

Combination treatments in first-line mCRPC

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BMUC 2025

bmuc.be/bmuc2025



**12th Belgian Multidisciplinary
Meeting on Urological Cancers**

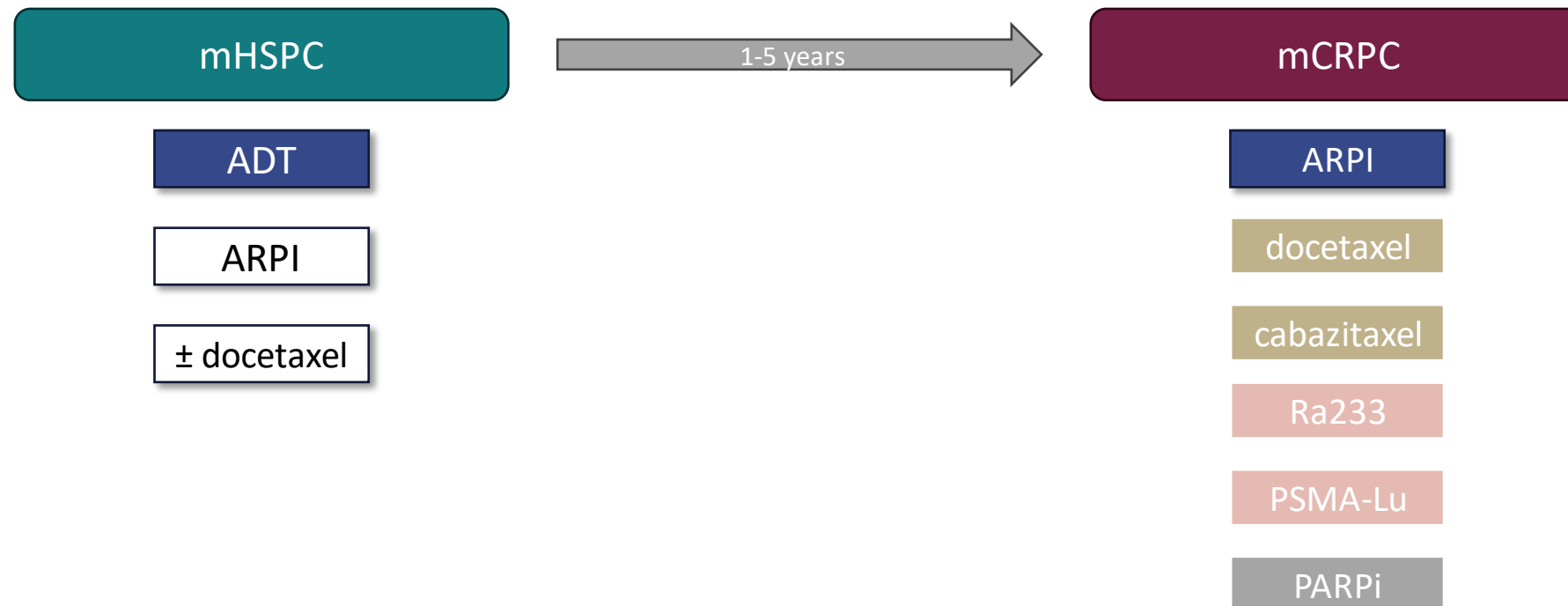
Conflicts of interest

- I have the following potential conflict(s) of interest to report

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports:	/
Receipt of honoraria or consultation fees:	AstraZeneca, Bayer, Bristol-Myers Squibb, Ipsen, Johnson & Johnson, MSD
Participation in a company sponsored speaker's bureau:	/
Stock shareholder:	/
Spouse/partner:	/
Other support (please specify):	/



mCRPC treatment landscape in 2025



PARP inhibitor in mCRPC



DDR gene alteration

DDR stands for “DNA damage repair”

Up to 30% of mCRPC patients harbor a DDR gene alteration.

➤ BRCA1/2 are the most frequent

Testing can be done :

➤ Germline : blood or saliva

➤ Somatic : tumour tissue

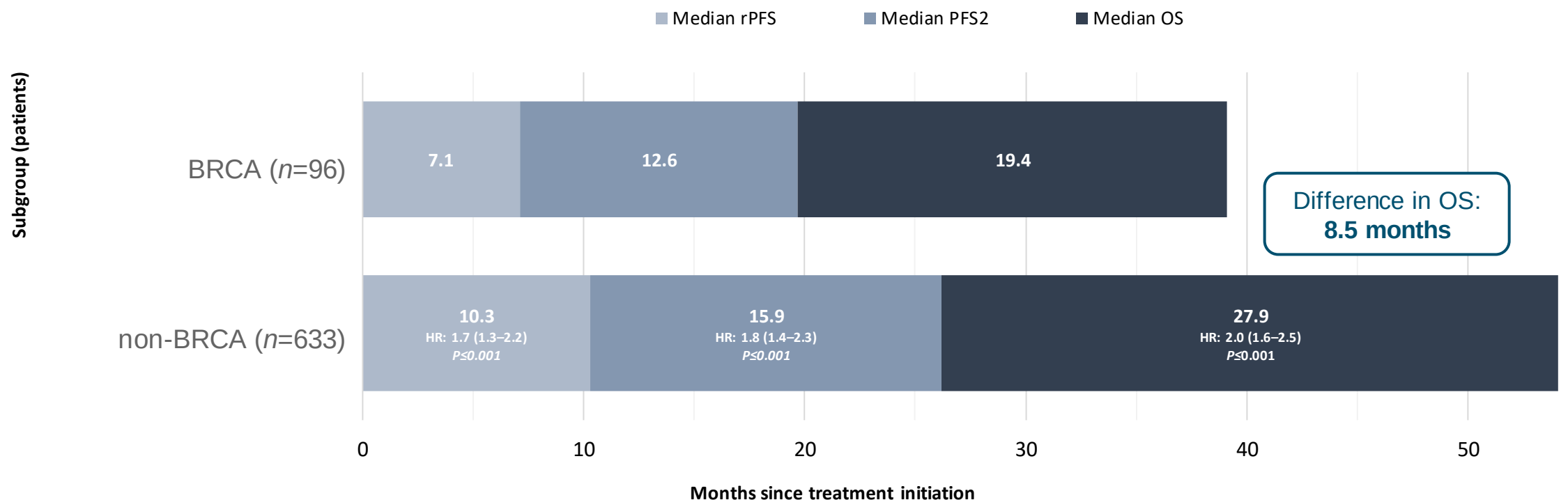
➤ < 5 years

➤ Preferably on a soft tissue biopsy



CAPTURE: BRCA1/2 mutations associated with shorter rPFS and OS in mCRPC1 (treated with either 1L NHT or taxanes)

Compared with non-BRCA patients*, BRCA patients had significantly worse rPFS, PFS2 and OS

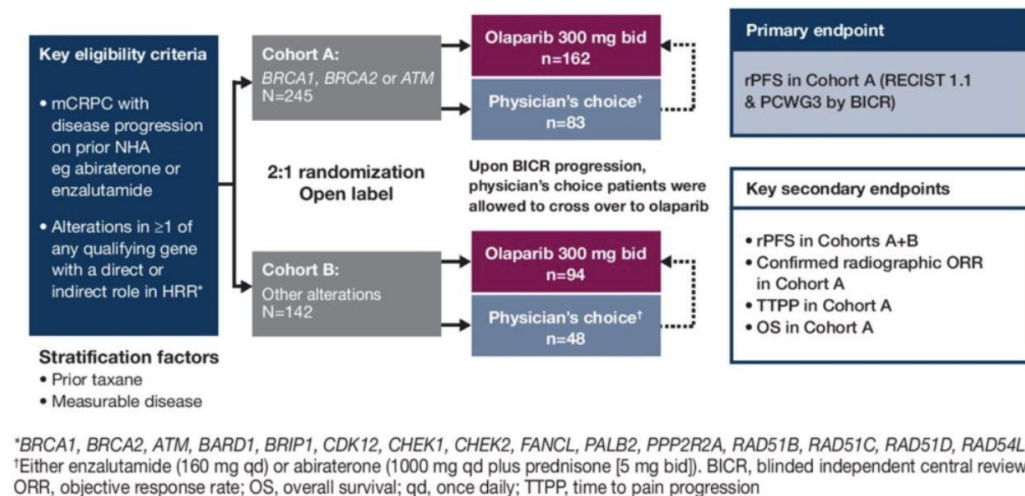


Based on the poorer prognosis for these patients, it is important to **identify** them (earlier as possible) and plan for an individualized treatment journey

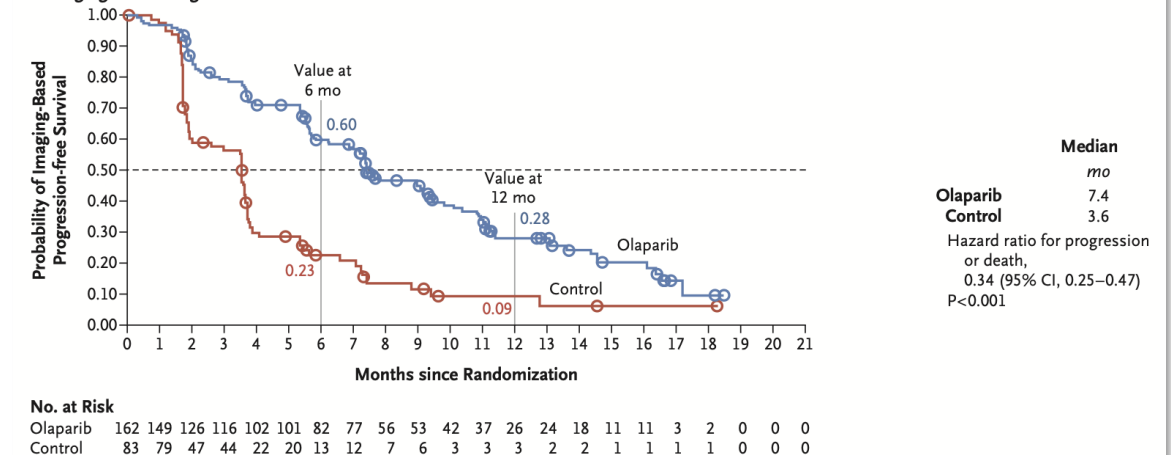
*non-BRCA patients include both non-HRR mutated patients as well as those with a HRR mutation different from BRCA)

