PARP Inhibitors in Earlier Stages of Prostate Cancer:

Current Data & Future Directions

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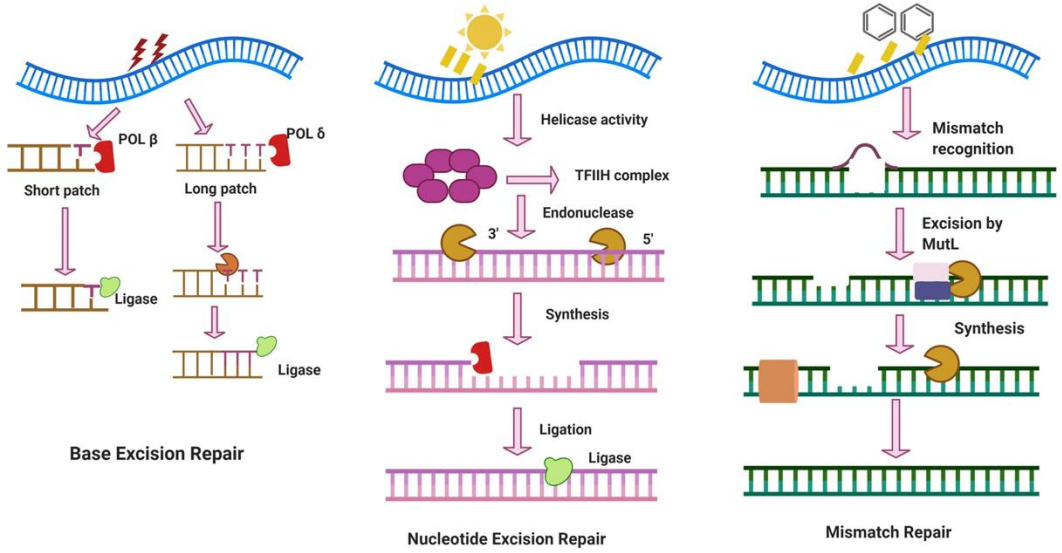
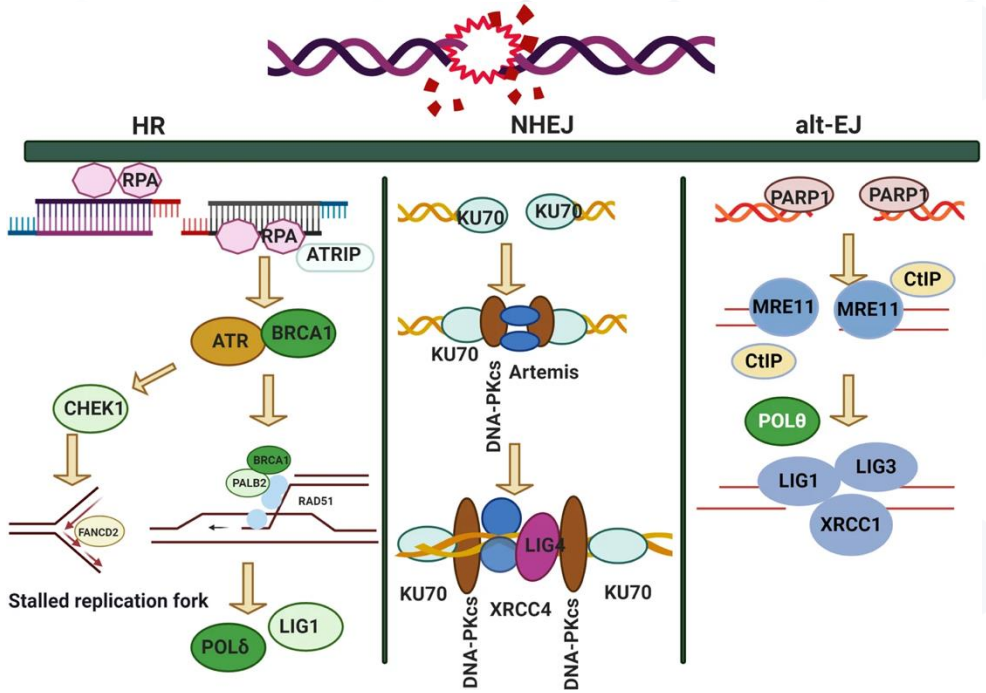
Where We Came From

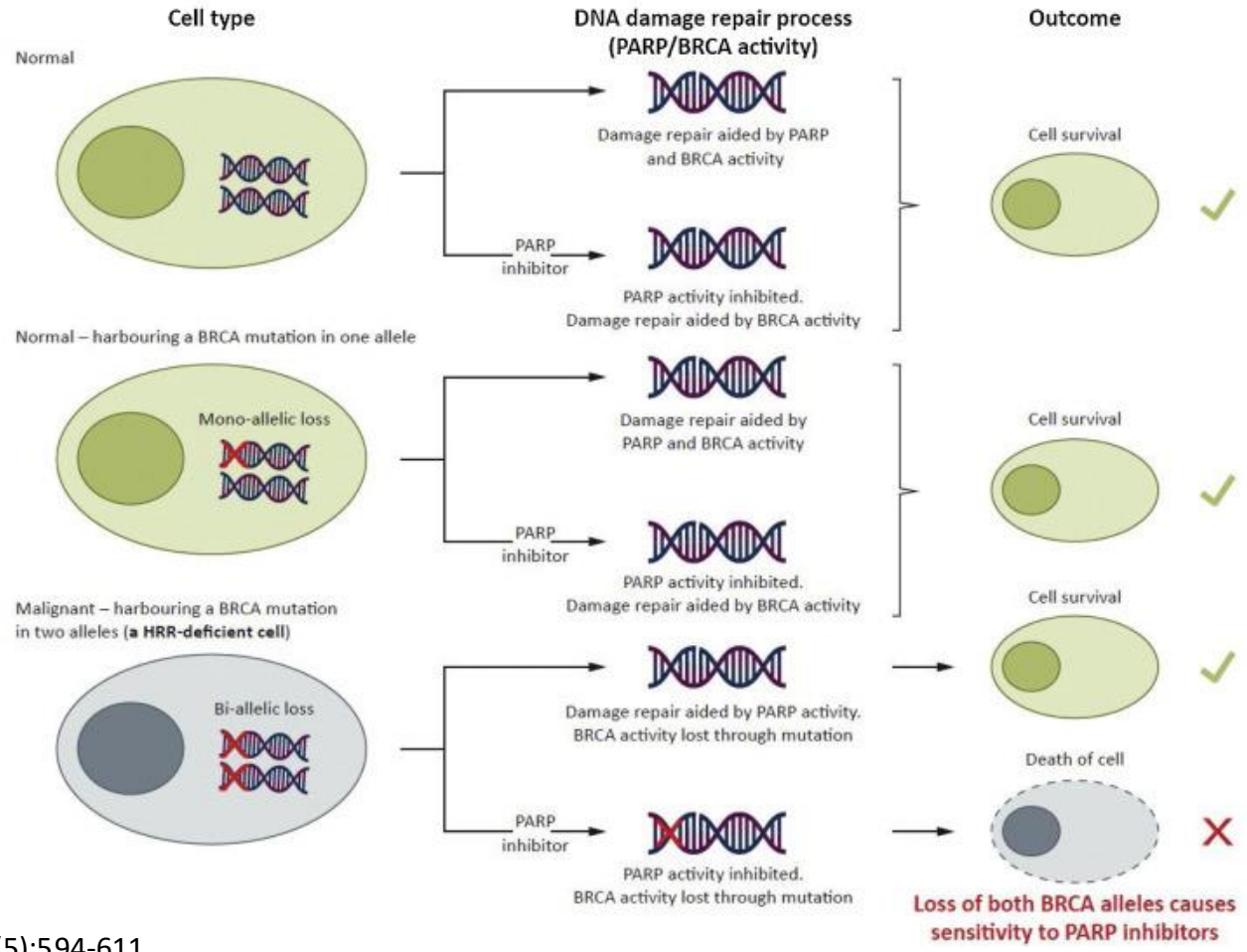
DNA Repair





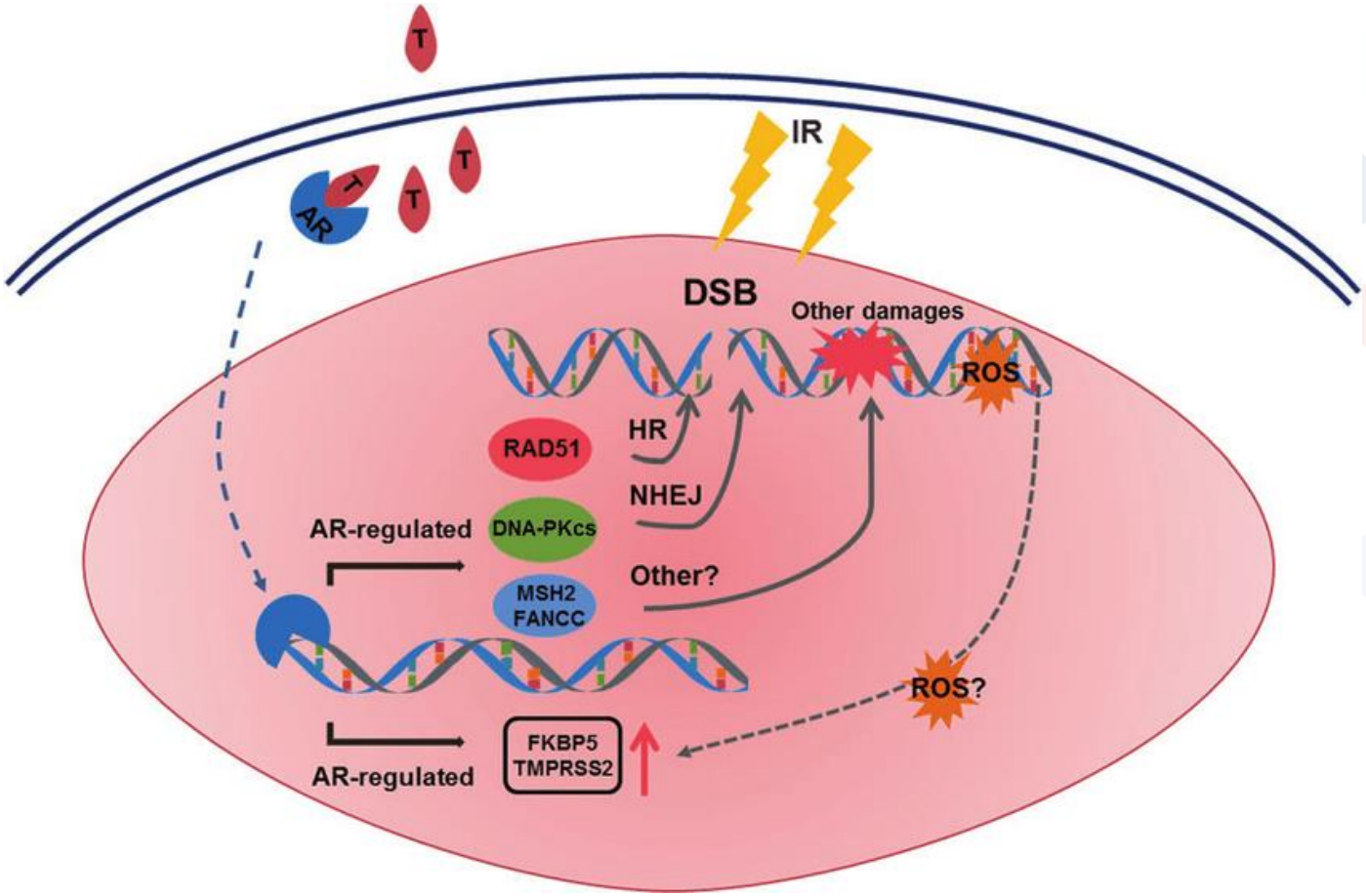
Huang, R et al. Signal Transduct Target Ther. 2021 Jul 9;6(1):254

