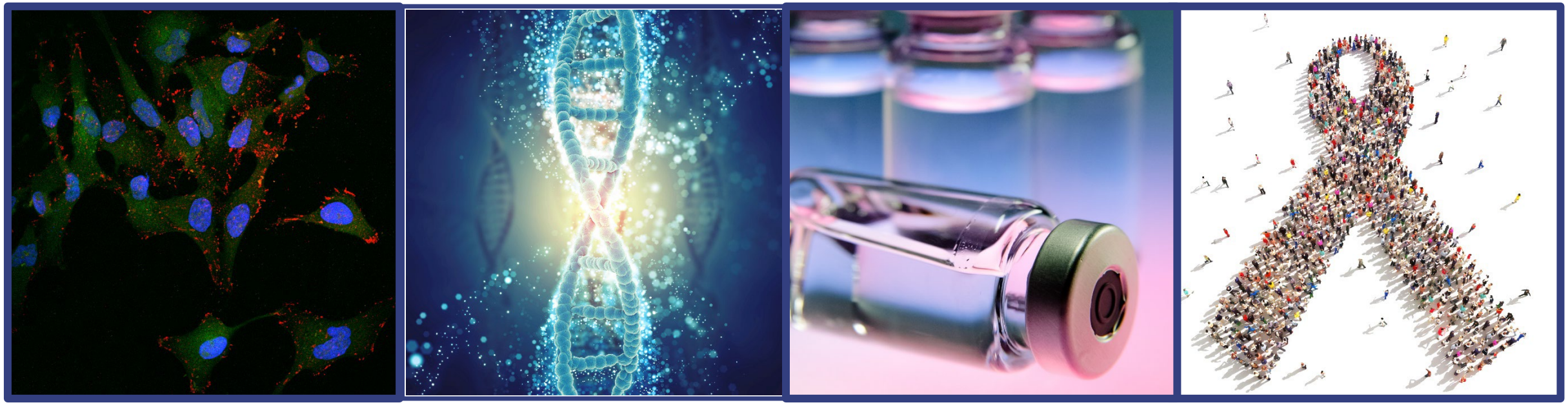

What is new in prostate cancer treatment?

Mehmet Asim Bilen, MD
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Winship Cancer Institute of Emory University

EMORY
WINSHIP
CANCER
INSTITUTE
National Cancer Institute-Designated
Comprehensive Cancer Center

Overview

- Advancement in upfront treatment of metastatic hormone-sensitive prostate cancer (mHSPC):
  - PEACE (2022)
  - ARASENS (2022)
- Updates in PARP inhibitors
- Radiopharmaceuticals: Lu-177 PSMA

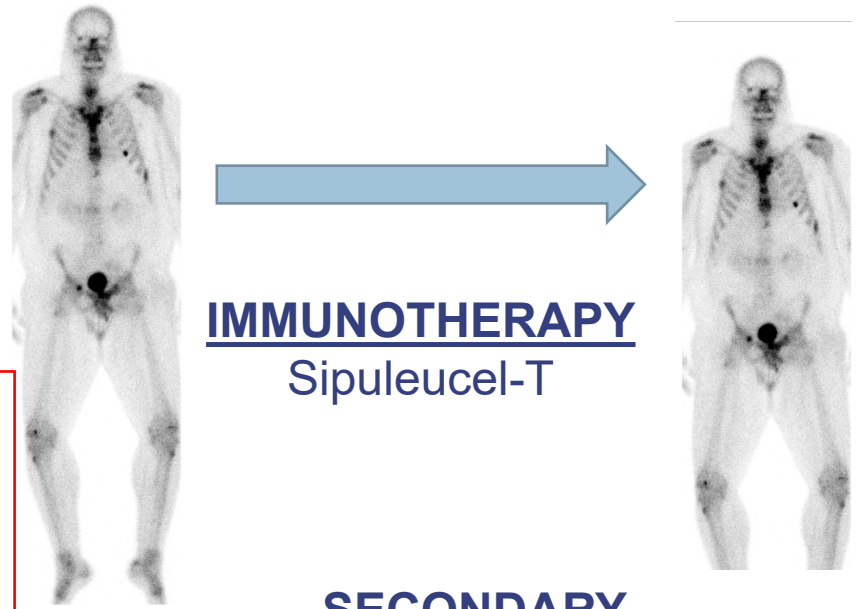
Case

- 55 y/o male patient
- Good health with no major health issue
- Recently diagnosed with prostate cancer, Gleason 4+5=9
- PSA > 1300
- Staging work-up showed >20 bone metastasis
- What is current treatment approach for this patient?

Therapeutic Options For Advanced Prostate Cancer 2022

CASTRATION SENSITIVE

CASTRATION RESISTANT



ANDROGEN DEPRIVATION
Orchiectomy / GnRH Agonists
GnRH Antagonist
Antiandrogens
Docetaxel
Enzalutamide
Apalutamide
Abiraterone+/- Docetaxel
Daralutamide+ Docetaxel

IMMUNOTHERAPY
Sipuleucel-T

SECONDARY HORMONAL TREATMENTS
Bicalutamide, flutamide, nilutamide
Ketoconazole
DES
Abiraterone
Enzalutamide

M0 CRPC AGENTS
Apalutamide
Enzalutamide
Daralutamide

Radiopharmaceuticals
Radium-223
Lu-177 PSMA

CHEMOTHERAPY
Docetaxel
Cabazitaxel

CRPC with DDR
Olaparib
Rucaparib
PARP inhibitor combinations

DES = diethylstilbestrol

How did we get here in mHSPC?

- CHAARTED & STAMPEDE (2015-2016):
  - 6 cycles of docetaxel +ADT
  - Improved OS over ADT alone
- LATIDUDE & STAMPEDE (2017):
  - Abiraterone+ADT
  - Improved OS over ADT alone
- ENZAMET & ARCHES (2019):
  - Enzalutamide+ADT
  - Improved OS over ADT alone (ENZAMET)
- TITAN (2019):
  - Apalutamide+ADT
  - Improved OS over ADT alone

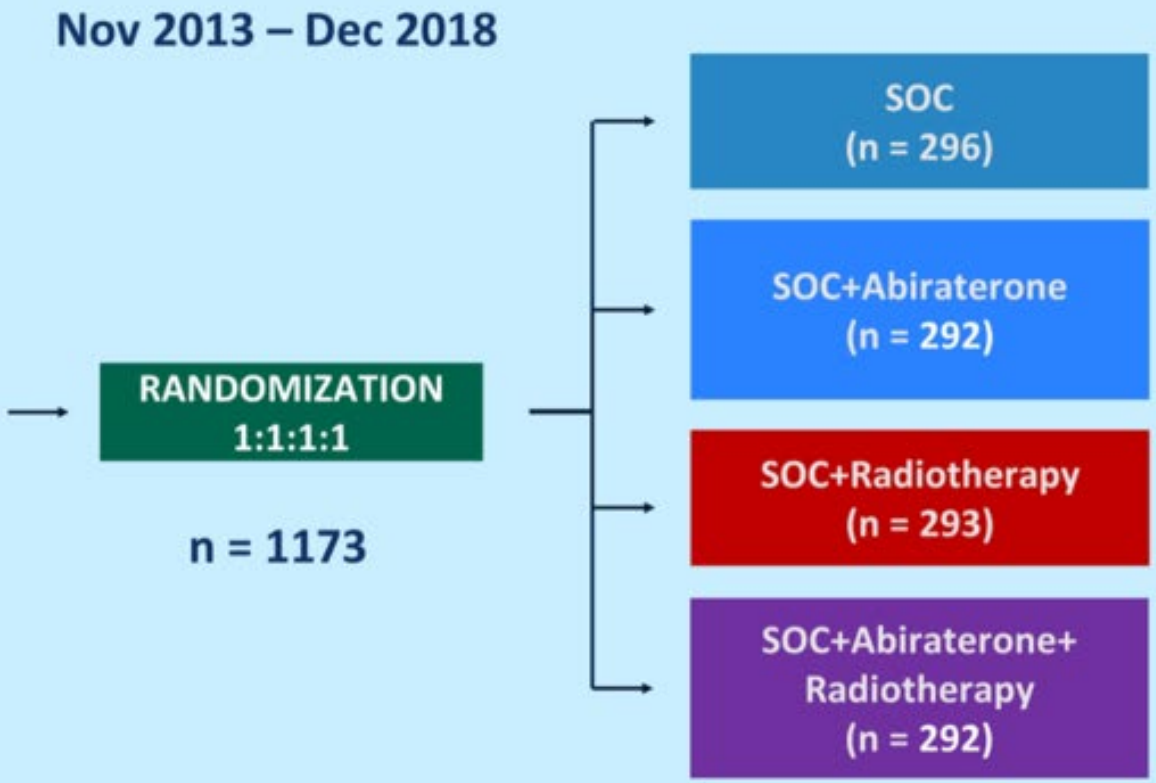
PEACE 1 trial

Key Eligibility Criteria
De novo mCSPC
Distant metastatic disease by ≥ 1 lesion on bone scan and/or CT scan
ECOG PS 0 -2

On-Study Requirement
Continuous ADT

Permitted
ADT ≤ 3 months

Stratification
ECOG PS (0 vs 1-2)
Metastatic sites (LN vs bone vs visceral)
Type of castration (orchidectomy vs LHRH agonist vs LHRH antagonist)
Docetaxel (yes vs no)