PARP inhibitor in monotherapy

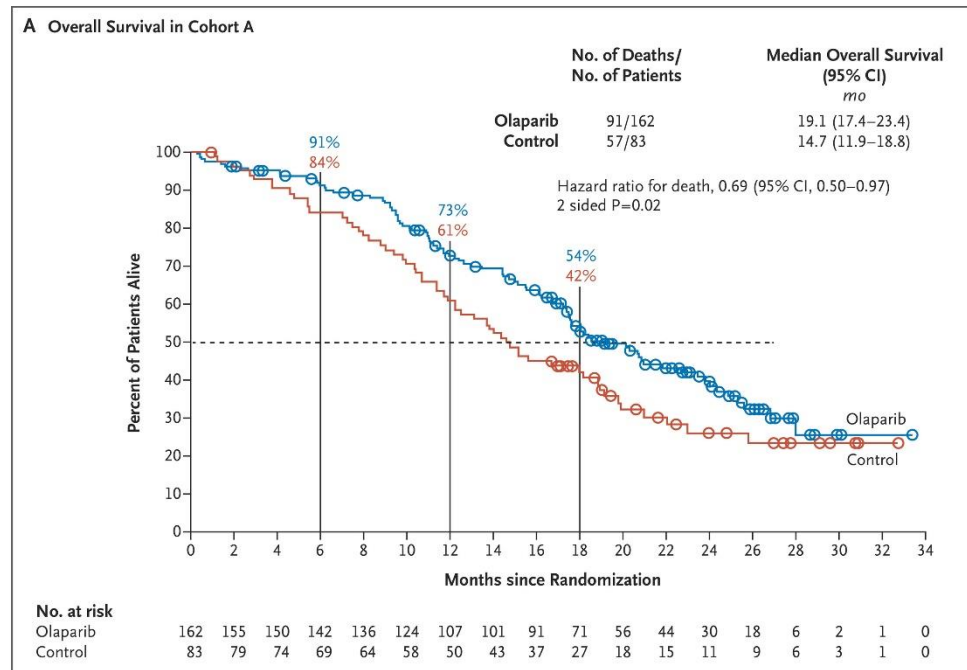
Figure 1. PROfound study design



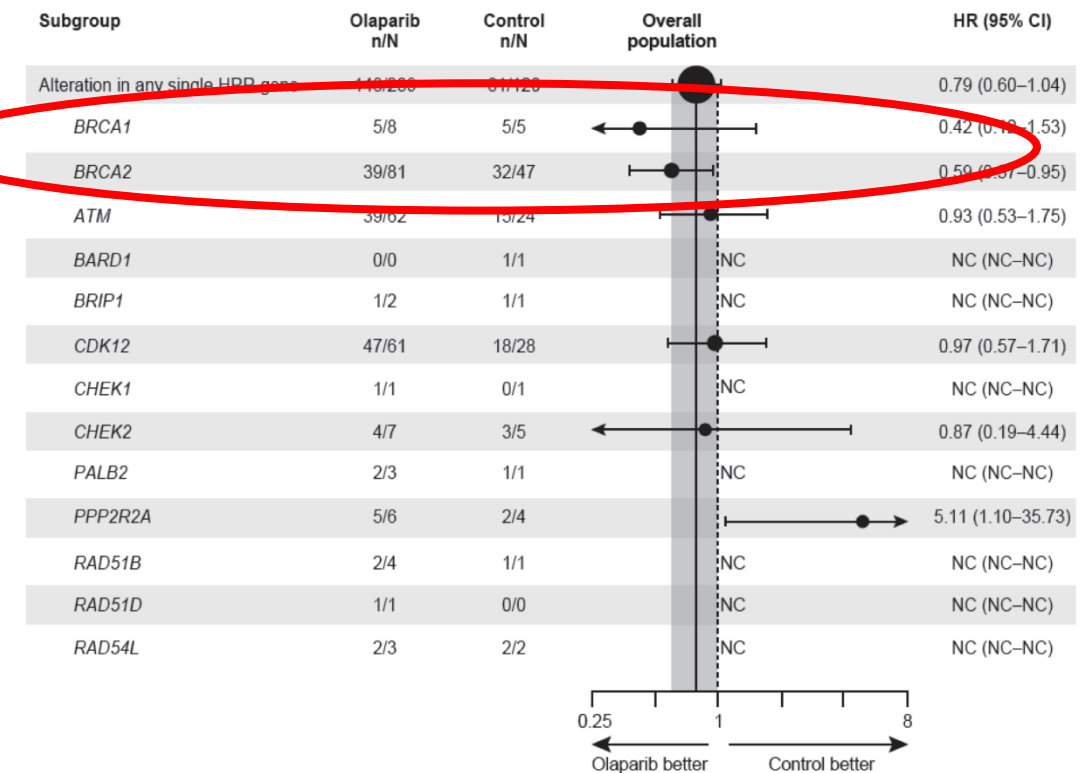
A Imaging-Based Progression-free Survival in Cohort A