Synergy



Antonarakis E, et al. Eur Urol Oncol. 2020 Oct;3(5):594-611

Synergy



Zhang W, et al. Prostate Cancer Prostatic Dis. 2020 Mar;23(1):24-37

Synergy

Table 3 Prevalence of selected DDR genes alteration in mCRPC

	DDR pathway involved	Grasso et al. [54]	Robinson et al. [55]	Total
Number of patients		59	150	209
ATM	General	11.8% (7)	5.3% (8)	7.2% (15)
ATR		5% (3)	8.6% (13)	7.7% (16)
BRCA1	HR		0.7% (1)	0.5% (1)
BRCA2		11.8% (7)	9.3% (14)	10.0% (21)
RAD51		1.7% (1)	2.0% (3)	1.9% (4)
PARP1	BER	3% (2)	2.7% (4)	5.5% (6)
MLH1	MMR	1.7% (1)	1.3% (2)	1.4% (3)
MSH2		3.3% (2)	2.7% (4)	2.9% (6)
FANCD2	FA	3.3% (2)	2.7% (4)	2.9% (6)
All genes		41.6%	35.3%	40%

Data was acquired from The Memorial Sloan Kettering cBioportal database (http://cbioportal.org)

Zhang W, et al. Prostate Cancer Prostatic Dis. 2020 Mar;23(1):24-37

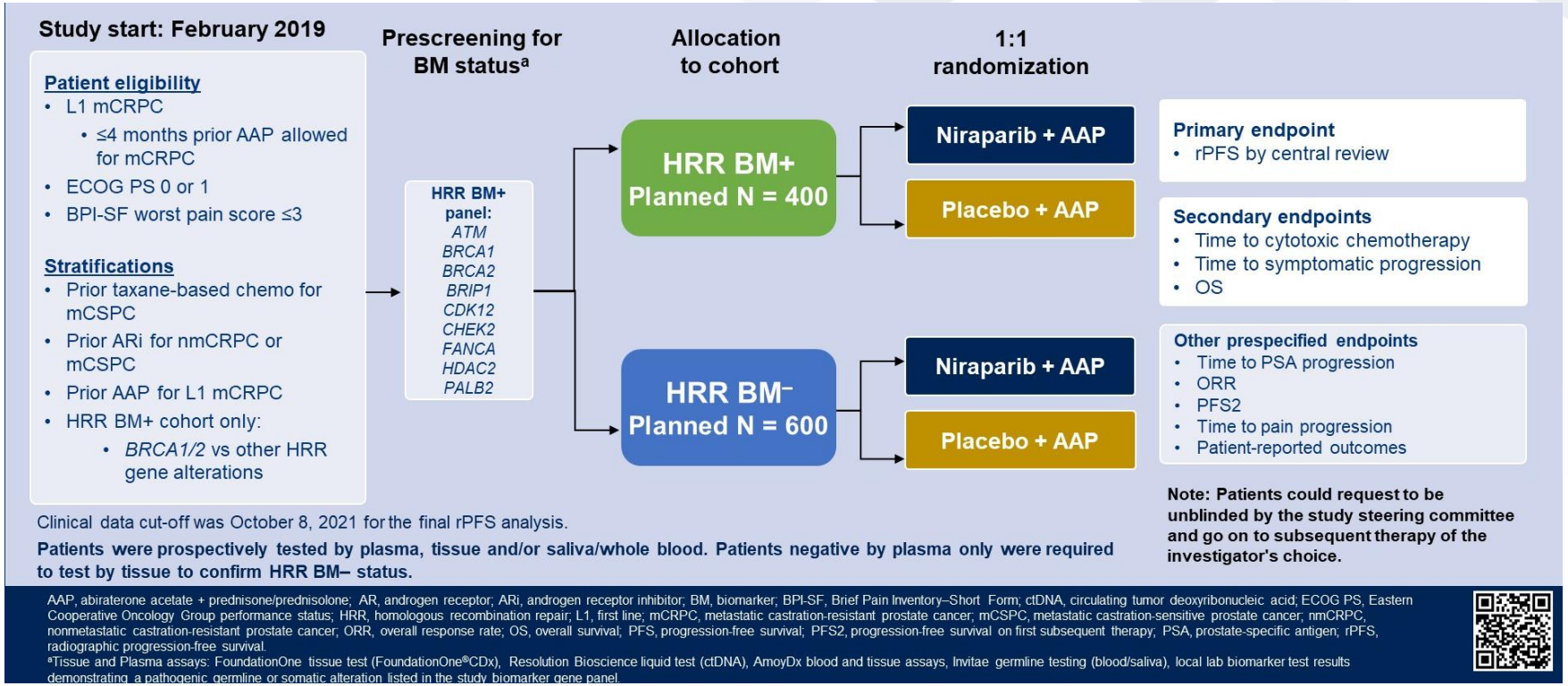
Where We Are Presently

Phase 3 Trials in mCRPC

- MAGNITUDE[1,2]
  - 69% negative by tissue and ctDNA
  - 30% unknown by tissue testing but neg by ctDNA
  - 0% unknown by ctDNA and tissue (1/247)
  - 20% prior docetaxel; 3% prior ARPI
- PROpel[3]
  - 33% with unknown tissue testing
  - 8% with unknown ctDNA testing
  - 25% prior docetaxel; <1% prior ARPI
- TALAPRO-2[4,5]
  - 27% unknown by tissue testing
  - 115/805 with any ctDNA results
  - 22% prior docetaxel; 5% prior ARPI

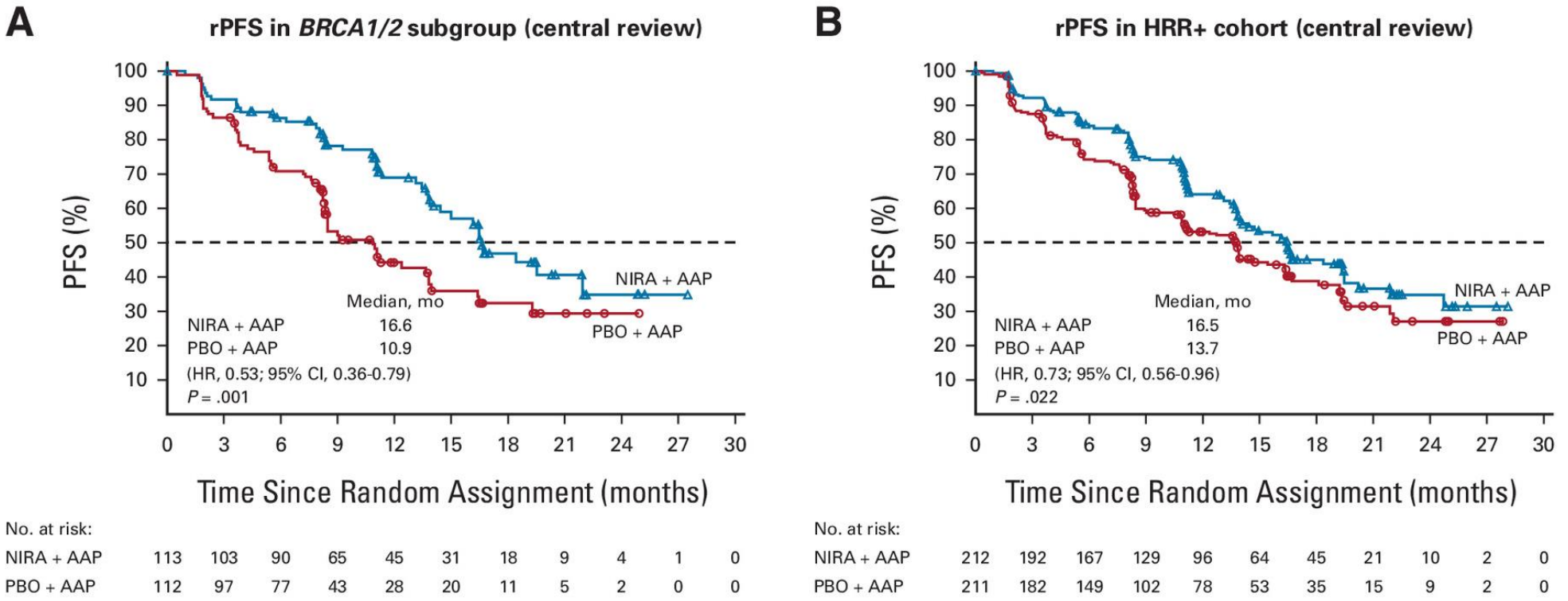
1. Chi KN, et al. J Clin Oncol. 2023 Jun 20;41(18):3339-3351
2. Chi KN, et al. J Clin Oncol 40, 2022 (suppl 6; abstr 12)
3. Saad F, et al. Lancet Oncol. 2023 Oct;24(10):1094-1108
4. Agarwal N, et al. Lancet. 2023 Jul 22;402(10398):291-303
5. Agarwal N, et al. J Clin Oncol 43, 2025 (suppl 5; abstr LBA18)

