Prostate Cancer: Targeted Therapy, PSMA, and More

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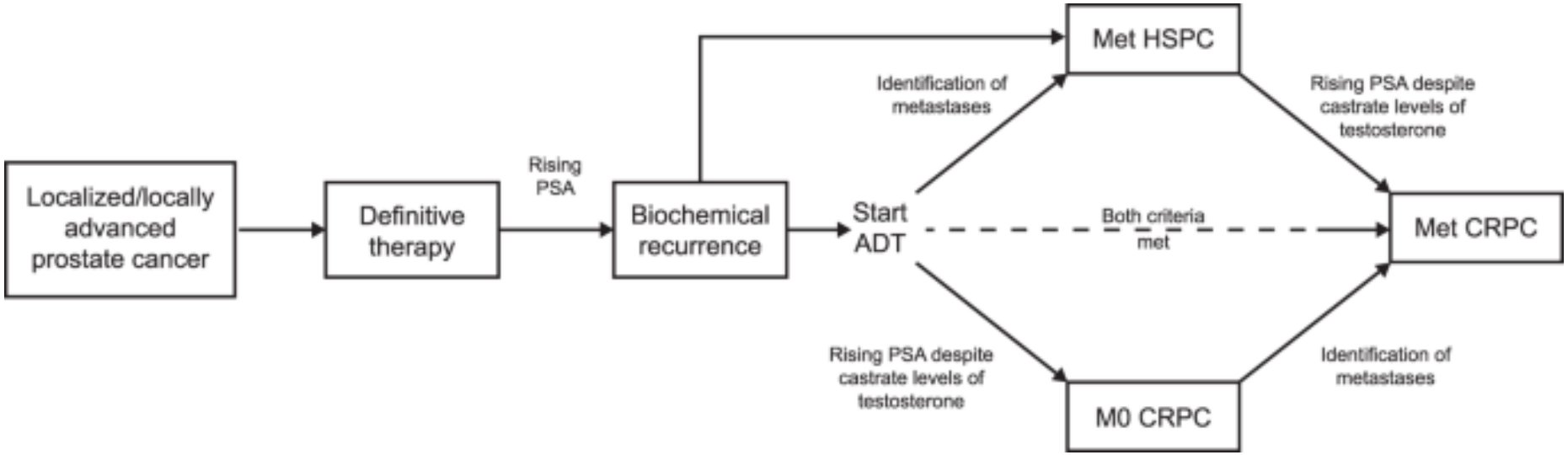
MLS New Orleans: Updates in Oncology from the Masters