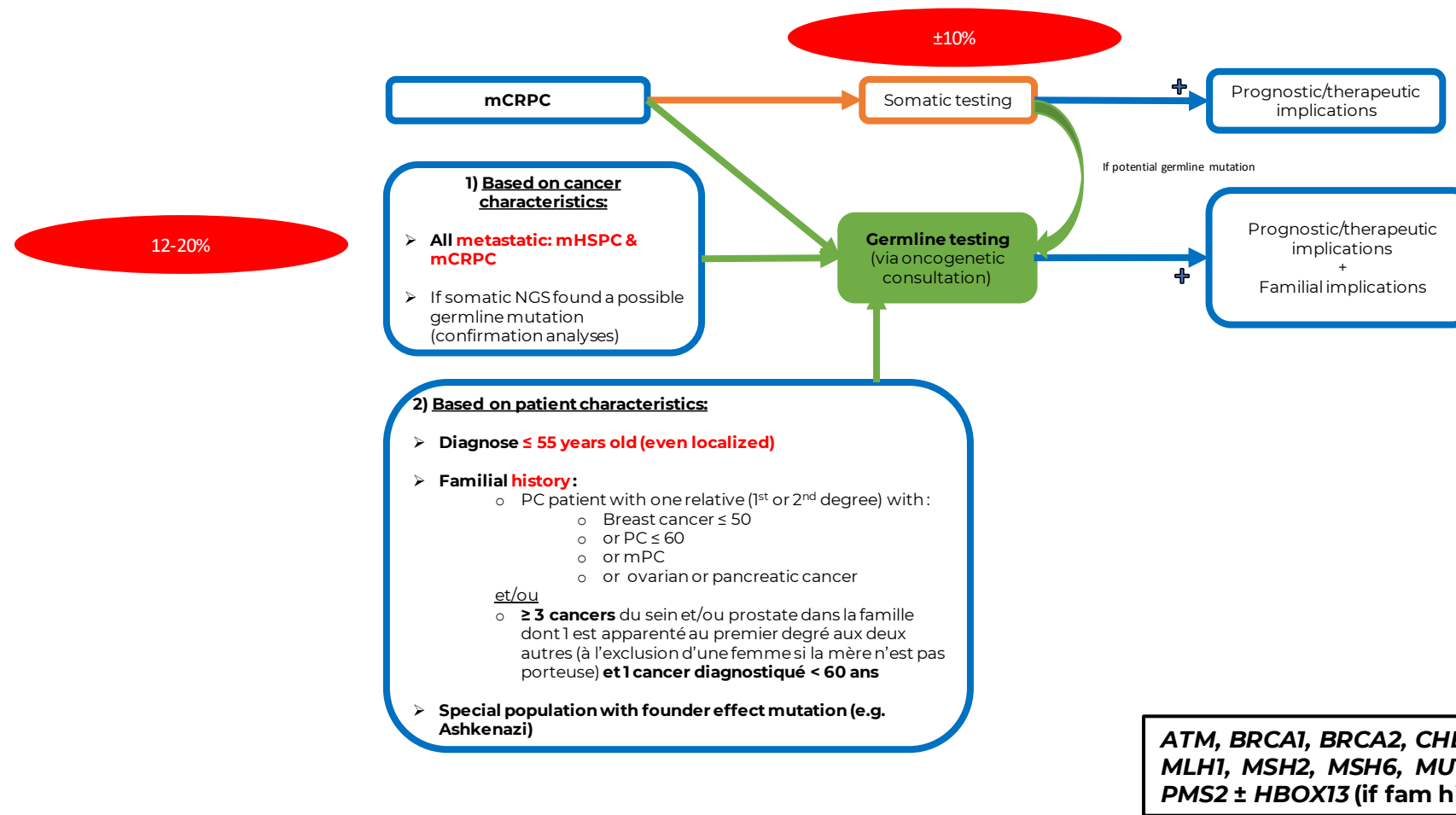
PARP inhibitor in monotherapy



B OS in Patients with Alterations in a Single HRR[†] Gene

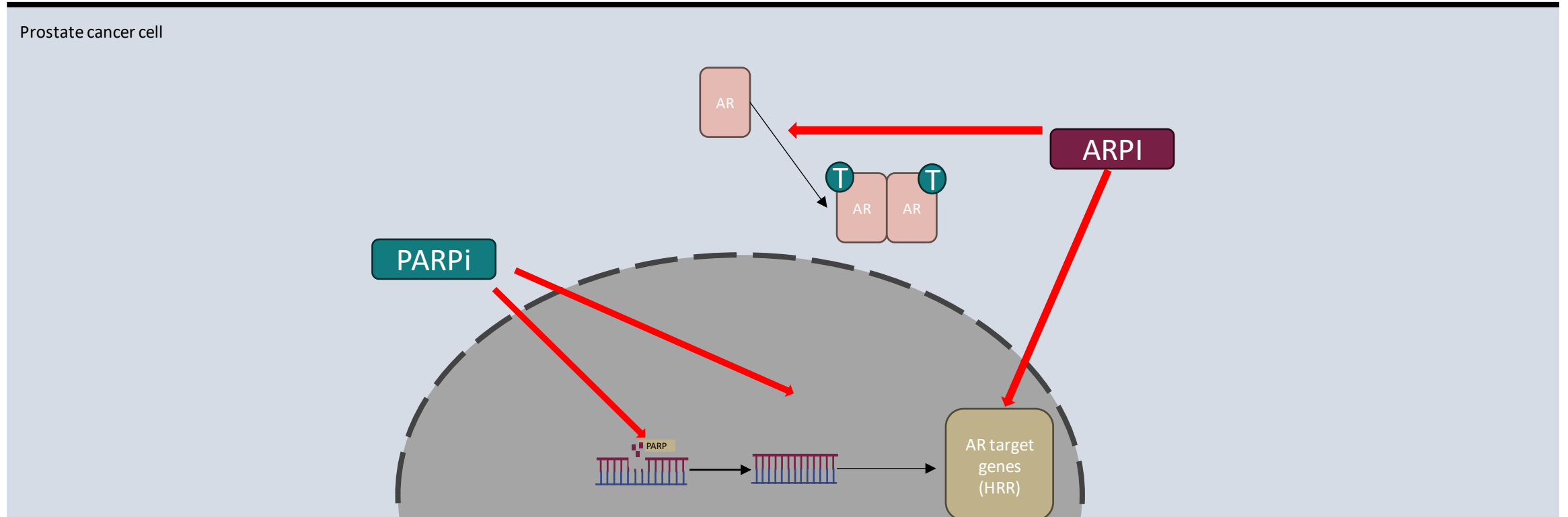


Germline testing indication in Belgium



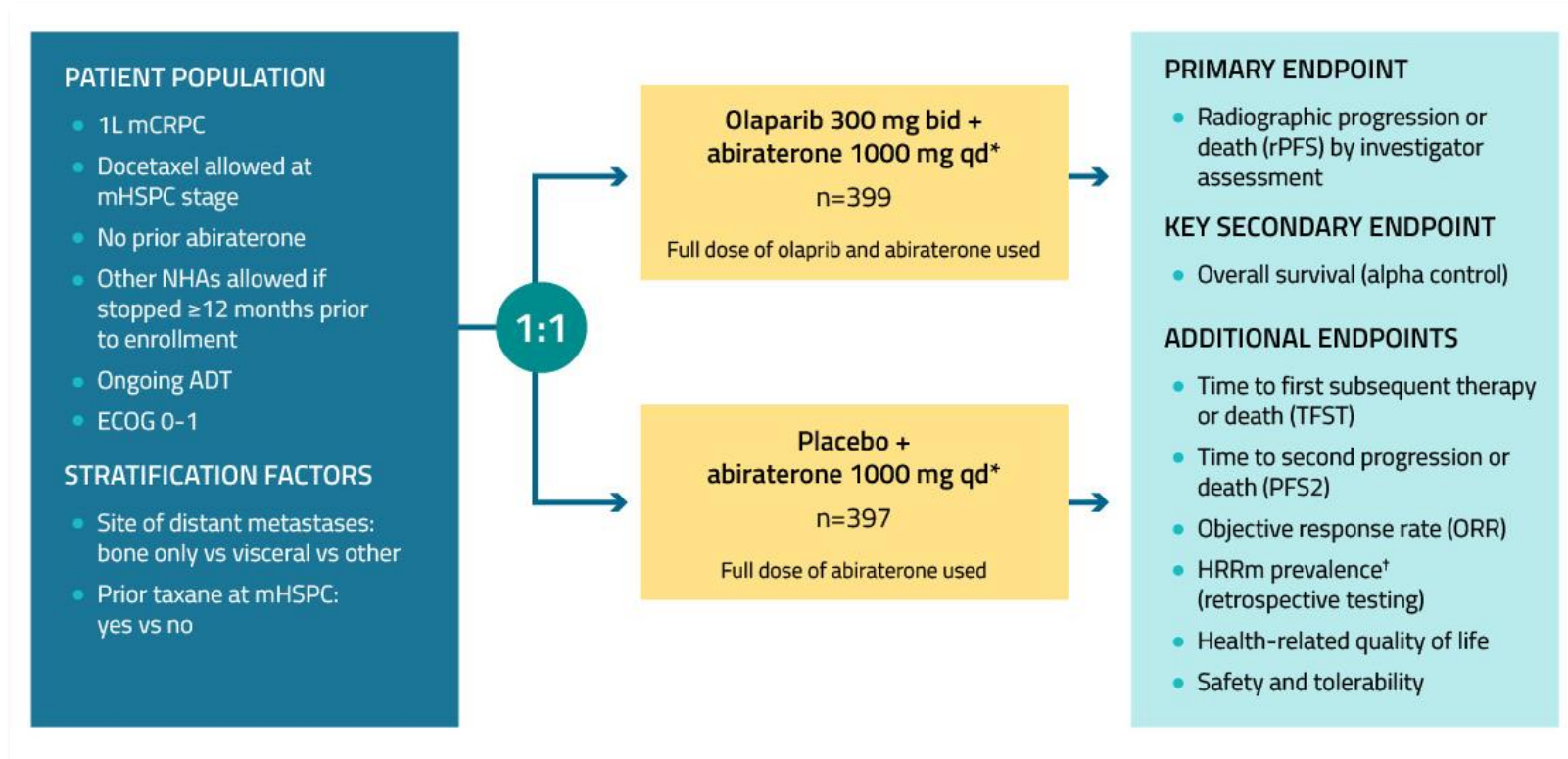
PARP inhibitors + ARPI : rationale

T



PARP inhibitors + ARPI combination

- PROpel : olaparib + abiraterone acetate/prednisone

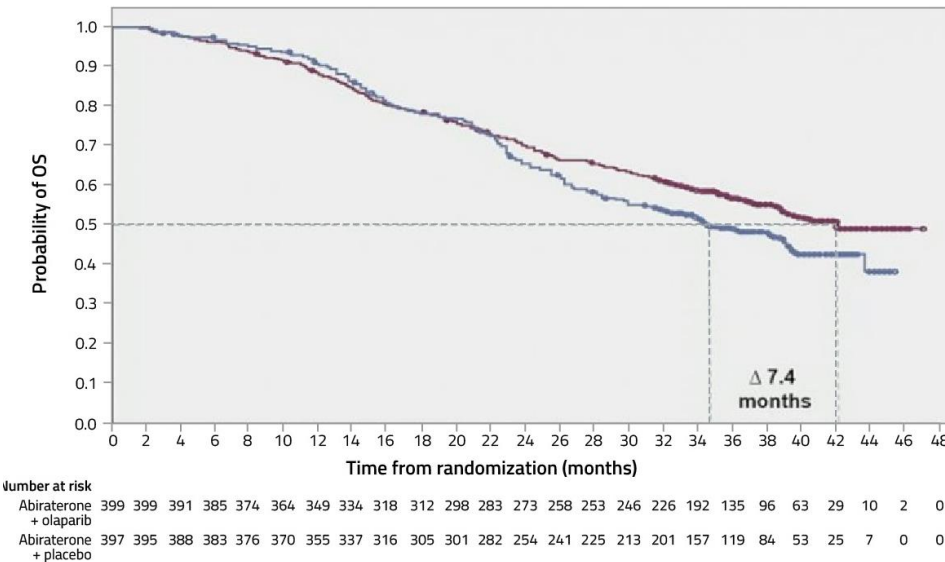
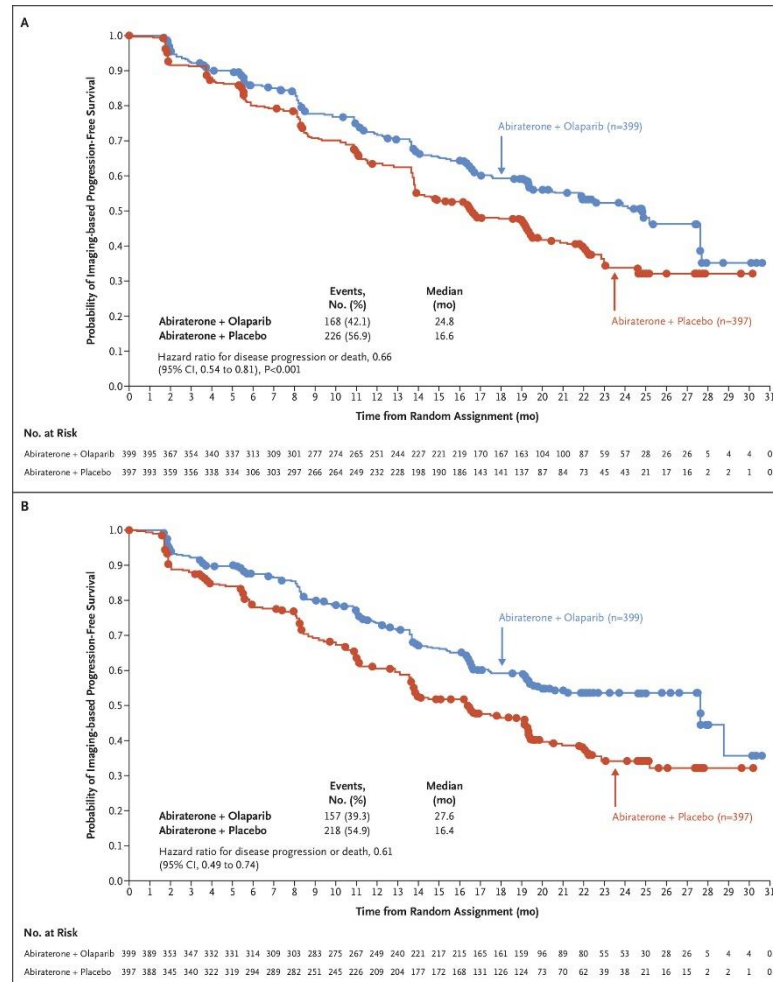


No HRR status
known at
enrollment.