MAGNITUDE



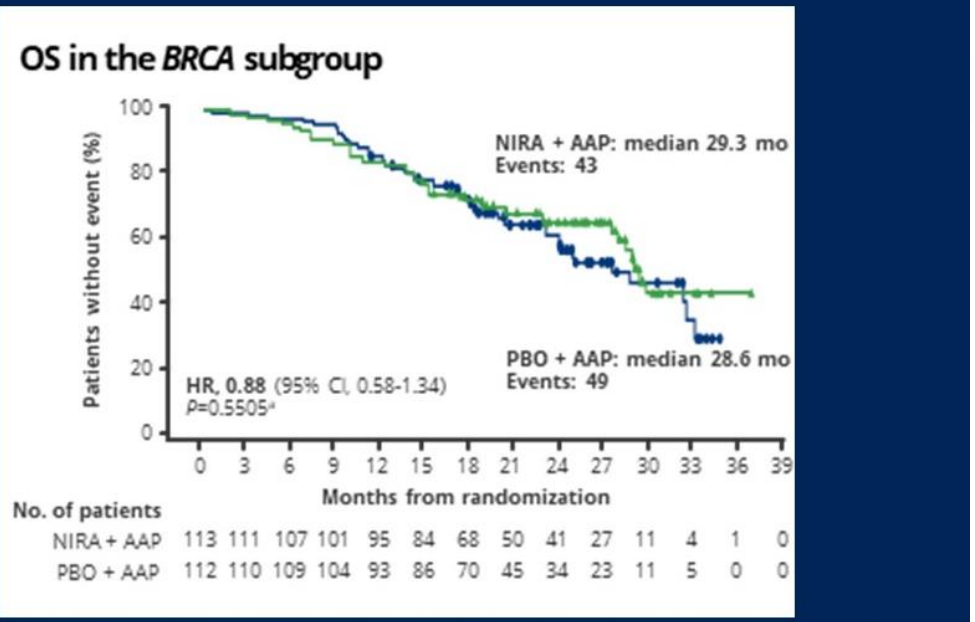
Chi KN, et al. J Clin Oncol 40, 2022 (suppl 6; abstr 12)

MAGNITUDE: PFS (HRR BM+)



Chi KN, et al. J Clin Oncol. 2023 Jun 20;41(18):3339-3351

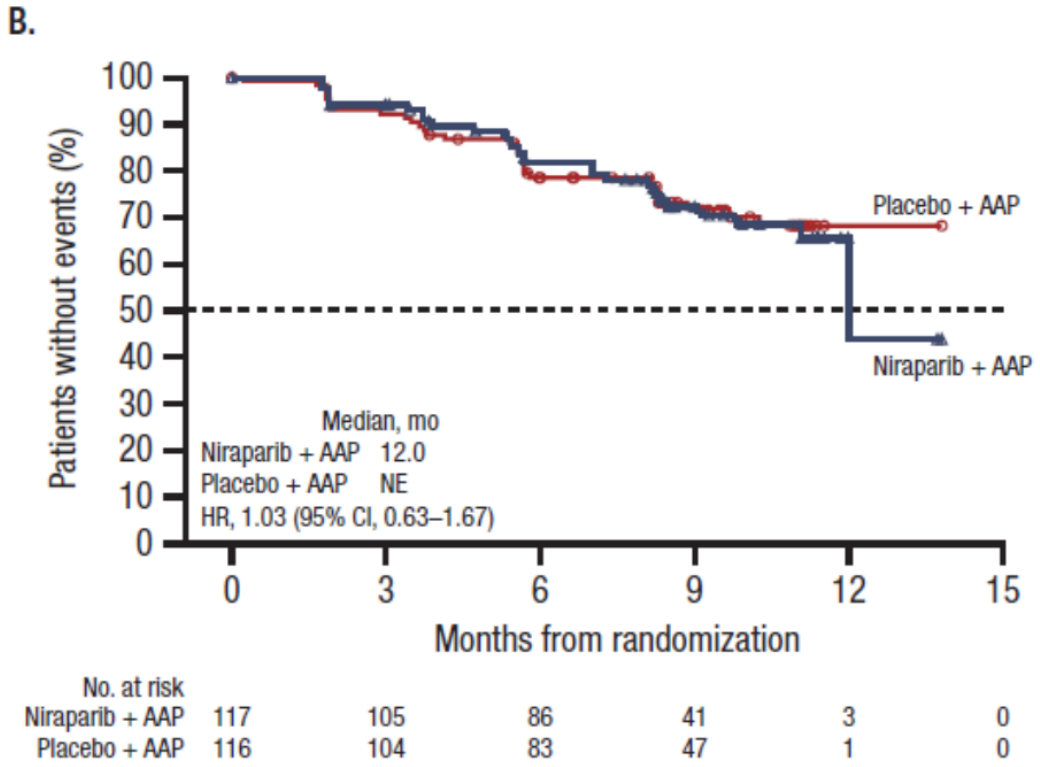
MAGNITUDE: OS (HRR BM+)



- IPCW analysis of OS showed a 46% reduction in the risk of death with niraparib + AAP compared with placebo + AAP (HR, 0.54 [95% CI, 0.33-0.90])
- The OS stratified analysis HR was 0.88 (95% CI, 0.58-1.34), with a trend toward improvement in OS observed in the IPCW analysis (HR=0.54 [95% CI, 0.33-0.90])

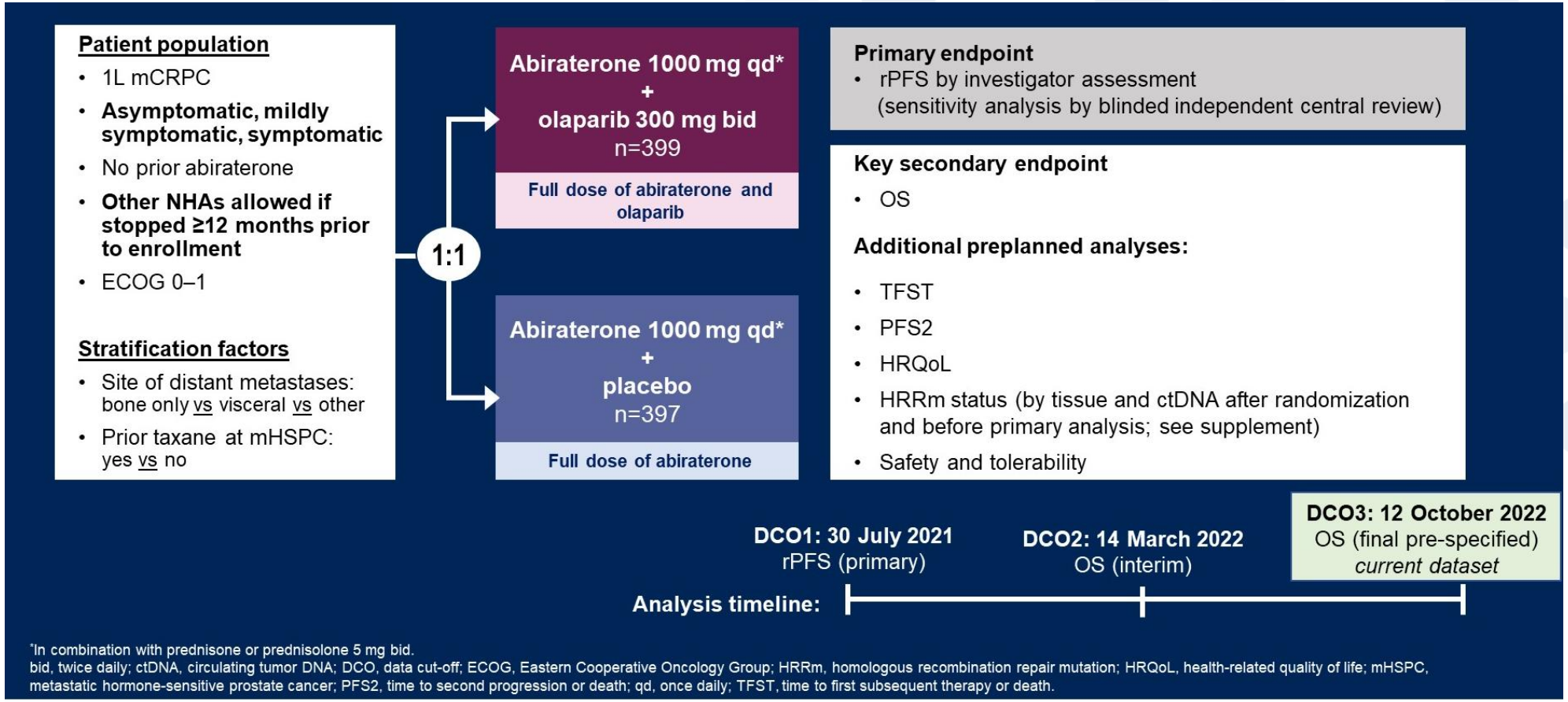
Efstathiou E, et al. J Clin Oncol 41, 2023 (suppl 6; abstr 170)

MAGNITUDE: PFS (HRR BM-)



