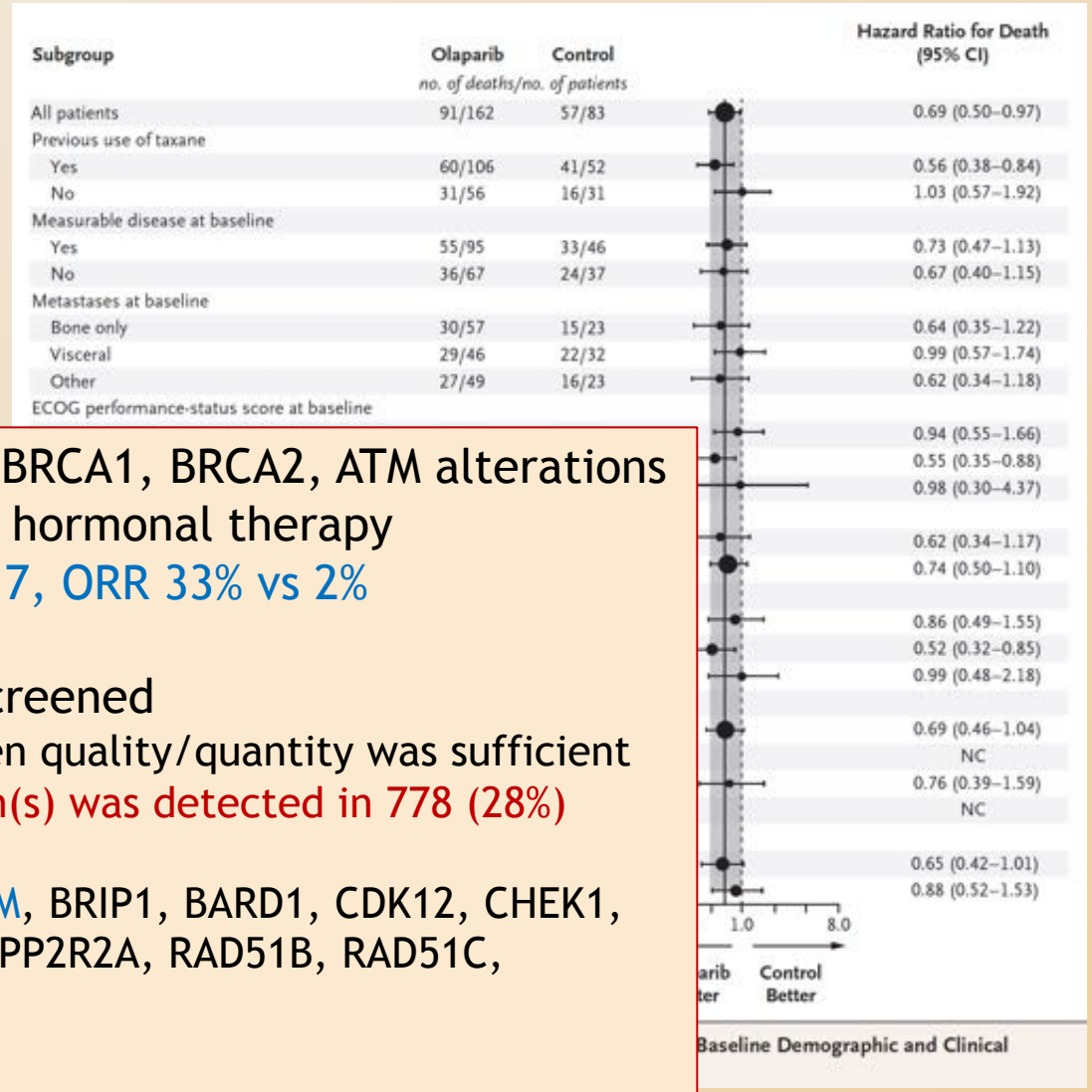



- Consider olaparib for BRCA1, BRCA2, ATM alterations after next generation hormonal therapy
- Median OS 19.1 vs 14.7, ORR 33% vs 2%