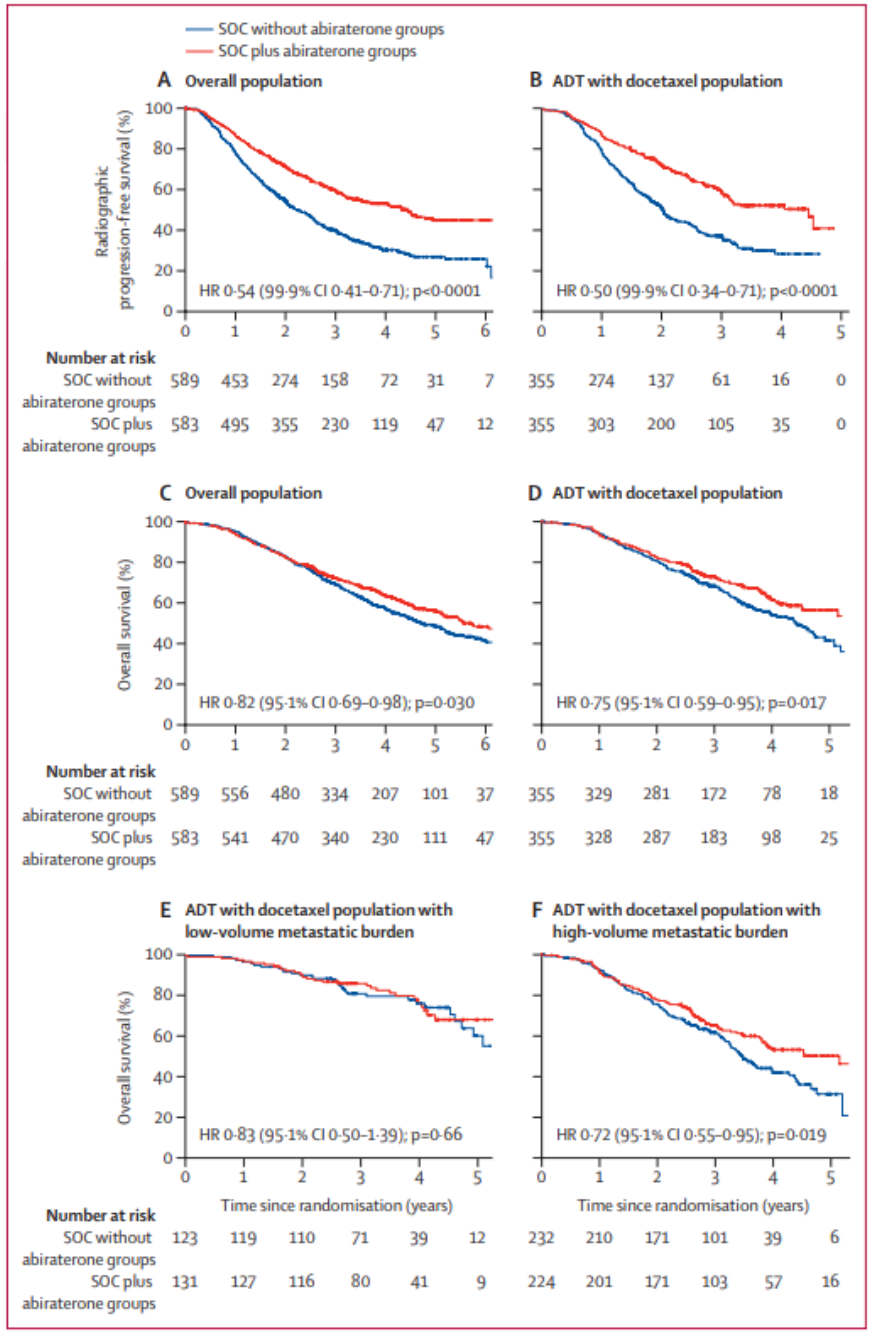
ECOG PS, Eastern Cooperative Oncology Group performance status

PEACE 1 trial

	Patients assessed, n		Median, years		Median difference, years	Hazard ratio	p value
	SOC with abiraterone groups	SOC without abiraterone groups	SOC with abiraterone groups	SOC without abiraterone groups			
Primary outcomes in the overall population							
Overall survival	583	589	5·7	4·7	0·9 (95·1% CI 0·0–2·0)	0·82 (95·1% CI 0·69–0·98)	0·030
Radiographic progression-free survival	583	589	4·5	2·2	2·1 (99·9% CI 0·7–2·9)	0·54 (99·9% CI 0·41–0·71)	<0·0001
Secondary outcomes in the overall population							
CRPC-free survival	583	589	3·8	1·5	2·3 (95% CI 1·6–3·0)	0·40 (95% CI 0·35–0·47)	<0·0001
Prostate-cancer-specific survival	583	589	NR	5·8	NA	0·75 (95% CI 0·61–0·91)	0·0038
Primary outcomes in the ADT with docetaxel population							
Overall survival	355	355	NR	4·4	NA	0·75 (95·1% CI 0·59–0·95)	0·017
Radiographic progression-free survival	355	355	4·5	2·0	2·2 (99·9% CI 0·6–2·8)	0·50 (99·9% CI 0·34–0·71)	<0·0001
Secondary outcomes in the ADT with docetaxel population							
Overall survival in patients with low-volume metastatic burden	131	123	NR	NR	NA	0·83 (95·1% CI 0·50–1·39)	0·66
Overall survival in patients with high-volume metastatic burden	224	232	5·1	3·5	1·1 (95·1% CI 0·2–1·9)	0·72 (95·1% CI 0·55–0·95)	0·019
Radiographic progression-free survival in patients with low-volume metastatic burden	129	122	NR	2·7	NA	0·58 (99·9% CI 0·29–1·15)	0·0061
Radiographic progression-free survival in patients with high-volume metastatic burden	225	231	4·1	1·6	2·2 (99·9% CI 0·6–3·2)	0·47 (99·9% CI 0·30–0·72)	<0·0001
CRPC-free survival	355	355	3·2	1·4	2·0 (95% CI 1·5–3·1)	0·38 (95% CI 0·31–0·47)	<0·0001
Prostate-cancer-specific survival	355	355	NR	4·7	NA	0·69 (95% CI 0·53–0·90)	0·0062

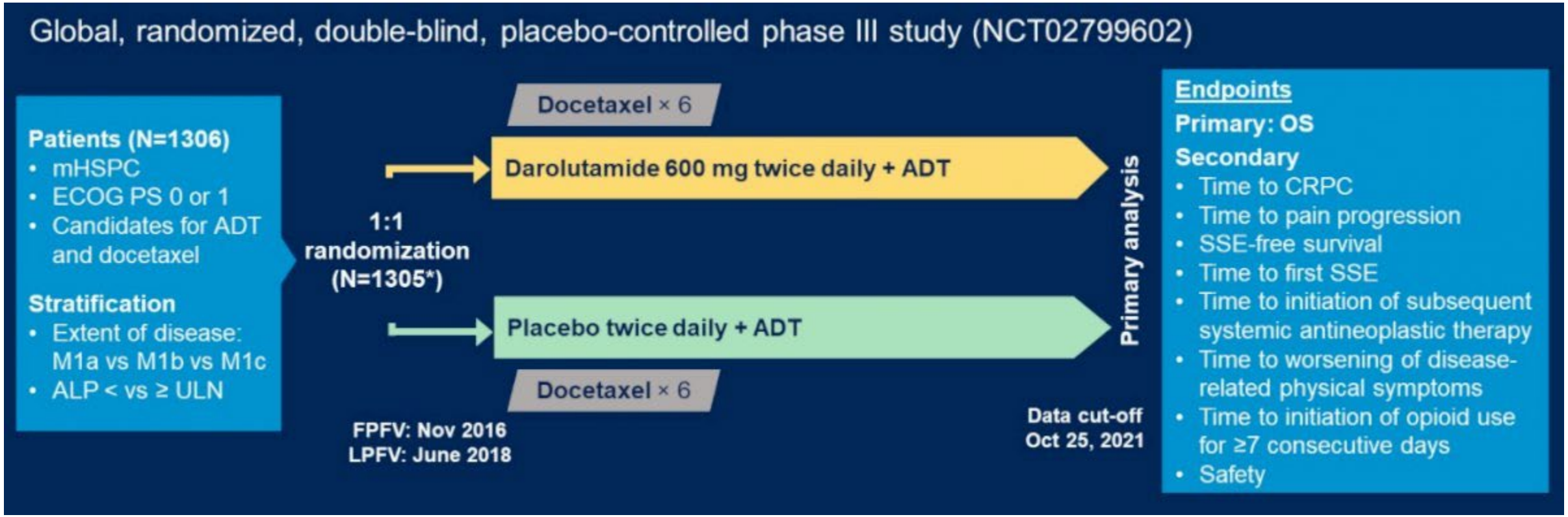
ADT=androgen deprivation therapy. CRPC=castration-resistant prostate cancer. NA=not available. NR=not reached. SOC=standard of care (with or without radiotherapy).