Chi KN, et al. J Clin Oncol. 2023 Jun 20;41(18):3339-3351

PROpel

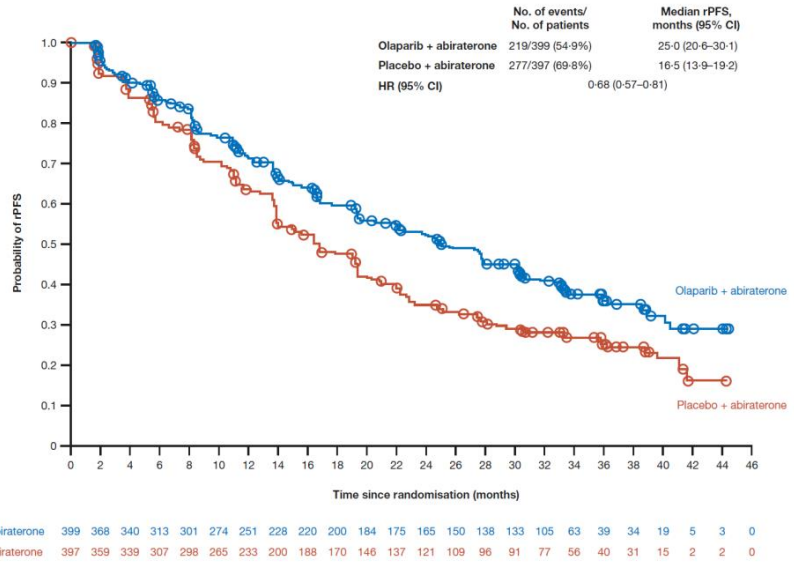


Noel C, et al. J Clin Oncol 41, 2023 (suppl 6; abstr LBA16)

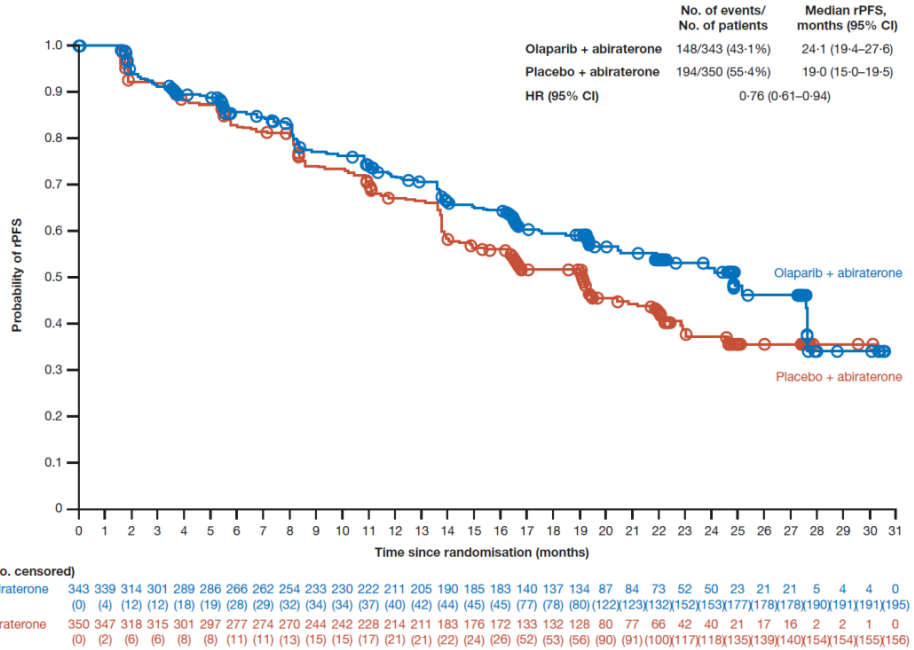
PROpel: PFS

Figure S2: **Kaplan–Meier estimates of updated radiographic progression-free survival by investigator assessment in the ITT population at final prespecified OS analysis (DCO: 12 October 2022).**

rPFS analysis at this final prespecified OS analysis was descriptive as rPFS at the primary analysis was statistically significant.

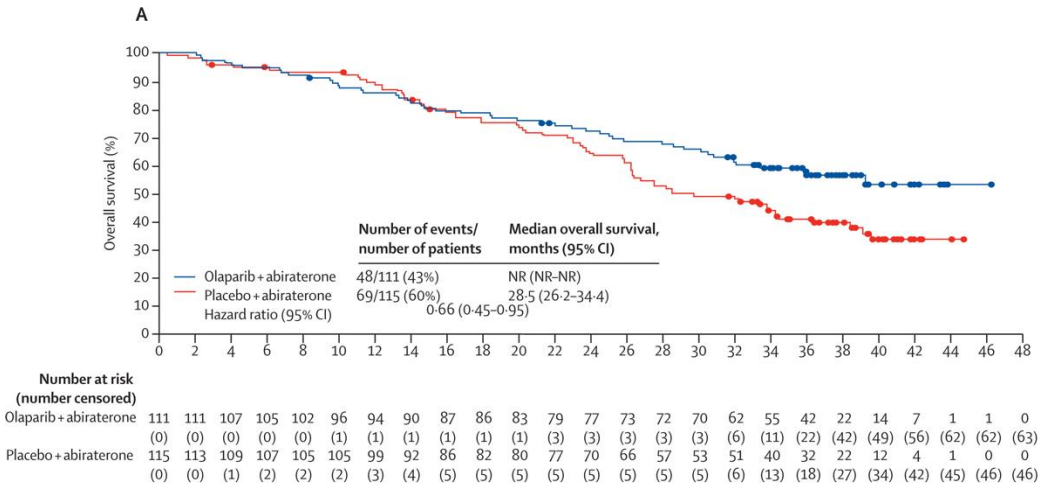


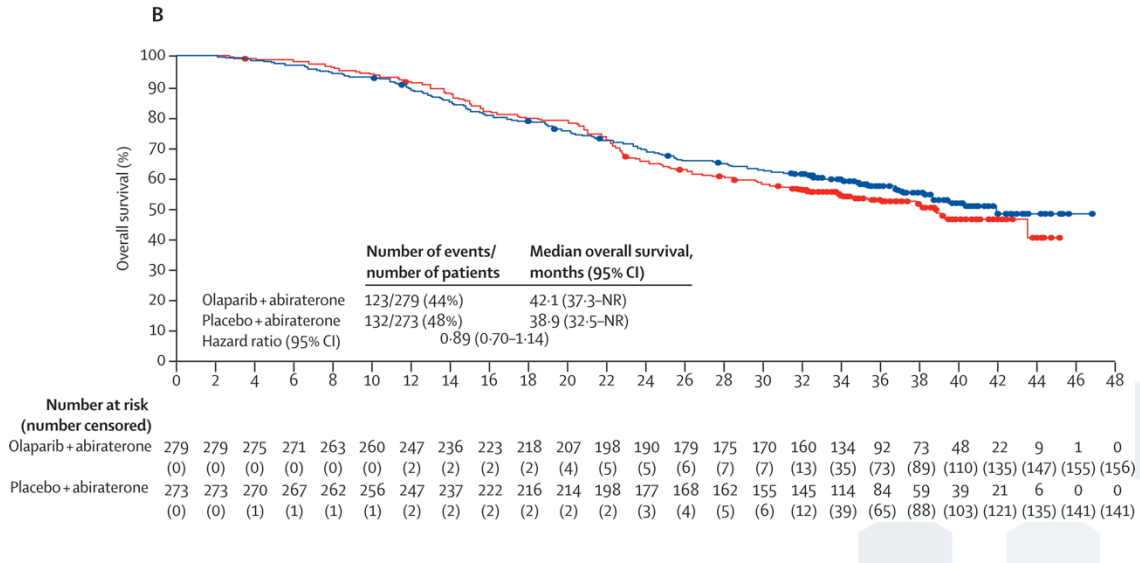
B. Radiographic progression-free survival in the non-BRCAm subgroup