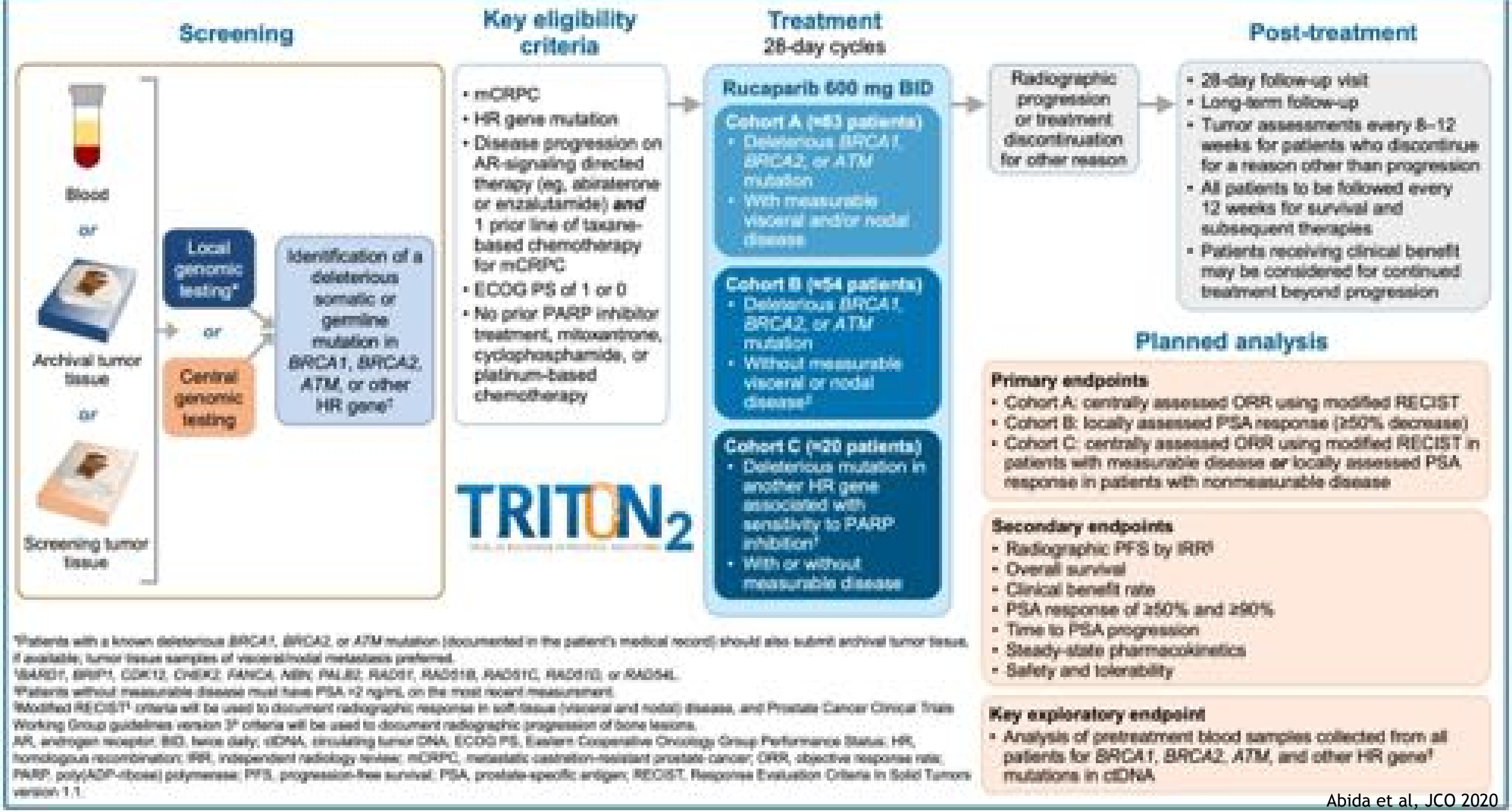
- 4425 patients were screened
  - 2792 (69%) specimen quality/quantity was sufficient
    - HRR alteration(s) was detected in 778 (28%)