Table 2: **Efficacy outcomes in the intention-to-treat population**



Fizazi et al. Lancet 2022

ARASENS trial



Smith et al. NEJM 2022

ARASENS trial

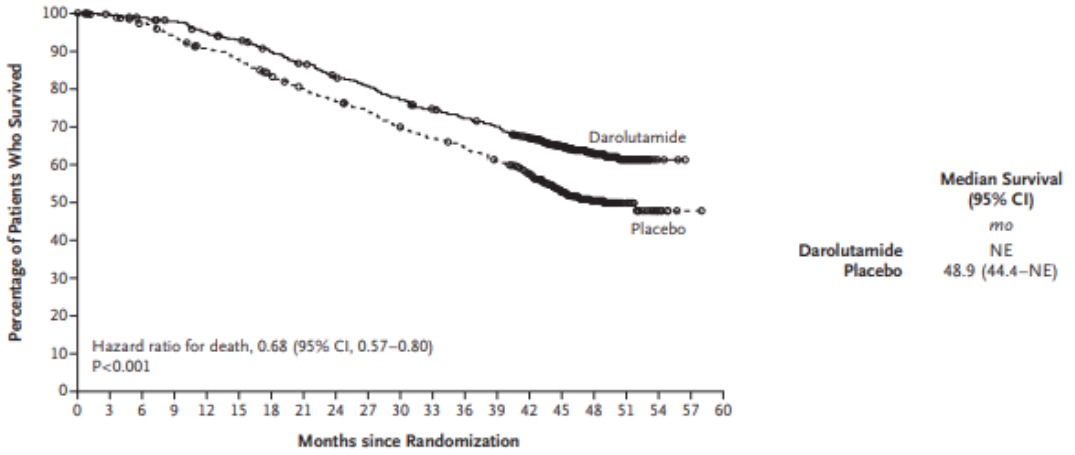
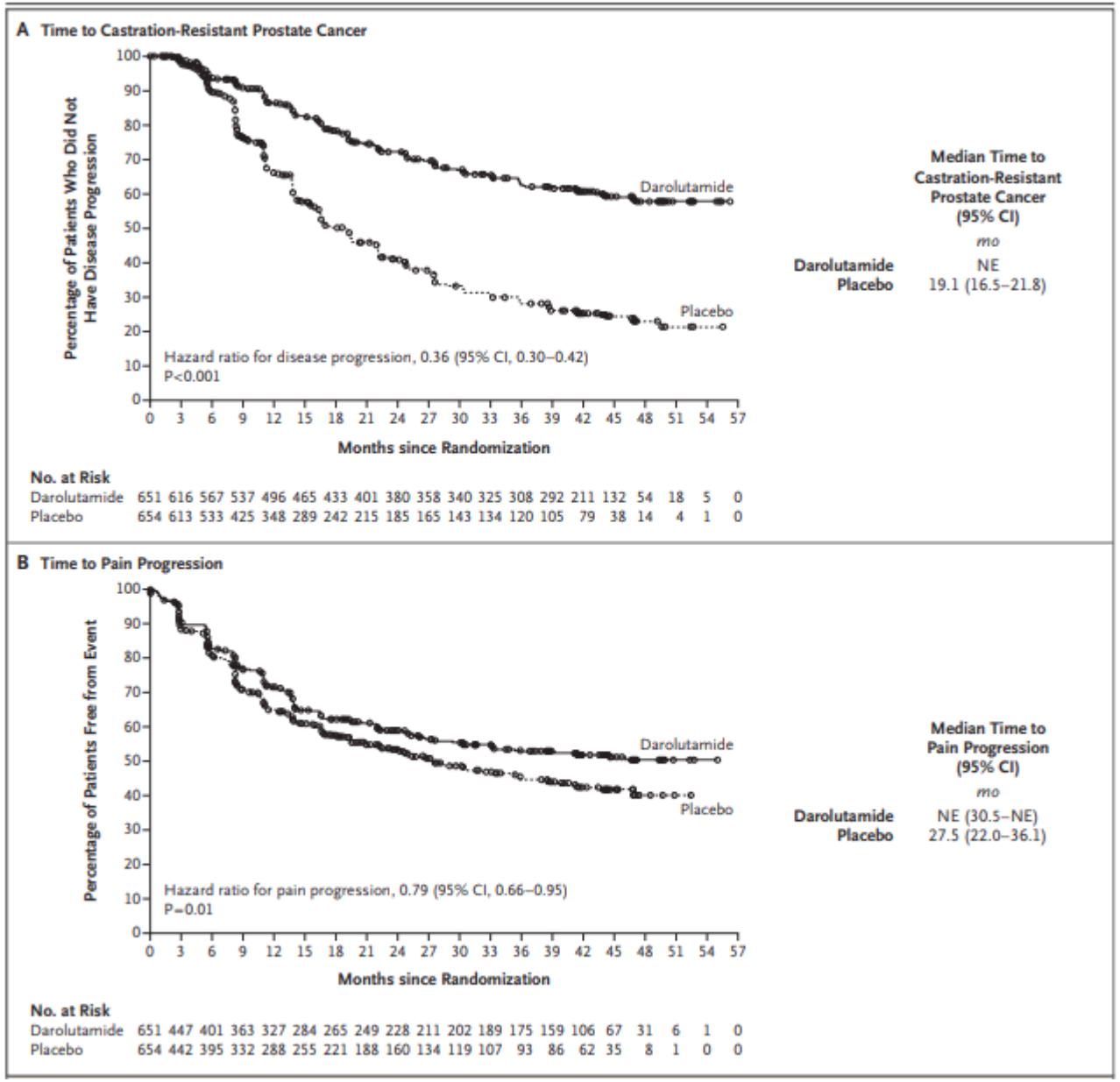


Figure 1. Overall Survival (Full Analysis Set).

Kaplan–Meier estimates of overall survival are shown. For the analysis of overall survival, data were censored as of the last known date the patients were alive. One patient who was randomly assigned to the placebo group but received darolutamide was included in the placebo group in the full analysis set. CI denotes confidence interval, and NE not estimable.



Smith et al. NEJM 2022

What Do We Achieve?

- Break the old taboo, which is advanced prostate cancer initially treated with hormone deprivation alone
- Push the bar of OS with more intense upfront treatment in metastatic hormone naïve prostate cancer (~3 years→ 4+ years)
- There is no one way of treatment; able to offer more options for patients based on their strength, preferences, comorbidities, etc

What Is Still Not Answered?

- There are still no tools available to match our patients with the right treatment
  - Who benefits from chemo vs NHA (abiraterone, enzalutamide, apalutamide, daralutamide)?
  - Biomarker based patient selection is still missing

- **Using old-school stratification, number of bone mets, presence of visceral disease**
  - **Need a better method in the era of advance imaging, such as PSMA or fluciclovine F 18 PET**

- Still not able to cure people with any of those treatments

PSMA = prostate-specific membrane antigen; PET = positron emission tomography

How do I choose treatment for newly diagnosed mHSPC?

Disease Volume	ADT+Docetaxel	ADT+Abiraterone	ADT+Enzalutamide	ADT+Apalutamide	ADT+Abiraterone+ Docetaxel	ADT+Daralutamide +Docetaxel (soon)
Low volume	Likely no	Yes	Yes	Yes	Likely no	Likely no
High volume	Yes	Yes	Yes	Yes	Likely Yes	Likely Yes
When I don`t use	Poor PS	Poorly control diabetes, or cardiac issues	Drug-drug interaction such as HIV med, DOACs, etc	Drug-drug interaction such as HIV med, DOACs, etc	Poor PS	Poor PS

mHSPC =metastatic hormone sensitive prostate cancer

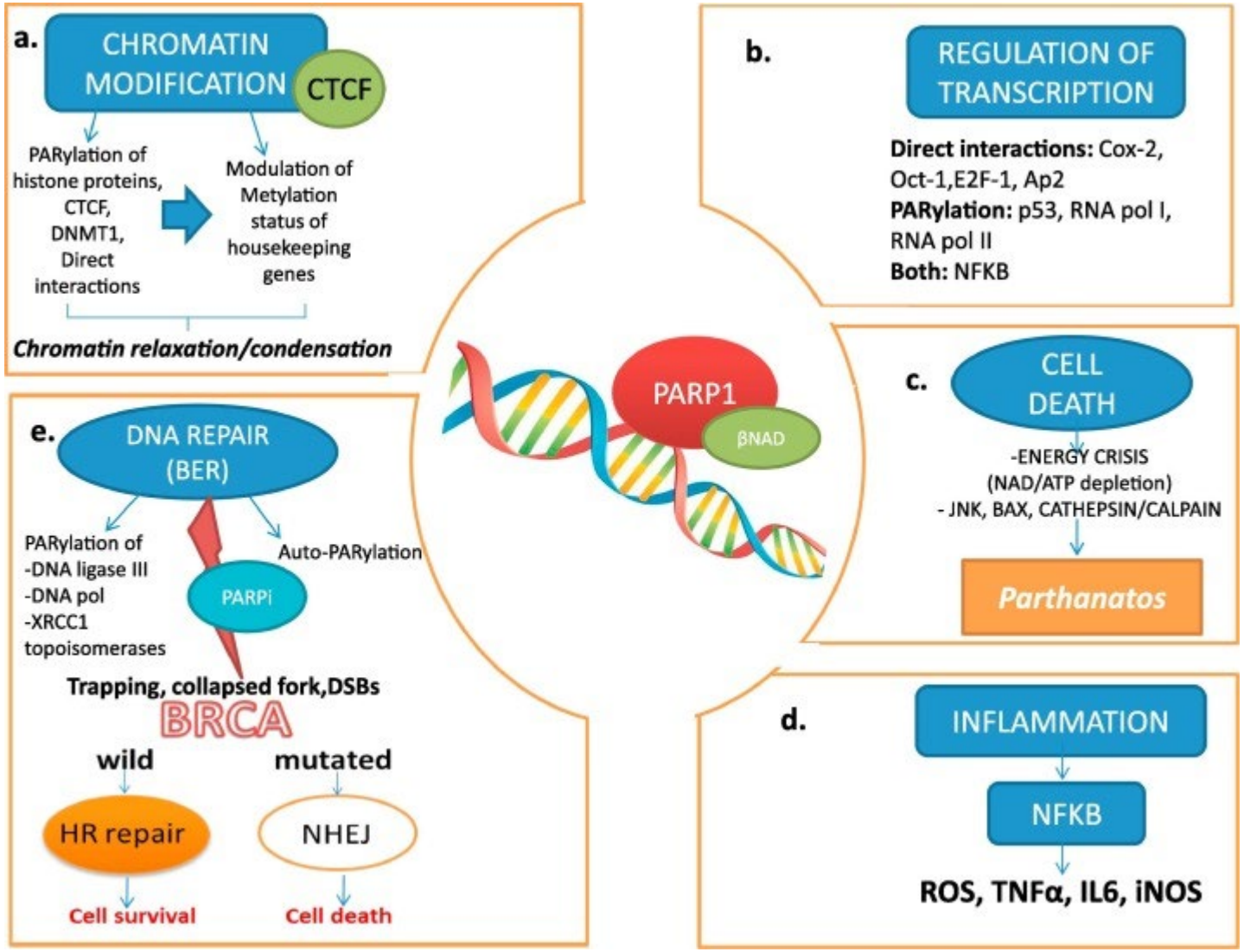
How do I choose treatment for newly diagnosed mHSPC?