Pts progressed on
ADT $\pm$ docetaxel
(ARPI stopped ≥ 12
months)

PARP inhibitors + ARPI combination

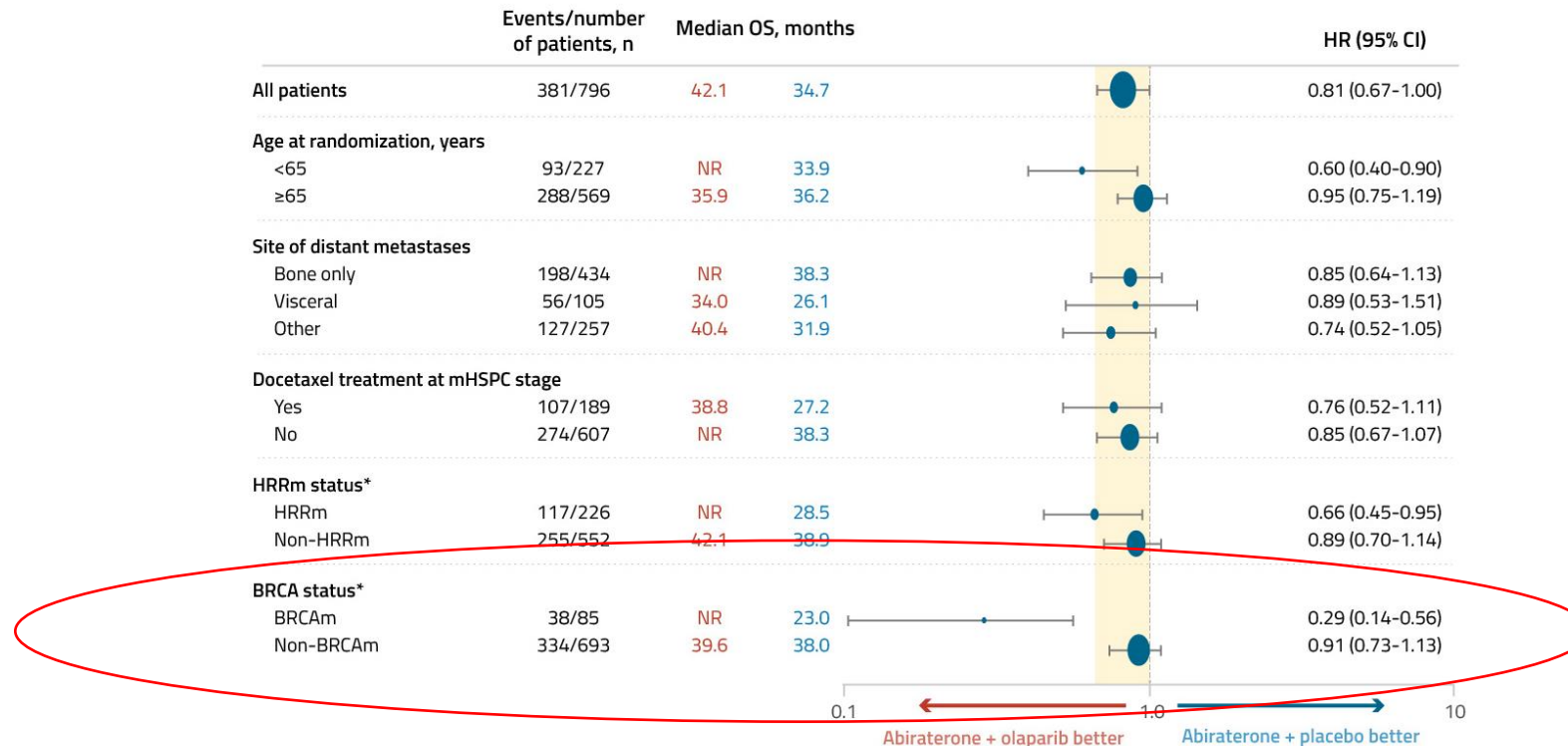
- PROpel : olaparib + abiraterone acetate/prednisone



HR 0.81
 $p=0.05$

PARP inhibitors + ARPI combination

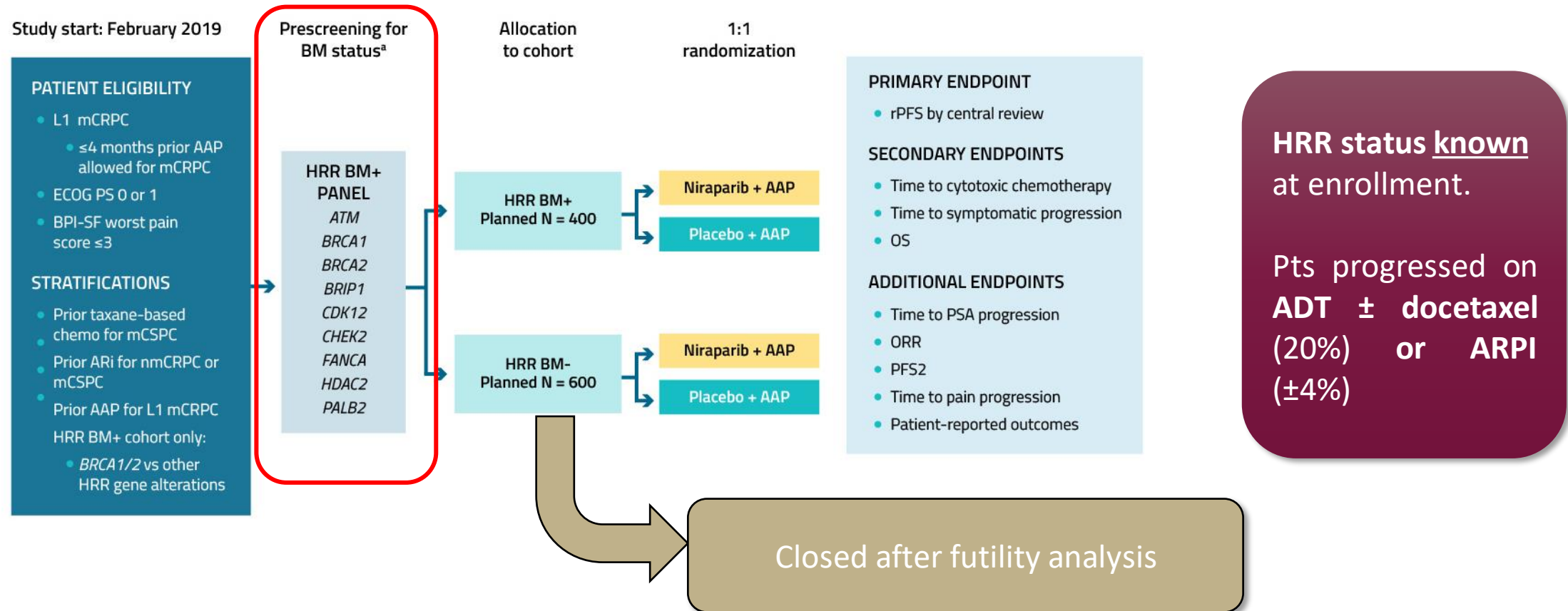
- PROpel : olaparib + abiraterone acetate/prednisone



All the OS benefit is driven by BRCAm pts (±10%)

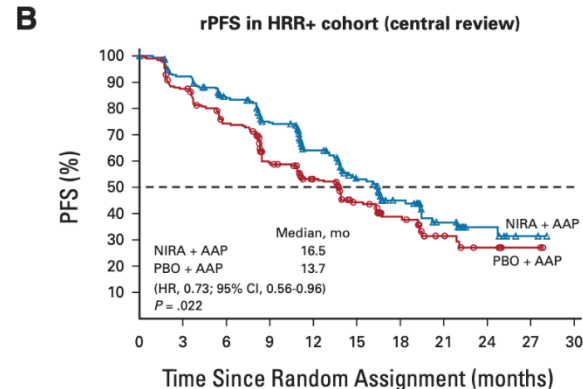
PARP inhibitors + ARPI combination

- Magnitude : niraparib + abiraterone acetate/prednisone



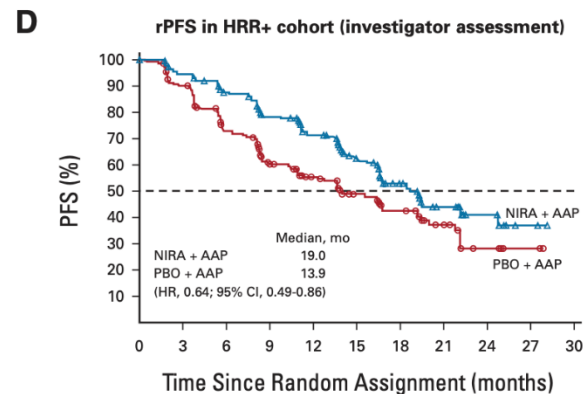
PARP inhibitors + ARPI combination

- Magnitude : niraparib + abiraterone acetate/prednisone



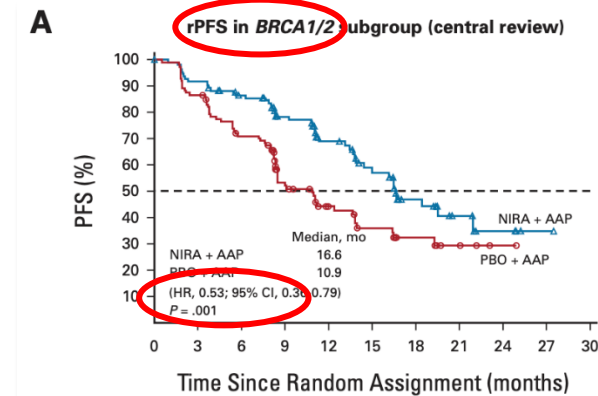
No. at risk:

NIRA + AAP	212	192	167	129	96	64	45	21	10	2	0
PBO + AAP	211	182	149	102	78	53	35	15	9	2	0



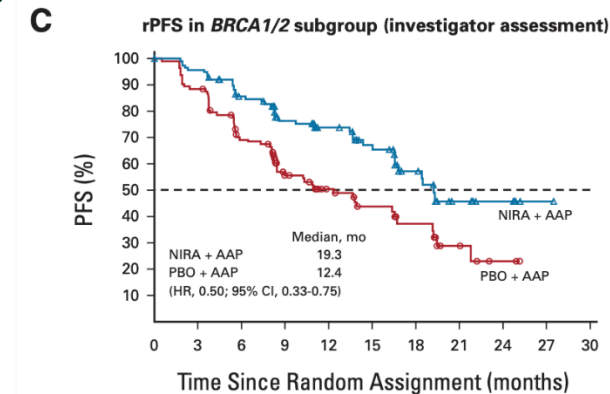
No. at risk:

NIRA + AAP	212	197	174	136	108	75	50	23	11	2	0
PBO + AAP	211	187	145	103	81	58	41	20	9	2	0



No. at risk:

NIRA + AAP	113	103	90	65	45	31	18	9	4	1	0
PBO + AAP	112	97	77	43	28	20	11	5	2	0	0



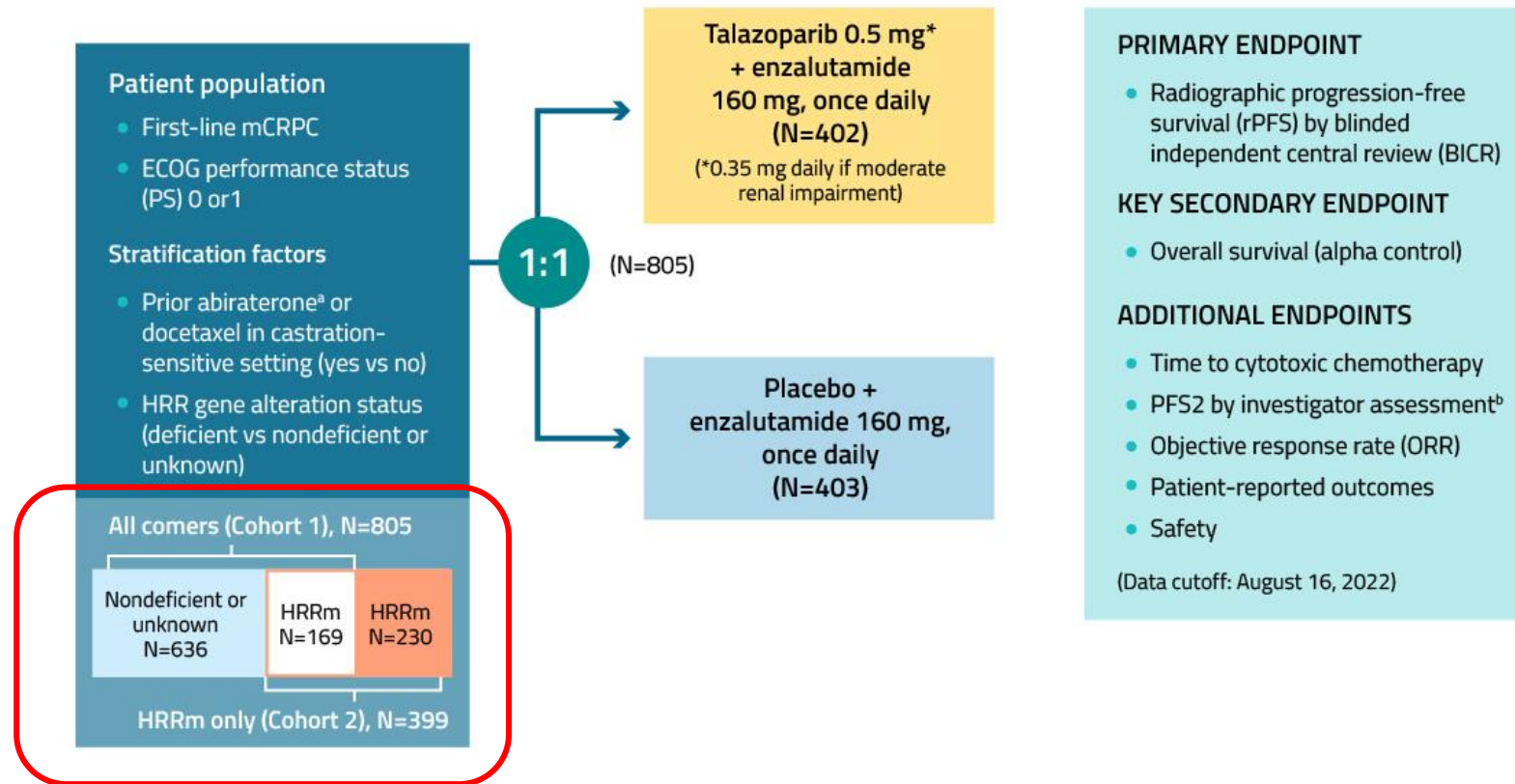
No. at risk:

NIRA + AAP	113	107	90	64	49	36	23	10	5	1	0
PBO + AAP	112	99	73	45	32	23	14	6	2	0	0

HR 0.50.66 (p=0.02) in
BRCA1/2 pts

PARP inhibitors + ARPI combination

- TALAPRO-2 : talazoparib + enzalutamide

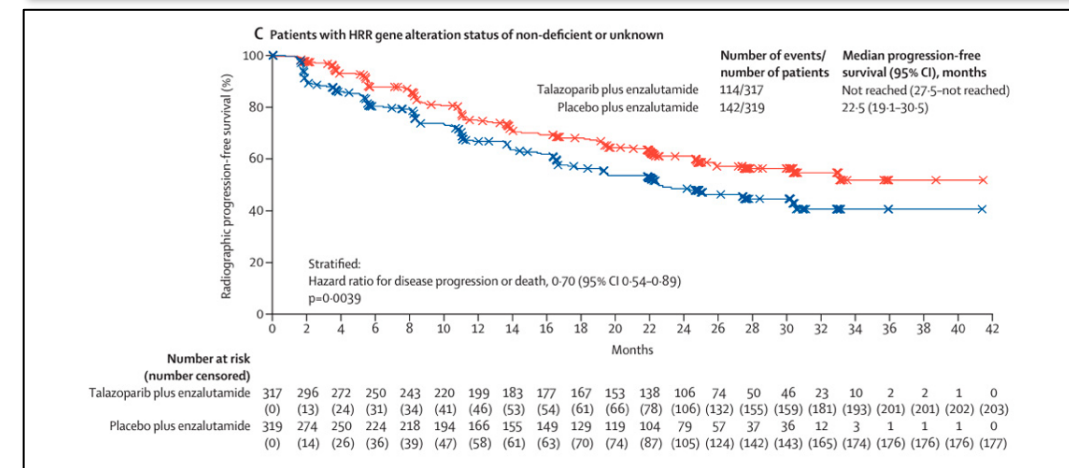
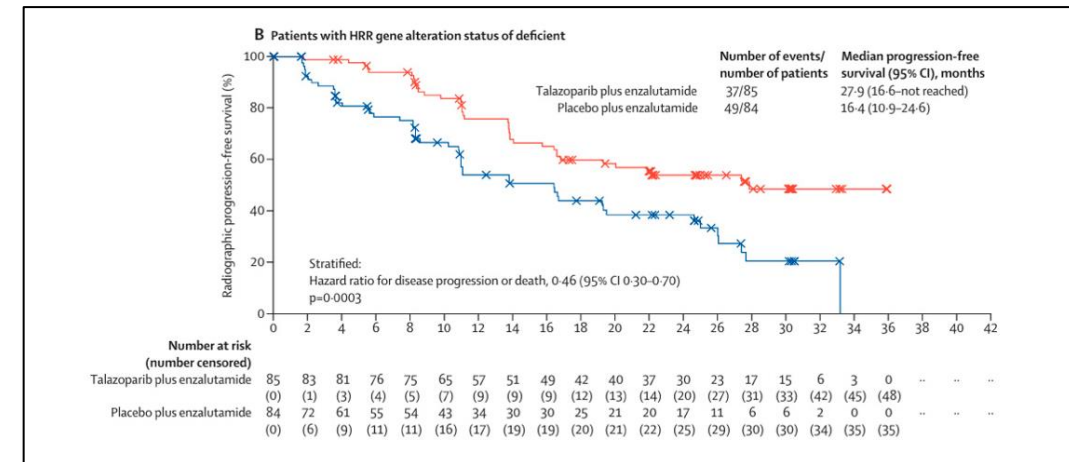
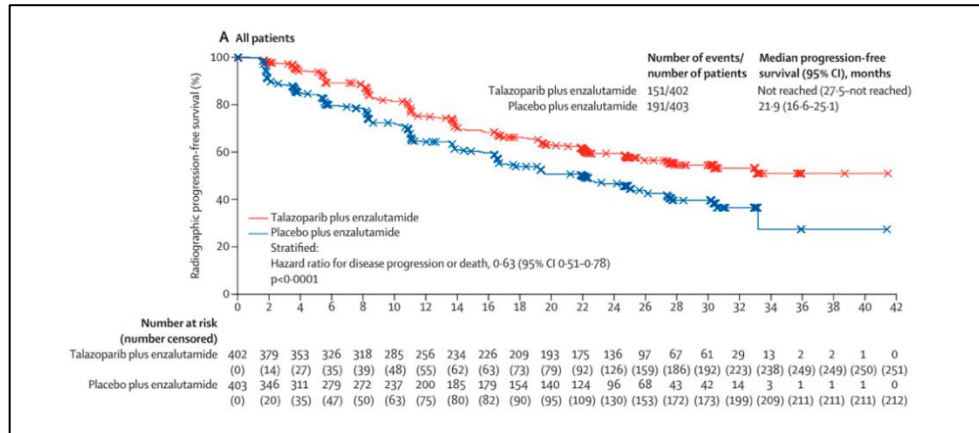


HRR status known
at enrollment in
cohort 2.