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




De Wit et al, NEJM 2019

# Figure 2. TRITON2 Trial Schema



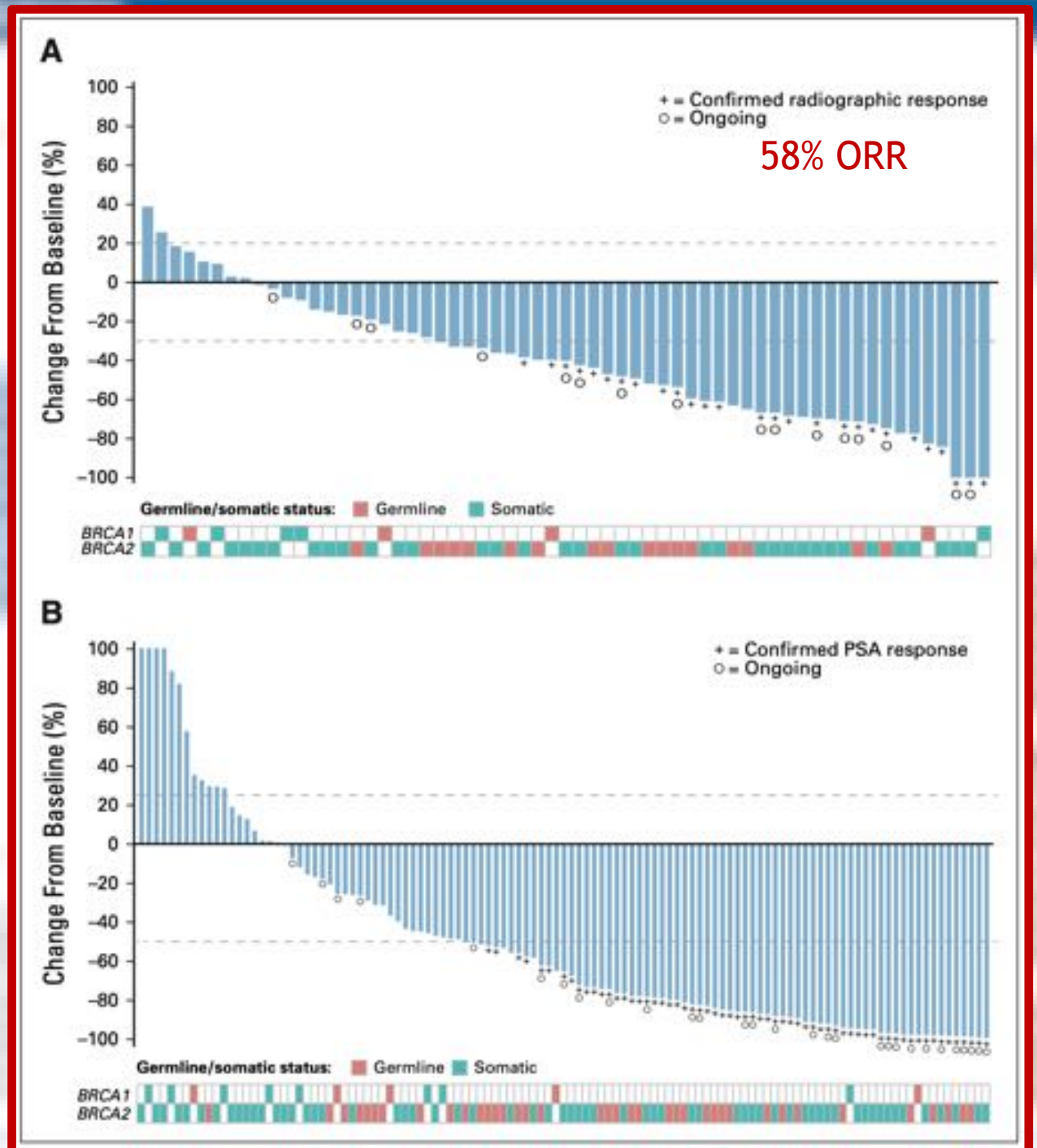

## Planned analysis

**Primary endpoints**
- Cohort A: centrally assessed ORR using modified RECIST
- Cohort B: locally assessed PSA response (≥50% decrease)
- Cohort C: centrally assessed ORR using modified RECIST in patients with measurable disease *or* locally assessed PSA response in patients with nonmeasurable disease

**Secondary endpoints**
- Radiographic PFS by IRR§
- Overall survival
- Clinical benefit rate
- PSA response of ≥50% and ≥90%
- Time to PSA progression
- Steady-state pharmacokinetics
- Safety and tolerability

**Key exploratory endpoint**
- Analysis of pretreatment blood samples collected from all patients for *BRCA1*, *BRCA2*, *ATM*, and other HR gene† mutations in cDNA

*Patients with a known deleterious *BRCA1*, *BRCA2*, or *ATM* mutation (documented in the patient's medical record) should also submit archival tumor tissue, if available; tumor tissue samples of visceral/nodal metastases preferred.
†*BARD1*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *NBN*, *PALB2*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*.
‡Patients without measurable disease must have PSA ≥2 ng/mL on the most recent measurement.
§Modified RECIST[1] criteria will be used to document radiographic response in soft tissue (visceral and nodal) disease, and Prostate Cancer Clinical Trials Working Group guidelines version 3[2] criteria will be used to document radiographic progression of bone lesions.
AR, androgen receptor; BID, twice daily; cDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, homologous recombination; IRR, independent radiology review; mCRPC, metastatic castration-resistant prostate cancer; ORR, objective response rate; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors version 1.1.