All agents look similar, lack of biomarker:

- Cost: Docetaxel (~ 75$ per vial)
- Poor performance status: Abiraterone or Enzalutamide or Apalutamide
- Compliance issue: Docetaxel (IV vs PO)
- Chemotherapy anxiety: Abiraterone or Enzalutamide or Apalutamide
- Consider comorbidities, such as diabetes, seizure disorder
- Several adverse features: Triplet
- PATIENT PREFERENCE

mHSPC =metastatic hormone sensitive prostate cancer

PARP Inhibitors

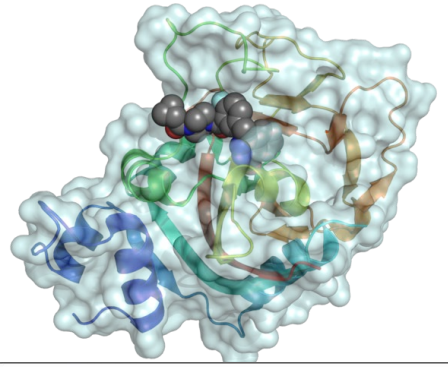


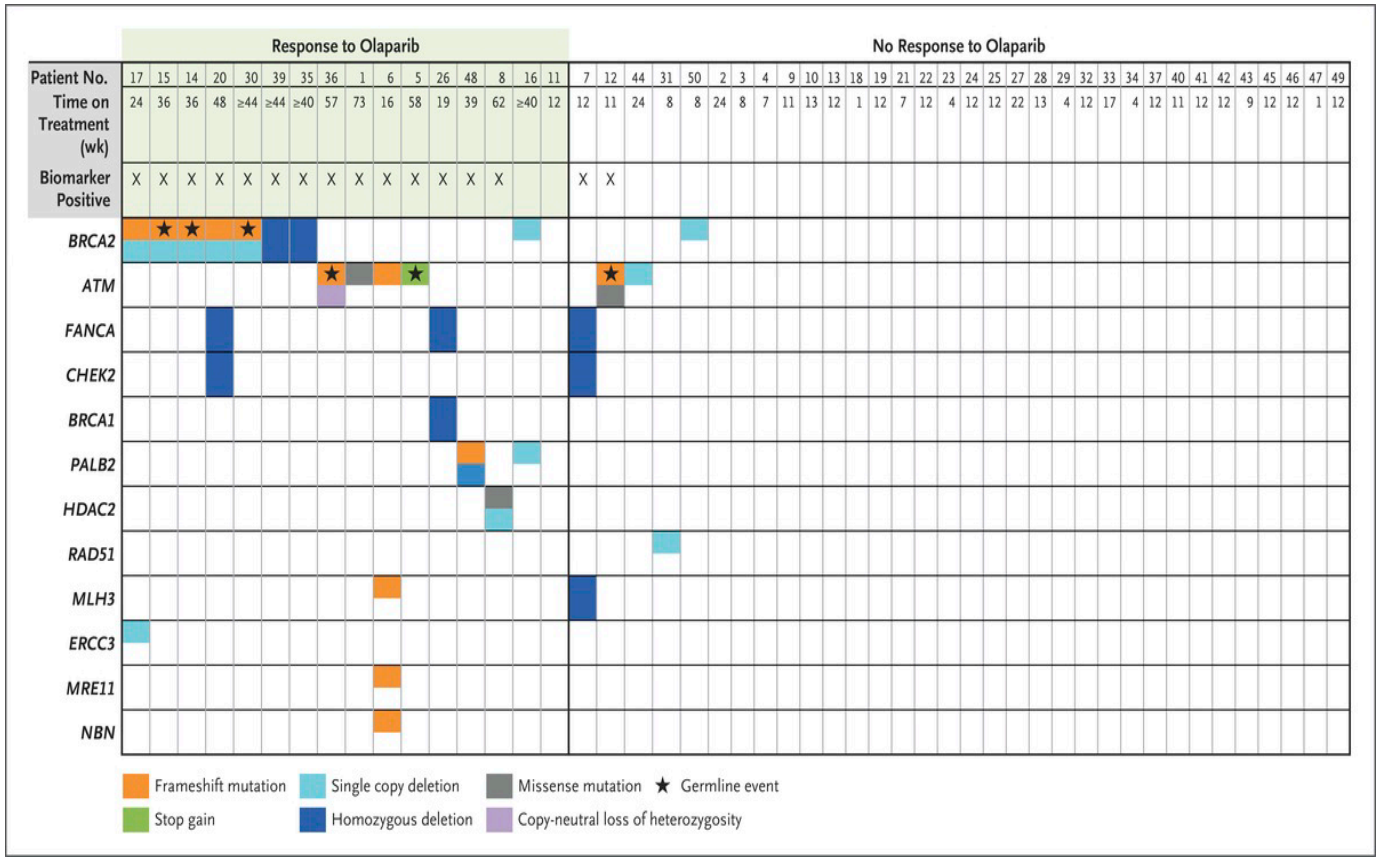
https://www.cancertreatmentreviews.com/article/S0305-7372%2818%2930200-7/fulltext

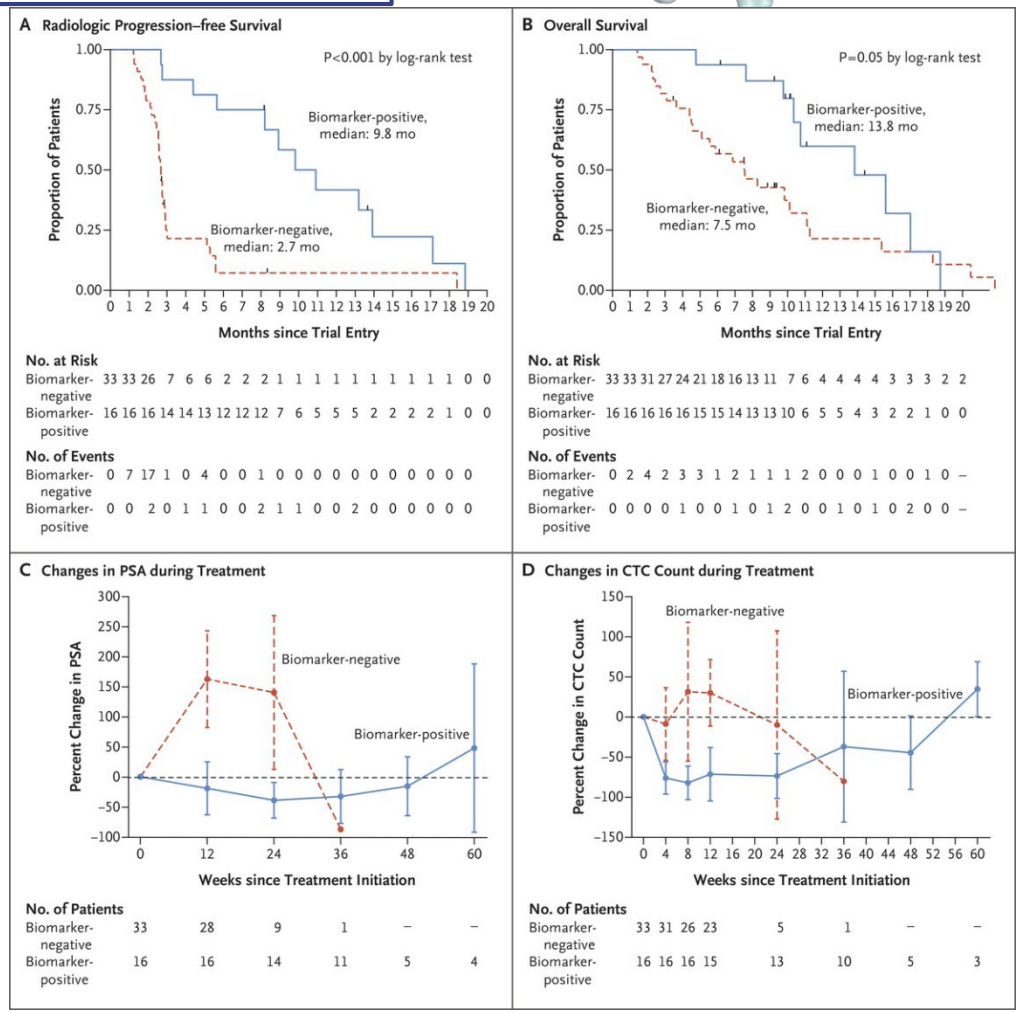
ORIGINAL ARTICLE

DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

Joaquin Mateo, M.D., Suzanne Carreira, Ph.D., Shahneen Sandhu, M.D., Susana Miranda, B.Sc., Helen Mossop, M.Math.Stat., Raquel Perez-Lopez, M.D., Daniel Nava Rodrigues, M.D., Dan Robinson, Ph.D., Aurelius Omlin, M.D., Nina Tunariu, M.D.Res., Gunther Boysen, Ph.D., Nuria Porta, Ph.D., et al.







Mateo J, et al. *N Engl J Med.* 2015;373:1697-1708.

How did we get here in PARP inhibitors?