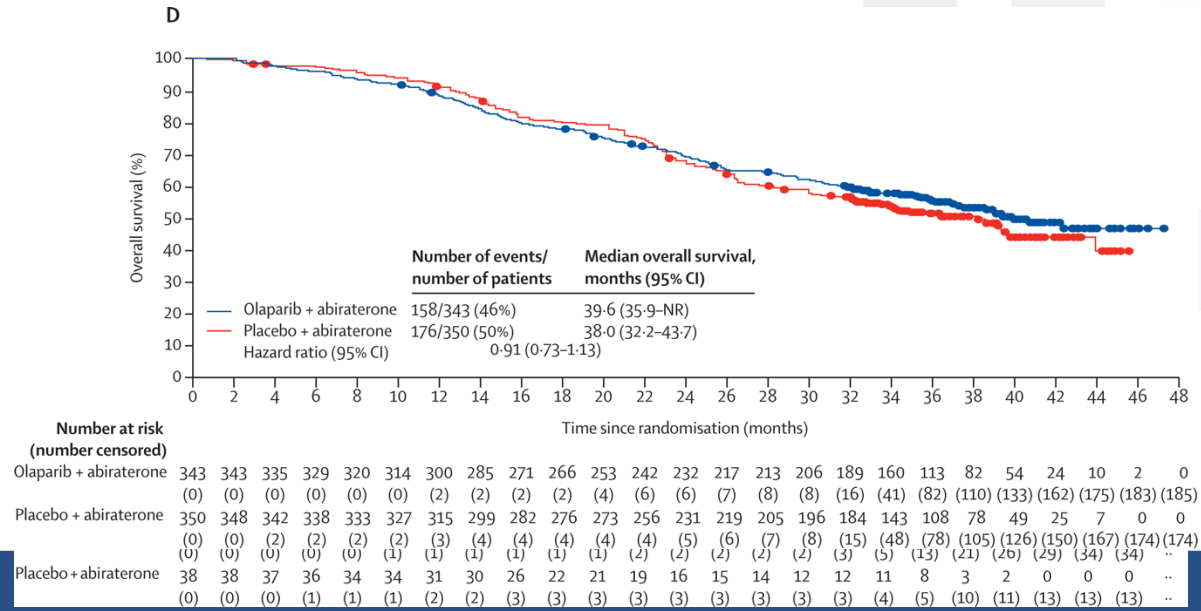


Saad F, et al. Lancet Oncol. 2023 Oct;24(10):1094-1108

PROpel: OS



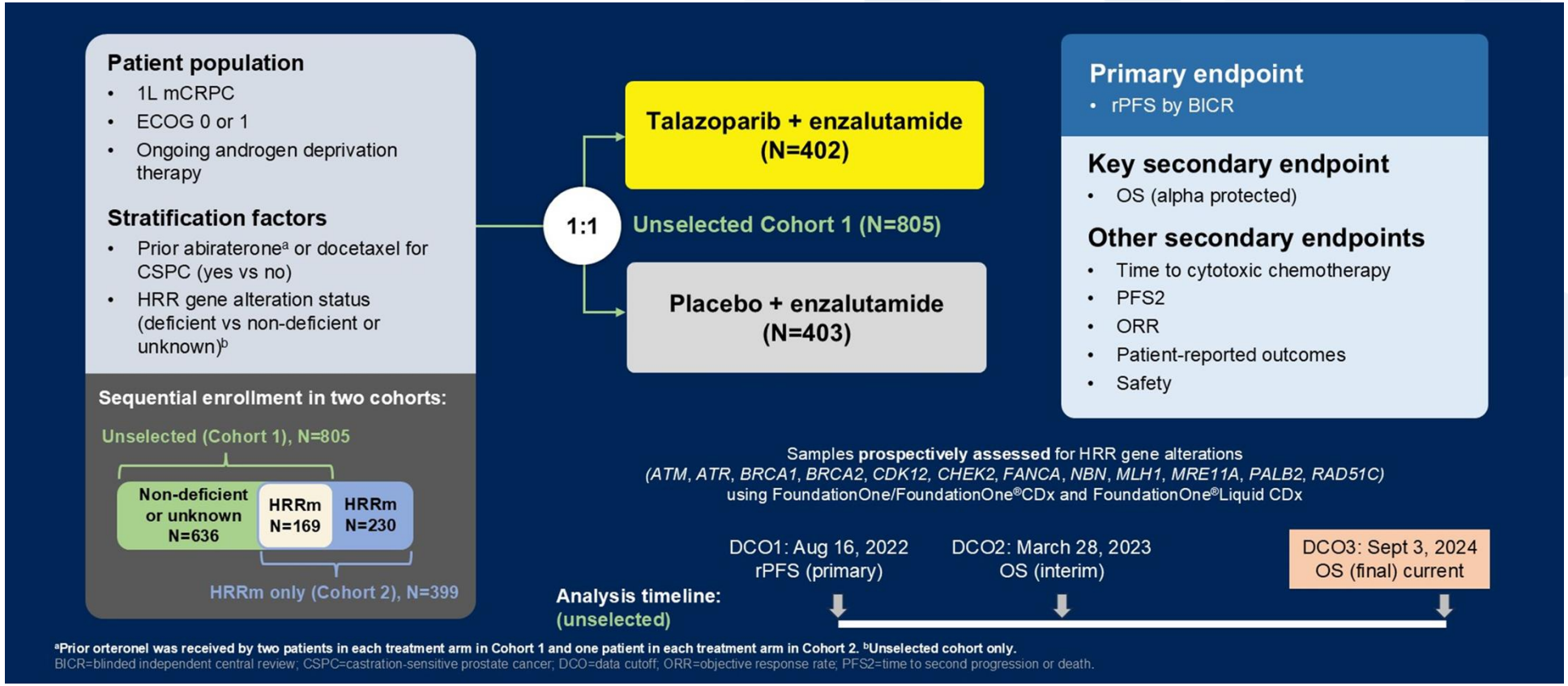




A. OS HRRm
B. OS non-HRRm
C. OS BRCA-mutated
D. OS non-BRCA-mutated

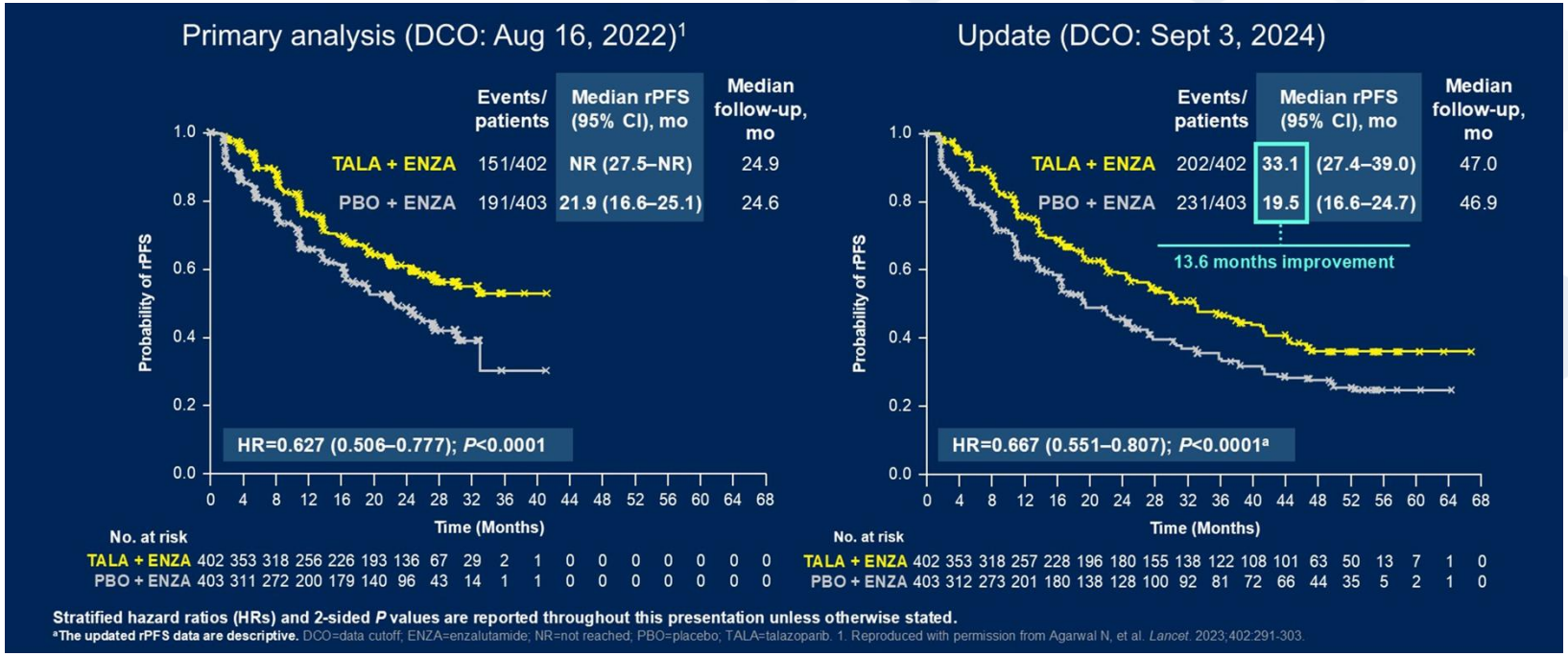
Saad F, et al. Lancet Oncol. 2023 Oct;24(10):1094-1108

TALAPRO-2



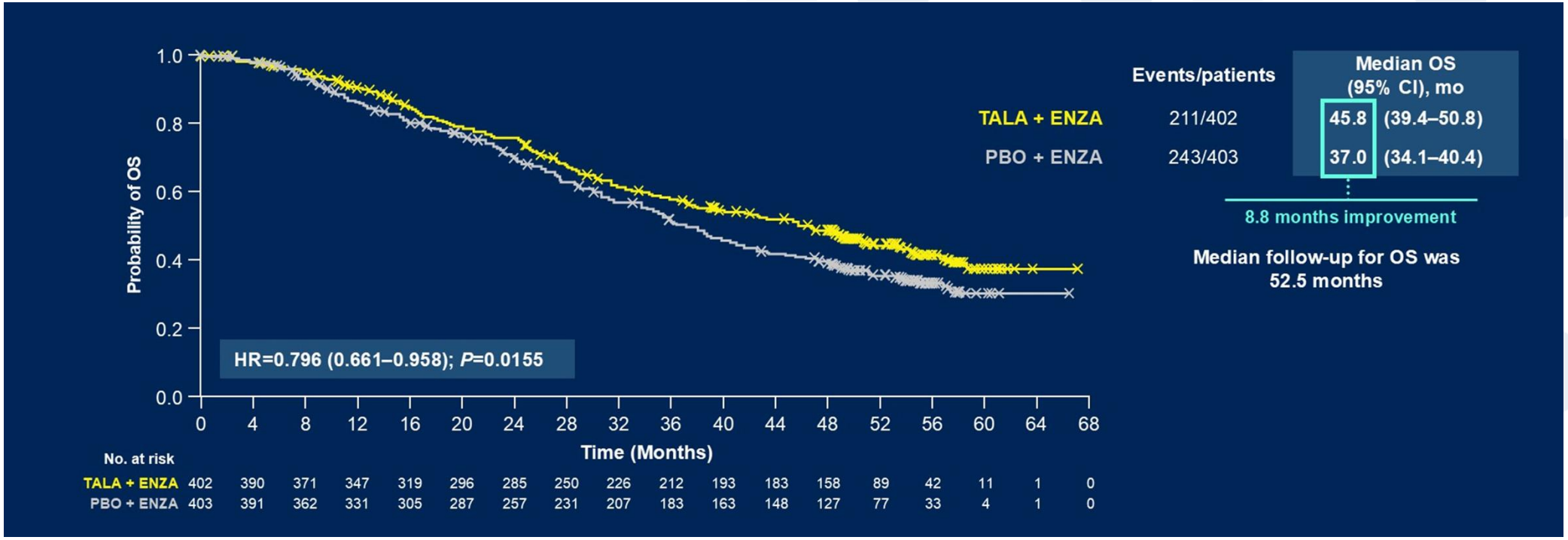
Agarwal N, et al. J Clin Oncol 43, 2025 (suppl 5; abstr LBA18)