Progression of Prostate Cancer

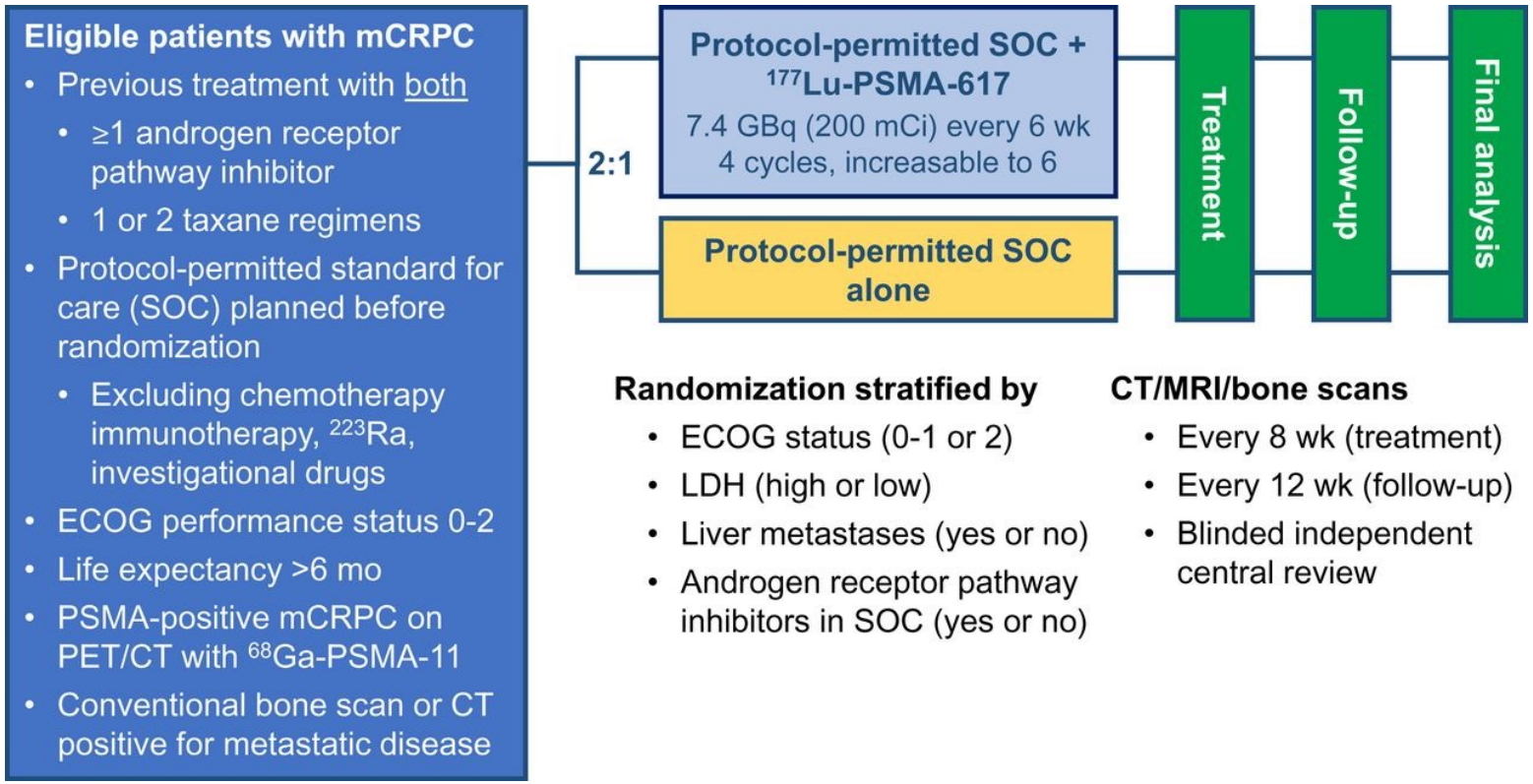


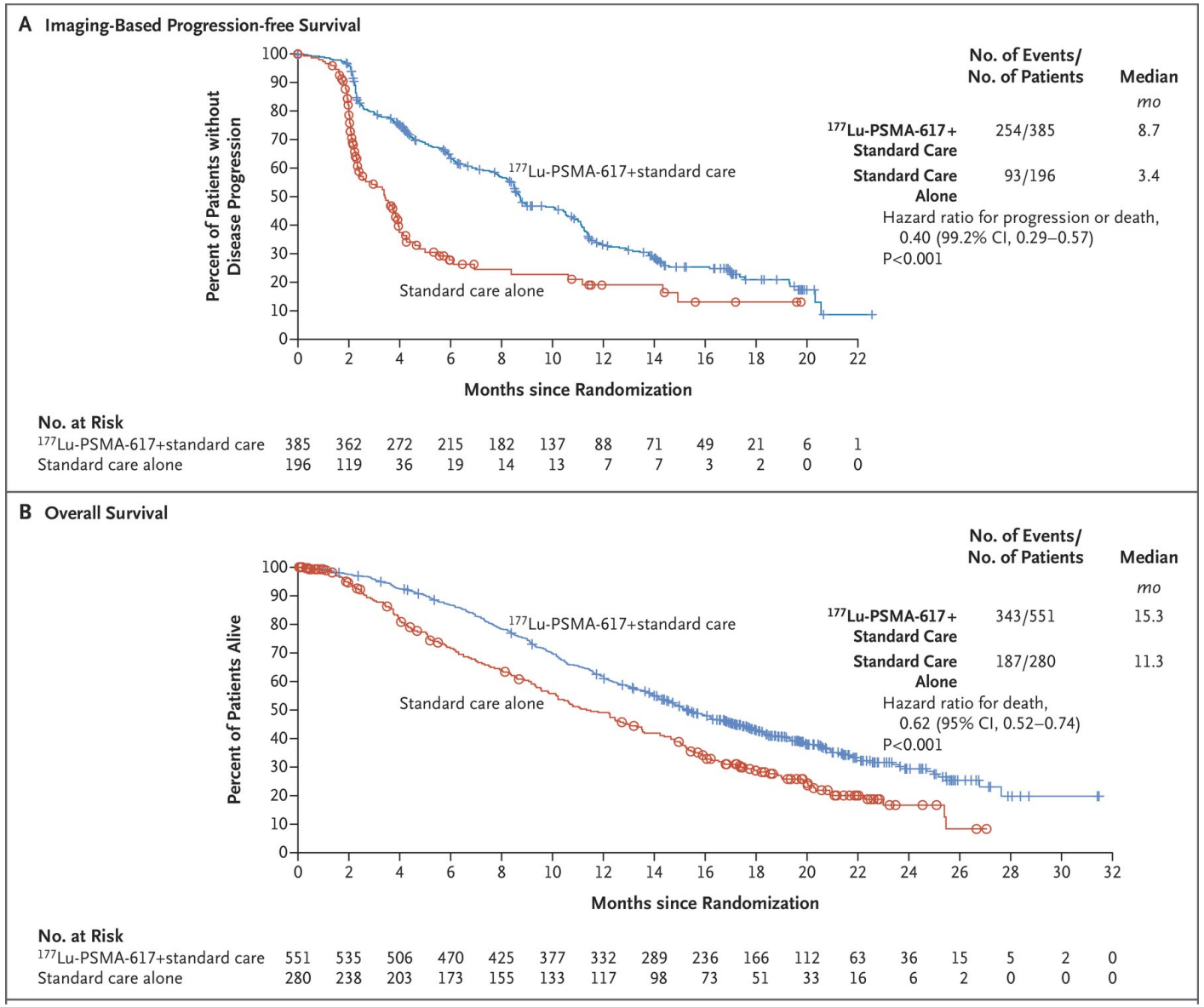
Advanced Imaging

- PSMA PET-CT
  - Much more accurate (92% vs 65%) at detecting metastases than conventional imaging.
  - Decreasing non-metastatic, biochemical recurrence cases, and increasing oligometastatic disease.
    - EA8191 / INDICATE Trial – evaluating targeted XRT and apalutamide in this setting

Theranostics

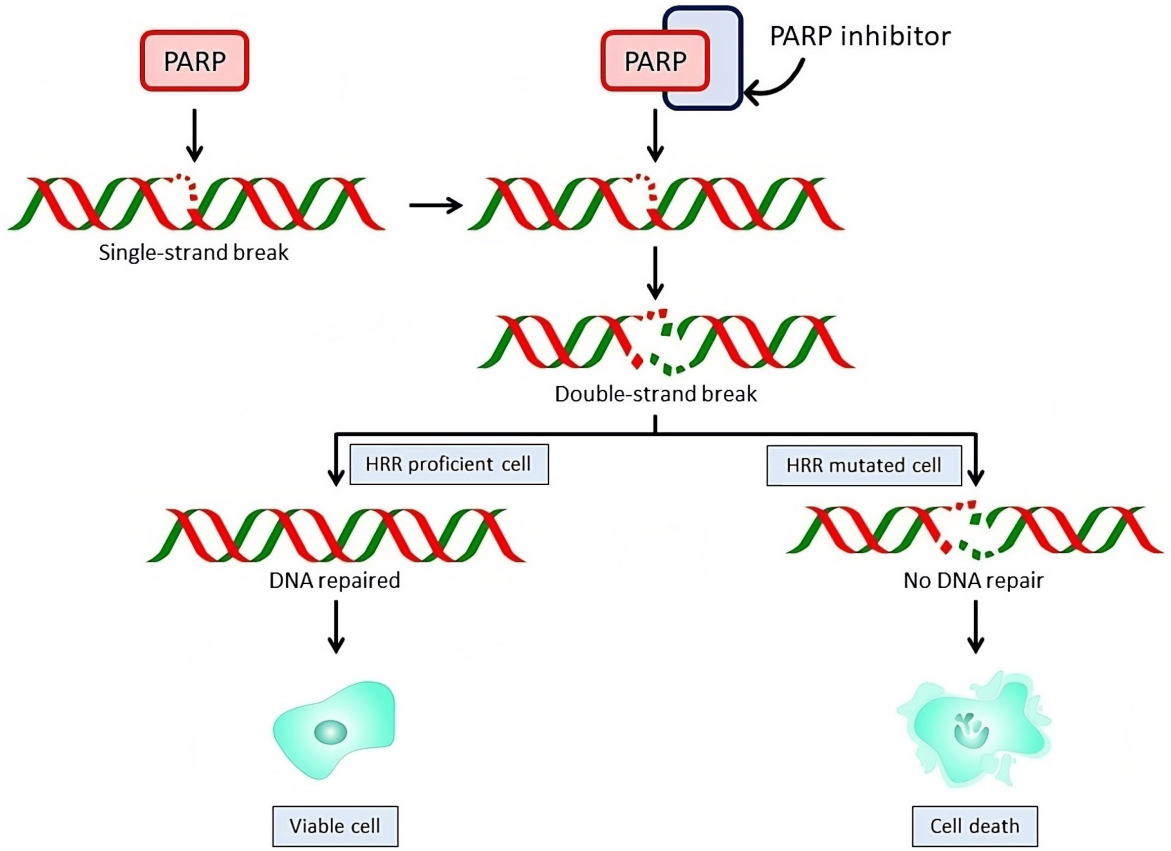
- Lutetium-177 vipivotide tetraxetan PSMA therapy