Abida et al, JCO 2020

# What to Consider to Arrive at the Optimal Approach?

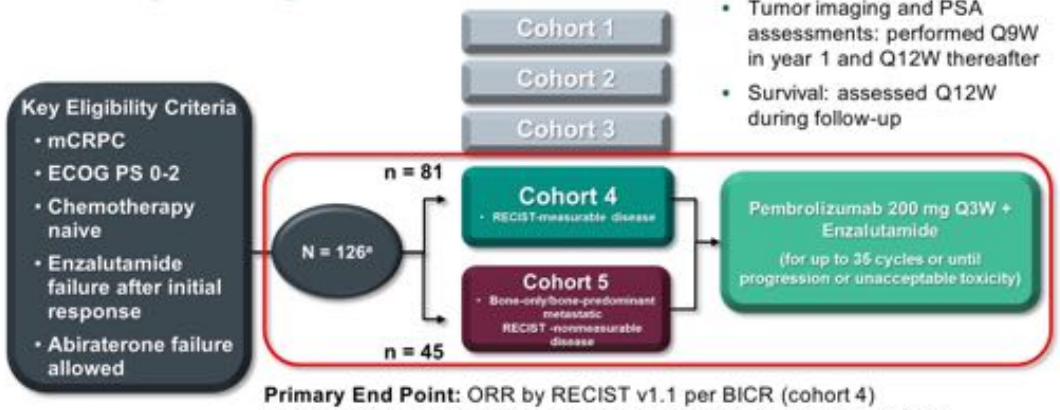
- Treatment history has an impact
- Consider M0 treatment for PSADT $\leq$ 10 months
- Use as many agents with OS benefit as possible
- Consider Sipuleucel T and Ra223 earlier in the course
- Recognize combinations that don’t work
- Avoid using abiraterone after enzalutamide or vice versa
- PSMA-Lu177 is approved for CRPC in addition to SOC
- Combination of PSMA-Lu177 with ARPI may work
- Look for BRCA2/1, ATM etc; 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



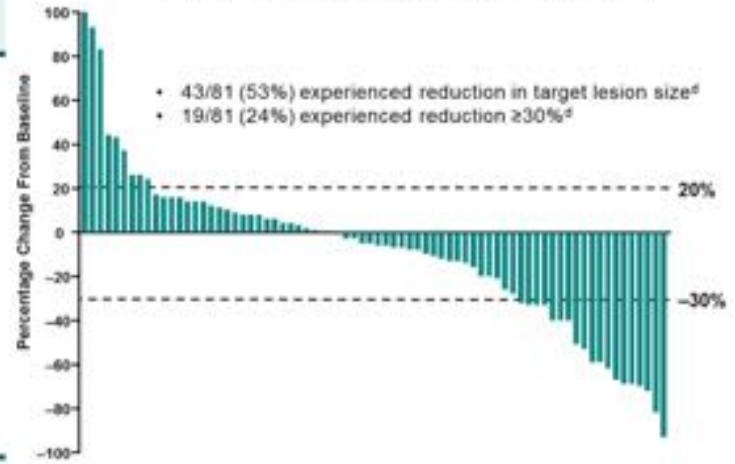

**Primary End Point:** ORR by RECIST v1.1 per BICR (cohort 4)
**Secondary End Points:** DCR (RECIST v1.1), rPFS (PCWG3-modified RECIST v1.1), PSA response rate, OS, and safety (cohorts 4 and 5); DOR (RECIST v1.1, cohort 4)

[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?

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- Consider Sipuleucel T and Ra223 earlier in the course
- Recognize combinations that don’t work
- Avoid using abiraterone after enzalutamide or vice versa
- PSMA-Lu177 is approved for CRPC in addition to SOC
- Combination of PSMA-Lu177 with ARPI may work
- Look for BRCA2/1, ATM etc; consider olaparib and rucaparib
- Consider pembrolizumab for DNA MMR deficiency

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