TALAPRO-2: PFS



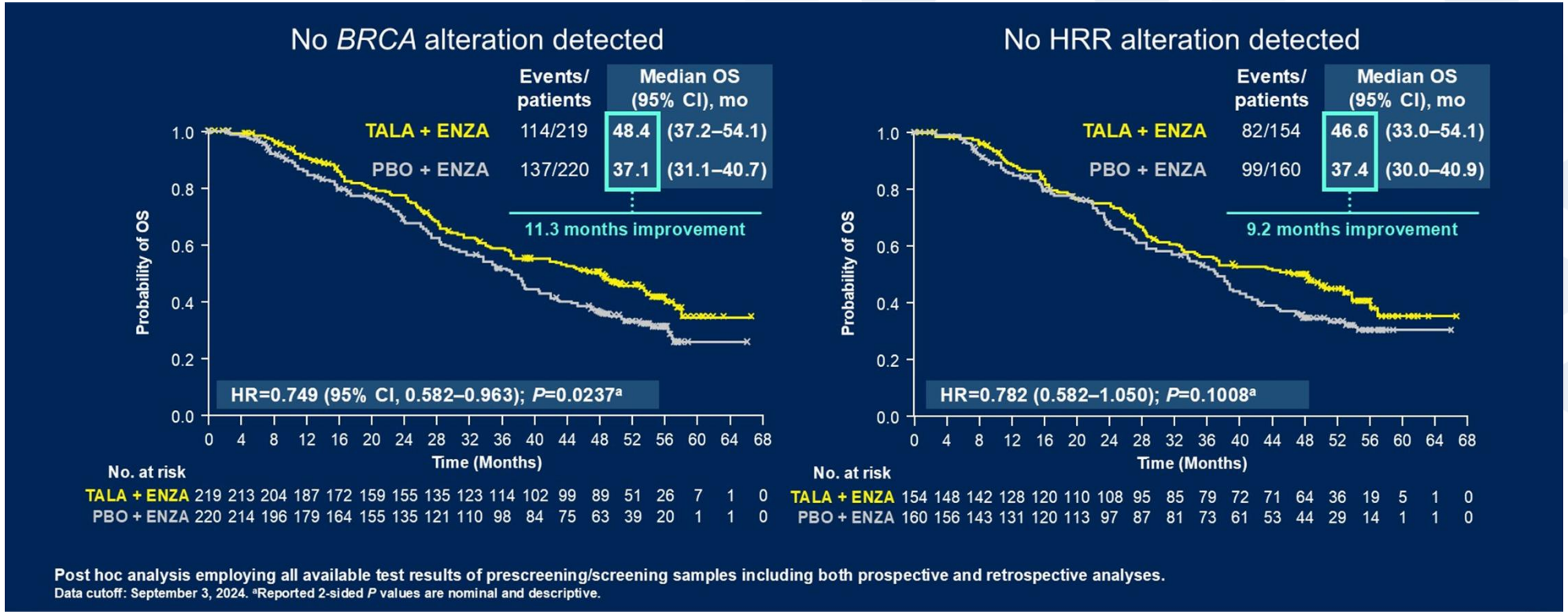
Agarwal N, et al. J Clin Oncol 43, 2025 (suppl 5; abstr LBA18)

TALAPRO-2: OS



Agarwal N, et al. J Clin Oncol 43, 2025 (suppl 5; abstr LBA18)

TALAPRO-2: OS



Agarwal N, et al. J Clin Oncol 43, 2025 (suppl 5; abstr LBA18)

Why Different Results?

Why Different Results?

- Differences in niraparib versus talazoparib/olaparib?
- Differences in testing (excluding more CHIP)?
- Other factors?

ML

06/2016 PSA 17.1 ng/mL; biopsy Gleason 5+4=9 Left prostate

08/2016 ADT and bicalutamide started (neoadjuvant)

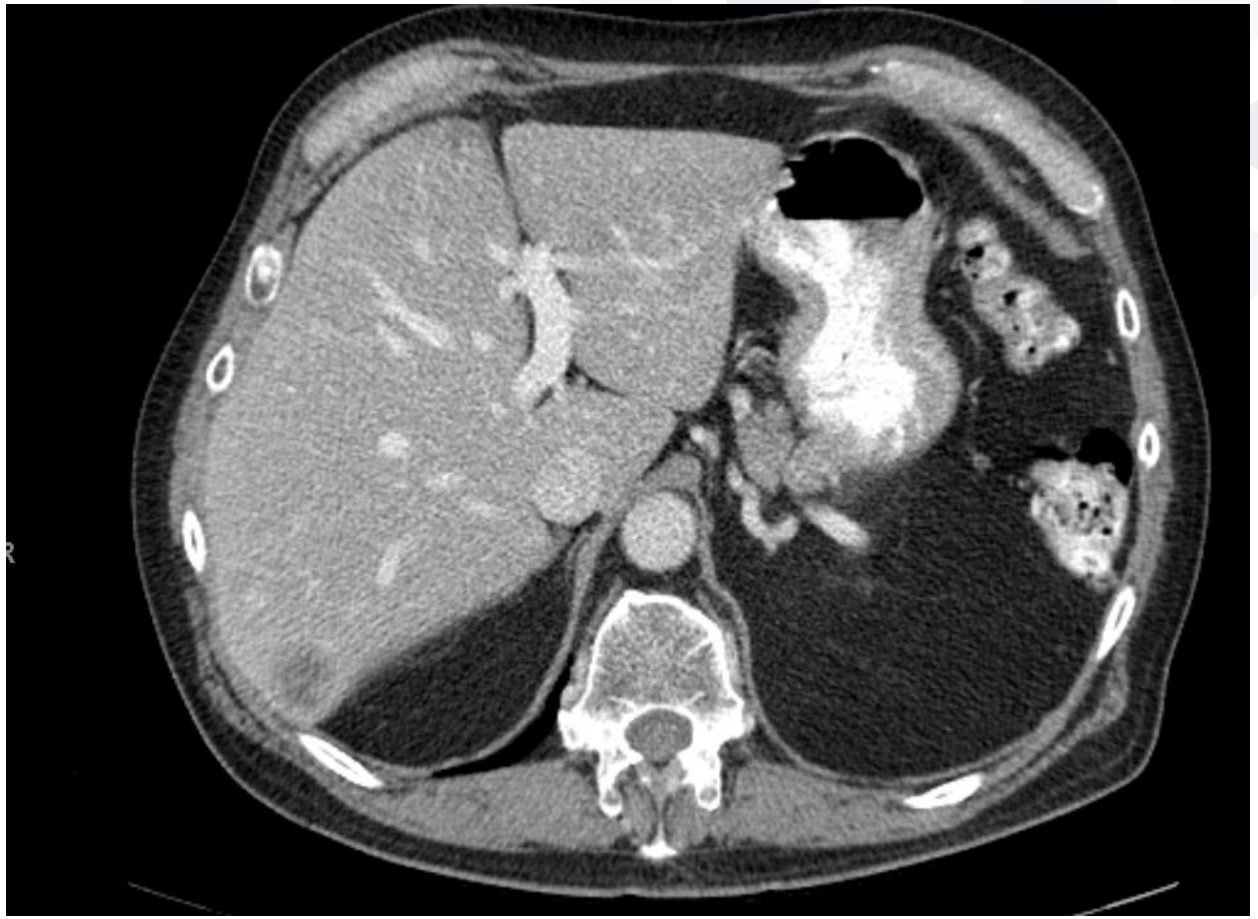
03/2017 PSA 1.63 ng/mL; cystoprostatectomy, pT4, positive margins

05/2017 PSA 4.77 ng/mL

07/2017 PSA 10.2 ng/mL; fluciclovine-PET/CT: Bony metastases to the left inferior sacrum and coccyx. As well as multiple PET positive new liver lesions

07/21/2017 - CT A/P with progressive liver lesions consistent with metastasis

ML



ML

08/2017 Started docetaxel 75mg/m2 plus ADT

8/2017 NGS testing

Genetic testing performed by Invitae

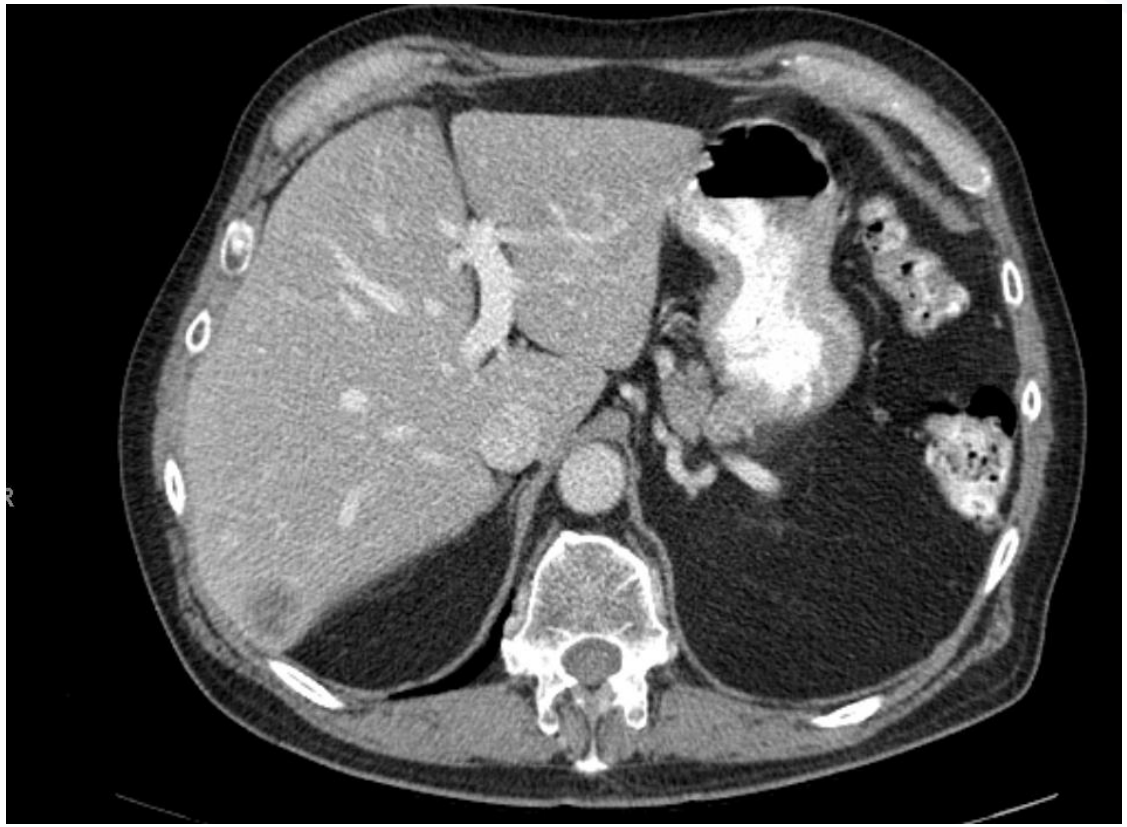
BRCA2 c.1834_1835delGAinsTT (p.Glu612Leu) **VUS**
CDKN2A C.382G>A (p.Ala128Thr) **VUS**
MRE11 c.1462C>G (p.Arg488Gly) **VUS**