- PROFOUND (2020):
  - Phase 3: Olaparib vs physician's agents of choice
  - Cohort A: *BRCA1*, *BRCA2*, *ATM*
  - Cohort B: Other DDR alterations
  - OS and rPFS improvement
  - FDA approved broadly

- TRITON 2 (2020):
  - Single arm, phase 2
  - Post NHA, and Taxane
  - *BRCA1/BRCA 2* cohort
  - Positive ORR
  - FDA approval for *BRCA1/2*

PROpel trial

PROpel Trial: First-line Olaparib + Abiraterone in mCRPC

- Ongoing, randomized, double-blind, international phase III study

Stratified by metastatic disease (bone only vs visceral vs other); docetaxel for mHSPC (yes vs no)

Patients with progressing mCRPC; no prior therapy for mCRPC; docetaxel for mHSPC allowed; ECOG PS 0/1; no prior abiraterone (N = 796)†

→ **Olaparib** 300 mg BID + **Abiraterone*** 1000 mg QD (n = 398)

→ **Placebo** + **Abiraterone*** 1000 mg QD (n = 398)

→ *Until radiographic progression or unacceptable toxicity*

Crossover from placebo to olaparib not permitted

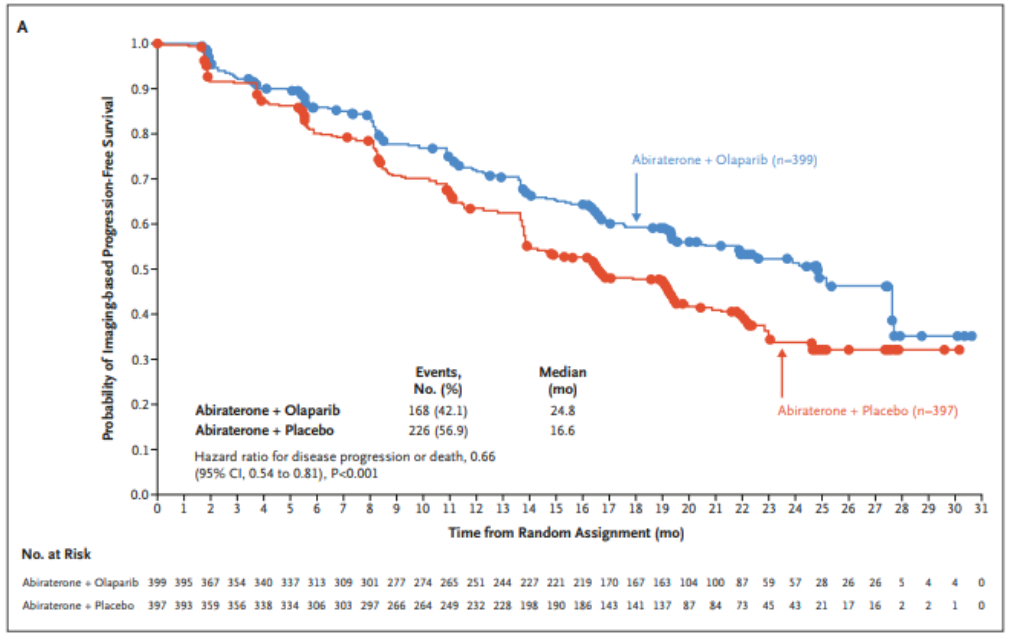
* Prednisone/prednisolone (5 mg) given with abiraterone.

† An additional 108 patients will be randomized 1:1 in China.

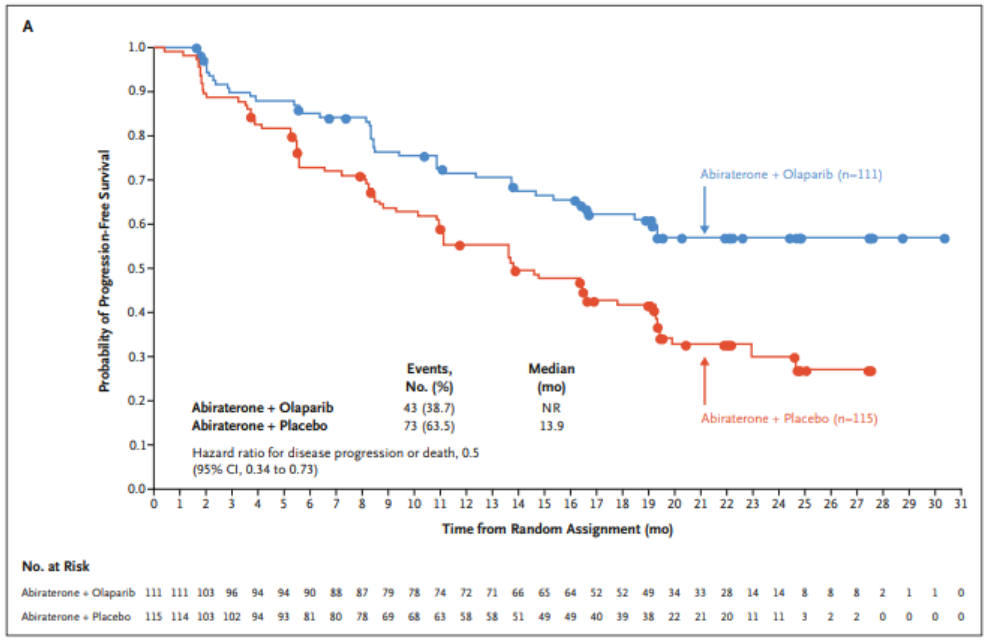
- Primary endpoints: rPFS by investigator
- Key secondary endpoints: OS, time to subsequent therapy or death, time to pain progression

NCT03732820.