Pts progressed on
ADT ± docetaxel
(20%) **or**
abiraterone (±5%)

PARP inhibitors + ARPI combination

- TALAPRO-2 : talazoparib + enzalutamide



PARP inhibitors + ARPI combination

- TALAPRO-2 : talazoparib + enzalutamide

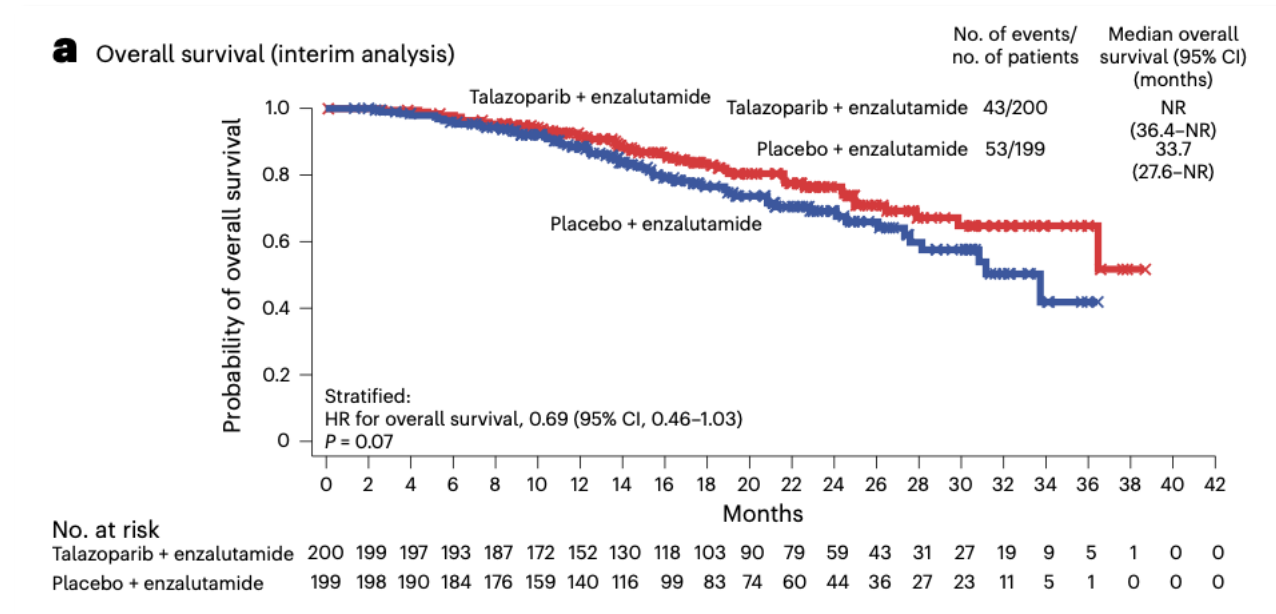
b By selected gene subgroups[†]

Subgroup	Talazoparib + enzalutamide No. of events/no. of patients	Placebo + enzalutamide No. of events/no. of patients	Talazoparib + enzalutamide Median (months)	Placebo + enzalutamide Median (months)	Hazard ratio (95% CI)	Two-sided P value
All HRR-deficient	65/198	104/197	NR	13.8	0.44 (0.32–0.60)	<0.0001
Only <i>BRCA1</i>	2/8	5/9	20.0	11.7	0.17 (0.02–1.51)	0.07
Only <i>BRCA2</i>	11/55	40/60	NR	11.0	0.19 (0.10–0.38)	<0.0001
Only <i>PALB2</i>	3/6	4/5	NR	8.6	0.56 (0.12–2.51)	0.44
Only <i>CDK12</i>	12/28	18/30	21.9	13.8	0.49 (0.23–1.02)	0.05
Only <i>ATM</i>	12/35	7/22	NR	27.7	0.76 (0.30–1.94)	0.58
Only <i>CHEK2</i>	8/24	8/24	22.1	NR	0.90 (0.34–2.39)	0.83

Once again, benefit mainly driven by BRCA(1/2)-altered patients

PARP inhibitors + ARPI combination

- TALAPRO-2 : talazoparib + enzalutamide



PARP inhibitors + ARPI combination

- Incidence of the most frequently reported Aes

	Grade	PROpel (abi + ola vs abi + placebo)	MAGNITUDE (abi + nira vs abi + placebo)	TALAPRO-2 (enza + talazo vs enza + placebo)
Drug interruption		49% vs 25%	49.1% vs 27.5%	65.3% vs 24.7%
Dose reduction		22.6% vs 5.6%	20.3% vs 3.8%	54.5% vs 24.7%
Discontinuation		17.3% vs 7.8%	18.4% vs 8.1%	21.6% vs 13%
Any AEs	Any	97% vs 95 %	99% vs 94%	98% vs 95%
	≥3	47% vs 38%	56% vs 43%	75% vs 45%
Fatigue	Any	38% vs 28%	30% vs 19%	33% vs 27%
	≥3	2.3% vs 1.5%	5% vs 4%	2% vs 1%
Anemia	Any	48% vs 18%	50% vs 23%	65% vs 16%
	≥3	16% vs 3%	29% vs 9%	41% vs 5%
Thrombocytopenia	Any	NA	23% vs 10%	25% vs 3%
	≥3	NA	4% vs 2%	7% vs 1%
Neutropenia	Any	NA	15% vs 7%	32% vs 7%
	≥3	NA	5% vs 2%	19% vs 1%
Nausea	Any	28% vs 13%	25% vs 15%	21% vs 17%
	≥3	1% vs 1%	1% vs 1%	2% vs 1%
Vomiting	Any	13% vs 9%	15% vs 8%	NA
	≥3	1% vs 1%	1% vs 1%	NA
Diarrhea	Any	17% vs 9%	NA	12% vs 11%
	≥3	1% vs 1%	NA	0% vs 0%
VTE & PE		8% vs 2.5% 6% vs 1.5%		
MDS/AML		2 cases	2 cases	0

PARP inhibitors + ARPI combination

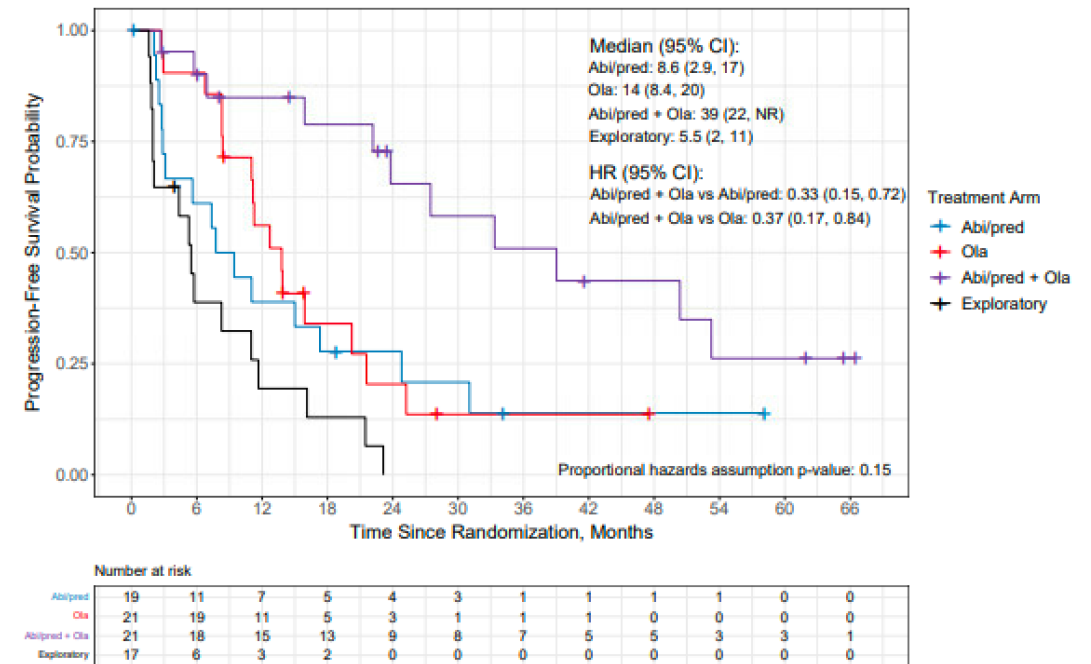
- Does the sequence matter ? (BRCAAWAY)

3 arm trials :

- Arm I : abiraterone -> olaparib
- Arm II : olaparib -> abiraterone
- Arm III : Abiraterone + olaparib

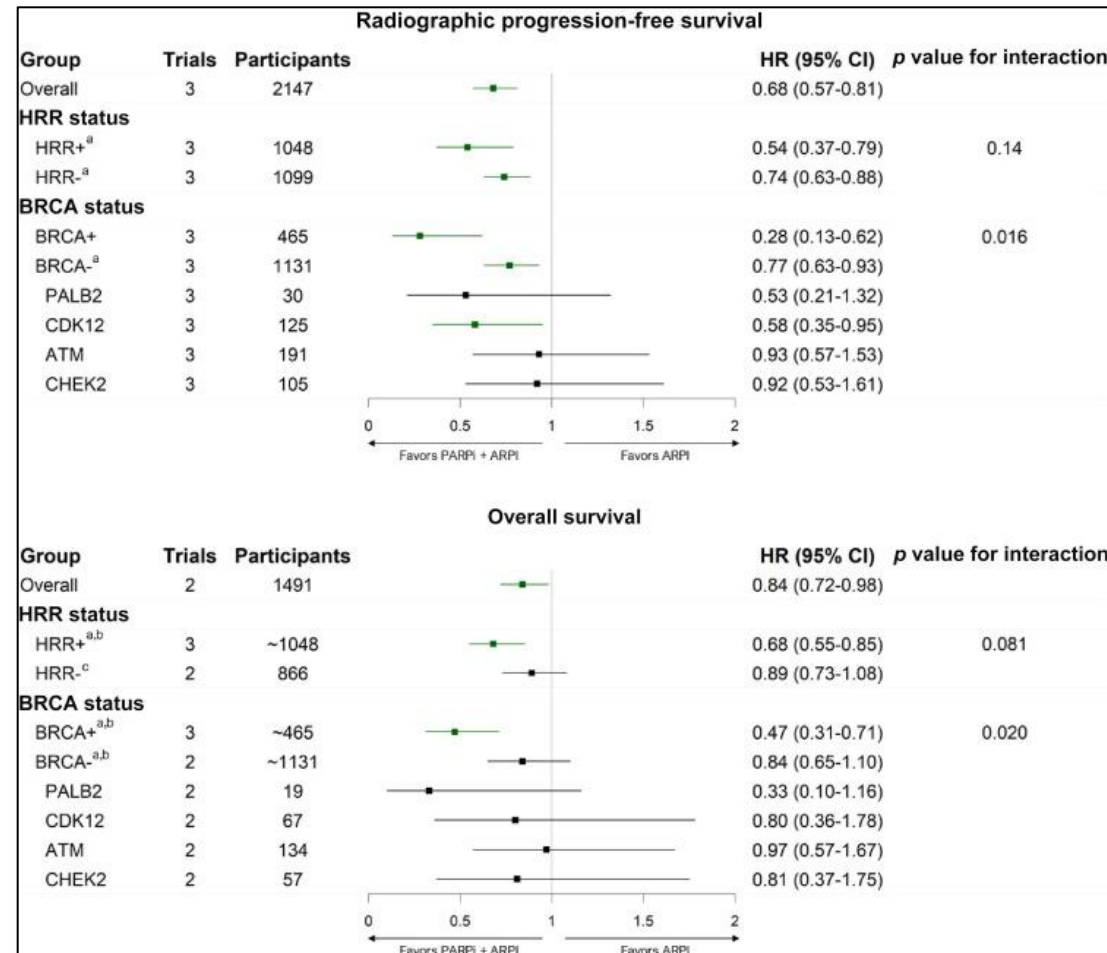
Combination >>> sequential treatment

A.