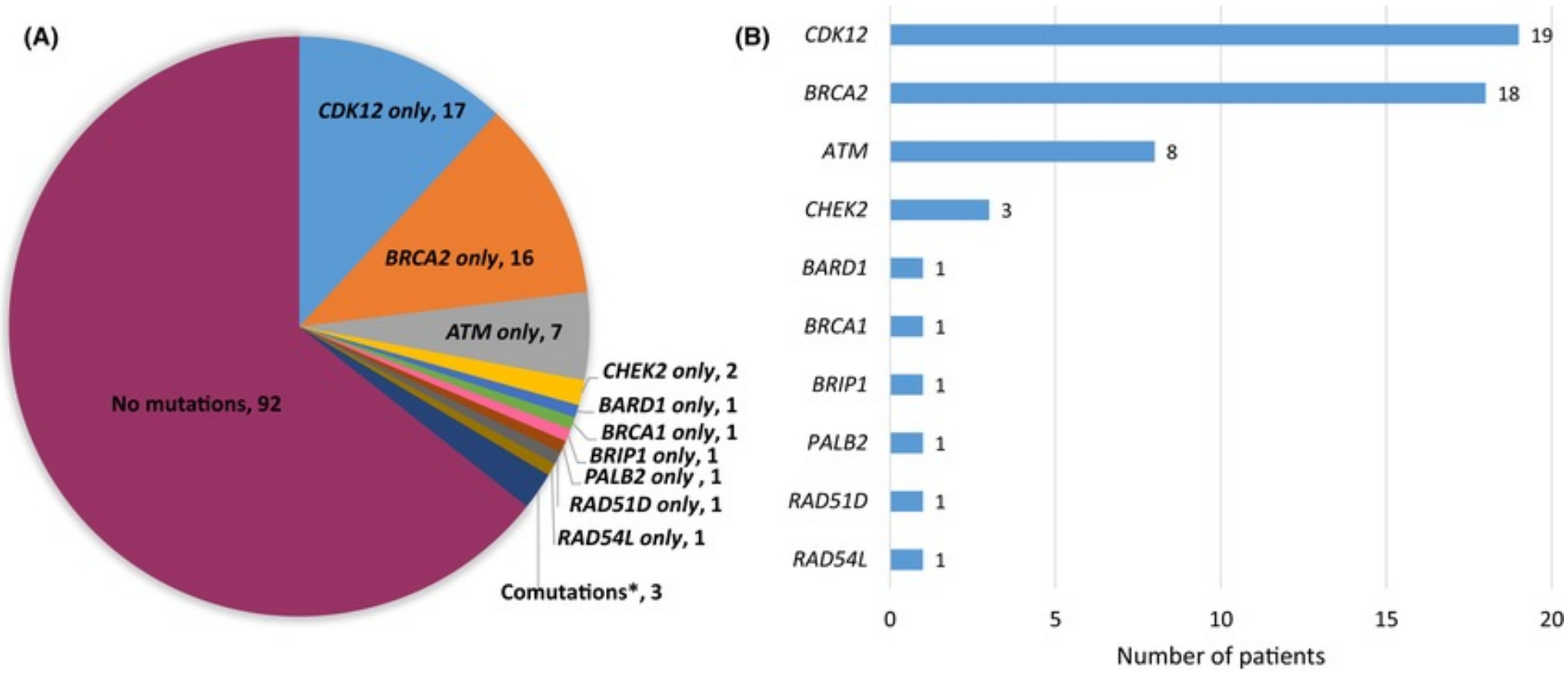


https://www.nejm.org/doi/full/10.1056/nejmoa2107322

PARP inhibitors

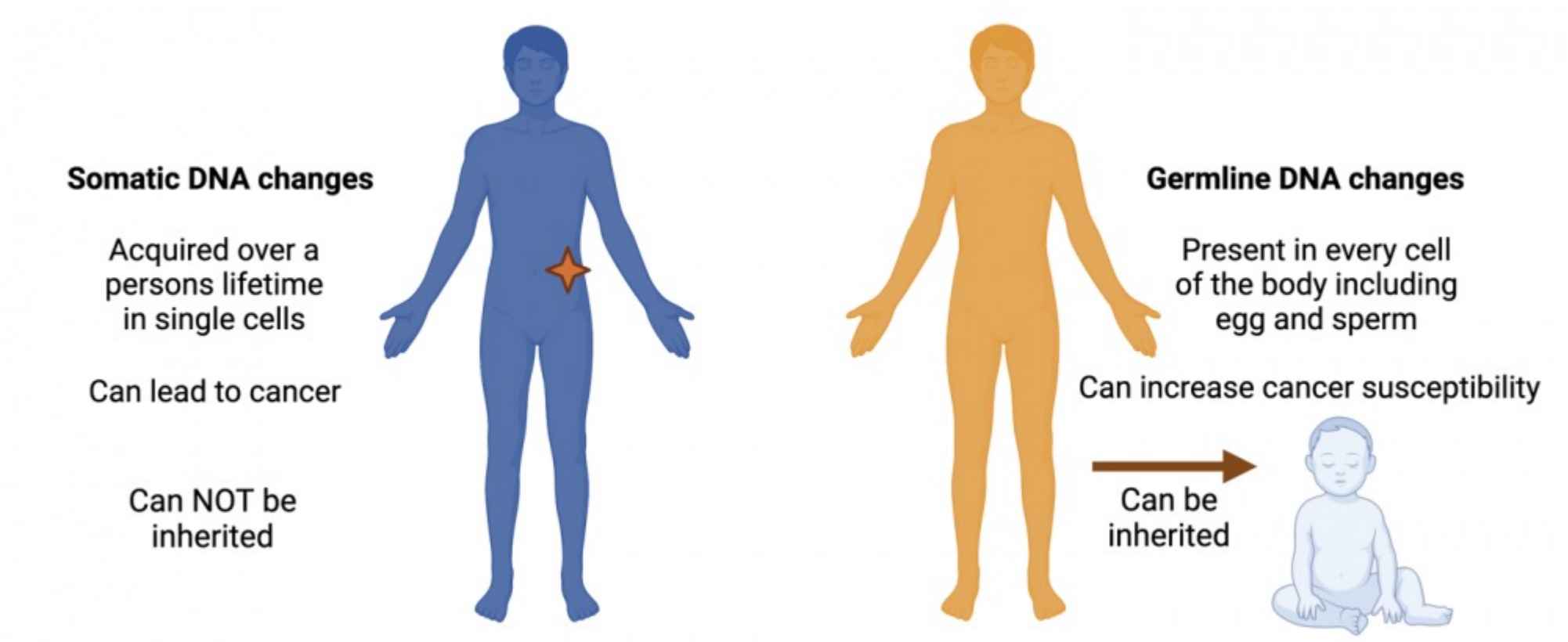


Rate of HRR gene mutations in men with metastatic prostate cancer



https://www.researchgate.net/figure/Landscape-of-HRR-related-gene-mutations-in-mCRPC-A-Frequency-of-mutations-for-the_fig2_365315921