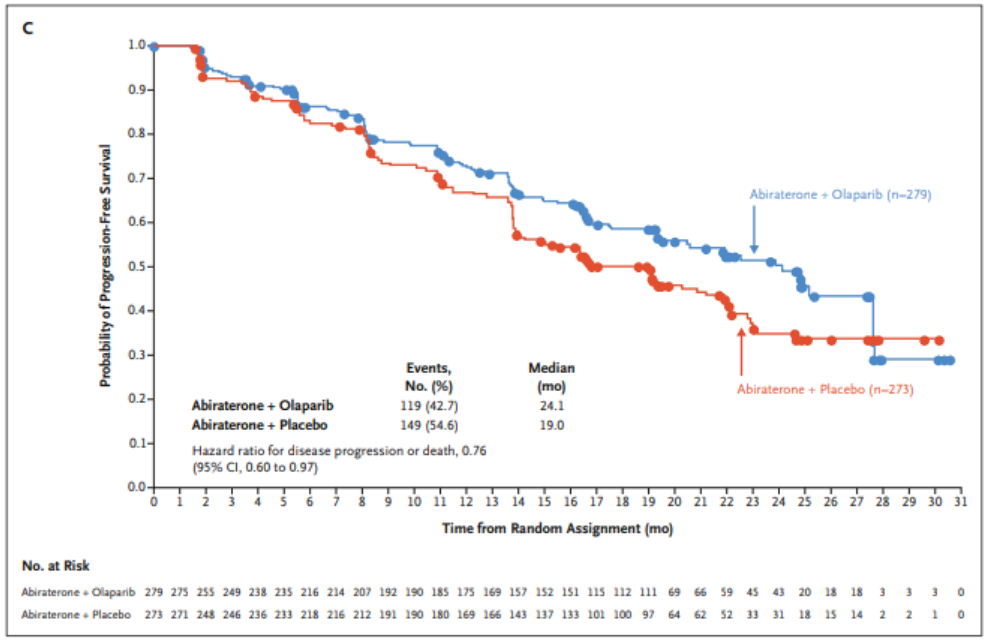
PROpel trial: rPFS



rPFS

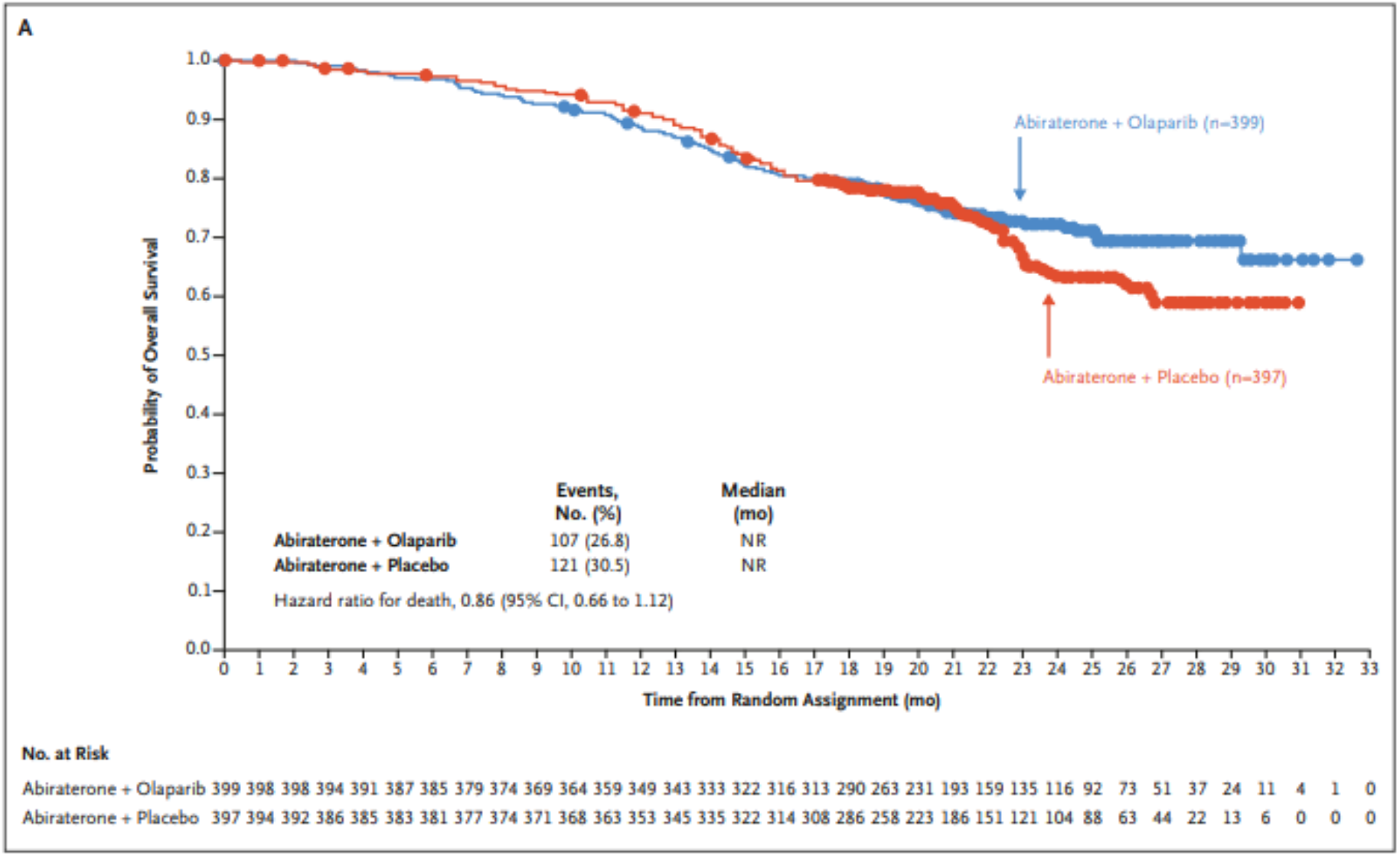


rPFS in HRR+

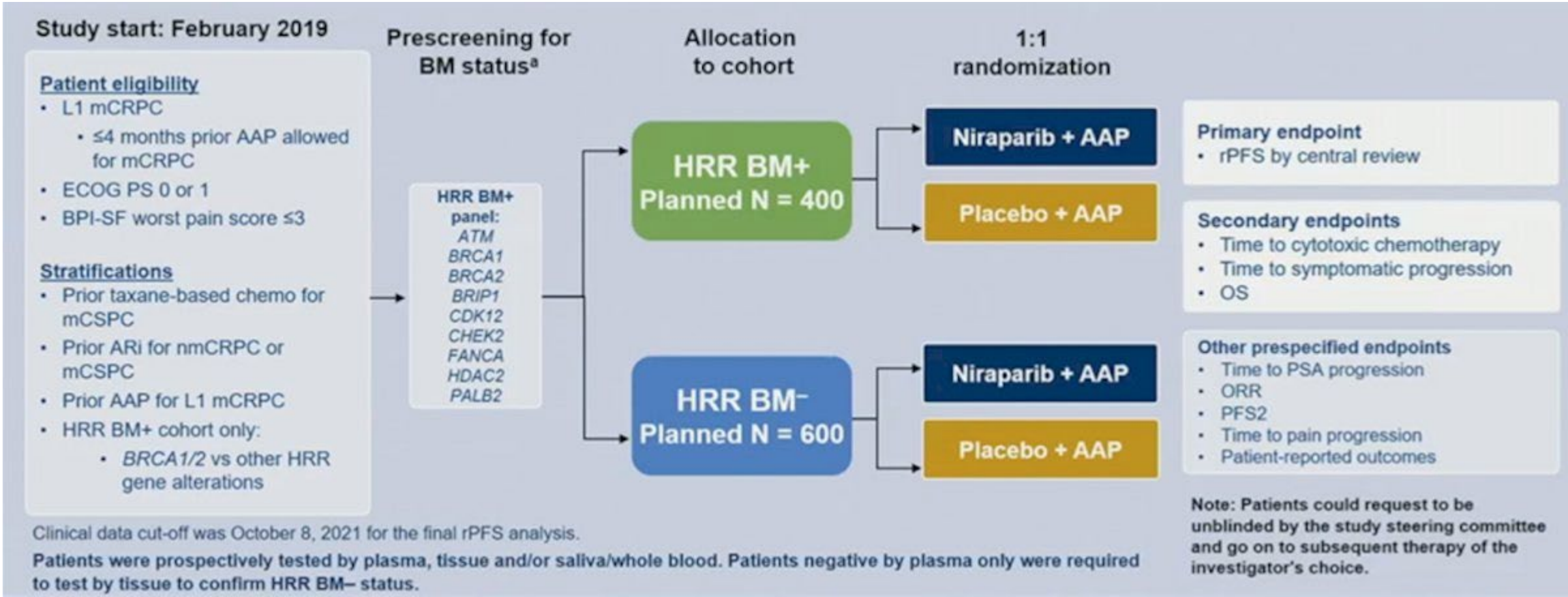


rPFS in HRR-

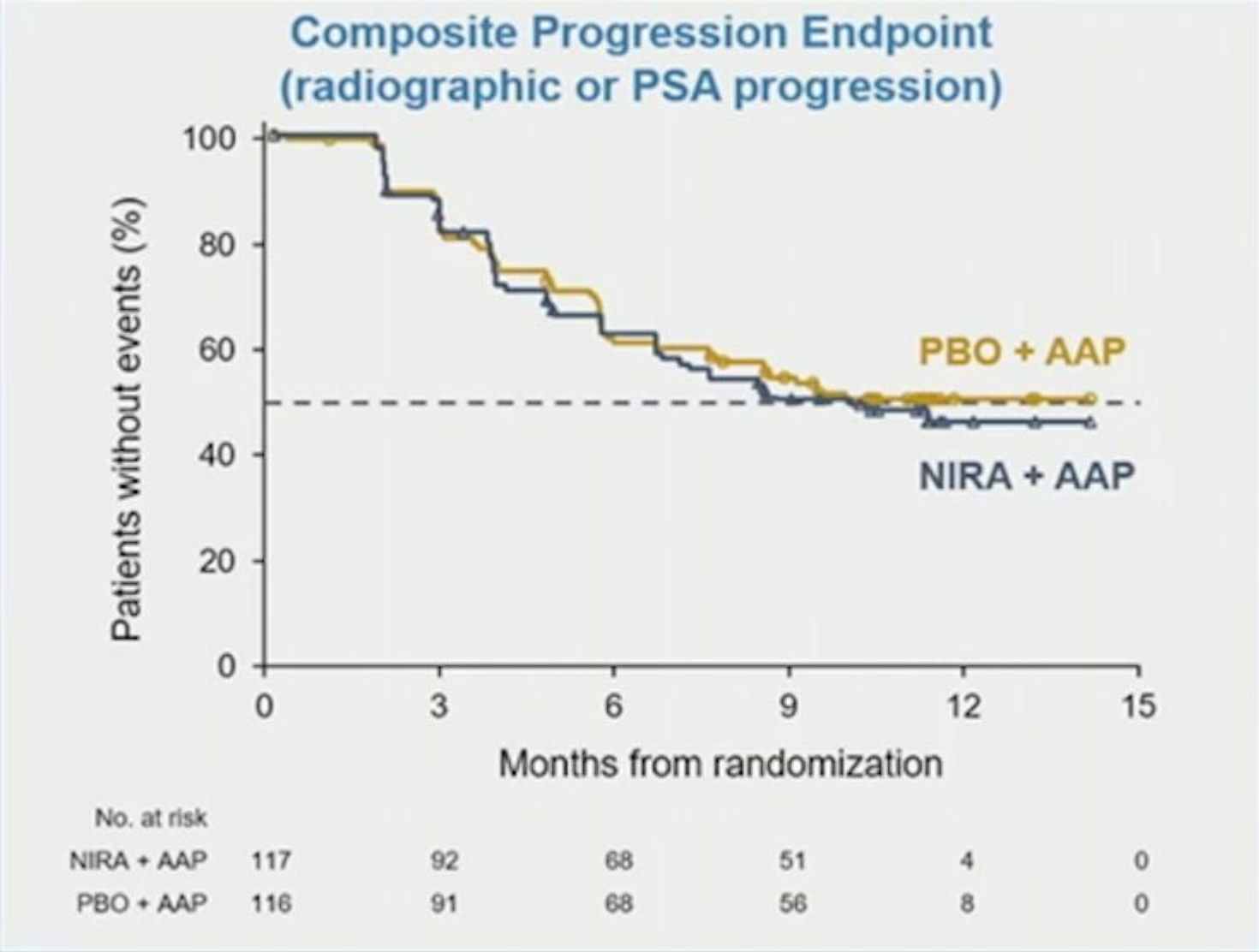
PROpel trial: OS



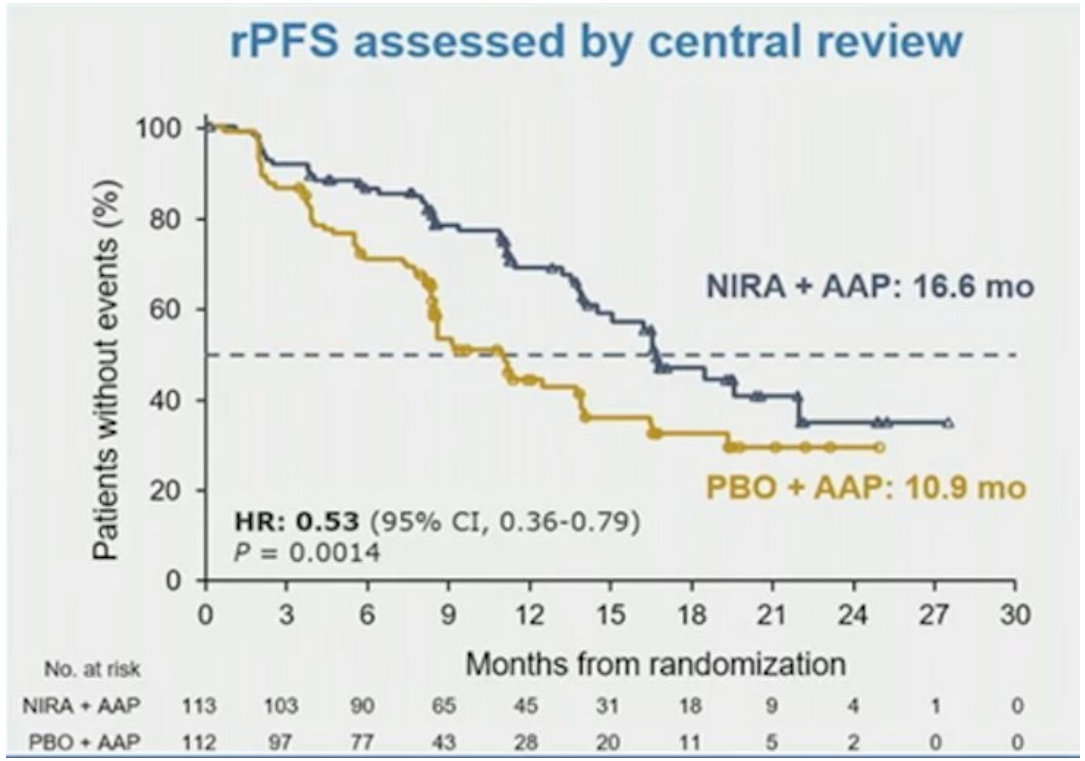
MAGNITUDE trial



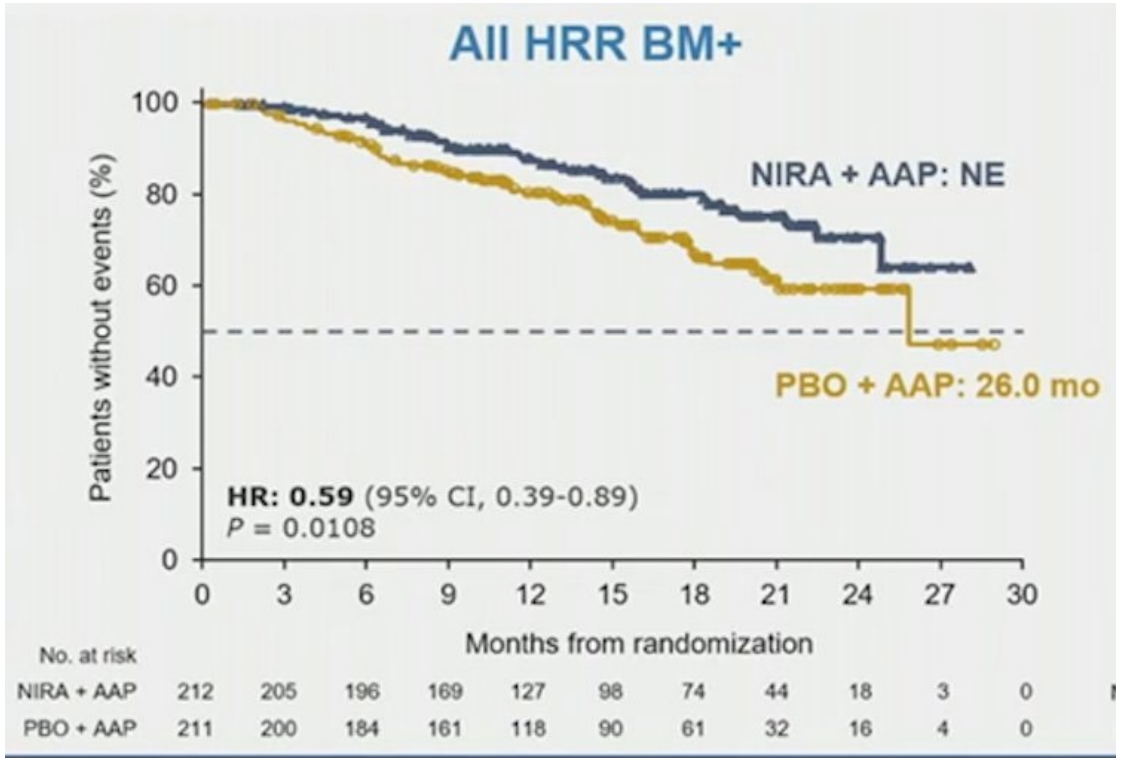
MAGNITUDE trial



MAGNITUDE trial



***BRCA1/2* Subgroup**

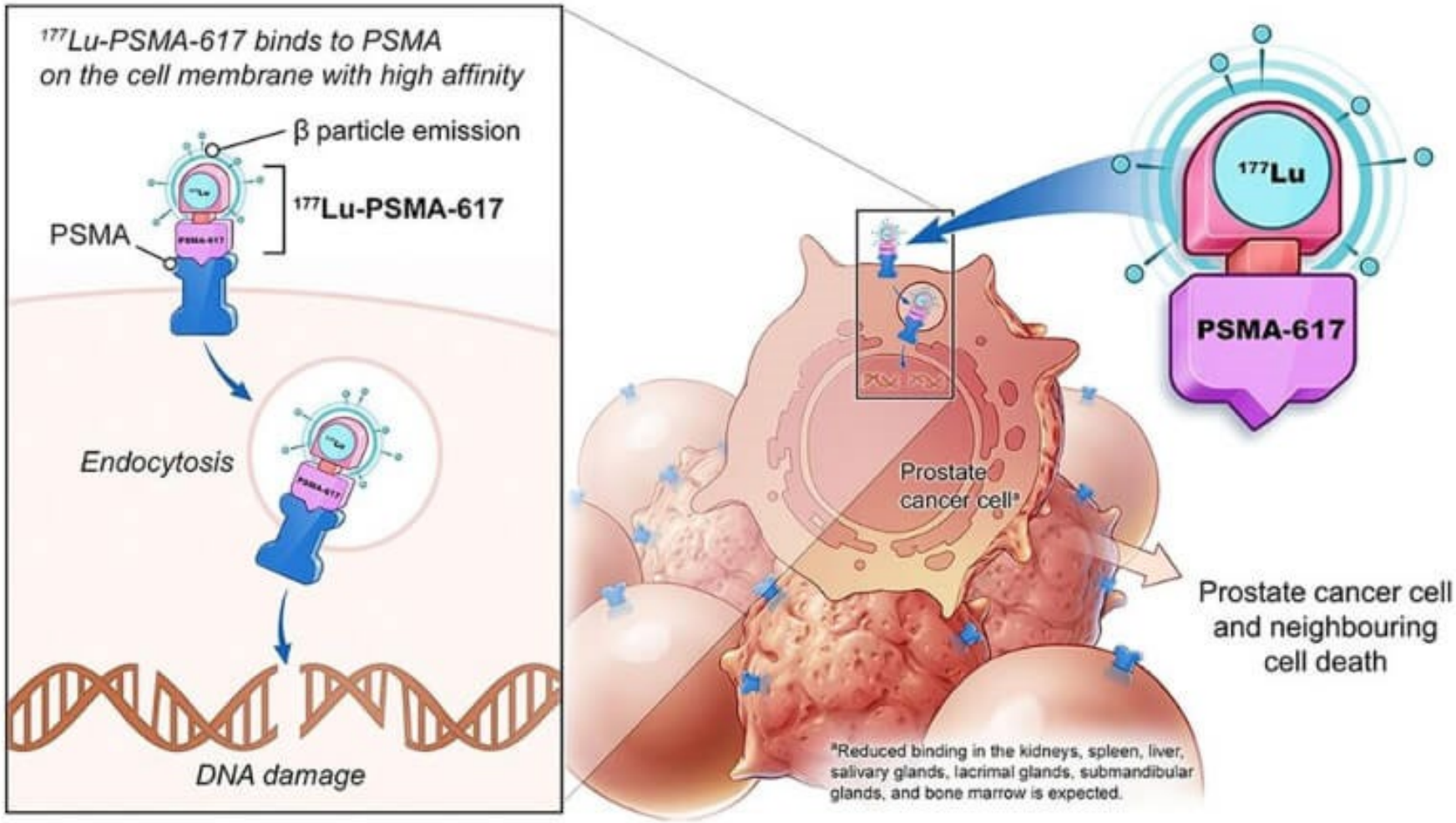


All HRR

PARP inhibitors

- DNA repair gene alterations are seen in metastatic prostate cancer
  - Both germline and somatic testing is required