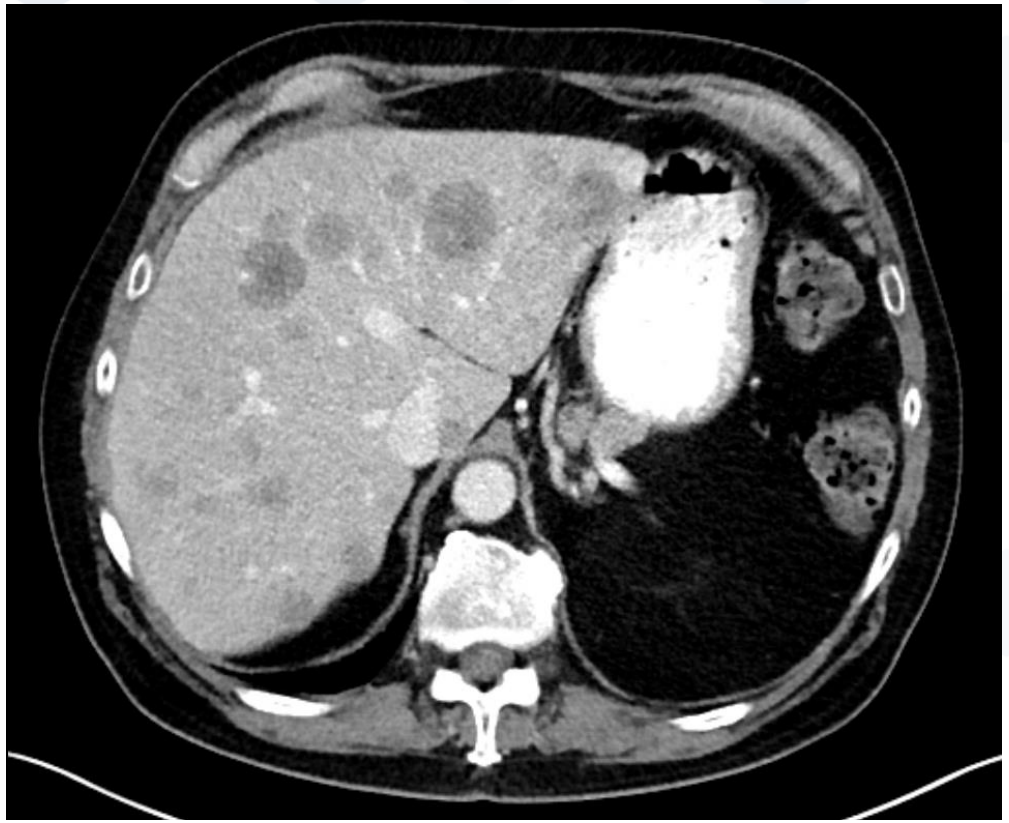
Somatic testing performed by Foundation Medicine from prostatectomy

BRCA del
PTEN del
CTNNB1 S45F
TMPRSS2-ERG fusion
PIK3R1, truncation intron 7
TP53 L114fs*32

01/2018 PSA rise to 6.4 ng/mL, CT c/a/p with progressive disease including new liver metastasis

ML



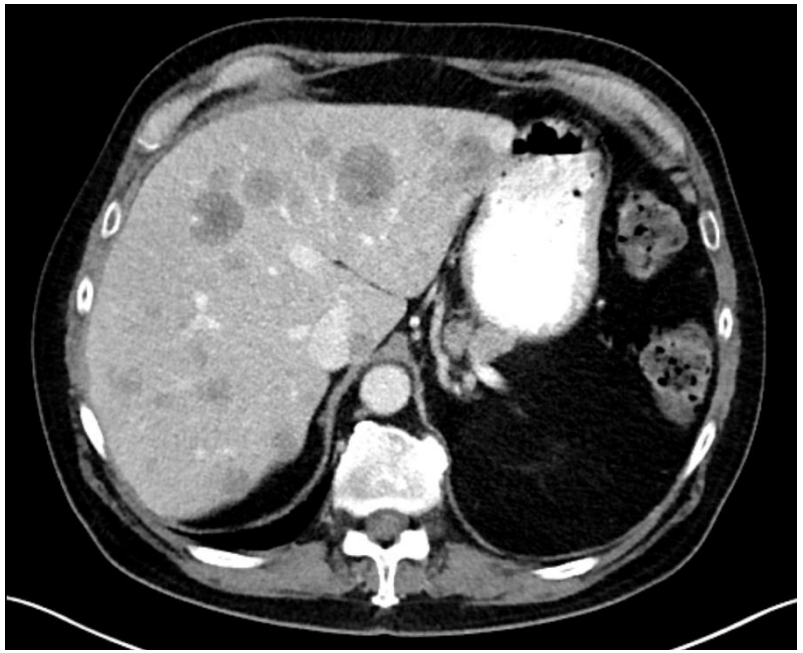


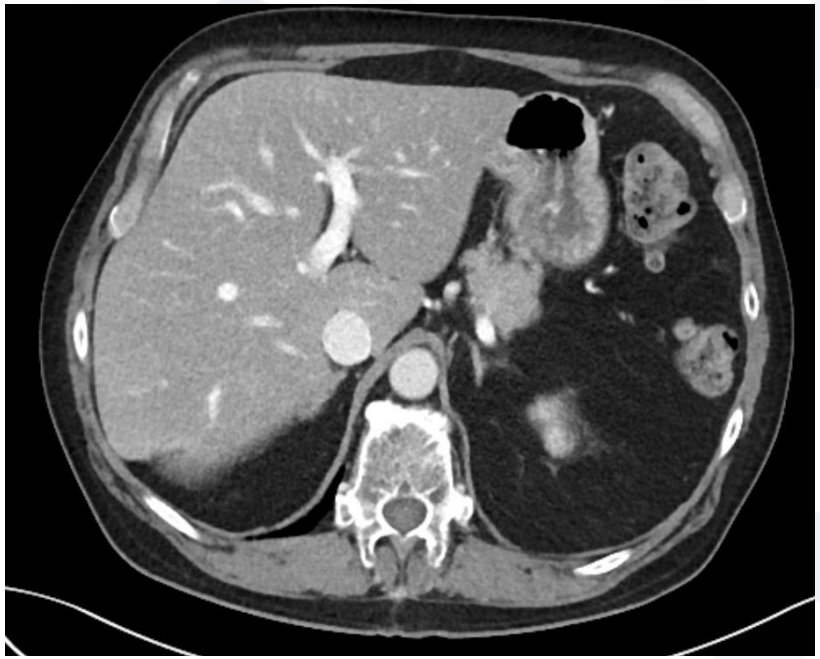
ML

01/2018 Started olaparib 300mg twice daily

06/2018 PSA <0.1 ng/mL; CT a/p resolution of previously visible liver metastasis. CT chest Decreased size of multiple pulmonary nodules

ML





ML

1/2020 Olaparib held for neutropenia (ANC 3.0 -> 1.18)

2/2020 Restart olaparib (ANC 2.6); PSA <0.1 ng/mL

6/2022 PSA <0.1 ng/mL; olaparib dose held due to ongoing fatigue, progressive lymphopenia and ongoing anemia

08/2022 PSA <0.1 ng/mL; Re-started olaparib 300 mg BID

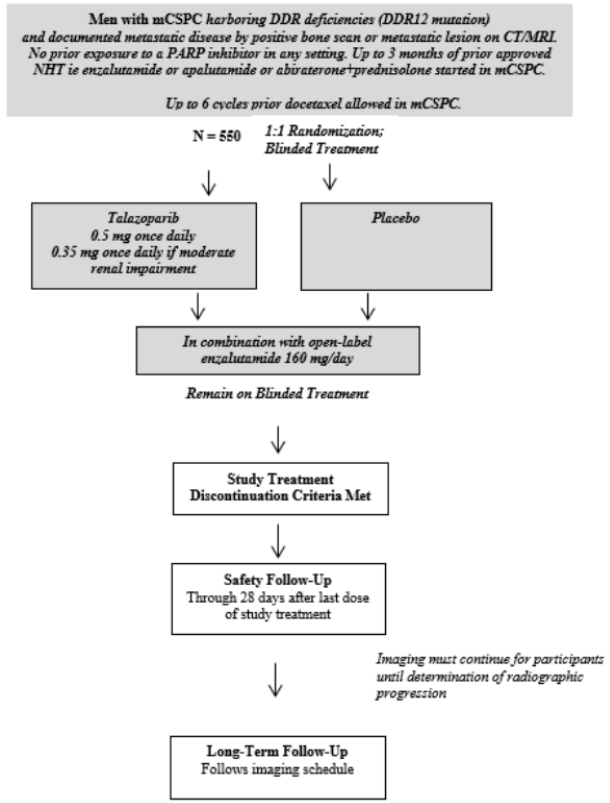
12/2024 NM bone scan negative for metastasis. CT a/p negative for metastasis. CT chest unchanged sclerosis of 10th rib, no metastasis. PSA <0.1 ng/mL