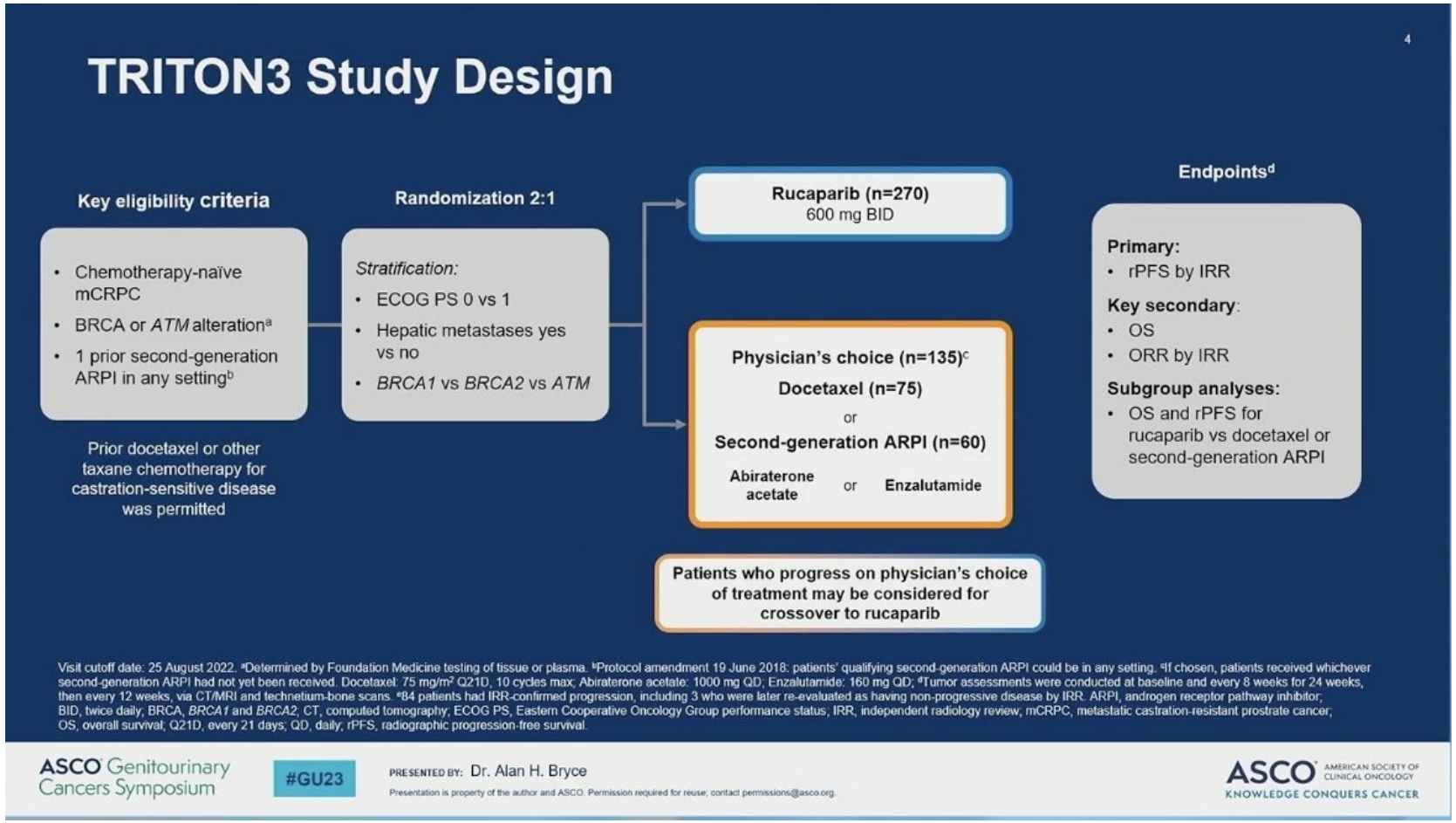
Somatic vs Germline Mutations

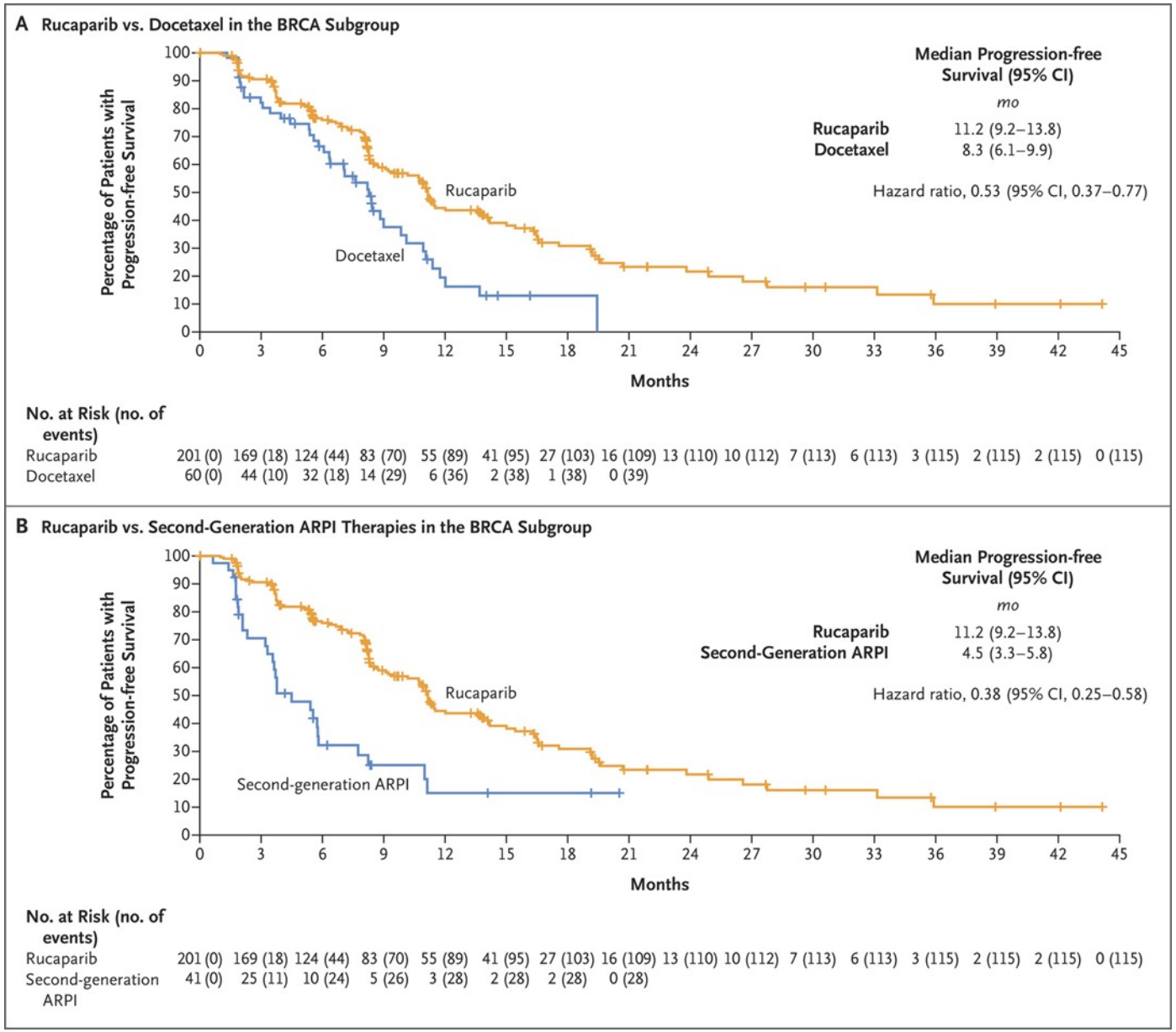


Single agent PARPi

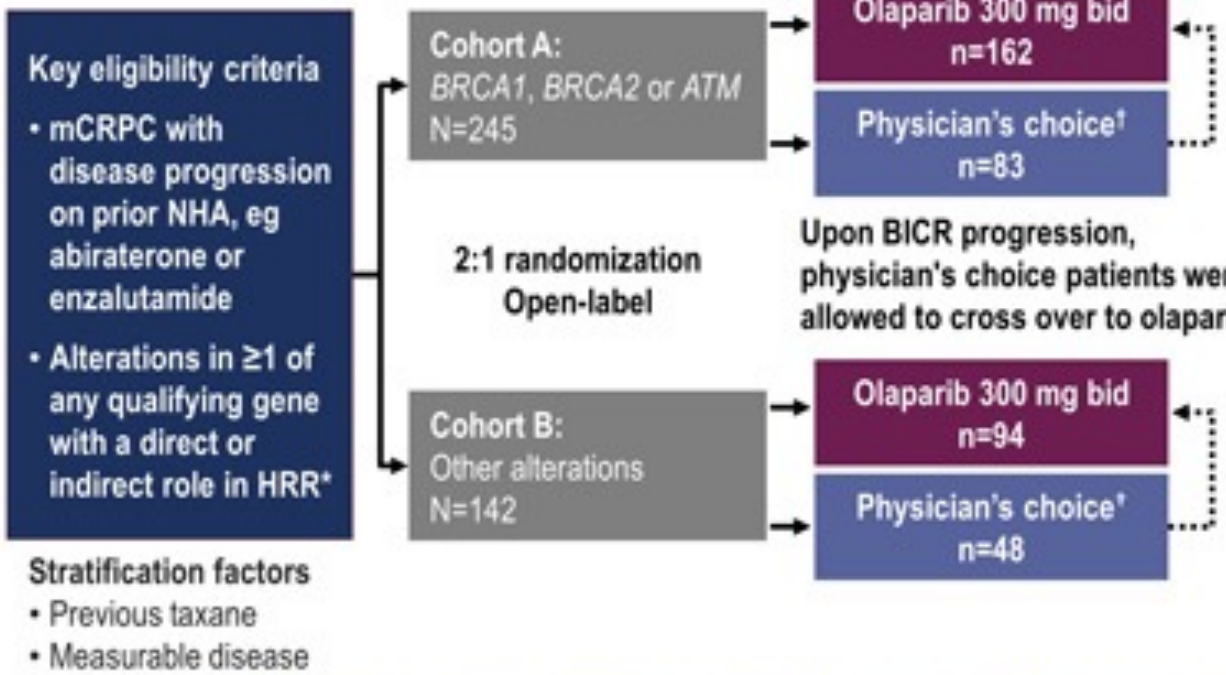
- Rucaparib – BRCA mutations
- Olaparib – HRR gene mutations

Triton3 Study




A Rucaparib vs. Docetaxel in the BRCA Subgroup
Percentage of Patients with Progression-free Survival
Median Progression-free Survival (95% CI)
mo
Rucaparib 11.2 (9.2–13.8)
Docetaxel 8.3 (6.1–9.9)
Hazard ratio, 0.53 (95% CI, 0.37–0.77)
Rucaparib
Docetaxel
Months
No. at Risk (no. of events)
Rucaparib 201 (0) 169 (18) 124 (44) 83 (70) 55 (89) 41 (95) 27 (103) 16 (109) 13 (110) 10 (112) 7 (113) 6 (113) 3 (115) 2 (115) 2 (115) 0 (115)
Docetaxel 60 (0) 44 (10) 32 (18) 14 (29) 6 (36) 2 (38) 1 (38) 0 (39)
B Rucaparib vs. Second-Generation ARPI Therapies in the BRCA Subgroup
Percentage of Patients with Progression-free Survival
Median Progression-free Survival (95% CI)
mo
Rucaparib 11.2 (9.2–13.8)
Second-Generation ARPI 4.5 (3.3–5.8)
Hazard ratio, 0.38 (95% CI, 0.25–0.58)
Rucaparib
Second-generation ARPI
Months
No. at Risk (no. of events)
Rucaparib 201 (0) 169 (18) 124 (44) 83 (70) 55 (89) 41 (95) 27 (103) 16 (109) 13 (110) 10 (112) 7 (113) 6 (113) 3 (115) 2 (115) 2 (115) 0 (115)
Second-generation ARPI 41 (0) 25 (11) 10 (24) 5 (26) 3 (28) 2 (28) 2 (28) 0 (28)