PARP inhibitors + ARPI combination

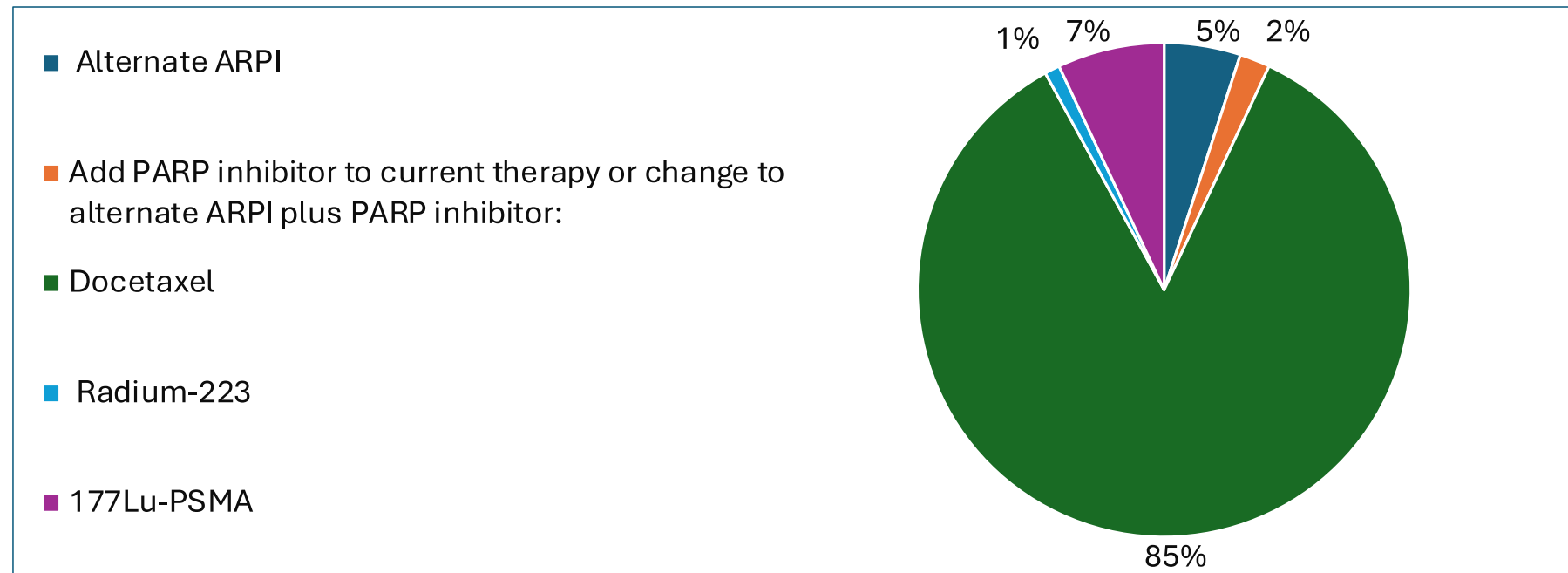
- Specific gene alteration benefit : meta-analysis



Benefit only in *BRCA*-altered patients (in rPFS & OS)

PARP inhibitors + ARPI combination

APCCC 2024 : For the majority of patients with mCRPC and **somatic genetic testing not available** what is your treatment recommendation in the first-line setting when they received ADT+ARPI for mHSPC?



RLT + ARPI in mCRPC



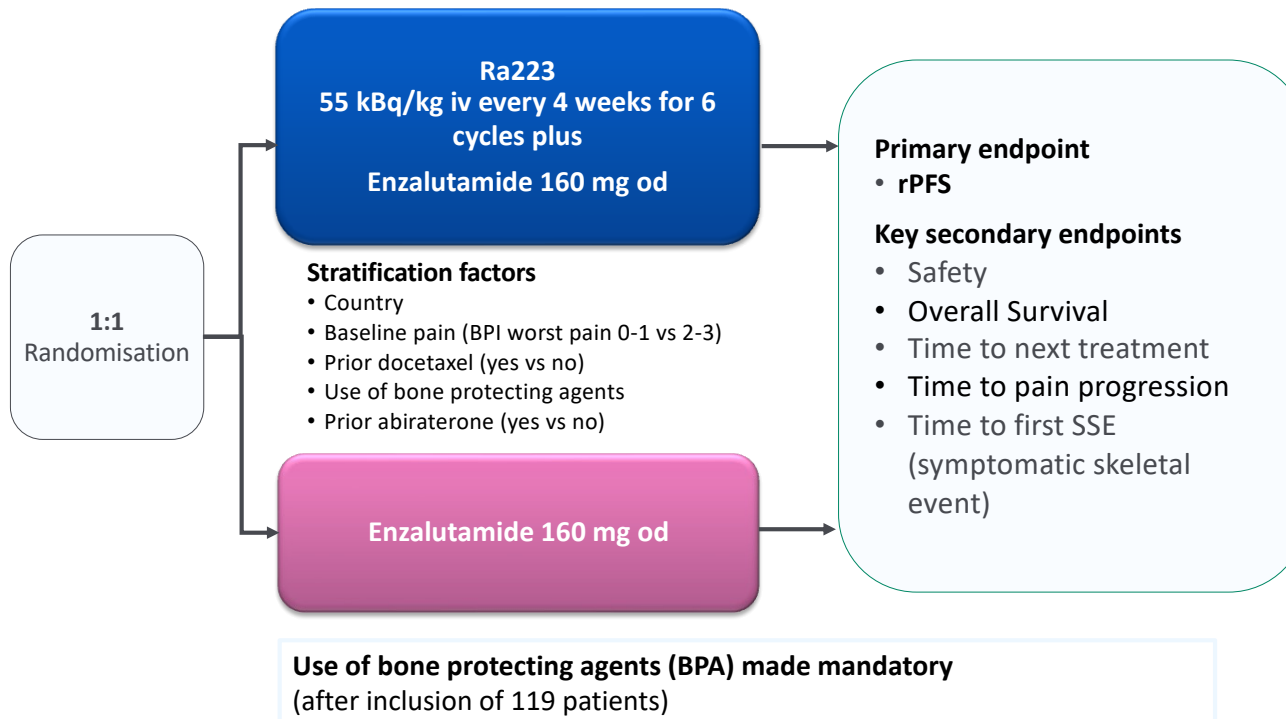
PEACE-3 : Radium 223 + enzalutamide

EORTC-GUCCG 1333 (PEACE-3)

Updated design

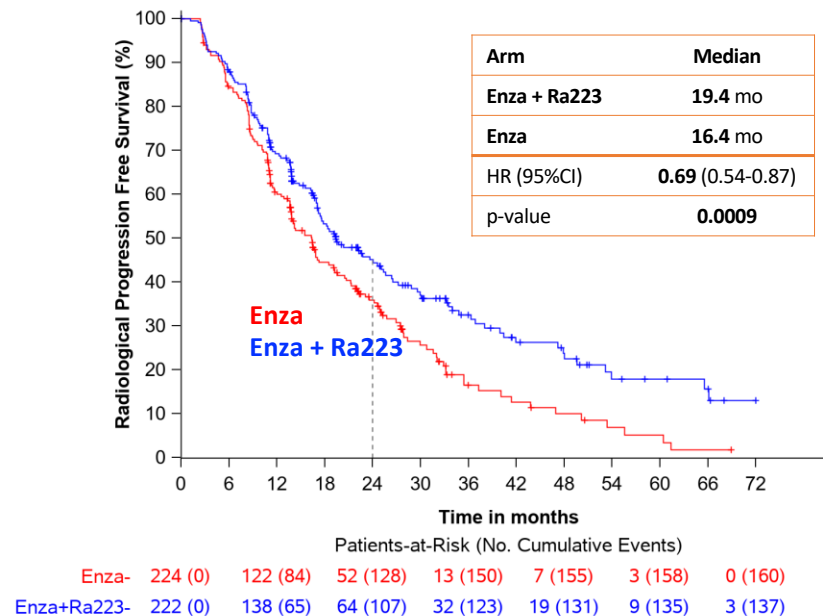
Study population

- Patients with mCRPC and bone metastases (≥ 4 bone metastases)
- Asymptomatic or mildly symptomatic*
- WHO PS of 0 or 1
- No prior treatment with enzalutamide or Ra223
- No known visceral metastases
- Ongoing ADT
- Prior treatment with abiraterone in mHSPC allowed