Where We Are Going

mHSPC

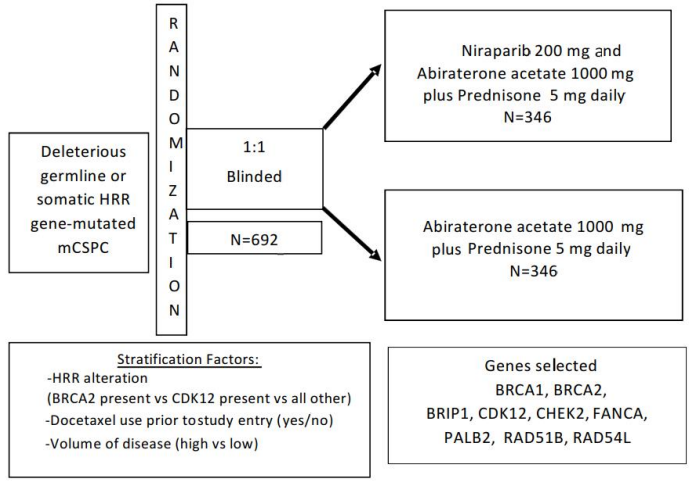
TALAPRO-3

- NCT04821622
- N = 550
- Primary Endpoint rPFS
- Blood or tissue NGS testing



- ***ATM/ATR****/BRCA1*
- *BRCA2/CDK12/CHEK2*
- *FANCA/**MLH1/MRE11A***
- ***NBN****/PALB2/**RAD51C***

AMPLITUDE



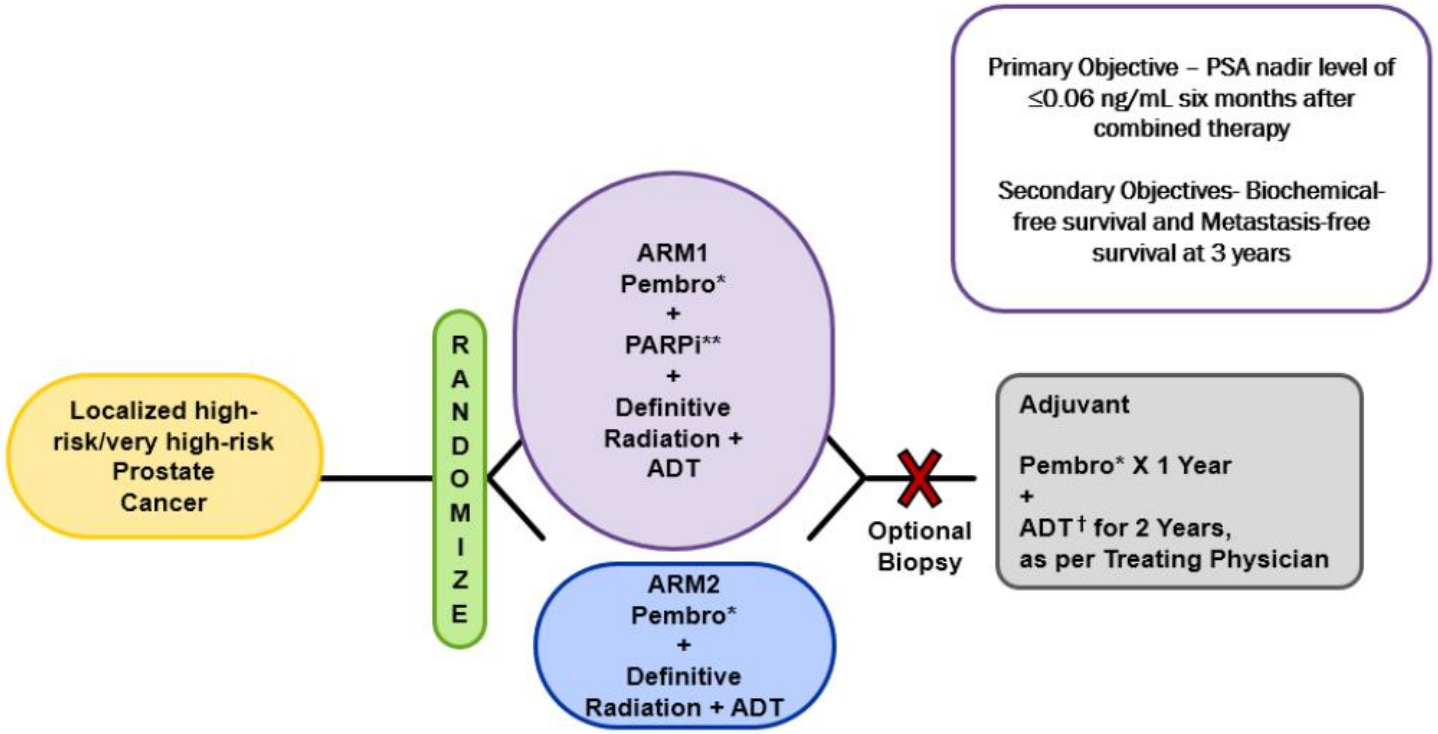
- NCT04497844
- N = 692
- Primary Endpoint rPFS
- Blood or tissue NGS testing

- *BRCA1/BRCA2/**BRIPP1***
- *CDK12/CHEK2/FANCA*
- *PALB2/**RAD51B/RAD54L***

Localized Prostate Cancer

UK/HCI IIT

- Any HRD/DDR status
- N = 64
- NCT05568550
- BRCA1, BRCA2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L



Localized Prostate Cancer

NADIR

- Any HRD/DDR status
- Niraparib/XRT/ADT
- N=22
- NCT04037254
- 95 locations across the US and Canada

ASCLEPIuS

- Any HRD/DDR status
- Niraparib/Abi/XRT/ADT
- N=102
- NCT04194554
- 6 Locations in US

MDACCC IIT

- Any HRD/DDR status
- Neoadj Apa/ADT → Apa/ADT/XRT → Good response will continue; Poor response randomized to Abi/Nira/ADT vs Apa/ADT
- N=200
- NCT04947254

Increasing Complexity

1. Will this replace chemotherapy for mHSPC?

Combined Functional Groups of Primary, Secondary, and Other Endpoints

Single-gene alteration, HR (95% CI)	NIRA + AAP (N)	PBO + AAP (N)	rPFS, HR (95% CI)	TCC, HR (95% CI)	TSP, HR (95% CI)	OS, HR (95% CI)	TPSA progression, HR (95% CI)	ORR (risk ratio) NIRA vs PBO
BRCA1/2	113	112	0.53 (0.36, 0.79)	0.58 (0.33, 1.01)	0.68 (0.42, 1.11)	0.96 (0.57, 1.63)	0.46 (0.30, 0.69)	1.65 (1.02, 2.71); 29/56 (52%) vs 15/48 (31%)
HRR-Fanconi group	17	14	0.59 (0.23-1.45)	0.68 (0.17-2.74)	0.90 (0.24-3.37)	0.43 (0.12-1.50)	0.65 (0.27-1.59)	1.5 (0.38-6.00); 3/6 (50%) vs 2/6 (33%)
BRIP1	4	4	0.23 (0.02-2.26)	NE	1.14 (0.10-13.27)	NE	0.98 (0.14-7.00)	0.5 (0.13-2.00); 1/2 (50%) vs 1/1 (100%)
FANCA	5	6	1.07 (0.18-6.44)	0.51 (0.05-5.16)	1.23 (0.17-8.74)	NE	0.66 (0.13-3.47)	NE; 0/1 (0%) vs 0/2 (0%)
PALB2	8	4	0.59 (0.15-2.22)	0.39 (0.02-6.19)	0.41 (0.03-6.62)	0.27 (0.05-1.66)	0.59 (0.16-2.20)	2 (0.33-11.97); 2/3 (67%) vs 1/3 (33%)
HRR-associated group	20	23	0.64 (0.26-1.58)	0.72 (0.19-2.69)	0.58 (0.17-2.00)	0.43 (0.13-1.38)	0.43 (0.17-1.10)	6.4 (0.96-43.25); 5/7 (71%) vs 1/9 (11%)
CHEK2	18	20	0.66 (0.25-1.75)	0.36 (0.07-1.88)	0.54 (0.14-2.25)	0.44 (0.12-1.71)	0.37 (0.14-0.99)	NE; 5/7 (71%) vs 0/6 (0%)
HDAC2	2	3	0.71 (0.06-8.02)	NE	0.71 (0.04-11.79)	0.44 (0.04-5.13)	NE	NE; 0/0 (0%) vs 1/3 (33%)
ATM	43	42	1.11 (0.63-1.99)	0.26 (0.08-0.80)	0.75 (0.28-2.00)	1.07 (0.44-2.65)	0.73 (0.39-1.36)	3 (1.12-8.13); 14/17 (82%) vs 3/11 (27%)
CDK12	11	16	1.32 (0.43-3.92)	1.13 (0.27-5.70)	1.05 (0.28-3.94)	1.61 (0.49-5.33)	0.66 (0.24-1.80)	2.25 (0.64-7.97); 3/4 (75%) vs 2/6 (33%)

- Patients with genes alterations in *PALB2*, *CHEK2* and *HDAC2* showed benefit across all endpoints, similar to results seen in patients with *BRCA1/2* gene alterations

HR, hazard ratio; CI, confidence interval; NIRA, niraparib; AAP, abiraterone acetate and prednisone; PBO, placebo; rPFS, radiographic progression-free survival, TCC, time to cytotoxic chemotherapy; TSP, time to symptomatic progression; OS, overall survival; TPSA, time to prostate-specific antigen; ORR, overall response rate; HRR, homologous recombination repair; NE, not estimable.

Sandhu S, et al. J Clin Oncol 40, 2022 (suppl 16; abstr 5020)

Increasing Complexity

1. Will this replace chemotherapy for mHSPC?

2. What about long-term toxicity with BM failure?

Increasing Complexity

Cohort A:

3,527 patients first-line maintenance treatment with PARPi after platinum

Cohort B:

356 patients treated with PARPi after platinum-sensitive relapse

Control:

1,503 patients underwent to at least two lines of a platinum-based chemotherapy and never treated with a PARPi

Results

Cohort A vs Control

Propensity scoring (1,282 matched pairs)

Incidence (1.25% vs 0.86%): HR = 2.06 (95% CI 0.94 - 4.51, p=0.064)

Cohort B vs Control

Propensity scoring (263 matched pairs)

Incidence (10% vs 3.8%), HR = 1.76 (95%CI 0.42-7.37, p = 0.432)

Farolfi A, et al. Int J Gyn Cancer. Volume 34, Supplement 3, October 2024, Page A18

Increasing Complexity

1. Will this replace chemotherapy for mHSPC?

2. What about long-term toxicity with BM failure?

3. NGS testing increasingly important
    - HRD status
    - PI3K/PTEN

4. …or maybe not? (Radioligand Therapy)

Conclusions

1) The significance of response is related to HRD status determined from either tissue or liquid biopsy

2) Some synergy exists with PARPi and ARPI
   a. This may not be true after ARPI exposure

3) Three phase 3 trials are ongoing in mHSPC with PARPi/ARPI

4) PARPi/ARPI combinations are being tested in the localized disease setting concurrently with XRT in multiple phase 2 studies

Questions?