PROfound STUDY DESIGN



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, and developed in partnership with Foundation Medicine Inc, was used to prospectively select patients harboring alterations in the following genes in their tumor tissue: *BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D* or *RAD54L*

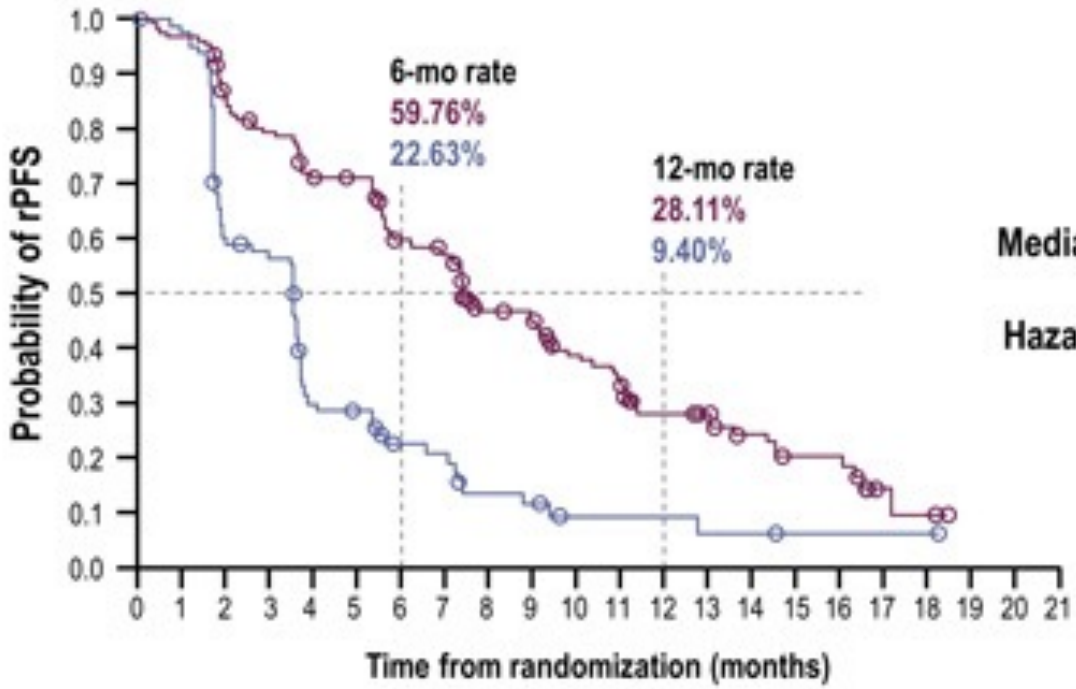
†Physician's choice of either enzalutamide (160 mg qd) or abiraterone (1000 mg qd plus prednisone [5 mg bid])

BICR, blinded independent central review; PCWG3, Prostate Cancer Working Group 3; RECIST, Response Evaluation Criteria in Solid Tumors

NCT02987543

PROfound Primary endpoint

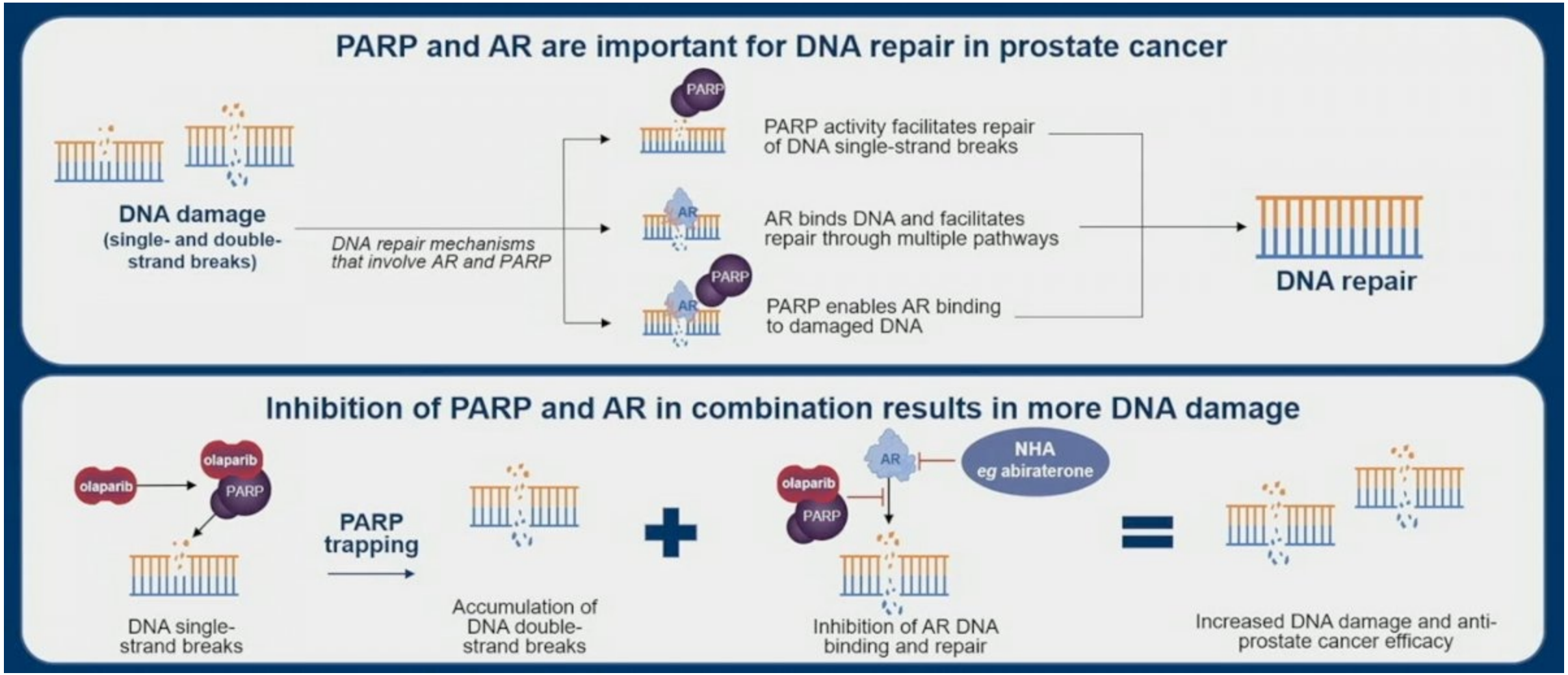
rPFS BY BICR IN PATIENTS WITH ALTERATIONS IN *BRCA1*, *BRCA2*, OR *ATM* (COHORT A)



	Olaparib (N=162)	Physician's choice (N=83)
Events (%)	106 (65.4)	68 (81.9)
Median PFS (months)	7.39	3.55
Hazard ratio (95% CI)	0.34 (0.25, 0.47) *P*<0.0001	