- PARP inhibitors have demonstrated efficacy in mCRPC
  - Olaparib and rucaparib are now FDA approved
- PROPEL and MAGNITUDE trials tested PARP inhibitors +NHA
  - PROPEL + in rPFS regardless of HRR status
  - MAGNITUDE only for patients with HRR+
  - Although OS is secondary end point, still pending
  - Drug and financial toxicity need to be considered

Radiopharmaceuticals: Lu-177 PSMA



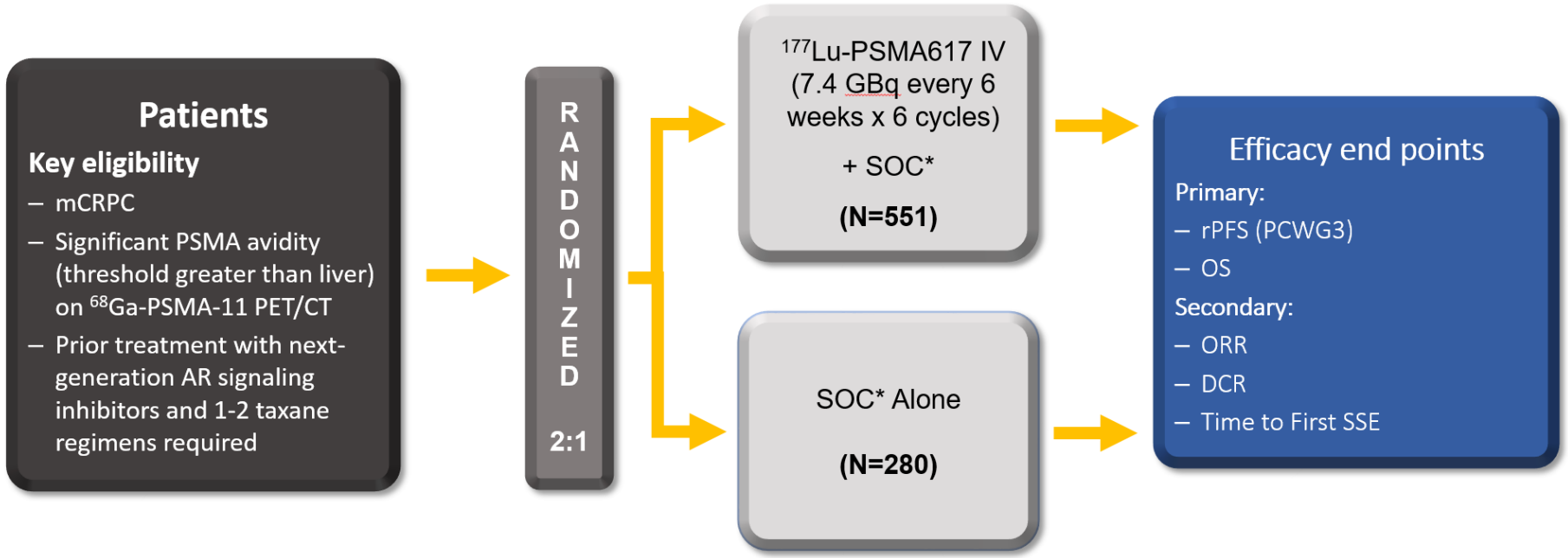
VISION Trial: Lu-177 PSMA

ASCO Annual Meeting 2021, Abstract #LBA4

Phase III study of lutetium-177-PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION).