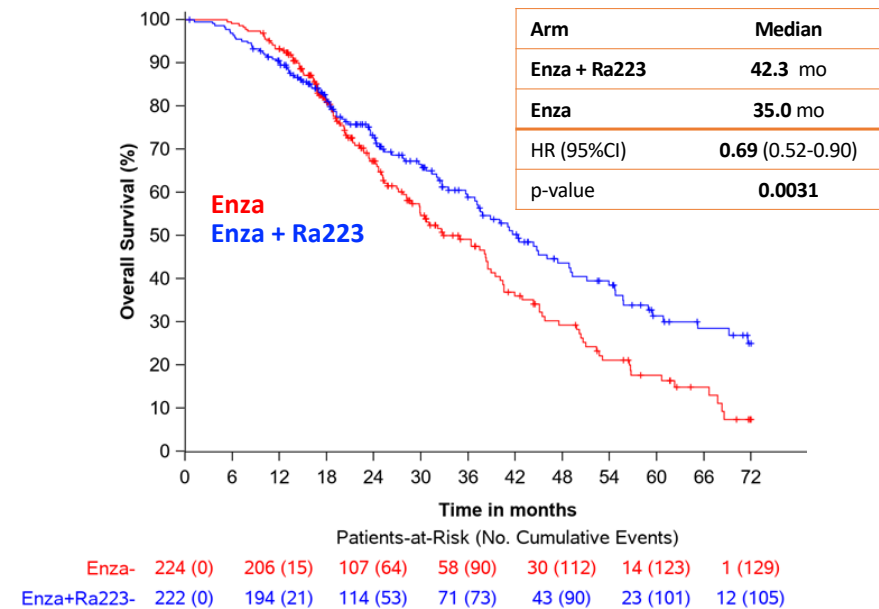


PEACE-3 : Radium 233 + enzalutamide

Primary endpoint: rPFS

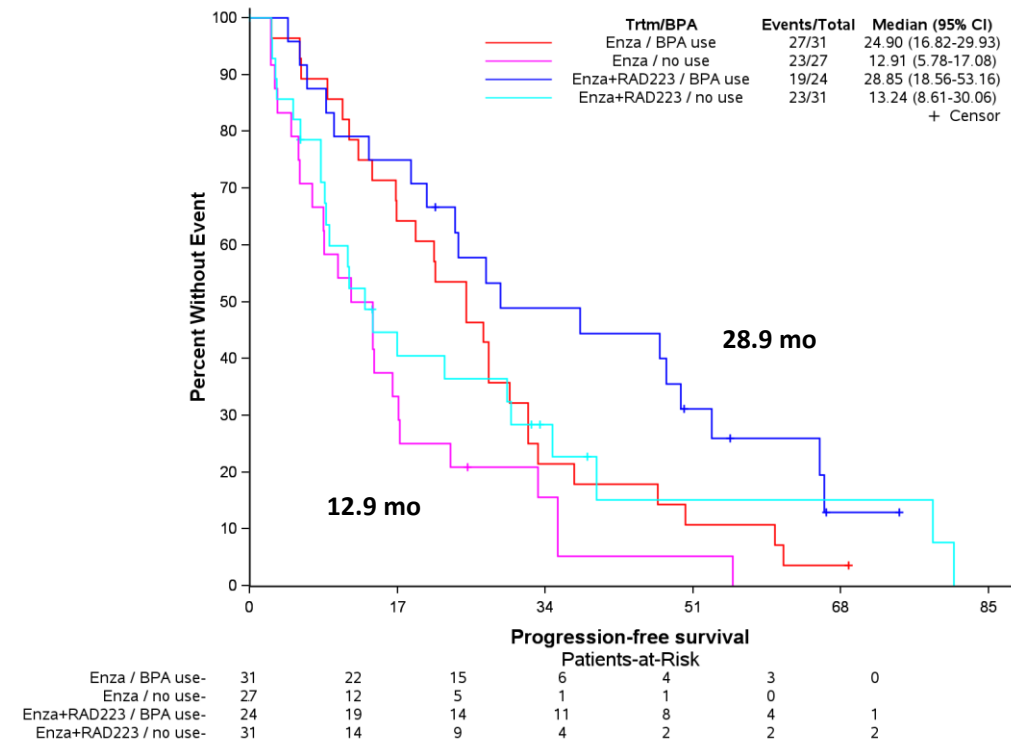
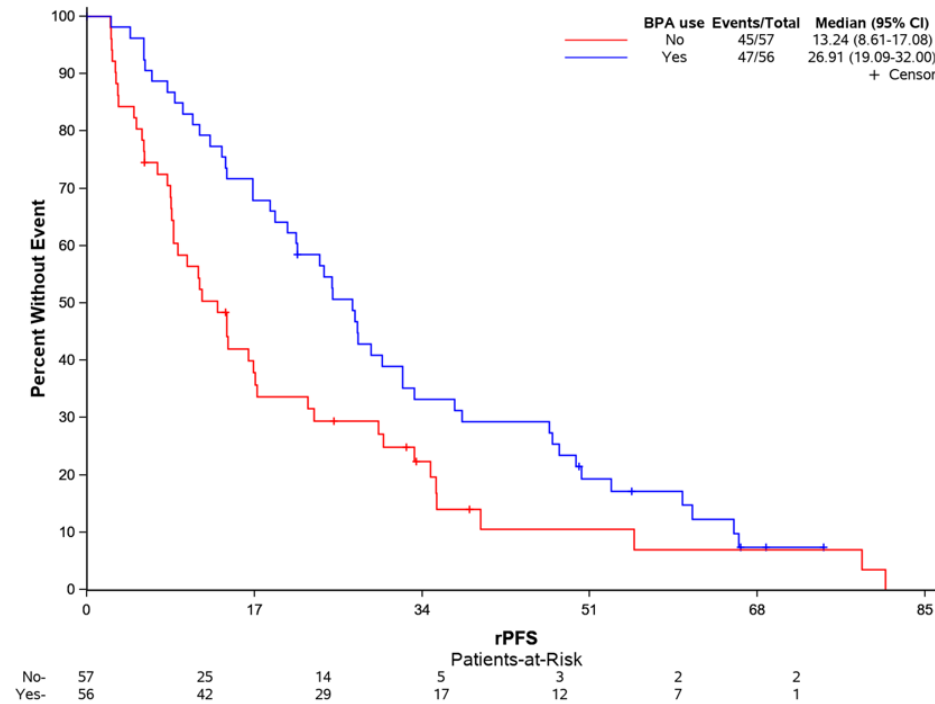


Secondary endpoint: OS (interim analysis at 80% of events)



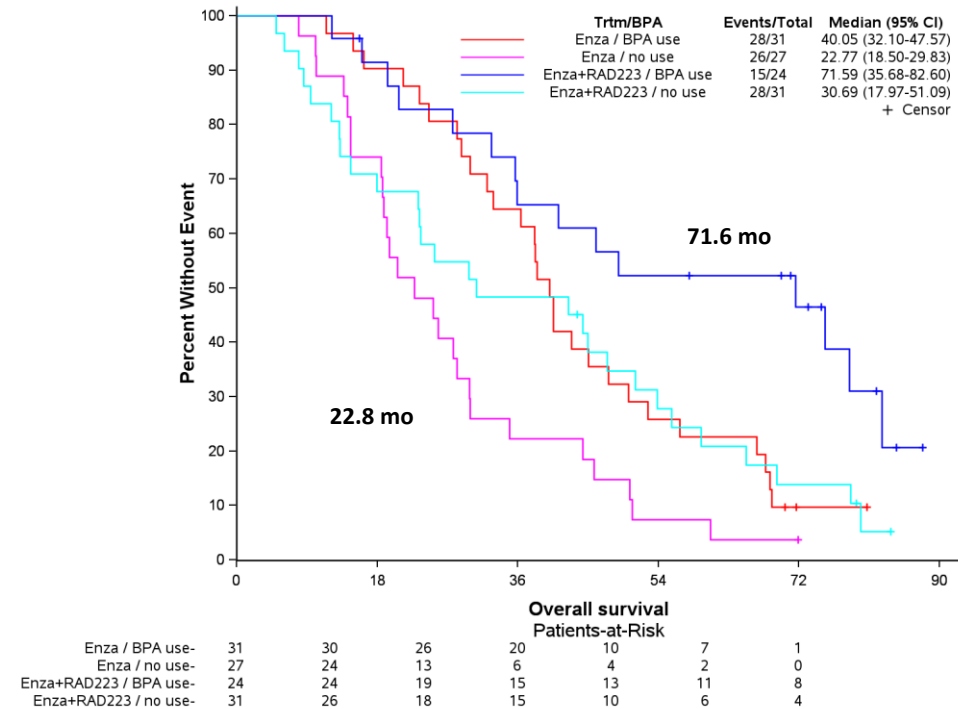
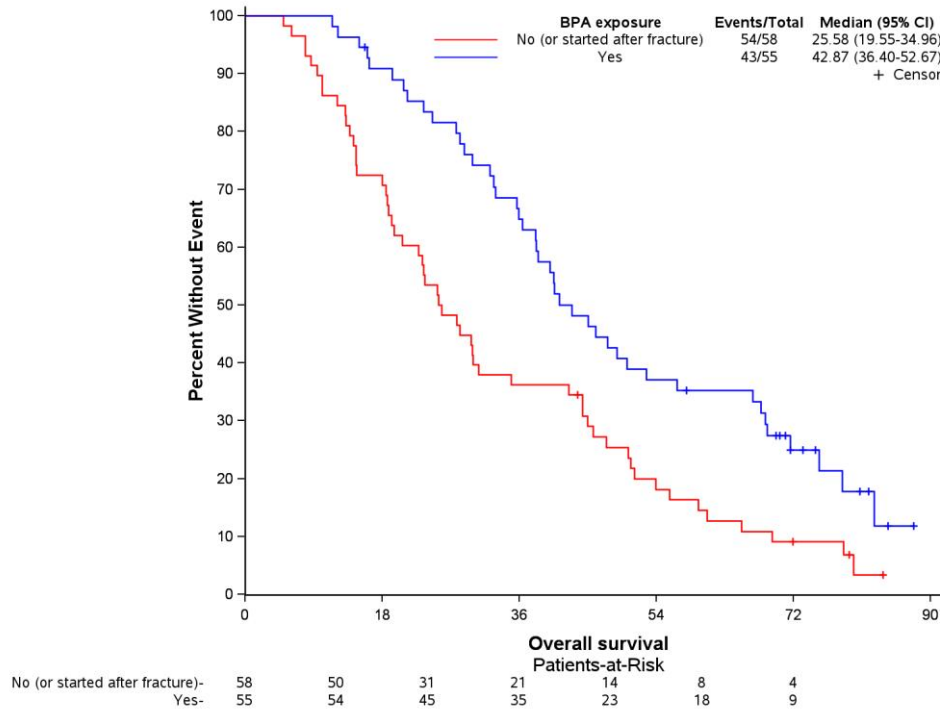
Combination of Radium-233 and enzalutamide improves rPFS (HR 0.69) and OS (HR 0.69)

PEACE-3 : Radium 233 + enzalutamide



The use of BPA increases rPFS by 14 months (HR 0.6)

PEACE-3 : Radium 223 + enzalutamide



The use of BPA increases OS by 17 months (HR 0.56)

Take home messages



Take home messages

- Combination of an ARPI and a PARPi in all comers progressing on ADT alone ? **NO benefit if not *BRCA(1)/2*** ;
- Combination in *BRCA*-altered progressing on ADT + ARPI ? **No data**
- Combination of Radium-233 and enzalutamide (+BPA), if EMA approved, **might be an interesting 1st line mCRPC for patient not previously treated** with an ARPI.





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