NCT02987543

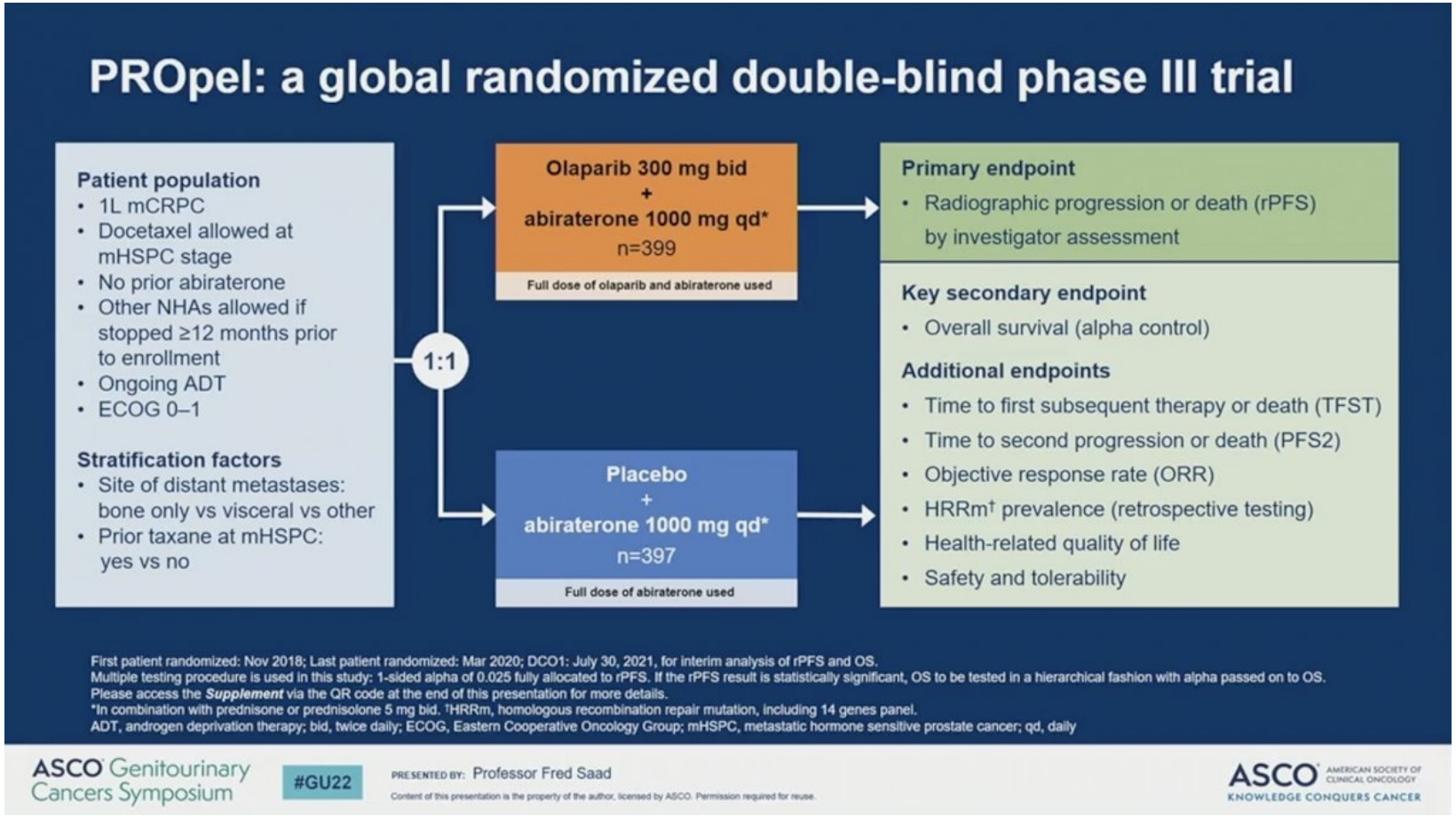
Prespecified sensitivity analysis based on investigator assessment: Hazard ratio 0.24 (95% CI 0.17, 0.34); *P*<0.0001


PARP and AR are important for DNA repair in prostate cancer
DNA damage
(single- and double-strand breaks)
DNA repair mechanisms that involve AR and PARP
PARP
AR
PARP
AR
PARP activity facilitates repair of DNA single-strand breaks
AR binds DNA and facilitates repair through multiple pathways
PARP enables AR binding to damaged DNA
DNA repair
Inhibition of PARP and AR in combination results in more DNA damage
olaparib
olaparib
PARP
DNA single-strand breaks
PARP trapping
Accumulation of DNA double-strand breaks
AR
NHA
eg abiraterone
olaparib
PARP
Inhibition of AR DNA binding and repair
Increased DNA damage and anti-prostate cancer efficacy

PARPi+NHT Combos

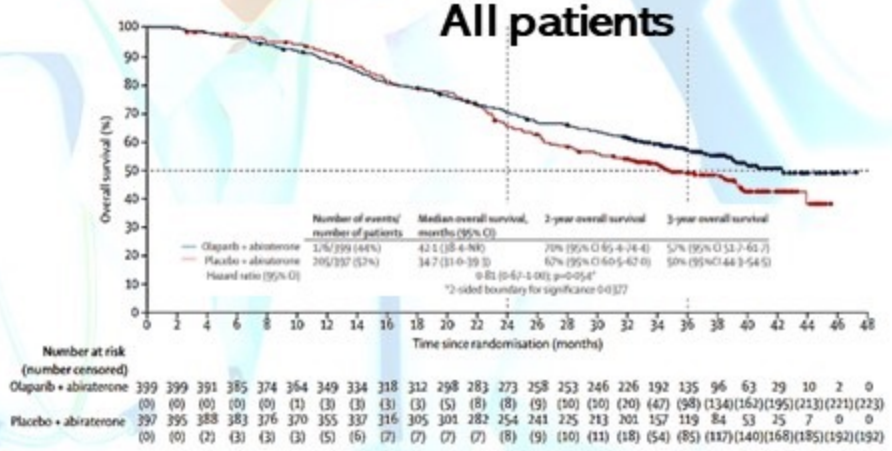
- Olaparib/abiraterone – BRCA mutations
- Niraparib/abiraterone – BRCA mutations
- Talazoparib/enzalutamide – HRR gene mutations