Presenting Author: Michael J. Morris, MD

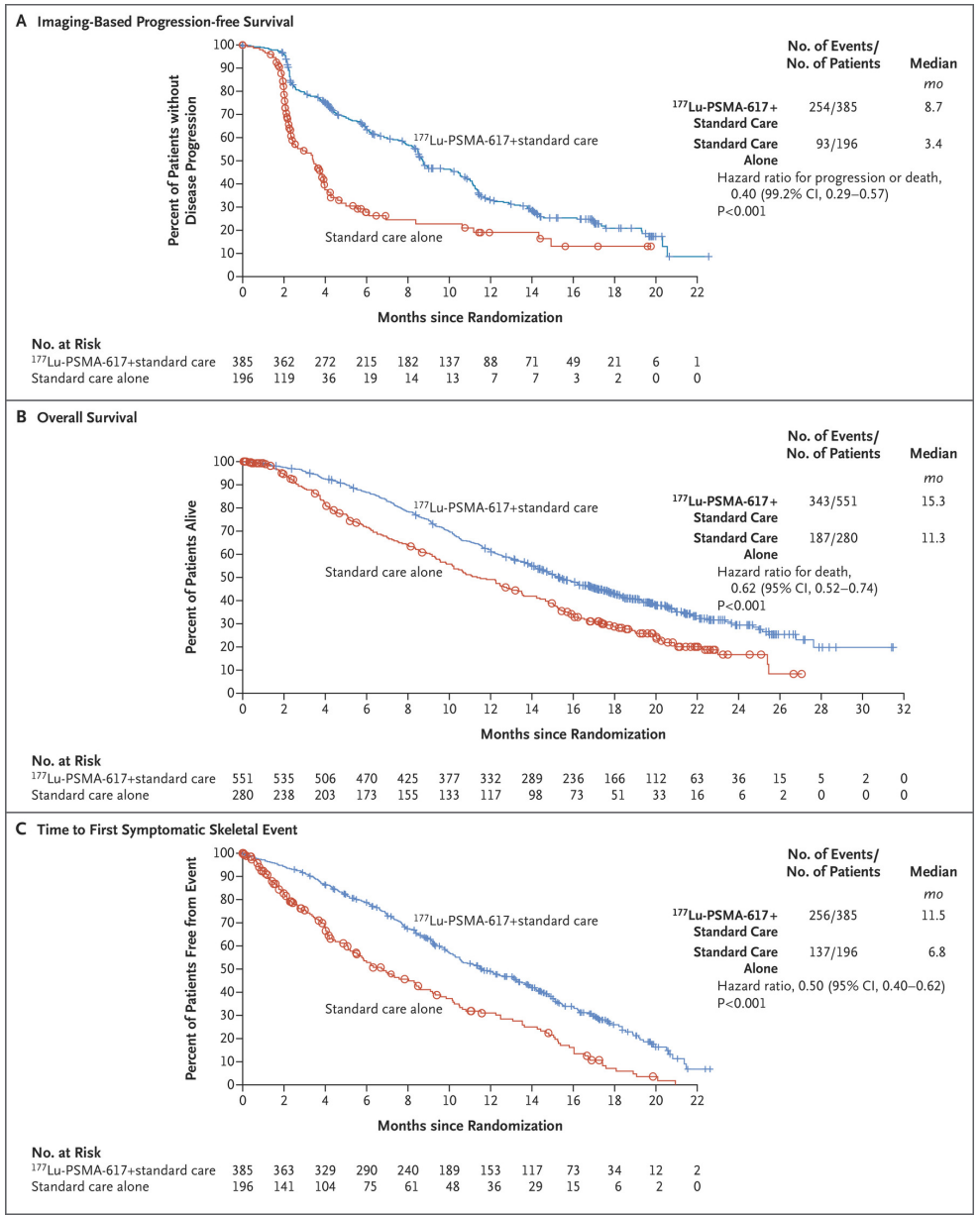
Hypothesis: To investigate the clinical benefit of ^{177}Lu-PSMA-617 plus SOC treatment in men with advanced-stage PSMA-positive mCRPC.



*SOC was investigator determined but excluded cytotoxic chemotherapy and radium-223

www.clinicaltrials.gov: (NCT03511664)

VISION Trial: Lu-177 PSMA



Sartor NEJM 2021

VISION Trial: Lu-177 PSMA

Table 2. Adverse Events.*

Event	^{177}Lu-PSMA-617 plus Standard Care (N=529)		Standard Care Alone (N=205)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Any adverse event	519 (98.1)	279 (52.7)	170 (82.9)	78 (38.0)
Adverse event that occurred in >12% of patients				
Fatigue	228 (43.1)	31 (5.9)	47 (22.9)	3 (1.5)
Dry mouth	205 (38.8)	0	1 (0.5)	0
Nausea	187 (35.3)	7 (1.3)	34 (16.6)	1 (0.5)
Anemia	168 (31.8)	68 (12.9)	27 (13.2)	10 (4.9)
Back pain	124 (23.4)	17 (3.2)	30 (14.6)	7 (3.4)
Arthralgia	118 (22.3)	6 (1.1)	26 (12.7)	1 (0.5)
Decreased appetite	112 (21.2)	10 (1.9)	30 (14.6)	1 (0.5)
Constipation	107 (20.2)	6 (1.1)	23 (11.2)	1 (0.5)
Diarrhea	100 (18.9)	4 (0.8)	6 (2.9)	1 (0.5)
Vomiting	100 (18.9)	5 (0.9)	13 (6.3)	1 (0.5)
Thrombocytopenia	91 (17.2)	42 (7.9)	9 (4.4)	2 (1.0)
Lymphopenia	75 (14.2)	41 (7.8)	8 (3.9)	1 (0.5)
Leukopenia	66 (12.5)	13 (2.5)	4 (2.0)	1 (0.5)
Adverse event that led to reduction in ^{177}Lu-PSMA-617 dose	30 (5.7)	10 (1.9)	NA	NA
Adverse event that led to interruption of ^{177}Lu-PSMA-617†	85 (16.1)	42 (7.9)	NA	NA
Adverse event that led to discontinuation of ^{177}Lu-PSMA-617†	63 (11.9)	37 (7.0)	NA	NA
Adverse event that led to death‡	19 (3.6)	19 (3.6)	6 (2.9)	6 (2.9)

* Shown are data for all the patients who underwent randomization and received at least one dose of their assigned treatment (standard care, with or without ^{177}Lu-PSMA-617). Adverse events during the treatment period were those that occurred on or after the start of randomized treatment and up to 30 days after the last administration of the randomized treatment (standard care or ^{177}Lu-PSMA-617, whichever was later) or before subsequent anticancer treatment. Adverse events were coded with the use of Common Terminology Criteria for Adverse Events, version 5.0, and terms from the *Medical Dictionary for Regulatory Activities*, version 23.1. NA denotes not applicable.

† Patients who had been randomly assigned to receive ^{177}Lu-PSMA-617 plus standard care and who did not receive ^{177}Lu-PSMA-617 but did receive standard care were included in the control group (standard care alone) of the safety population; 3 patients had adverse events during cycle 1 of ^{177}Lu-PSMA-617 therapy that led to the interruption (in 2 of 205 patients [1.0%]) or discontinuation (in 1 [0.5%]) of that therapy.

‡ Five adverse events that led to death in the ^{177}Lu-PSMA-617 group were considered by the investigators to be related to the drug: pancytopenia (in 2 patients), bone marrow failure (in 1), subdural hematoma (in 1), and intracranial hemorrhage (in 1).

Sartor NEJM 2021

Radiopharmaceuticals: Lu-177 PSMA

- Lu-PSMA is FDA approved as of March 2022 for patients with PSMA positive mCRPC who received NHA and taxane based chemo

- As of July 2022, it is available at Emory; the eligibility criteria include:
  - Ga-68 PSMA scan (initially, later plan to expend PyL PSMA PET scan)
  - Any systemic anti-cancer therapy within 28 days
  - Radionuclide therapy (Strontium-89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223, hemi-body irradiation) within 6 months
  - Unmanageable urinary tract obstruction or hydronephrosis;
  - Progressive deterioration of organ function (GFR < 30 mL/min or creatinine > 2-fold upper limit of normal (ULN); liver enzymes > 5-fold ULN).
  - Myelosuppression: a. Total white cell count less than 2.5 × 109 /L b. Platelet count less than 75 × 109 /L

- This opens new era with different combinations, such as IO, and also coming to front line

Future Directions

- PSMA- BITE: AMG 160 trial
- PSMA- ADC: ARX-517 trial
- Novel immunotherapy combinations:
  - For CRPC: Nivolumab+ TLR, XL092+Atezolizumab
  - For HSPC: Dual PD1/CTLA4 antibody+ standard of care
- CAR-T cell: BP-012 trial (PSCA-CAR-T cells)
- TROP2-ADC: DS-1062a

Acknowledgment

Medical Oncology:

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- Bassel Nazha
- Jackie Brown
- Wayne Harris

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- David Schuster
- Saima Muzahir

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Urology

- Viraj Master
- Haydn Kissick
- Martin Sanda
- John Petros
- Ken Ogan
- Shreyas Joshi
- Aaron Lay
- Vikram Narayan

Biostatistics

- Yuan Liu

Pathology

- Adeboye Osunkoya
- Lara Harik

Lots of good memories at Sea Island……

Thank you…

2017

2021

Born in 6/28/2021

2022