PROpel Study

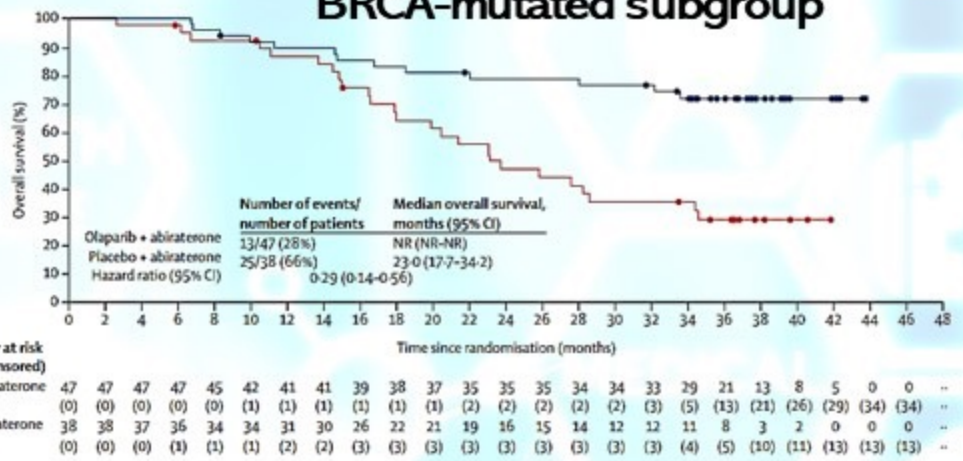


Olaparib plus abiraterone in metastatic castration-resistant prostate cancer

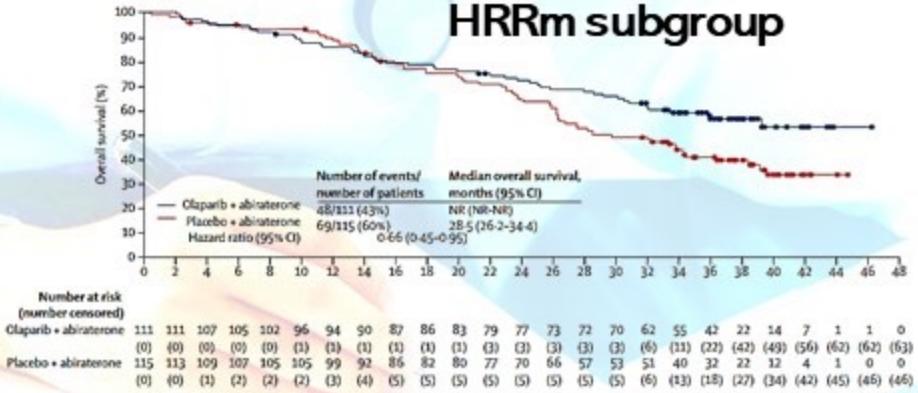
All patients



BRCA-mutated subgroup



HRRm subgroup

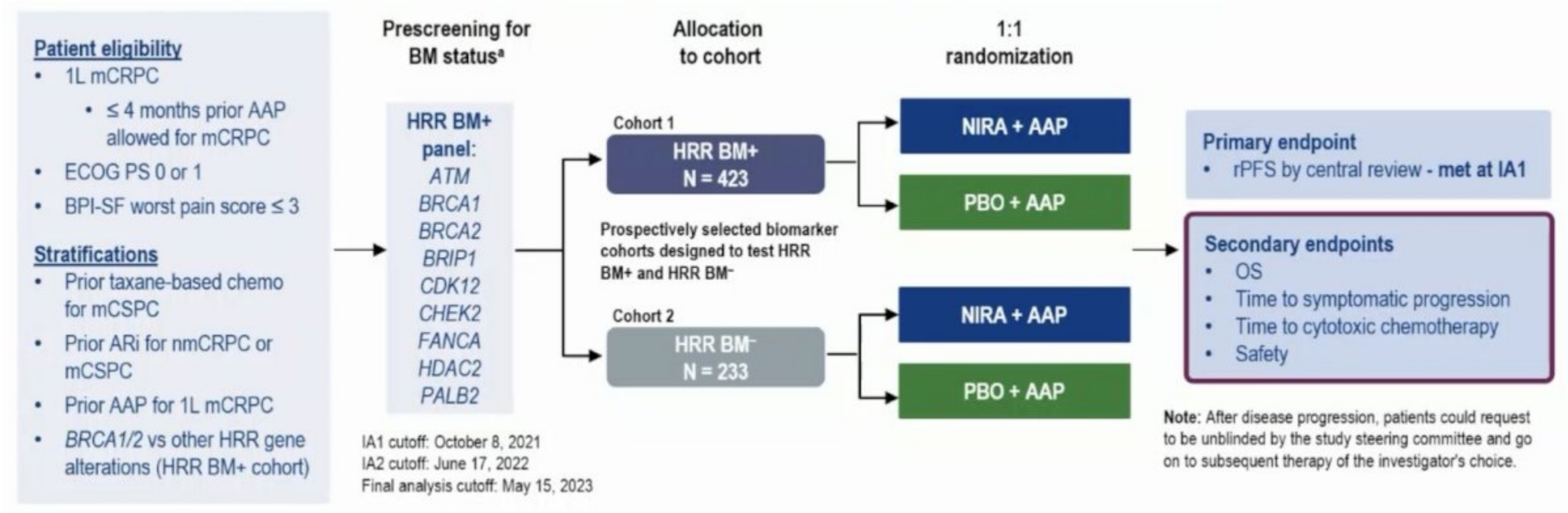


Median overall survival	Olaparib + abiraterone	Placebo + abiraterone	Hazard ratio
All patients	42·1 months	34·7 months	0·81
HRRm subgroup	NR	28·5 months	0·66
BRCA-mutated subgroup	NR	23·0 months	0·29

In the phase 3 PROpel trial, a significant improvement in overall survival is observed for olaparib with abiraterone compared to placebo with abiraterone in patients with mCRPC. The improvement observed was primarily attributable to patients with BRCA mutation.

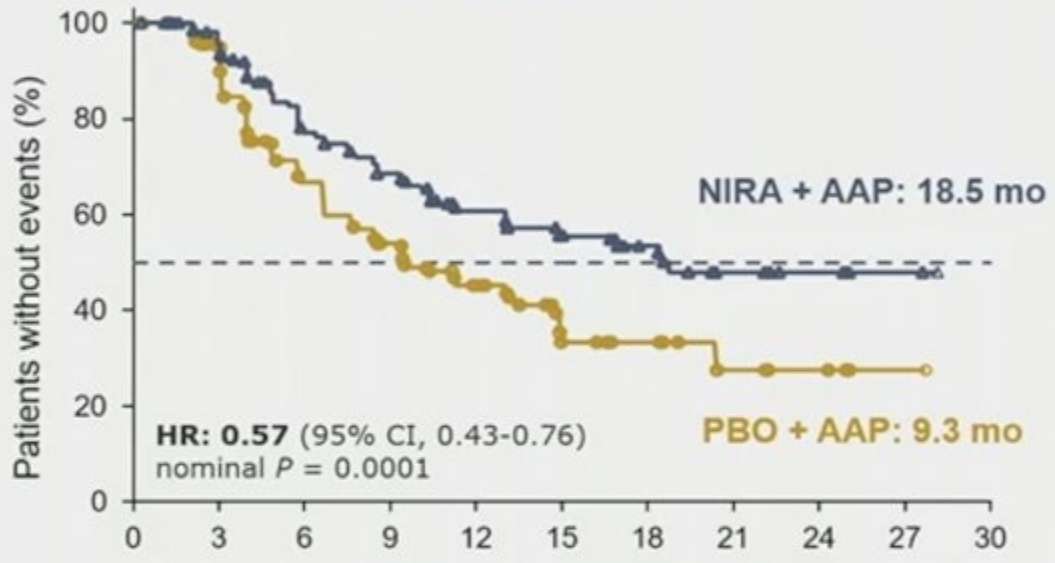
Ref: Saad F, et al. Lancet Oncol. Sep 12 ,2023

MAGNITUDE Study



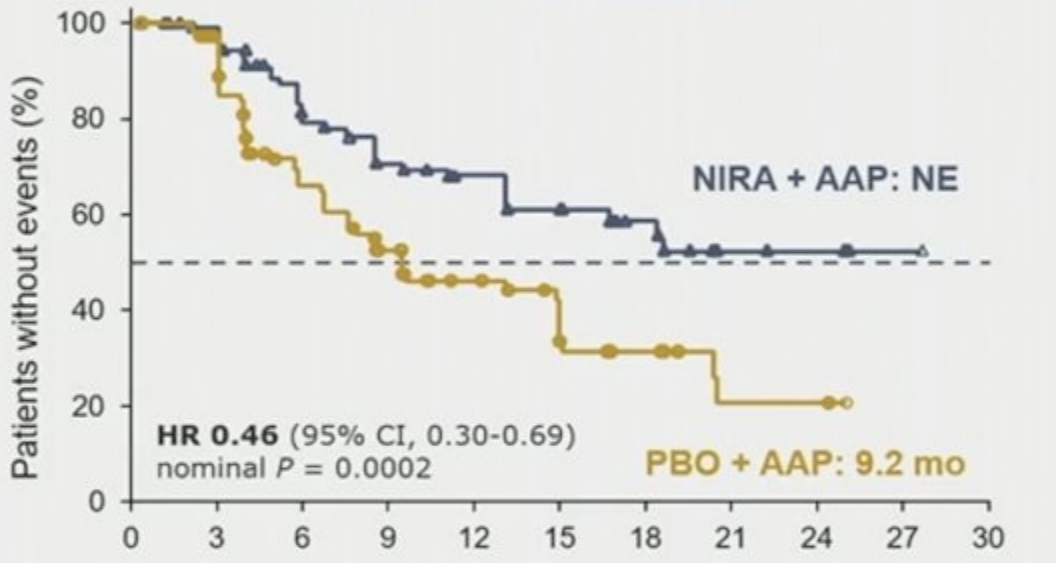
MAGNITUDE: NIRA + AAP Consistently Prolongs Time to PSA Progression Across Gene Alterations

All HRR BM+



No. at risk											
NIRA + AAP	212	182	145	118	85	58	45	20	10	2	0
PBO + AAP	211	162	118	91	61	34	25	11	8	1	0

BRCA1/2-mutated

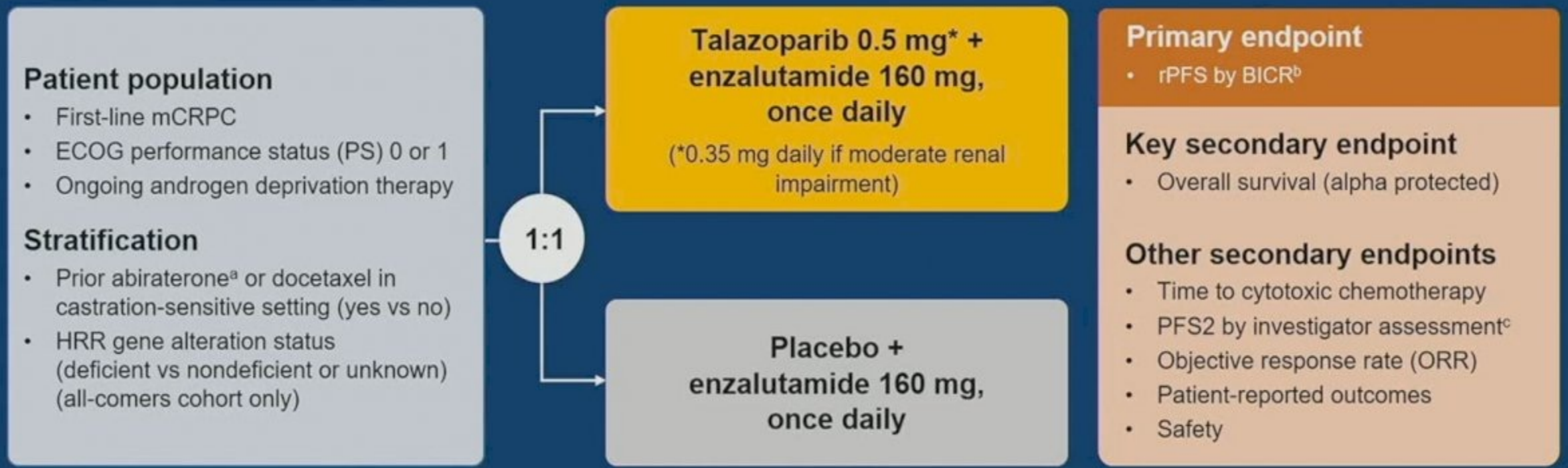


No. at risk											
NIRA + AAP	113	107	100	85	62	43	30	15	6	1	0
PBO + AAP	112	107	91	80	49	40	21	11	6	1	0

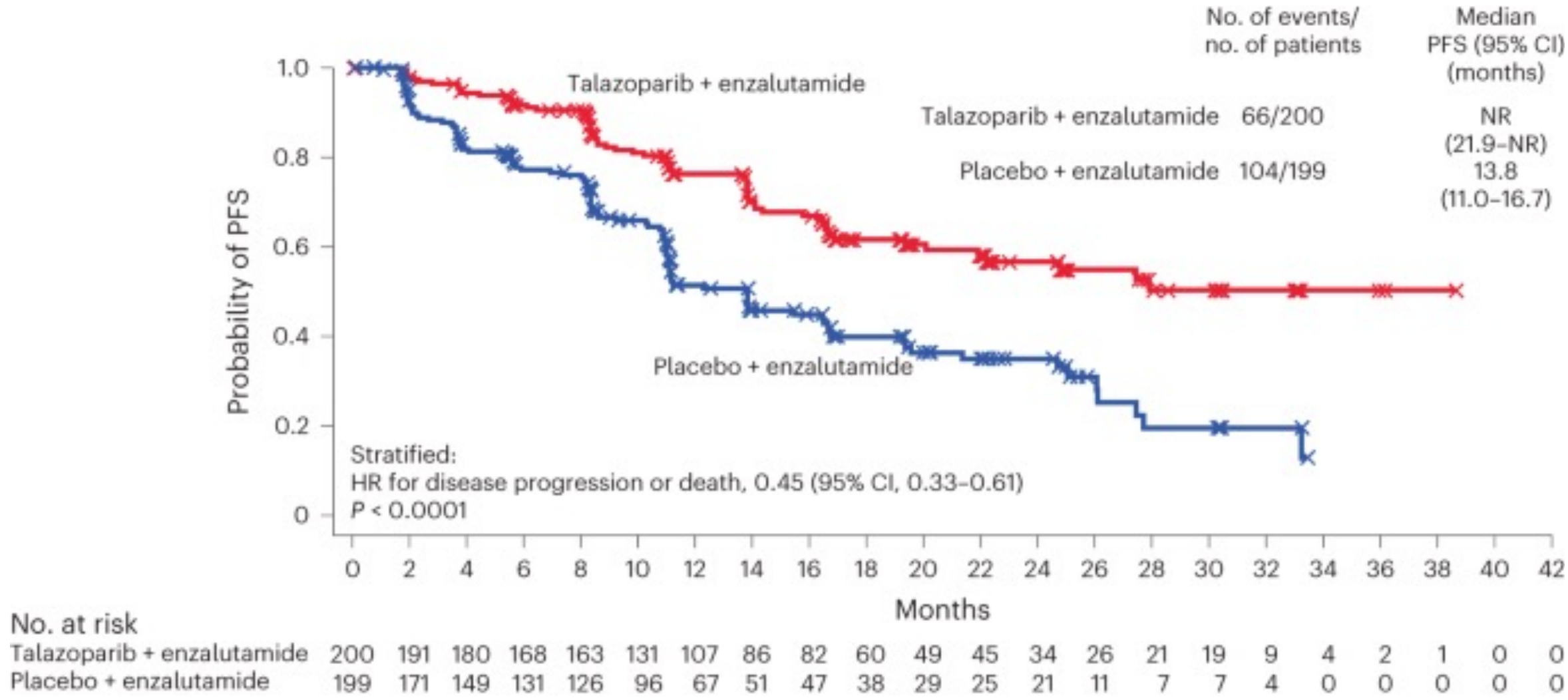
NIRA + AAP nearly doubles the median time to PSA progression with 43% improvement

AAP, abiraterone acetate plus prednisone; CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; NE, not estimable; PSA, prostate-specific antigen.

TALAPRO-2: A Randomized, Double-blind, Placebo-Controlled Study



Samples prospectively assessed for HRR gene alterations *(BRCA1, BRCA2, PALB2, ATM, ATR, CHEK2, FANCA, RAD51C, NBN, MLH1, MRE11A, CDK12)* using FoundationOne®CDx and/or FoundationOne®Liquid CDx


No. of events/ no. of patients
Median PFS (95% CI) (months)
Talazoparib + enzalutamide 66/200 NR (21.9–NR)
Placebo + enzalutamide 104/199 13.8 (11.0–16.7)
Talazoparib + enzalutamide
Placebo + enzalutamide
Probability of PFS
1.0
0.8
0.6
0.4
0.2
0
Stratified:
HR for disease progression or death, 0.45 (95% CI, 0.33–0.61)
P < 0.0001
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42
Months
No. at risk
Talazoparib + enzalutamide 200 191 180 168 163 131 107 86 82 60 49 45 34 26 21 19 9 4 2 1 0 0
Placebo + enzalutamide 199 171 149 131 126 96 67 51 47 38 29 25 21 11 7 7 4 0 0 0 0 0

Immunotherapy for advanced prostate cancer

- Pembrolizumab for MSI-H, dMMR, or TMB ≥10 mut/Mb

Immunotherapy for advanced prostate cancer

- Combination immunotherapy in prostate cancer:
  - Phase 3 KEYNOTE-641 and KEYNOTE-789 (pembrolizumab + enzalutamide) were discontinued early due to lack of efficacy
  - Phase III KEYLYNK-010 (pembrolizumab + olaparib) did not meet PFS or OS endpoints
  - Phase II trial of pembrolizumab + Lu177 is currently enrolling

Conclusions

- New treatment modalities (theranostics, targeted therapy, and immunotherapy) offer new hope to patients with advanced prostate cancer.

- Defining novel molecular targets and new biomarkers of response will allow us to better personalize innovative treatments options for patients with advanced prostate cancer.